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Triplet-Triplet Energy Transfer in Indolylketones

Larry E. Hewitt
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TRIPLET-TRIPLET ENERGY TRANSFER
IN INDOLYLKETONES

by

Larry E. Hewitt

A Dissertation
Submitted to the
Faculty of The Graduate College
in partial Fulfillment
of the
Degree of Doctor of Philosophy

Western Michigan University
Kalamazoo, Michigan
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Larry E. Hewitt
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INTRODUCTION
Absorption and Emission Processes

Triplet-triplet energy transfer is a basic process in both photochemistry and molecular spectroscopy. Understanding the transfer of triplet energy, first observed spectroscopically with organic molecules in 1952, has made possible many of the new developments in synthetic photochemistry during the past decade. It has also been useful for elucidating the mechanisms of photochemical reactions. Because the results would be of interest to many synthetic photochemists, work on intermolecular triplet energy transfer has been investigated very actively. However, the first work on intramolecular triplet-triplet energy transfer was apparently not done until 1963 with no major follow-up until 1967. Most of the studies on intramolecular transfer are directed toward the elucidation of the fundamental nature of and the requirements for triplet energy transfer in general, since many of the basic prerequisites are not known or well understood. Triplet-triplet energy transfer is, however, already becoming a useful tool (phosphorescent probes) for the investigation of enzymatic reactions and for structure elucidation of proteins and nucleic acids. These applications will be discussed later.

Once a molecule has absorbed radiation and is promoted from the ground electronic state (designated as $S_0$), various

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processes can occur before it returns to $S_0$. These will be reviewed briefly by means of the schematic energy level diagram (Fig. 1).

In the absorption process the molecule is excited from the ground state to any of the vibrational states of a higher singlet electronic state $S_n$. The radiationless process whereby a molecule passes from a low vibrational level of an upper state $S_2$ to a high vibrational level of a lower electronic state having the same total energy is known as internal conversion (denoted by wavy lines in the diagram). Loss of excess vibrational energy ultimately puts the molecule in the lowest vibrational level of the first excited state $S_1$. Internal conversion can also occur to the ground state $S_0$. Another radiationless process allowing a molecule to pass from the lower vibrational level of $S_1$ to a high vibrational level of the first triplet state $T_1$ is called intersystem crossing (dashed line). This is the process by which the triplet state is populated since direct absorption $S_0 \rightarrow T_1$ is forbidden by quantum mechanical spin rules.

A molecule can return to the ground state by radiative transitions. Fluorescence is defined as the light emitted as a result of a transition between states of the same multiplicity while phosphorescence describes a radiative transition between states of different multiplicities. For organic molecules in fluid or rigid solutions only the lowest
Figure 1. Schematic energy level diagram indicating radiative and radiationless transitions.

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triplet and lowest singlet states are found to emit. For all practical purposes fluorescence is due to the transition $S_1 \rightarrow S_0$ and phosphorescence to $T_1 \rightarrow S_0$. The following sequential outline summarizes the various processes. Approximate lifetimes are indicated. Reflecting the forbidden nature of the transition, the phosphorescence lifetimes are considerably longer than fluorescence.

**Absorption**

$S_0 \rightarrow S_n$  

**Internal conversion**

$S_n \xrightarrow{10^{-11} - 10^{-14} \text{sec}} S_1$

**Fluorescence**

$S_0 + h\nu \rightarrow T_n \xrightarrow{10^{-9} \text{sec}} S_0$

**Intersystem crossing**

$S_0 \xrightarrow{10^{-8} \text{sec}} T_n \xrightarrow{10^{-5} - 10^{-7} \text{sec}} S_0$

**Internal conversion**

$T_1 \xrightarrow{10^{-3} \text{sec}} S_0$

$S_0 \xrightarrow{10^{-3} \text{sec}} S_0$

**Internal conversion**

Initial Studies of Triplet-triplet Energy Transfer

Triplet-triplet electronic energy transfer can be described by the following equation in which initially,

\[ D^* (\text{triplet}) + A (\text{singlet}) \rightarrow D (\text{singlet}) + A^* (\text{triplet}) \]

the donor molecule $D$ is in an excited triplet state; in the final state the acceptor $A$ has been promoted to a triplet and the donor has been demoted to its ground state.
The electronic energy transferred is denoted by the asterisk. The triplet acceptor can now react or emit as if it had been excited directly. If it phosphoresces while going from the lowest triplet state to the ground state, the overall process is called sensitized phosphorescence. The radiationless transfer of triplet electronic energy involves the simultaneous de-excitation of the donor and excitation of the acceptor: a one-step process which does not involve the intermediacy of a photon.

In order to demonstrate unambiguously triplet-triplet energy transfer the donor and acceptor energy levels must be arranged appropriately. The ideal arrangement is indicated in the following diagram (Fig. 2). With a suitable cutoff filter direct excitation of the acceptor molecule

![Energy level diagram](image)

Figure 2. Energy level diagram illustrating an ideal case of triplet-triplet electronic energy transfer.
is excluded, and only the donor is excited. Any possibility of singlet-singlet energy transfer is prevented. The donor is chosen so that its $S_1$ and $T_1$ energy levels are between those of the acceptor. Donor molecules having a small energy difference between $S_1$ and $T_1$ are good candidates for much of the experimental work. Carbonyl compounds make especially good donor molecules.

The first demonstration of sensitized phosphorescence with organic compounds in rigid media at $77^°K$ was provided by the classic experiment of Terenin and Ermolaev. These investigators studied solutions of anthracene (A) and benzophenone (D). A solution of anthracene in ethanol at $77^°K$ excited by radiation of 366 nm wavelength exhibits no phosphorescence since the onset of the absorption spectrum lies at 327 nm. However, irradiation of a mixture of benzophenone-anthracene under the same conditions leads to emission from anthracene, and the spectrum is identical with that of anthracene phosphorescence. The energy level scheme for this example parallels the ideal conditions above and is illustrated in Figure 3. Excitation at 366 nm corresponds to an energy of 27,300 cm$^{-1}$. The only way phosphorescence from anthracene could have occurred is by triplet-triplet energy transfer.

Another confirmation of energy transfer is provided by observation of quenching of the donor. Ermolaev and Terenin found that the value of $I_0/I - 1$ increased (where

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Figure 3. Energy level diagram for triplet-triplet energy transfer from benzophenone to naphthalene at 77°K.

$I_0$ and $I$ represent the donor phosphorescence intensity in the absence and presence of the quencher, i.e., naphthalene) as the concentration of naphthalene increased. This result indicated benzophenone quenching. Analogously, the relative yield of the naphthalene-sensitized phosphorescence should increase as its concentration increases. The ratio $I_A/I_D$ (obtained by graphical integration of the spectral curves of the phosphorescence of the acceptor and donor) was found to increase rapidly as the naphthalene concentration increased.

An extension of this work to many other donor-acceptor pairs has been done.$^5$

The first documented case of intramolecular sensitized phosphorescence in organic molecules was reported in 1963 by Leermakers, et. al.$^2$ who investigated the compound

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4-(1-naphthylmethyl)benzophenone (I, n = 1). Interestingly, this compound contains the same chromophores studied intermolecularly by Ermolaev and Terenin. The singlet and triplet energies of the two moieties are the same as those discussed before. The only emission detected from an equimolar mixture of 1-methylnaphthalene (II) and 4-methylbenzophenone (III) under excitation with 366 nm light was that of 4-methylbenzophenone. Apparently, intermolecular energy transfer is negligible at this concentration (5 x 10⁻³ M). However, at the same concentration, the phosphorescence spectrum of 4-(1-naphthylmethyl)benzophenone (I, n = 1) is almost identical to that of 1-methylnaphthalene even when only the benzophenone moiety is excited (366 nm excitation). The phosphorescence spectra are reproduced in Figure 4.

Later this work was extended to a study of triplet-triplet energy transfer in a series of compounds containing the benzophenone and naphthalene moieties separated by a
Equimolar mixture of II & III

1-Methylnaphthalene (II)

17000 19000 21000 23000 25000
Wavelength (cm⁻¹)

Figure 4. Comparison of phosphorescence spectrum of I with those of model compounds.

series of methylene groups (I, n = 1, 2, 3). The absorption spectra of all three compounds were nearly identical to that of an equimolar mixture of 1-methylnaphthalene (II) and 4-methylbenzophenone (III) demonstrating that the two absorbing chromophores are independent. The phosphorescence emission spectra of the three compounds are nearly identical to that of 1-methylnaphthalene. Quenching experiments showed that every quantum absorbed by a benzophenone chromophore resulted in the formation of a quenchable triplet. Combining these data with other results led to the following conclusion. Irradiation of compounds I with 366 nm light leads to excitation of the lowest n→π* singlet state of benzophenone. After completely efficient intersystem crossing resulting in the corresponding n→π* triplet, transfer of the triplet energy to the naphthalene moiety takes place with 100% efficiency.
The increase in the number of methylene groups in the "bridge" connecting the two chromophores apparently does not place the chromophores farther apart. Molecular models were constructed by the authors and little difference in the distance was noted for the three molecules. Moreover, many conformations are probable that place the chromophores in van der Waals contact. Of course, an infinite number of intermediate conformations are possible. Also, the relatively large sizes of the chromophores give more chance of contact. It is this contact (or more specifically, the overlap of the electron clouds) that is believed to be responsible for triplet-triplet energy transfer. Before discussing further studies involving intramolecular transfer, the nature of the interaction responsible for the transfer should be examined.

Theoretical Work on Triplet-triplet Energy Transfer

In 1924 Perrin,\textsuperscript{7} while investigating fluorescence quenching in dyes, introduced the concept of the "active sphere." Extended to intermolecular triplet-triplet electronic energy transfer, the theory suggests that, if an acceptor molecule has an excited donor molecule in the triplet state within its "sphere of interaction," the donor is quenched "instantaneously." On the other hand, donor molecules located outside the given volume $v$ about the acceptor exert no effect on the acceptor. It is assumed that the molecules do not change their positions during the
lifetime of the excited state, and a rigid solution assures this. In such a case the only donors which transfer triplet energy are those whose "active volumes" contain acceptor molecules. If $v$ is the volume of the active sphere of each acceptor molecule and $n = N \times 10^{-3}$ is the number of acceptor molecules per cm$^3$, the probability that an excited donor will lie within an active sphere is

$$p = e^{-nv}$$

The quenching of the donor phosphorescence yield $\Phi_{pt}$ by triplet-triplet energy transfer as a function of the acceptor concentration is described by the formula

$$\frac{(\Phi_{pt})_0}{(\Phi_{pt})} = e^{\alpha[A]}$$

where $(\Phi_{pt})_0$ is the phosphorescence quantum yield of the donor in the absence of the acceptor, $\Phi_{pt}$ is the quantum yield in the presence of acceptor at concentration $[A]$, and $\alpha$ is a constant. Since $p$ is proportional to $\Phi_{pt}$,

$$\frac{(\Phi_{pt})_0}{\Phi_{pt}} = e^{nv}$$

The volume of the active sphere is therefore,

$$v = \frac{\ln[(\Phi_{pt})_0/\Phi_{pt}]}{N[A] \times 10^{-3}}$$
and, assuming the molecules approximate the size of spheres, the radius of the active sphere $R$ is

$$R = \left[ \frac{3v}{4} \right]^{1/3}$$

For the benzophenone-naphthalene case, $v = 8.6 \times 10^{-21} \text{ cm}^3$ and $R = 13 \AA$ is the distance between the centers of the interacting molecules. Studies with other molecules\(^5\) give critical transfer distances around $15 \AA$. The distances calculated from Perrin's model are slightly more than the van der Waals radii expected for donor-acceptor collision complexes depending upon the particular molecules.

Several inadequacies can be found with the model. It assumes that no complex forms between D and A molecules. Some workers have found complex formation to be negligible\(^8,9\) under the conditions employed while studying triplet transfer although the evidence is not unequivocal. The possibility remains that a random distribution of molecules is not achieved since more polar interactions could lead to molecules being closer than the critical transfer distance. This would lead to greater transfer efficiency. The spherical assumption for molecular shapes also seems inadequate for molecules in rigid solutions, since, for example, naphthalene has molecular dimensions of approximately $9 \AA \times 7 \AA \times 3.5 \AA$. The distance between the electron cloud of naphthalene and a donor would depend on its orientation. Microco-precipitation could also occur at the low temperatures.
employed and especially at the relatively high concentra-
tions (0.5 M)\textsuperscript{10} needed to observe the phenomena. Finally,
local melting of the glass matrix may occur because of the
heat evolved in radiationless transitions of the excited
molecules. This could decrease the actual distance of approach
with respect to a random distribution in glassy solutions at
low temperatures.

Triplet-triplet electronic energy transfer has been
treated theoretically by Dexter.\textsuperscript{11} In this formalism
transfer is seen possible when the excited donor and accep-
tor are close enough for overlap of their electron clouds.
In the region of overlap the electrons are indistinguish-
able so that an excited electron on D\textsuperscript{*} may also appear on A.
This exchangeability of electrons leads to the exchange
mechanism for energy transfer. Dexter has shown that the
probability of energy transfer is proportional to the square
of an exchange integral which represents the electrostatic
interaction between the electron clouds of the donor and
acceptor. Since both functions leading to the electron
interactions fall off exponentially with distance from D\textsuperscript{*}
or A, it is clear that their product will be very small
throughout all space unless D\textsuperscript{*} and A have a small separa-
tion distance. If the separation is small, both functions
will be sizable in the same region of space, namely, between
D\textsuperscript{*} and A where the distance between interacting electrons is
small. The integral may well be sizable (for small separations)
even though the overlap integrals, which enter in normalization, are negligibly small.

The separation and concentration dependencies are included in a term whose quantity can not be directly related to optical experiments. Thus, spectroscopic measurements, unfortunately, will not give values of donor to acceptor distances.

The selection rules in the exchange integrals allow triplet-triplet transfer to occur by this mechanism.

Since Dexter's original paper on the exchange mechanism little work on the theoretical basis of triplet energy transfer has been done. To our knowledge only one report of an actual calculation using Dexter's transfer probability expression has been done.$^{12}$ This gave an order-of-magnitude agreement with an experimentally determined transfer efficiency, but the value of the exchange integral can vary by $10^{13}$ eV depending on the type of orbitals used in the calculation. Thus any calculations for the exchange mechanism with present knowledge of orbital interactions, are, for the most part, not too reliable and little confidence can be placed in them. The mechanism seems to depend on the orientation, and although theoretical work is lacking, experimental work has been done with intramolecular transfer in suitably oriented rigid molecules. These will be discussed below along with attempts at determining distance requirements for triplet-triplet transfer.
Further Studies of Triplet-triplet Transfer Using Emission Spectroscopy

A study of triplet-triplet energy transfer paralleling that of Hammond, et al., used a similar series of compounds. Keller and Breen prepared the compounds which contain a

\[ \text{IV, } n = 0, 1, 2, 3 \]

naphthalene moiety as the acceptor and phthalimide as donor. The energy levels of the chromophores were not ideally situated since at the excitation wavelength used (297 nm), both chromophores absorb nearly equally. Energy transfer was determined by comparing the intensities of the phosphorescence of compounds IV with that of 1-methylnaphthalene. The intensity of the phosphorescence of IV was found to be twice that of 1-methylnaphthalene alone. This is what would be expected if the triplet energy of phthalimide were transferred completely to naphthalene and quantum yields were unchanged.

Any satisfactory correlation of the transfer efficiency to the structure of the molecules IV is difficult since the work suffers from the same problems associated with Hammond's work, i.e., the framework of methylene groups does not allow any rigidity to keep the chromophores apart. The increase in the number of methylene groups would tend
to place the chromophores farther away from one another. However, this assumes that an "extended" model is one of the more preferred conformations. Although Keller and Breen\textsuperscript{3} seem to think that an extended model is more reasonable (for IV, n = 3, the chromophores would be about 5 Å apart), the conformations which allow energy transfer to occur most efficiently are probably those that place the chromophores in contact or near contact. Polar interactions between the chromophores could bring them close together especially in rigid solution. Little is known about the preferred conformatons of such molecules. It seems unusual that these workers think it improbable that the molecules exist in a conformation in which a complex is formed between the chromophores.

Keller later investigated triplet-triplet energy transfer in a system which was the first attempt at studying a relatively rigid molecule.\textsuperscript{13} The two compounds V and VI contain the anthrone moiety as the donor and naphthalene as acceptor held apart by a spiro linkage. The absorption spectra of each double molecule agree very well with the sum of the spectra of the two isolated parts. The orientation of the plane of the naphthalene chromophore with respect to the plane of the anthrone chromophore differs by 90\(^\circ\) in V and VI. The energy level scheme involved is given in Figure 5. The phosphorescence spectra of both compounds V and VI when excited with energy of 366 nm

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Figure 5. Energy level diagram of singlet and triplet states for model compounds V and VI.

wavelength show only emissions characteristic of the naphthalene chromophore indicating complete transfer of triplet energy. Anthrone phosphorescence could have been seen since it phosphoresces over a wide wavelength region where naphthalene does.

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not emit. Other data indicate that little of the triplet energy is lost during the transfer to the naphthalene.

Triplet energy transfer in the same two compounds V and VI was studied by Hudson and Hedges in a later report. They obtained significantly different phosphorescence results than that reported by Keller. The compounds were prepared in essentially the same manner. Upon excitation at 369 nm where only anthrone absorbs, the phosphorescence spectrum of both compounds show that emission is occurring from both chromophores and not just from naphthalene indicating that triplet transfer is not complete! Hudson and Hedges were able to reproduce Keller's naphthalene-only emission by employing conditions likely to cause aggregation of molecules, and, therefore, intermolecular transfer of the remaining anthrone triplet energy. The aggregation is apparently caused by the insolubility of the spirans V and VI relative to compounds like naphthalene. Hudson and Hedges used spirane concentrations an order of magnitude lower than the previous study and even then had to be careful to avoid suppressing the anthrone phosphorescence. They concluded that these results of only partial transfer of triplet energy must be due to the near orthogonality of the transition moments in the two chromophores. The orthogonality of the planes of the two moieties probably is involved in the lack of total transfer, but the transition moments of the chromophores, according to Dexter, are not involved in
the exchange mechanism of triplet-triplet energy transfer. When models are constructed of the spiranes V and VI, the spiro linkage is seen to be not entirely rigid. Two conformations are possible that bring the H-1 and H-8 of the anthrone within the $\pi$ orbital system of the naphthalene. Whether this is the overlap that is responsible for the triplet-triplet energy transfer is uncertain, but it could explain the subtle change in anthrone emission in V and VI upon solvent changes. Therefore, it is probably not a valid assumption to consider that the $n,\pi^*$ lowest triplet energy level is localized exclusively in the carbonyl group.

Other workers studied further examples of intramolecular energy transfer in rigid molecules and again obtained conflicting results. Demember and Filipescu$^{15}$ prepared 1,4-dimethoxy-5,8-methano-6,7-exo-[fluorene-9'-spiro-1"-cyclopropane]naphthalene (VII) which contains the p-dimethoxybenzene (DB) and fluorene (F) chromophores on an inflexible norbornane-spirocyclopropane frame. According to the authors, the uv absorption spectrum of VII coincided with that of an equimolar mixture of VIII and dimethoxybenzene.
Using a mixture of VIII and p-dimethoxybenzene, phosphorescence and excitation spectra indicated that efficient energy transfer was taking place from F to DB because only a triplet emission from DB was seen at the concentrations employed (10^{-3} M). At these concentrations and the resulting large distances between chromophores these results are compatible only with singlet-singlet resonance transfer. With the rigid model compound VII no singlet or triplet transfer could be detected. This suggested that, although the two systems are only 7 Å apart and thus well within the 15 Å distance reported for intermolecular exchange interaction, an orientation preference must be satisfied before efficient transfer occurs.

Lamola restudied the same compound\textsuperscript{16} because he was skeptical of the results of Filipescu's work. One minor improvement was to use the compound IX as the model donor instead of p-dimethoxybenzene. The combined absorption spectra of VIII and IX were significantly different from the spectrum of the double chromophore compound (VII). In addition to intensity differences, distinct spectral shifts were present indicating that interactions between
the chromophores are not negligible. In addition the emission band for compound IX attributed to the phosphorescence by DeMember and Filipescu was assigned erroneously. Instead, according to Lamola, it is probably involved with the quenching of the fluorene-like fluorescence. Lamola examined the fluorescence of fluorene itself and noted that the intensity was nearly 200 times as intense as in the spirocyclopropane-linked fluorene (VIII). The bridging network exerts a profound quenching of fluorene fluorescence. Filipescu reported also that no singlet-singlet energy transfer was detected in compound VII. However, Lamola found evidence for efficient singlet-singlet transfer from the p-dimethoxybenzene group to the fluorene moiety, and because this transfer was fast, triplet excitation transfer was precluded. Consideration of both papers indicates that the choice of compound VII is not a good one for transfer studies because of an interaction between the chromophores and because the spiro-cyclopropane structure seems to affect the emission properties of the fluorene moiety. Indeed, in a later report by Filipescu a photorearrangement was

![Diagram](image.png)

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detected for the spiro-cyclopropane fluorene VIII in which a dibenzofulvene X was formed. These compounds exhibit an intense $S_1 \rightarrow S_0$ emission, and for photoproduct X, it appears at the same wavelength as the anomalous fluorescence peak in Lamola's paper$^{16}$ and the mistaken phosphorescence peak in Filipescu's work.$^{15}$

Keller and Dolby$^{18}$ prepared and examined the absorption and emission of compounds containing chromophores separated by a rigid steroid bridge. 3-Naphthyl-5$\alpha$-androstane-17$\beta$-(p-benzoylbenzoate) (XI) contains an ester of benzoylbenzoic acid as the triplet donor and the naphthalene chromophore as the acceptor. Another compound XII

![Chemical structure of compounds](attachment:image.png)

contains carbazole as the donor chromophore. The choice of chromophores is nearly ideal since the energy levels are

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situated such that both donor chromophores in XI and XII can be excited by long wavelength radiation which is not absorbed by the acceptor naphthalene chromophore. When compound XI was excited by radiation only absorbed by the donor chromophore, the phosphorescence spectrum showed some naphthalene emission in the presence of strong phosphorescence characteristic of the triplet donor. No naphthalene emission is seen from an equimolar mixture of model donor XIII and naphthalene. Comparison of the phosphorescence intensities indicates that 35% of the triplet excitation energy is transferred to naphthalene in compound XI. For compound XII comparison of intensities from triplet-donor chromophore and triplet-acceptor chromophore indicate that about 30% of the triplet energy is transferred from the carbazole chromophore to the naphthalene. For both compounds XI and XII the absorption spectra agreed favorably with the sum of the spectra of the separated chromophores.

The main conclusion of Keller and Dolby was that triplet energy transfer is a relatively short-ranged process. The distance between chromophores in XI and XII as measured from molecular models is approximately 15Å. Presumably,
this is in an "extended" model placing the chromophores
the maximum distance apart. However, many conformations
are possible which bring the chromophores considerably
closer together because the steroid backbone is not entirely
rigid and the benzophenone-4-carboxylate chromophore has
considerable rotational freedom. Galley and Stryer\textsuperscript{19} have
also noted this lack of rigidity and variable distance.
Compound XII was purified by thin-layer chromatography from
a mixture containing three other impurity spots. The
purity and identification of the compound seems to be in
some question since all emission studies were done on 0.03 mg
obtained from the thin-layer chromatogram. Also, the carbon-
hydrogen elemental analysis was performed before this
purification.

A bis-steroid backbone served to separate chromophores
in a compound (XIV) prepared by Leermakers, et. al.\textsuperscript{20} A

\[
\begin{array}{c}
\text{XIV}
\end{array}
\]
naphthoate chromophore acted as the donor and anthranoate as the triplet energy acceptor. The energy level scheme is depicted in Figure 6. The intensity of phosphorescence for compound XIV excited at a wavelength equivalent to an energy of 95.4 kcal/mole was compared to the intensity of an equimolar mixture of methyl 1-naphthoate and methyl 9-anthroate.

\[
\begin{align*}
S_1 & \quad 89.4 \text{ (320 nm)} \\
S_2 & \quad 74.3 \text{ (385 nm)} \\
T_1 & \quad 61.5 \\
T_2 & \quad 45
\end{align*}
\]

Figure 6. Energy level diagram for chromophores in model compound XIV. Excitation at 300 nm.

Their equipment was incapable of recording the low energy triplet emission from anthroate although naphthoate emission could be observed. The intensity of the naphthoate phosphorescence was nearly equal for both XIV and the mixture. They thought that this intensity from XIV was somewhat greater than expected since 80% of the naphthoate's excitation energy had already been dissipated through singlet-singlet transfer which was examined in the same paper. If any
triplet-triplet transfer to anthroate had occurred, an attenuation in naphthoate phosphorescence intensity should have been observed. In addition phosphorescence lifetimes were recorded for XIV, an equimolar mixture of donor and acceptor, and for the donor alone. In all three cases the lifetime was 0.15 sec. The absence of any decrease in the lifetime in XIV and the equal phosphorescence intensities indicate that no triplet-triplet transfer is occurring in XIV. The distance between the two chromophores as measured from molecular models is approximately 20 Å and, therefore, the exchange mechanism can not occur at distances greater than 20 Å, at least when these two chromophores are involved. The evidence is not entirely unequivocal because there are many conformations possible which bring the chromophores closer together. As the authors admit, weak interactions could stabilize the "folded" forms relative to the "extended" conformations. Also, unambiguous evidence would have been obtained only by exciting the donor and observing an acceptor phosphorescence. However, the energy levels are not appropriate for this.

Investigating further aspects of intramolecular triplet-triplet energy transfer, Filipescu, DeMember and Minn\textsuperscript{12} prepared 1,4-methano-2,3-exo-[fluorene-9'-spiro-1"-cyclopropane]-9,10-diketoanthracene (XV). In this system, the planes of the triplet donor chromophore, tetralin-1,4-dione (XVI) and acceptor chromophore, fluorene, are oriented
perpendicularly. From molecular models the distance between the van der Waals radii of the two chromophores is 5.2 Å. These radii are of the oxygen of the carbonyl groups and the 1' (or 8') carbon atom of fluorene. The energy level diagram is indicated in Figure 7. The separate chromophore model compounds (XVII and VIII) have characteristic phosphorescence.

Figure 7. Energy level diagram for chromophores in compound XV.

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spectra that are significantly different. In a 1:1 mixture of XVII and VIII each chromophore could be excited selectively and display characteristic phosphorescence. Upon excitation at 304 nm (32900 cm\(^{-1}\)) only fluorene is excited and consequently only fluorene phosphorescence is seen. However, upon selective excitation of the tetralin-1,4-dione chromophore in XVII at 251 nm (39900 cm\(^{-1}\)), the phosphorescence emission resembles that of the fluorene model (VIII) with only a minor contribution from the dione. The transfer efficiency at 251 nm (where \(\varepsilon\) for tetralin-1,4-dione model equals 12000 and for the fluorene model equals 6000 \(\text{1 mole}^{-1}\ \text{cm}^{-1}\)) was 83±5%. This appears to be the first good example of triplet-triplet energy transfer in a system in which the chromophores are not in contact. However, whether the transfer is dependent on the mutual orientation between the chromophores in XVII, is dependent on the separation only, or both is not clear. A compound in which one of the chromophores in XVII can assume different orientations yet remain at approximately the same distance from the fixed chromophore would help resolve this. So far no compounds with these structural characteristics have been examined; however, other molecules with mutually perpendicular chromophores have been examined.

Filipescu and Bunting\(^{21}\) have prepared a compound XVIII containing cyclopentenone (C) and phenanthrene (P). The model compounds containing the single chromophores are

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indicated by structures XIX and XX. Excitation and emission spectra gave values for the energies of the $S_1$ and $T_1$ states of both model chromophores. The energy level diagram for the relevant compounds is given in Figure 8. The emission spectrum of the double chromophore compound XVIII under excitation of the phenanthrene chromophore shows a substantial quenching of phenanthrene fluorescence relative to XX and a total absence of cyclopentenone phosphorescence. The phosphorescence spectrum was identical to that from the phenanthrene.

Figure 8. Energy level diagram for model compound XVIII.

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model \( (XX) \). The results are interpreted as a partial coupling of the \( S_1^P \) level to an upper vibrational level of \( S_1^C \) \( (\text{singlet-singlet transfer}) \) followed by total back-transfer from \( T_1^C \) to \( T_1^P \) after intersystem crossing. This result of efficient energy transfer seems to parallel the results of the previous system studied \( (\text{compound XV}) \).

Filipescu, et. al. in two separate papers studied energy transfer in two compounds having p-dimethoxybenzene \( (D) \) as the triplet donor chromophore and phenanthrene \( (P) \) as the triplet acceptor attached to rigid sigma-bond frames. The first compound examined \( (XXI)^{22} \) uses the spirocyclopropane-norbornane frame to separate the chromophores. As was noted in the previous work\(^{21} \) the phenanthrene-on-the-frame chromophore \( (XX) \) is an efficient emitter from the triplet state and avoids the problems associated with the analogous spiro-linked fluorene \( (VIII) \) in which fluorescence and phosphorescence were substantially quenched. The lowest triplet states of \( D \) and \( P \) are obtained from the 0-0 bands of the phosphorescence spectra \( (23260 \text{ and } 21190 \text{ cm}^{-1} \) respectively) and are well suited for triplet-triplet

\[
\text{XXI}
\]

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energy transfer. From the emission studies in which phosphorescence from both chromophores was seen, they concluded that in spite of the favorable energy level and separation distance ($6 \text{ Å}$), no triplet-triplet energy transfer occurred.

The second compound (XXII) examined contained the same chromophores, but separated by one more norbornane unit.  

![Chemical Structure](image)

As in the previous compound, the uv absorption of compound XXII was compared to the sum of the spectra of the constituent chromophores. This established that there was no delocalization or even weak electronic interaction between the two moieties. Special attention was devoted to insure the photostability of the phenanthrene-on-the-frame XX. Although a photoisomerization occurred at 298°K in fluid

![Chemical Structure](image)
solution, the quantum yield for the rearrangement to the tribenzofulvene XXIII was only $10^{-4}$ at 77°K in rigid solution.

As with compound XXI, model compound XXII also demonstrated no evidence of triplet-triplet energy transfer. According to the exchange mechanism, this implies a vanishing exchange integral for both molecules. Although the interchromophoric separation is close enough (6-7 Å) to be within the "sphere of quenching," a zero exchange integral appears to result. According to Filipescu this lack of triplet transfer must be due to the symmetrical properties of the two compounds. The mutual orthogonality of the planes of the two chromophores seems to be the most conspicuous feature.

These cases are undoubtedly the best examples yet published recording an absence of triplet-triplet energy transfer even though the prerequisites for Dexter's exchange mechanism seem to be fulfilled. Again, it is not clear whether the lack of transfer is due to the separation and/or the orientation of the two chromophores.

Work by Zimmerman provided an example of a model compound in which the chromophores are separated but are free to assume many orientations by rotations about sigma bonds. The compound 1-benzoyl-4-(α-naphthyl)bicyclo[2.2.2]-octane (XXXIII) has the benzoyl group as the triplet donor and naphthalene as the acceptor chromophore. The energy levels for the first excited singlet and triplet states
provide an ideal case for the study of triplet-triplet energy transfer. Upon irradiation of a 0.0002 M solution of the model compound at 350 nm at 77°K, only the benzoyl group is excited. The phosphorescence spectrum shows only emission from naphthalene. Solutions of the isolated chromophores pivalophenone (XXXIV) and 1-methylnaphthalene up to 0.01 M exhibit only emission from the benzoyl group under the same conditions. Intermolecular triplet transfer can only begin to be noticed at 0.1 M. Thus, the naphthalene emission in the model compound XXXIII must be due to intramolecular transfer. Reference to extended Huckel molecular orbital calculations for the 1,4-diaryl bicyclo-[2.2.2]octane led Zimmerman to believe that the sigma framework is possibly responsible for the triplet transfer. If the sigma bonds indeed participate in the triplet transfer, many of the previous studies would have to be reexamined or reinterpreted. Most workers assume that the sigma framework contributes little if anything to chromophoric interaction. Whatever the interpretation, triplet-triplet energy transfer occurs easily in model compounds such as XXXIII even with the separation. If the same two chromophores could
be oriented perpendicularly upon a rigid framework, such as described in much of Filipescu's work, the emission studies would be valuable. Such a study has not been carried out to our knowledge.

Photochemical Studies on Triplet-triplet Energy Transfer

Most work on intramolecular energy transfer between nonconjugated chromophores has been carried out by selective excitation of the donor and observation of emission from the acceptor. However, several studies have used a photochemical reaction in the acceptor to monitor intramolecular transfer. Filipescu$^{17,25,26}$ has reported studies on several rigid molecules which undergo a photochemical reaction following a transfer of triplet energy. For example, upon irradiation with light absorbed only by the 1,4-tetralindione chromophore (D), the norbornylene compound $XXIV$ undergoes a cyclization to form the cage structure $XXVI$. The sequence of events leading to $XXVI$ in fluid solution at room temperature seems to be (1) excitation to
S₁ of the 1,4-tetralin chromophore, (2) intersystem crossing to T₁, (3) a conformational change leading to XXV, (4) triplet energy transfer to the norbornylene (N) chromophore, and (5) cyclization. A conformational change giving XXV is required for this reaction, but whether the triplet transfer occurs before or after the change is uncertain. The authors argue that whenever N is excited by transfer of energy from D or from an external sensitizer, the excess vibrational energy is sufficient to cause this conversion. In rigid solution at 77°K, XXIV does not react to give the cage compound presumably because the conformation XXV can not be achieved. However, the phosphorescence quantum efficiencies of the 1,4-tetralindione moiety in XXIV and the saturated analogue XXVII are identical at 77°K in rigid solution. If

triplet-triplet transfer occurs in XXIV under these conditions, the intensity of the phosphorescence from D should be lower than for the saturated norbornane. This evidence seems to indicate that a conformation change needs to precede the triplet transfer. The absence of quenching of the 1,4-tetralindione chromophore in XXIV seems to suggest to the authors
that even though the van der Waals radii of the \( \pi \) systems of the two chromophores are well within the "sphere of quenching," an orientation dependence must be required for the transfer.

The spirocyclopropane-fluorene (VIII) \( \rightarrow \) dibenzofulvene (X) photorearrangement served as a chemical detector of triplet energy transfer in rigid model compound XXVIII. The quantum yield of the fluorene\( \rightarrow \) dibenzofulvene conversion under excitation of only the F chromophore when compared to the yield when only the cyclopentenone is excited selectively indicated that an efficient transfer of triplet energy occurred from the \( T_1 \) of C to the \( T_1 \) of F. The results are complicated somewhat by the uncertainty of the energy of the \( T_1 \) state of cyclopentenone. The spectroscopic triplet obtained from the 0-0 band of the phosphorescence

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spectrum places the emitting triplet in cyclopentenone itself at 72.5 kcal/mole or above the \( T_1 \) of fluorene (65 kcal/mole). Separate quenching experiments in a different reaction place the \( T_1 \) much lower at ca. 61 kcal/mole or about 4 kcal/mole lower than the \( T_1 \) of fluorene. The spectroscopic triplet at 72.5 kcal would then be \( T_2 \). With Filipescu's work the existence of the lower \( T_1 \) is in doubt since no back transfer of triplet energy occurs (\( T_1^{F} \rightarrow T_1^{C} \)).

The fluorene \( \rightarrow \) dibenzofulvene photorearrangement was used to advantage in another compound which had previously been studied spectroscopically.\(^5\) Menter and Filipescu\(^7\) followed the reaction of compound XV to XXIX. The photo-

\[
\text{XV} \xrightarrow{hv} \text{XXIX}
\]

chemical quantum yield of the intramolecularly sensitized reaction in XV was comparable to that of the intermolecularly sensitized reaction of VIII to X. An efficient energy transfer from the \( \pi \rightarrow \pi^* \) triplet of the ketone to the lowest \( \pi \rightarrow \pi^* \) state of the fluorene chromophore was seen to account for the results. The triplet transfer for this isomerization supports the previous spectroscopic study discussed
before, and, therefore, seems to indicate that triplet-triplet energy transfer can occur in some compounds in which the donor and acceptor moieties are rigidly separated and perpendicularly oriented.

Alternate Approaches for Studying Triplet-triplet Energy Transfer

Several alternate approaches have been carried out to determine just how close donor and acceptor molecules must come to promote exchange interaction. A steric hindrance to triplet-triplet energy transfer has been examined by monitoring photocyclizations of $\alpha,\alpha$-dimethylvalerophenone (XXX) and 3,3-dimethyl-1,2-butanedione (XXXI).$^{27}$

It was thought that perhaps quenching of the ketone $n\rightarrow\pi^*$ triplet would be significantly lower for the "hindered" ketones XXX and XXXI than for the "unhindered" valerophenone. This assumes that a closer approach to the carbonyl group would lead to greater quenching. Chloronaphthalene, 1,3-pentadiene, and other dienes were used as triplet quenchers. Quenching of the two "hindered" tertiary alkyl-ketones and for the "unhindered" valerophenone was found to vary with solvent viscosity in parallel fashion. Therefore,
triplet energy transfer for the hindered ketone triplets is just as "diffusion controlled" as transfer from the unhindered ketone triplet. Tertiary alkylketones are resistant to nucleophilic addition because of steric hindrance. Since the results here show that the bulky tertiary alkyl groups do not hinder triplet energy transfer from the carbonyl group, the donor and acceptor must not have to approach to within bonding distance in order to achieve the required orbital overlap for the exchange mechanism to operate.

A model for steric hindrance to triplet energy transfer emerges from these studies assuming a maximum overlap, preferred orientation, and a distance between the donor and acceptor molecules close to the van der Waals radii. The diagrams below (Figure 9) indicate these models and incorporated assumptions. For 1,3-pentanediolone the X group would be hydrogen and a sideview (Figure 10) of the complex indicates that it would offer no interference to maximum overlap. However, for 2,3-dimethylhexadiene as quencher, a methyl group would be present and its size would require that the
distance between the molecules must increase, or, more likely, the molecules must tilt. This would explain the slightly different quenching efficiencies of several dienes toward XXX. The model is very simplified and may not represent the situation at all since energy transfer occurs at greater distances, even with completely separated chromophores as presented before.

A search for a steric hindrance to triplet electronic energy transfer has also been conducted by Wamser and Chang who measured quenching rates of triplet triphenylene by a series of azo compounds with a variety of steric properties. The structures of some of the azo compounds are indicated below. The quenching rates dropped off significantly as

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the steric bulk around the azo function increased. Triplet energy transfer from triphenylene to azo-n-butane proceeds at a diffusion-controlled rate since the donor and acceptor molecules may come into direct contact. However, with azo-tert-butane, the rate is an order-of-magnitude less than diffusion-controlled. This is explained by the presence of the bulky substituent keeping the donor and acceptor chromophore (van der Waals radii) separated by about 1 Å. This model of triplet energy transfer assumes that the azo compound lies flat over the plane of the triphenylene molecule.

The orientation dependence for triplet-triplet transfer has been examined by using magnetophotoselection. A discussion of the method is not pertinent to this work; however, the results are of interest. The primary conclusion is that the probability of transfer has small, if any, dependence on the orientation of the donor-acceptor pairs. The pairs used in the study were phenanthrene-d_{10} and benzophenone as donors and naphthalene-d_{8} as the acceptor. This result was rationalized for the exchange mechanism. Because the intermolecular distance for such an interaction has a large exponential dependence, the rate of change of transition probability would be sufficiently large that the effect of pair configuration would be masked. Even though the overlap of perpendicularly oriented benzophenone-naphthalene would be much smaller than for a parallel alignment, the overlap for the perpendicular situation is sufficiently
large at the effective transfer distance that the probability of transfer remains unity. Other magnetophotoselection experiments have supported the lack of observation of orientation effects. Obviously, conclusions of these experiments conflict with the steric hindrance work and with the assumptions made by most workers in intramolecular energy transfer; that is, that a suitable orientation (generally thought to be a parallel situation) is necessary for efficient transfer.

A similar technique was used by Eisenthal to study benzophenone-phenanthrene and anthrone-phenanthrene pairs. Contrary to the results of the previously described magnetophotoselection experiments, Eisenthal observed an orientation dependence for triplet-triplet transfer. In this work the axis of benzophenone was found to be parallel to the molecular plane of phenanthrene. However, no preferred angular orientation with respect to the long and short axes of phenanthrene was found. For the anthrone-phenanthrene pair, the molecular planes likewise were found to be parallel, and, in this parallel configuration, no angular orientation was preferred.

Applications of Triplet-triplet Energy Transfer

A few groups have applied the phenomena of triplet-triplet energy transfer to the elucidation of structures of biological macromolecules, primarily proteins. In most of
this work a suitable chromophore (phosphorescent probe) is introduced into the system such as a substrate or inhibitor for a particular enzyme and changes in the enzyme phosphorescence are noted. Galley and Stryer\textsuperscript{19} examined the active site of bovine carbonic anhydrase by introducing a triplet donor molecule, m-acetylbenzene sulfonamide (XXXII), an inhibitor that binds to the zinc atom at the active site. The triplet acceptor was a tryptophan residue of the enzyme. The phosphorescence of the inhibitor is characteristic and

\[
\begin{align*}
\text{XXXII} \\
\begin{array}{c}
\text{O} \\
\text{SO}_2\text{NH}_2 \\
\text{CH}_3
\end{array}
\end{align*}
\]

and can be excited at 330 nm where the protein is not excited. Carbonic anhydrase has a phosphorescence characteristic of tryptophan when excited at 280 nm. The energy level scheme is ideal for triplet-triplet energy transfer. Upon irradiation at 77°K at 350 nm the enzyme-inhibitor complex exhibited only a phosphorescence characteristic of tryptophan indicating that the triplet energy of m-acetylbenzene sulfonamide was transferred to a tryptophan residue in the enzyme. m-Acetylbenzene sulfonamide (MABS) next was displaced by acetazalamide, an inhibitor known to bind with high affinity to the zinc atom at the active site and which
does not phosphoresce in the region of interest. The phosphorescence of this mixture excited at 330 nm showed only an emission from MABS. Galley and Stryer concluded from this evidence and from other studies of triplet-triplet energy transfer that the indole chromophore of the tryptophan residue must be within 12 Å of the zinc atom to be in van der Waals contact with MABS. One of the tryptophans then must be involved at the binding site of the aromatic sulfonamide inhibitor.

In contrast to carbonic anhydrase, the enzyme-inhibitor complex of α-chymotrypsin and MABS shows no evidence of transfer of triplet energy to tryptophan residues indicating that none of the eight tryptophan residues in α-chymotrypsin is involved in the portion of the active site probed by the phosphorescent donor.

The initial work of Galley and Stryer on carbonic anhydrase has been extended by McCarville and Hauxwell to other inhibitors including ones which have different arrangements of singlet and triplet energy levels relative to those of tryptophan. Many of the ligands exhibited triplet-triplet energy transfer to a tryptophan residue. The work increases greatly the number of compounds suitable as phosphorescent probes.

Galley has examined transfer of triplet excitation in complexes of calf thymus DNA and a dye, 9-aminoacridine. A highly efficient transfer from the bases of native DNA.
to the dye was observed. Comparison with data of triplet transfer in small molecules led to the conclusion that the dye can not be bound on the outside of the DNA helix. The evidence is consistent with a model that places the dye molecule between the DNA bases. Upon denaturation of the DNA there was a detectable loss of triplet energy transfer indicating that the rigid helical structure is needed in order for the dye to "trap" the triplet-excited base in the DNA molecule. Apparently, a decrease in orbital overlap occurs between the dye and the bases. This work suggests that phosphorescent probes may be useful for monitoring conformational changes in which only small changes in geometry occur, i.e., when the distance changes between the chromophores are less than 14-15 Å.
OBJECTIVES AND RATIONALE FOR RESEARCH

Considering the work done on intramolecular triplet-triplet energy transfer as reviewed in the previous section, nearly all of the study has involved chromophores which are only of inherent interest for investigating the general principles of the transfer. No work has been done, to our knowledge, on chromophores which have been used as phosphorescent probes in the elucidation of enzyme active sites other than the probe studies themselves. A study of the isolated chromophores in the absence of the enzyme may allow more definite conclusions regarding the distances involved in the active site-probe interactions. Of particular interest would be compounds which contain a phosphorescent chromophore present in enzymes and perhaps a chromophoric substrate or inhibitor. In most enzymes and proteins the only phosphorescent amino acid residues are phenylalanine, tyrosine, and tryptophan. Of these triplet emission from tryptophan is the most efficient and it has the lowest triplet level of the three. Since the only enzyme which has been examined to any extent by phosphorescent probes is carbonic anhydrase, interest was directed at tryptophan and one of the inhibitors studied, m-acetylbenzenesulfonamide.

If compounds could be constructed containing both of these moieties separated by a nonchromophoric bridge, triplet-triplet energy transfer between MABS and tryptophan could
be studied. A series of such compounds in which the distance between the chromophores would be varied would provide good models for a study of the distance requirements for the transfer. Presumably in such a series the efficiency of the transfer would decrease as the separation distance increased. A correlation between the efficiency and distance could provide a means of measuring distances involved in inhibitor-active site complexes.

Since one of the requirements of the compounds would be a relatively inflexible interconnecting framework, the synthesis of these compounds would be a major obstacle to such a study. The chromophores themselves should be relatively rigid and free from substantial rotational freedom, particularly about sigma bonds. The incorporation of tryptophan and a molecule such as MABS into a rigid framework poses some problem in this consideration not to mention synthetic difficulties. A more reasonable approach would be to consider only the chromophore itself which is responsible for the absorption and emission characteristics of these two molecules. For tryptophan this would be indole and for MABS-like molecules, the carbonyl group. Disregarding the remainder of the tryptophan molecule in this study seems reasonable since the only other important chromophore, the carboxyl group (or in the protein, the peptide bond) has its absorption maximum near 200 nm, or much higher in energy than the indole ($\lambda_{\text{max}} = 280$ nm). The region of the

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ultraviolet spectrum being excited in MABS in the Galley-Stryer study corresponded to the forbidden $n \rightarrow \pi^*$ transition of the carbonyl group. The molecule has a weak absorption beyond 300 nm (ca. 50 l mole$^{-1}$ cm$^{-1}$ at 320 nm). An isolated carbonyl group as exemplified by acetone also has a weak absorption at this wavelength, but the intensity is much less ($\ll 5$ l mole$^{-1}$ cm$^{-1}$). The weaker absorption at the wavelength of concern appears to be the only disadvantage to the use of a saturated carbonyl group to represent the MABS chromophore in this study of triplet-triplet energy transfer.

To our knowledge triplet energy transfer in indole compounds containing an unconjugated "isolated" carbonyl group has not been examined. While such compounds would be of interest because of the analogy to the enzyme active site-inhibitor complex, they are good models for a study of energy transfer in general because of the small size of the carbonyl group. Its small size would permit a very localized region of excitation. Compare this to the much larger size of the donor moieties in previous studies such as benzophenone, anthrone, cyclopentenone, etc.

The synthesis of a series of indolylketones covering a wide range of chromophore separation distances (preferably from 0-15 Å) would be a difficult task. In this study emphasis is placed on relatively simple structures with small separation distances (0.5-6.5 Å). The compounds in
the accompanying table (Figure 11) were considered as possible candidates for triplet energy transfer. Only one of these compounds was commercially available (3-indolylacetone) so nearly all would have to be synthesized. The preparation of compounds whose synthesis has been reported in the literature was emphasized first and other compounds were synthesized as time permitted.

The compounds do not provide a wide range of distances, and the series of compounds with the chromophores separated by a series of methylene groups suffers from the same structural problem, i.e., nonrigidity, as earlier studies. Again, however, the small size of the carbonyl may allow a complete separation of the chromophores in the extended conformations of the compounds. The compounds with a cyclohexane bridge are also not absolutely rigid, but they do keep the chromophores separated, and the twisting the ring undergoes will not alter the distance substantially. Also, at 77°K the more stable conformation should be frozen out placing the chromophores in a fixed position. The important aspect of many of these model compounds is that the van der Waals radii of the two chromophores do not come in contact. If a van der Waals contact is necessary for the efficient transfer of triplet energy, these molecules may show a decreased transfer efficiency.
Figure 11. Indolylketones considered for triplet-triplet energy transfer studies.
SYNTHESIS OF INDOYLKETONES

Historical

Our first efforts to synthesize the indolylketones desired for this study focused on the nucleophilic addition of the indole nucleus to a carbonyl group. The addition of indole to a suitably substituted cyclohexanone would be a convenient method for introducing the cyclohexane bridge in several of the compounds in Figure 11. The conversion of a suitable X group in the resultant alcohol XLV to a carbonyl group would give the indolylketones. The presence of the -OH group would not interfere with the energy transfer studies.

Reactions of indole have been reviewed\textsuperscript{34,35,36} including reactions with ketones. In general, nucleophilic reactions of indoles with acetone in acetic acid gives bis-indolylalkanes (XLVII)\textsuperscript{37} and not the expected hydroxy derivatives (XLVIII) from simple nucleophilic addition to the carbonyl group. Other ketones react similarly to give diindolylmethanes.

51
More pertinent to the objectives in this work is the reaction of cyclohexanone with indole. The hydroxy product is not obtained. Instead compound L\text{I} results from further condensation. The same compound is obtained from condensation of indole with 1,3-cyclohexanedione. Reaction of one equivalent of indole with one equivalent of 1,4-cyclohexanedione might yield a desired indolylketone L\text{II}. However, the dione again forms the diindolyl derivative L\text{IV} with 2-methylindole (L\text{III}).
Since condensations of this type did not appear promising for construction of indolylketones, attention was directed towards reactions of indolylanions with carbonyl groups. This approach appeared to be more promising after a study of previous workers' results. Organometallic derivatives of indoles are good sources of indolylanions. Indole Grignard reagents can be easily prepared and reactions with
alkylating agents generally lead to 3-substituted indoles after hydrolysis. For example, reaction of the indole Grignard reagent \( \text{LV} \) with methyl iodide affords predominantly 3-methylindole (\( \text{LVI} \)) and with ethylene oxide yields 3-indolyl-ethanol (\( \text{LVII} \)). Reactions of indolyl magnesium derivatives with ketones, however, do not in general lead to the hydroxyl compounds. 2-Methylindolyl magnesium bromide reacts with acetone or acetophenone to give dimeric products (\( \text{LIX} \), \( R = \text{Ph or CH}_3 \)). Hoshino isolated a 1 : 1 adduct of indolyl magnesium iodide (\( \text{LV} \)) and acetone by a careful workup of the reaction mixture, but the substitution was apparently on the ring nitrogen. These results and others indicate a general instability of 3-indolylcarbinols, and their isolation will only be permitted by carefully controlled conditions.
Other organometallic derivatives of indole can be prepared and alkylated. Treatment of indole with n-butyl-lithium in ether yields the N-lithio derivative. Work on reactions of the lithium salt of indoles is mainly concerned with the lithio salt of N-methylindole. Apparently, it lithiates more smoothly than indole and undergoes reactions more readily. Shirley and Roussel\(^\text{43}\) prepared 2-lithio-1-methylindole (LXI) using a 4-fold excess of n-butyllithium in ether and carried out the reactions shown below as well as others. Of particular interest was the successful addition of the N-methylindole moiety to the carbonyl group of benzophenone giving the carbinol LXIV in 53% yield. Similar results were obtained by Kebrle and Hoffmann\(^\text{44}\) using several ketones especially aliphatic ketones. Pertinent to

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the synthesis of the indolylketones desired for energy transfer studies is the successful addition to a cyclohexanone (LXVI). Metallations of N-substituted indoles with n-butyllithium generally proceed in the 2-position.

However, lithiation of indole itself leads only to nitrogen substitution.\(^{43}\) Treatment of indole with a slight excess of n-butyllithium followed by carbonation yielded only 1-indolecarboxylic acid (LXVIII). Carbon substitution could not be effected with a 4-fold excess of n-butyllithium and reaction times up to 48 hours.
Attempted Reactions of Lithioindoles with Ketones

In spite of the previous lack of observation of carbon substitution with indole-lithium reagents, attempts were made to metallate indole with n-butyllithium in ether and to treat the resulting lithium salt with ketones. For example, treatment of indole with 1.1 equivalents of n-butyllithium was followed by stirring at room temperature or refluxing for up to 24 hours. To the resulting lithium salt was added cyclohexanone. This mixture was stirred at approximately 30° for up to 7 days. Thin layer chromatography (TLC) indicated that only starting material (indole and cyclohexanone) was present. Infrared spectra of the products obtained after workup of the reactions showed a strong carbonyl group absorption, and all other absorptions corresponded to those of indole or cyclohexanone.

Since this approach to some of the desired indolylketones did not appear promising, attention was focused on additions of 2-lithio-1-methylindole to ketones. Although only 2- or 3-substituted indoles were preferred for the

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energy transfer studies, a literature search indicated that the pertinent spectroscopic properties of N-methylindole are similar to those of indole. In particular, the phosphorescence emission of 1,2-dimethylindole is similar to that of 2-methylindole as indicated in Table 1. In addition, further confirmation of the greater synthetic utility of 1-methylindole was desired.

1-Methylindole was prepared by the method of Potts and Saxton as indicated below from indole and methyl iodide.

```
\[
\begin{align*}
\text{indole} & \rightarrow \text{na} \rightarrow \text{methyldiiodoindole} \\
\text{XLI} & \text{LXX} & \text{LXXI}
\end{align*}
\]
```

A small amount of indole was present in the sample as indicated by the N-H stretch of indole at 2.90 μ in the infrared spectrum. This could be removed by heating the product.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Excitation</th>
<th>Phosphorescence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-dimethylindole</td>
<td>288 nm</td>
<td>414 nm, 441 nm, 454 nm, 464 nm</td>
</tr>
<tr>
<td>2-methylindole</td>
<td>285 nm</td>
<td>408 nm, 434 nm, 446 nm, 458 nm</td>
</tr>
</tbody>
</table>

Table 1. Comparison of phosphorescence emission of 1,2-dimethylindole and 2-methylindole.
over sodium while redistilling. Following the procedure of Shirley and Roussel an ether solution of N-methylindole was treated with a 4-fold excess of n-butyllithium. After refluxing for 22 hours, cyclohexanone in ether was added. Workup yielded an oil from which the desired product (LXXII) fortuitously crystallized from ethanol (11% yield). Addition of 2-lithio-1-methyldindole to a more complex ketone, 6-methoxy-2-tetralone (LXXIII) was attempted. Following the reaction by TLC showed that no reaction was occurring except when the lithium salt was made with 4 equivalents of n-butyllithium. In this case two faint spots on TLC were present in addition to dense spots for starting materials. A purification by silica gel column chromatography gave negligible amounts of gums representing the supposed product spots.

These results seem to indicate that the addition of indolylanions to carbonyls will not be a very promising route to the desired indolylketones. In anticipation that

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this method would work, the synthesis had been attempted of possible cyclohexanones which would lead to the desired compounds after indole addition.

The monoethylene ketal of 1,4-cyclohexanedione (LXXVI) has been prepared by Mertes using the usual ketalization procedure, i.e., refluxing the ketone with ethylene glycol in benzene with a catalytic amount of p-toluenesulfonic acid. The monoketal LXXVI was isolated by low pressure distillation followed by crystallization. Upon repeating this reaction, we obtained a product which distilled over a wide temperature range with no substantial fraction boiling at a nearly constant temperature. Of the several fractions which were collected, recrystallization of these led to wide-range melting mixtures.

In another attempted preparation the crude product was chromatographed on silica gel. The separation was followed by TLC. Fractions containing the spot thought to be a product yielded a wide-range melting solid upon evaporation of the solvent. Recrystallization from ethanol gave a mixture of small rough crystals and long needles. The smaller crystals had a melting point close to that reported for LXXVI and a C=O infrared peak. The long needles had no peak in
the carbonyl stretch region of the ir spectrum. In addition they had a melting point (77-79°) close to a literature value for LXXVII (mp 79-79.5°).48 Since these crystalline products were separated manually, this method was not useful for producing synthetically useful quantities.

Courtot48 has also examined this reaction. Using one equivalent of ethylene glycol with the diketone LXXV, a mixture was obtained of about equal proportions of mono- (LXXVI) and bis-ketal (LXXVII) and unreacted diketone. The unreacted starting material was removed by dissolving it in water, and the 1,4-dioxaspiro[4.5]8-decanone (mp 72-73°) was obtained via the bisulfite addition compound. The sharp melting point for the pure compound indicates that Merte's47 compound (mp 65-73°) was probably a mixture.

Lambert49 used the same procedure and obtained a 1:2:1 mixture of ketone to ketal to bis-ketal which were separated by silica gel column chromatography in unstated yields.

The preparation of the similar monoethylene ketal of 5,5-dimethyl-1,3-cyclohexanedione (LXXVIII) was attempted using the same procedure. A solid was obtained which recrystallized from ethanol over three days. This crystalline solid consisted of only one product by gas chromatography. The elemental analysis did not correspond to that of the expected product. Instead, the analysis agreed with that of 3,3'-ethylenedioxy-bis-(5,5-dimethyl-2-cyclohexen-1-one) (LXXX). The nmr spectrum was consistent with this structure.
and with a literature nmr spectrum\(^50\) of the same compound prepared by an alternate method.

Efforts to synthesize the two monoketals above and any other potentially useful ones were abandoned when the indolyl anion additions failed. This method would have provided a convenient and short route to some of the desired compounds as indicated below for one of them. This was particularly discouraging since Mertes\(^47\) had prepared 8-phenyl-1,4-dioxaspiro[4.5]-8-decanol (LXXXIII) by the addition of phenyllithium to the monoketal of 1,4-cyclohexanedione (LXXVI).

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Following the abandonment of the initial general synthetic scheme, other syntheses were attempted, many of these following literature preparations and involving completely different pathways for the most part. The synthesis of the compounds used in the energy transfer studies will be presented for each compound. In nearly every case the yields were not optimized since only 50 mg of each indolylketone was sufficient for our studies.

4-(3'-Indolyl)-2-butanone (XXXVI)

3-Indolylacetone (XXXV) was purchased from Aldrich Chemical Company. The next higher homologue, 4-(3'-indolyl)-2-butanone (XXXVI) was prepared by the method of Szmuszkovicz who obtained the compound by the Michael addition of indole to methyl vinyl ketone (MVK) in acetic acid-acetic anhydride. Three molar equivalents of MVK were used in his preparation.

Upon attempting this reaction we obtained only gums which

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could not be crystallized. Using only one equivalent of MVK also gave an unrecrystallizable gum. The use of freshly distilled MVK also did not yield a solid precipitate upon hydrolysis of the reaction mixture. In view of these failures the procedure was rechecked. Szmuszkovicz had performed the reaction successfully with only acetic acid as the solvent. However, the addition of acetic anhydride gave a somewhat higher yield of the desired product in his work. When the reaction was run in the absence of acetic anhydride in the present work a precipitate of 4-(3'-indolyl)-2-butanone (XXXVI) was obtained which was recrystallized from benzene-petroleum ether in 30% yield. Thin layer chromatography indicated that only one substance was present.

5-(3'-Indolyl)-2-pentanone (XXXVII)

The next homologue in the series, 5-(3'-indolyl)-2-pentanone (XXXVII) had not been prepared to our knowledge. An available compound, 3-indolebutyric acid (LXXXV, R = H) has the required number of methylene groups and a potential aliphatic carbonyl group. The carboxyl group can be converted to a methylketone by a number of procedures. Of those

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of interest here, the Corey method\textsuperscript{52} converts esters to methylketones in a two-step sequence using the methylsulfinyl carbanion LXXXVI to prepare a $\beta$-ketosulfoxide LXXXVII, which is cleaved by aluminum amalgam to yield a methylketone (LXXXVIII). Because of the presence of an active hydrogen on the indole moiety of ethyl 3-indolebutyrate (LXXXV, $R = \text{CH}_2\text{CH}_3$), this is not a particularly attractive method. The methylsulfinyl anion would react with it in preference to the carbonyl group.

A more attractive procedure seemed to be the direct conversion of acid to the methyl ketone using methyllithium. Cyclohexyl methyl ketone has been prepared by making the lithium salt of cyclohexanecarboxylic acid (XC). Methyl-lithium addition followed by hydrolysis gives the methyl ketone (XCII).

Following this procedure, 3-indolebutyric acid suspended in dimethoxyethane was treated with two equivalents of lithium hydride to give the dilithio salt XCIII.

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Upon addition of an ether solution of methyllithium, a substantial amount of an insoluble brown gum formed. After stirring at room temperature for 2 hours followed by hydrolysis, starting material was recovered (70% recovery) from the aqueous phase, and a small amount of a gum was obtained from the organic phase. The use of TLC to follow another run indicated that little reaction was occurring.

A modification of this procedure by Wynberger was used to prepare 3-acetyl-5-methylpyrazole (XCVII) from 5-methylpyrazole-3-carboxylic acid (XCIV). In this method three equivalents of methyllithium in ether are added to an ether-tetrahydrofuran solution of the acid (XCIV). Two
molecules are needed to react with both active hydrogens, and the third molecule reacts with the carbonyl group. After hydrolysis the acetyl compound is obtained in 49% yield.

3-Indolebutyric acid (LXXXV) in ether-tetrahydrofuran was similarly treated with three equivalents of methyl-lithium. A brown gum formed soon after addition. After stirring for 8 hours and hydrolysis, an oil was obtained which was shown by TLC to contain substantial starting material. A silica gel column chromatography allowed a solid to be collected (9%) which was identified by elemental and spectroscopic analysis as the desired product, 5-(3'-indolyl)-2-pentanone (XXXVII). The low yield of the methyl ketone and the substantial amount of unreacted starting material probably are related to the insolubility of one of the lithium complexes which forms a gum. The gum is hydrolyzed to give mainly 3-indolebutyric acid.

\[
\text{LXXXV} \quad \text{XXXVII}
\]

Of the four possible oxotetrahydrocarbazole isomers, only the 2-oxo- and 3-oxo compounds (XL and XLI) are useful
for intramolecular triplet-triplet energy transfer studies because the carbonyl groups in both of these compounds are not conjugated with the indole aromatic system. 2-Oxo-tetrahydrocarbazole has been prepared by Teuber and Cornelius using a lithium/ammonia reduction of 2-methoxycarbazole (CII) followed by acid hydrolysis of the intermediate enol ether (CIII). 2-Methoxycarbazole (CII) is not commercially available and had to be synthesized for the present work. The procedure of Bradsher, et. al. appeared to be the most straightforward although four steps are involved starting with 4-hydroxybiphenyl (XCVII). The entire synthetic scheme for the preparation of 2-oxo-1,2,3,4-tetrahydrocarbazole is indicated below. The bromination of

![](image.png)

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4-hydroxybiphenyl (XCVIII) was carried out using the procedure of Bell and Robinson\textsuperscript{56} in 97\% yield (versus the literature yield of 84\%). 3-Bromo-4-hydroxybiphenyl (XCIX) was in turn smoothly methylated with dimethylsulfate in aqueous alkali in 90\% yield following the method of Hey and Jackson.\textsuperscript{57} The conversion of the bromocompound C to the amino derivative via a sodium amide-induced benzyne reaction was attempted following Bradsher's preparation.\textsuperscript{55}

Sodium amide was prepared in situ from sodium and ammonia. To this was added the bromo compound followed five hours later by hydrolysis of the reaction mixture. The procedure is rather unwieldy by requiring the extraction of the amine CI with 10 liters (on a 0.3 mole reaction) of 5\% hydrochloric acid in many portions. Basification, chloroform extraction, and low pressure distillation gave only a 10\% yield of the amine. This is in contrast to a reported yield of 65\% after distillation.\textsuperscript{55} Repeating the reaction gave crude yields of 18 and 33\%. Silica gel column chromatography was used to purify the amine in the latter run instead of distillation giving an overall yield of 31\%. Bradsher isolated a bis-(4-methoxybiphenylyl)amine CIV by acidification of the previous hydrochloric acid-extracted

\[
\begin{align*}
\text{CIV} & \\
\text{Ph} & \text{N} \quad \text{OCH}_3 \\
\text{Ph} & \text{Ph} \\
\text{OCH}_3 & \text{Ph}
\end{align*}
\]
solution. No attempt was made to isolate this secondary amine in this work. An increased yield of this amine would account for the low yield of the desired primary amine. Also, in general, reactions of amide ions with aryl halides in liquid ammonia do not give high yields. For example, o-bromoanisole (CV) and lithium amide give only a 22% yield of the amine CVI. A compound similar to the biphenyl C, 2-bromo-4-methylanisole (CVII) affords a 50% yield of amine CVIII.

2-Amino-4-methoxybiphenyl (CI) was diazotized and treated with sodium azide to afford the cyclized product, 2-methoxycarbazole (CII) in 53% yield. With this compound in hand, the Teuber and Cornelius procedure could be followed.

A Birch reduction of 2-methoxycarbazole using lithium in ammonia-ether is reported to give an 80% yield of the
dihydro compound CIII. Our first attempt returned only starting material. It appeared that the carbazole compound CII did not dissolve well in the ammonia/ether solution. Tetrahydrofuran was substituted for the ether. Most of the starting carbazole was again recovered. Since the reduction is proceeding to only a small extent, if any, the amount of lithium was doubled in hope of affecting the required reduction. The isolated product from this trial was not starting material as shown by TLC. An integrated nmr spectrum of the product revealed that over-reduction of 2-methoxycarbazole had occurred because the aromatic region of the spectrum did not integrate for four protons which compound CIII would require. The allylic region integrated for several protons. In addition, the material did not appear to be a pure compound because the melting point increased upon recrystallization, and the nmr spectrum did not correlate with any of the reasonable reduction products of 2-methoxycarbazole. The material was definitely over-reduced, however, because of the scarcity of aromatic protons in the nmr spectrum.

Finally, using the original procedure, the reduction time was extended from one to one and one-half hours. A product was obtained which corresponded to the desired compound, 2-methoxy-1,4-dihydrocarbazole (CIII) in 68% yield.

The final step in the synthesis of 2-oxo-1,2,3,4-tetrahydrocarbazole (XLI) proceeded in a straightforward way.
The enol ether CIII was hydrolyzed to the ketone in 52% yield. An elemental analysis agreed with the theoretical percentage composition, and the IR spectrum and melting point agreed with the literature values.\(^{54}\)

3-Oxo-1,2,3,4-tetrahydrocarbazole (XL)

Teuber and Cornelius\(^ {54}\) also prepared 3-oxo-1,2,3,4-tetrahydrocarbazole from 3-methoxycarbazole (CIX) using the same procedure as was described for the 2-oxo compound.

Because 3-methoxycarbazole is not readily available (nor is an easily adaptable derivative such as 3-hydroxycarbazole), it would have to be synthesized. Work was started on the synthesis following the three-step method of Campagne and Lake.\(^ {59}\) p-Anisidine (CXI) is condensed with 2-chlorocyclohexanone (CXII) to give CXIII which is in turn cyclized and aromatized to yield 3-methoxycarbazole.

2-Chlorocyclohexanone was prepared by the method of

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Newman\textsuperscript{60} in 51\% yield by the addition of gaseous chlorine to cyclohexanone. Condensation with p-anisidine following the literature preparation gave only a 24\% crude yield of 2-p-anisidinocyclohexanone (CXIII).

\[
\begin{align*}
\text{CXI} & \quad \text{CH}_3\text{O} & \quad \text{Cl} & \quad \text{CXII} & \quad \text{CH}_3\text{O} \\
& & & & \quad \text{MgCl}_2 \\
\end{align*}
\]

While this preparation was underway a different and shorter route to 3-oxo-1,2,3,4-tetrahydrocarbazole was attempted which is outlined below. Phenylhydrazine would condense and cyclize with 4-hydroxycyclohexanone (CXV) to give the 3-hydroxytetrahydrocarbazole CXVI which could be oxidized to the desired 3-oxodervative XL.

Harley-Mason and Pavri\textsuperscript{61} had prepared 3-hydroxy-1,2,3,4-tetrahydrocarbazole by condensing phenylhydrazine with 4-benzoyloxyxyclohexanone (CXVII) to give CXVIII followed by hydrolysis. In their paper they also mentioned that they failed to successfully oxidize the 3-hydroxy compound to the 3-oxo derivative XL. The oxidative methods that were attempted were not listed. Although any

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oxidations that use a strong acid might attack and decompose the indole moiety, other milder, and non-acidic oxidative procedures are available for converting secondary alcohols to ketones. In view of their failure to prepare the ketone, they do not seem to have attempted these methods. In addition, since 4-hydroxycyclohexanone was available from previous work on indolyl anion additions to ketones, this scheme was attempted.

4-Hydroxycyclohexanone (CXV)

When reactions of indolylanions were being investigated, 4-hydroxycyclohexanone was prepared as a compound which could lead to one of the desired indolylketones.
The procedure of Emmert and Lednicer\textsuperscript{62} for the preparation of this compound was attempted. 1,4-Dihydroxycyclohexane (CXIX) was acetylated in acetic anhydride to yield the diacetoxy compound CXX, of which only the trans isomer was isolated by fractional crystallization. A basic hydrolysis yielded 4-acetoxyxyclohexanol (CXXI) which was, in turn, oxidized with chromic acid in acetone to the cyclohexanone CXXII. Hydrolytic cleavage of the remaining acetyl group yielded 4-hydroxycyclohexanone in 13\% overall yield.

Soon after this procedure was completed, a two-step sequence was published which did not require the isolation of the intermediate compound. Since more material was needed, this procedure was attempted. Radlick and Crawford\textsuperscript{63}
used p-methoxyphenol as the starting material which was reduced in lithium/ammonia to the enol ether CXXIV. The enol ether was hydrolyzed to 4-hydroxycyclohexanone for an overall yield of 89% after purification by distillation.

\[
\begin{align*}
\text{CXXIII} & \xrightarrow{\text{Li/NH}_3} \text{CXXIV} & \xrightarrow{\text{H}_2\text{O}^+} \text{CXV}
\end{align*}
\]

Following this procedure, we obtained a yellow oil after distillation in 50% yield based on desired product. An infrared spectrum of this oil and TLC disclosed the presence of considerable p-methoxyphenol in the product. After standing several days at room temperature, the oil partially crystallized. Since 4-hydroxycyclohexanone is a liquid at room temperature, the crystals were probably p-methoxyphenol.

Increasing the reduction time again yielded a mixture of desired product and starting material. Since the four-step method of Emmert and Lednicer\textsuperscript{62} gives uncontaminated 4-hydroxycyclohexanone (by TLC and Gas chromatography), the lithium/ammonia reduction method was abandoned. Increasing the reduction time further beyond that recommended by Radlick and Crawford\textsuperscript{63} may be necessary for the reaction to succeed.
3-Hydroxy-1,2,3,4-tetrahydrocarbazole (CXVI) was prepared as proposed above by addition of phenylhydrazine to a hot acetic acid solution of 4-hydroxycyclohexanone (CXV). Isolation of the product and crystallization gave a 59% yield of the desired compound. When phenylhydrazine was added to a cold acetic acid solution of the cyclohexanone CXV, a high-melting yellow solid was obtained which is presumably the phenylhydrazone of 4-hydroxycyclohexanone CXXV.

Attempts to oxidize 3-hydroxy-1,2,3,4-tetrahydrocarbazole to the ketone using chromic acid prepared from sodium dichromate or chromium trioxide in acetone gave intractable gums from which no product could be isolated. Infrared spectra, however, did indicate the presence of a carbonyl group in the gums. In view of the sensitivity of the indole moiety to decomposition in the presence of strong acid, milder oxidation procedures were sought.

The indole alkaloid, yohimbine (CXXVI) has been oxidized to yohimbinone (CXXVII) using the non-acidic oxidation reagent, dicyclohexylcarbodiimide (DCC) in dimethylsulfoxide (DMSO) with orthophosphoric acid. Yields up to 80% were obtained.64
Adapting this procedure to the preparation of 3-oxo-tetrahydrocarbazole, the hydroxy compound CXVI was treated with three molar equivalents of DCC and 1.5 molar equivalents of crystalline ortho-phosphoric acid in DMSO. After standing at room temperature for 13.5 hours, a carbonyl (by ir spectroscopy) containing gum was obtained which could not be crystallized. According to Teuber and Cornelius the ketone recrystallized from ethanol.

Since one equivalent of the ortho-phosphoric acid was used to isolate the yohimbinone CXXVII as the phosphate salt, only 0.5 molar equivalent is really needed for the oxidation of yohimbine. Consequently, an excess of the acid was present in the oxidation. The reaction was repeated using only 0.5 molar equivalent of the acid catalyst and reaction times of 23.4.5, and 3.25 hours. In no cases could the oil or semi-solid obtained be crystallized. The ketone was probably present because the ir spectrum showed a strong peak in the carbonyl region.

The reaction was finally run in a dry box because of
possible water contamination being the cause of the failures. Crystalline phosphoric acid is very hygroscopic as is DMSO. Using three equivalents of DCC and 0.5 equivalents of the acid in DMSO in a dry box and a reaction time of 3 hours afforded a yellow solid in 84% crude yield. A crystallization from ethanol gave crystals of the desired product in 7% yield by slow evaporation of the ethanol. The 3-oxo-1,2,3,4-tetrahydrocarbazole had properties identical to those reported. Further evaporation of the solvent in the mother liquor afforded varying amounts of an oil. Since enough of the product was available for our studies, an increase in the yield of pure product was not sought.

3-(3'-Indolyl)cyclohexanone (XXXIX)

A Michael reaction used for the preparation of a previously described compound, 4-(3'-indolyl-2-butanone (XXXVI) could also be adapted for the preparation of 3-(3'-indolyl)cyclohexanone (XXXIX). Indole could add to 2-cyclohexenone (CXXVIII) as indicated.

\[
\begin{array}{c}
\text{XLIII} \\
\text{CXXVIII} \\
\text{XXXIX}
\end{array}
\]

Several attempts were made to achieve the addition. Most involved the introduction of one equivalent of
2-cyclohexen-1-one to an acetic acid solution of indole. The resulting solution was heated on a steam bath for 0.5, 1.5, 2.0, 3.0, and 5.0 hours. The reactions were worked up by pouring the mixtures into water and extracting the oily precipitate. Most of the product was found to be starting material by TLC and infrared spectroscopy. The carbonyl region indicated that a saturated cyclohexanone was present along with 2-cyclohexenone. Attempted purification by silica gel column chromatography have intractable gums in most of the runs.

For the 3-hour reaction the crude product was chromatographed and a yellow-brown oil was obtained from one of the non-starting material fractions. The oil solidified upon standing and was recrystallized from benzene-petroleum ether as small needles of the desired product in 5.5% overall yield. The low yield probably reflects the greater steric hinderance to addition at the β-carbon atom of 2-cyclohexen-1-one. This reaction is analogous to the addition product (CXXX) of indole and mesityl oxide (CXXIX). The 1,4-addition product is obtained in 2% overall yield (pure product).

\[
\begin{align*}
\text{Indole} + (\text{CH}_3)_2\text{C} &= \text{CHCH}_3 & \rightarrow \text{Product} \\
& & \text{CXXIX} & \text{CXXX}
\end{align*}
\]

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2-(4'-Oxopentyl)-3-methylindole (XXXVIII)

This compound was prepared following the procedure of Schlitter and Weber. 2-Methyl-1,3-cyclohexanedione (CXXXI) in benzene was condensed with phenylhydrazine to yield the tetrahydropyrido[1.2]indole CXXXII. Treatment of the isolated pure pyrido compound with methyl magnesium iodide gave the desired indolylketone XXXVIII.

\[
\text{CXXXI} + \text{CXXXII} \rightarrow \text{XXXVIII}
\]

Yohimban-17-one (XLII)

This alkaloid-derived indolylketone was prepared by the method of Albright and Goldman from yohimbine(CXXVI). The starting alkaloid was obtained from its hydrochloride by neutralization of an aqueous ethanol solution with concentrated ammonium hydroxide and collection of the precipitate. Yohimbine was oxidized to yohimbinone (CXXVII) as described previously using DCC-DMSO. Acidification and

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decarboxylation of yohimbinone in hot hydrochloric acid-acetic acid gave the desired product, yohimban-17-one (XLII).
Evidence for triplet-triplet energy transfer in the indolylketones prepared in this work was obtained by emission spectroscopy. As mentioned previously, the spectroscopic properties of indole and an aliphatic ketone provide an ideal situation for the study of triplet transfer. A schematic energy level diagram is presented in Figure 12. With the choice of a suitable cutoff filter direct excitation of indole can be prevented and only the ketone will be excited. A

![Schematic energy level diagram](image)

Figure 12. Schematic energy level diagram for lower singlet and triplet states of indole and an aliphatic ketone.

phosphorescence emission from indole would provide nearly unambiguous evidence for triplet-triplet energy transfer.

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Apparatus and Procedure

The absorption spectra of all the compounds used in this study were determined at room temperature on a Cary 14 recording spectrophotometer using EPA (ethyl ether, isopentane, and ethanol; 5:5:2 parts by volume respectively) as the solvent. Occasionally, for compounds not soluble in EPA, chloroform/methanol (1:4 v/v) was used. Ten mm quartz cells were used in all instances. The solvents used were reagent grade and were distilled prior to use. The compounds were of analytical purity.

The phosphorescent emission spectra were obtained using an Aminco-Bowman Spectrophotofluorometer equipped with an ellipsoidal condensing mirror system and a Hewlett-Packard Moseley 7035A X-Y recorder. The spectrophotofluorometer was fitted with a rotating cylindrical shutter having slits 180° apart to record in the phosphorescent mode. Each slit angle was 30° giving a phosphorimeter factor equal to six.

The lifetime measurements were determined using a time-base recorder, Honeywell Model 194, and by interrupting the exciting light with a manually operated shutter. The phosphorescent lifetimes were generally reproducible to at least ± 0.2 sec. Except where noted, all samples for the phosphorescent studies were run in a clear rigid glass of EPA at 77°K using a five millimeter I.D. quartz sample tube.

In order to assure uniformity and reproducibility of runs, all measurements were performed with the same tube.
In these experiments the quartz tube was lowered into a specially-made quartz dewar flask containing liquid nitrogen and measurements were performed after bubbling had subsided. The sample tube, dewar flask and dewar holder were aligned, and the same alignment maintained for each run to assure a constant reproducibility of phosphorescence intensity. The only deviations then were the normal ± 10% due to non-reproducibility of the rigid glasses at 77°C. In addition, the clarity of the liquid nitrogen was maintained to prevent loss of light intensity due to the formation of ice crystals.

The filter used was a 2 mm 295 nm sharp cutoff filter (Oriel). At 320 nm it transmitted approximately 30% of the exciting light which was sufficient for our studies. In addition, a 1 mm filter containing a 0.1 M indole solution in EPA was placed after the 295 nm filter, in some runs, to insure that indole was not being excited directly. Both the 295 nm glass filter alone and the combination of filters did not excite the indole chromophore singlet except in the case noted below. Consequently, only the glass filter was used.

The 1P28 photomultiplier tube was calibrated for wavelength response by manually comparing a fluorescence spectrum of anthranilic acid with a corrected spectrum for the same compound, a method with a reproducibility of ± 5%. Quantum efficiencies of phosphorescence (Φ_p) were obtained by comparison of the manually corrected spectra to that of anthranilic acid whose quantum efficiency of fluorescence
is known $\bar{\sigma}_f = 0.59$. The phosphorimeter factor of six was taken into account.

Absorption Spectra

The absorption spectra of the indolylketones used in these studies were determined as well as those of several model indoles and ketones. Indole, 2-methyl- and 3-methyl-indole, 2,3-dimethylindole, 1,2,3,4-tetrahydrocarbazole, and yohimbine were considered as model indoles, and acetone and cyclohexanone as model ketones. At $1.00 \times 10^{-4}$ M concentrations, the indolylketones and indoles exhibited an absorption in the wavelength range 250-300 nm attributed to the indole chromophore. The absorptions were nearly the same in all the compounds, and variations in the positions of the main peaks were only on the order of $\pm 1$ nm. The uv absorption spectra of 2,3-dimethylindole and yohimbine-17-one are representative examples and are shown in Figures 13 and 14 respectively. In Table 2 are listed the absorption wavelengths of several of the other compounds studied. At these concentrations the absorption at the wavelength of interest (320 nm) is very small for the indolylketones. Absorptions at 320 nm were determined using $1.00 \times 10^{-2}$ M solutions scanning the wavelength range 310-350 nm. The spectrum of 2-oxo-1,2,3,4-tetrahydrocarbazole was determined at $1.00 \times 10^{-3}$ M because the absorption at 320 nm is off-scale at $1.00 \times 10^{-2}$ M. Absorption spectra of yohimbine

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and yohimban-17-one were examined at 1.00 x 10^{-2} M in chloroform-methanol because of their insolubility in EPA above a concentration of ca.1-^{3} M. The spectra of all the compounds studied at 320 nm are shown in Figures 15-28 and the molar extinction coefficients \( \varepsilon_{320} \) are given in Table 2. The absorption of acetone and cyclohexanone in EPA are given also.

Solutions of equimolar amounts of indole and acetone in EPA (1.00 x 10^{-2} M each) gave an absorption spectrum in the 310-350 nm region that corresponded to acetone alone since indole has no absorption in this region.

**Emission Spectroscopy**

Indole, 2-methylindole, 3-methylindole, 2,3-dimethylindole, and tetrahydrocarbazole in EPA (1.00 x 10^{-2} M) all exhibited intense phosphorescent emissions characteristic of indole when excited near the wavelength of maximum absorption (290 nm). The emission spectrum (uncorrected) of indole is representative and is shown in Figure 29 and the wavelengths of emission of the indoles are listed in Table 3. The same compounds were also excited at 320 nm under the same conditions. Indole, 2-methyl- and 3-methylindole displayed no significant emission above background. However, 2,3-dimethylindole and tetrahydrocarbazole gave emissions in the indole region. The 2,3-dimethylindole emission from 380-550 nm was structureless but overlaps
Figure 13. Absorption spectrum of 2,3-dimethylindole in EPA (1.00 x 10^{-4} M).

Figure 14. Absorption spectrum of yohimban-17-one in EPA (1.00 x 10^{-4} M).
Figure 15. Absorption spectrum of 3-indolylacetone in EPA (1.00 x 10^{-2} M).

Figure 16. Absorption spectrum of 4-(3'-indolyl)-2-butanone (1.00 x 10^{-2} M).
Figure 17. Absorption spectrum of 5-(3'-indolyl)-2-pentanone in EPA (1.00 x 10^-2 M).

Figure 18. Absorption spectrum of 2-oxo-1,2,3,4-tetrahydrocarbazole in EPA (1.00 x 10^-3 M).
Figure 19. Absorption spectrum of 3-oxo-1,2,3,4-tetrahydrocarbazole in EPA (1.00 x 10^-2 M).

Figure 20. Absorption spectrum of 3-(7H-indolyl)cyclohexanone in EPA (1.00 x 10^-2 M).
Figure 21. Absorption spectrum of 2-(4'-oxopentyl)-3-methylindole in EPA (1.00 x 10^{-2} M).

Figure 22. Absorption spectrum of yohimban-17-one in chloroform/methanol (1.00 x 10^{-2} M).
Figure 23. Absorption spectrum of indole (1.00 x 10^{-2} M) in EPA.

Figure 24. Absorption spectrum of 2-methylindole (1.00 x 10^{-2} M) in EPA.
Figure 25. Absorption spectrum of 3-methylindole \((1.00 \times 10^{-2} \text{ M})\) in EPA.

Figure 26. Absorption spectrum of 2,3-dimethylindole \((1.00 \times 10^{-2} \text{ M})\) in EPA.
Figure 27. Absorption spectrum of 1,2,3,4-tetrahydrocarbazole in EPA (1.00 x 10^{-2} M).
Figure 28. Absorption spectrum of yohimbine in chloroform/methanol (1.00 x 10^-2 M).

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Table 2. Absorption wavelengths and molar extinction coefficients of several indoles and indolylketones and $\varepsilon_{320}$.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Wavelength (nm), $\varepsilon$</th>
<th>$\varepsilon_{320}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Indolylacetone</td>
<td>292 (6600)</td>
<td>157</td>
</tr>
<tr>
<td></td>
<td>282 (7900)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>275 (7500)</td>
<td></td>
</tr>
<tr>
<td>4-(3'-Indolyl)-2-butanone</td>
<td>292 (6400)</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>283 (7400)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>277 (6800)</td>
<td></td>
</tr>
<tr>
<td>5-(3'-Indolyl)-2-pentanone</td>
<td>292 (5100)</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>283 (6100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>277 (5600)</td>
<td></td>
</tr>
<tr>
<td>2-Oxo-1,2,3,4-tetrahydrocarbazole</td>
<td>292 (5700)</td>
<td>640</td>
</tr>
<tr>
<td></td>
<td>283 (7400)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>276 (7400)</td>
<td></td>
</tr>
<tr>
<td>3-Oxo-1,2,3,4-tetrahydrocarbazole</td>
<td>291 (6300)</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td>284 (8100)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>277 (8000)</td>
<td></td>
</tr>
<tr>
<td>3-(3'-Indolyl)cyclohexanone</td>
<td>292 (5700)</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>283 (6800)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>277 (6400)</td>
<td></td>
</tr>
<tr>
<td>2-(4'-Oxopentyl)-3-methylindole</td>
<td>292 (7300)</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>284 (8300)</td>
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</tr>
<tr>
<td></td>
<td>277 (7800)</td>
<td></td>
</tr>
<tr>
<td>Yohimban-17-one</td>
<td>291 (6400)</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>284 (7700)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>276 (7400)</td>
<td></td>
</tr>
<tr>
<td>Indole</td>
<td>292 (7200)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>283 (8200)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>274 (8500)</td>
<td></td>
</tr>
<tr>
<td>2-Methylindole</td>
<td>290 (5700)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>283 (7200)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>274 (7600)</td>
<td></td>
</tr>
<tr>
<td>3-Methylindole</td>
<td>292 (5200)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>283 (6000)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>276 (5600)</td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Compound</th>
<th>Wavelength (nm), $\varepsilon$</th>
<th>$\varepsilon_{320}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,3-Dimethylindole</td>
<td>292 (6100)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>283 (7000)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>276 (6600)</td>
<td></td>
</tr>
<tr>
<td>1,2,3,4-Tetrahydro-</td>
<td>292 (6400)</td>
<td>12</td>
</tr>
<tr>
<td>carbazole</td>
<td>283 (7500)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>275 (7200)</td>
<td></td>
</tr>
<tr>
<td>Yohimbine</td>
<td>292 (6400)</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>283 (7700)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>276 (7300)</td>
<td></td>
</tr>
</tbody>
</table>
the indole phosphorescence region. The tetrahydrocarbazole phosphorescence is characteristic of indole and has three distinct peaks when excited at 320 nm. The structure is nearly the same as when the compound is excited at 290 nm but much less intense. The significance of this result will be discussed later.

The indolylketones prepared in this work were examined at excitation wavelengths of 290 and 320 nm. At 290 nm, where the indole chromophore is being directly excited, the phosphorescence emission is distinctly characteristic of indole in general. For example the emission from 2-(4-oxopentyl)-3-methylindole is representative of these compounds, and the spectrum (uncorrected) is sketched in Figure 30.

Excitation of the indolylketones at 320 nm gave phosphorescence spectra characteristic of indole in many of the compounds. Since these are the spectra of concern for our study of triplet-triplet energy transfer, the corrected spectra of all of the indolylketones (320 nm excitation) are shown in Figures 31-41. The quantum efficiencies of phosphorescence ($\tilde{\alpha}_p$) of the compounds were calculated and are listed in Table 4.

Yohimbine and yohimban-17-one were examined in chloroform/methanol solution ($1.00 \times 10^{-2} \text{ M}$). At 77°K the solutions formed cracked, clear glasses. Reproducibility is

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therefore probably greater than ± 10%. The spectra under excitation at 290 nm exhibited a characteristic indole emission similar to those of the other indolylketones. Excitation at 320 nm gave a broad structureless emission of low intensity from 400-500 nm.

Acetone and cyclohexanone at 1.00 x 10⁻² M in EPA gave no emission under excitation at 320 nm or 290 nm. With a 1.00 M solution of acetone in EPA a weak acetone phosphorescence emission could be detected upon excitation at 320 nm. Under excitation at 290 nm this solution gave a broad structureless emission band characteristic of acetone. The uncorrected spectra are reproduced in Figure 42.

Phosphorescence emission from mixtures of indole and acetone were briefly examined. Solutions of 1.00 x 10⁻² M indole and acetone when excited at 320 nm showed no emission. Only at concentrations greater than 0.1 could a weak emission in the 400-500 nm region be seen.

Lifetime Measurements

Lifetimes were determined for the phosphorescence of all the model indoles and indolylketones at the maximum emission peaks under excitation at 290 nm. Lifetimes for the compounds examined at 320 nm excitation were obtained only when a measurable emission was present. These are listed also in Table 4. The symbol ___ indicates that there was either no or little emission under these conditions and that the determination could not be made.
Figures 29 and 30. Phosphorescence emission spectra of indole and 2-(4'-oxopentyl)-3-methylindole in EPA (1.00 x 10^-2). Excitation at 290 nm, photomultiplier x 0.01.

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Figure 31. CPK model and phosphorescence emission spectrum of 3-indolylacetone in EPA (1.00 x 10^{-2} M). Excitation at 320 nm, photomultiplier x 0.03.
Figure 32. CPK model and phosphorescence emission spectrum of 4-(3'-indolyl)-2-butanone in EPA (1.00 x 10^{-2} M). Excitation at 320 nm, photomultiplier x 0.003.

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Figure 33. CPK model and phosphorescence emission spectrum of 5-(3'-indolyl)-2-pentanone in EPA (1.00 x 10^-2 M). Excitation at 320 nm, photomultiplier x 0.003.

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Figure 34. CPK model and phosphorescence emission spectrum of 2-oxo-1,2,3,4-tetrahydrocarbazole in EPA (1.00 x 10^{-3} M). Excitation at 320 nm, photomultiplier x 0.01
Figure 35. CPK model and phosphorescence emission spectrum of 3-oxo-1,2,3,4-tetrahydrocarbazole in EPA (1.00 x 10^{-2} M). Excitation at 320 nm, photomultiplier x 0.03.
Figure 36. CPK model and phosphorescence emission spectrum of 3-(3'-indolyl)cyclohexanone in EPA (1.00 x 10^{-2} M). Excitation at 320 nm, photomultiplier x 0.01.

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Figure 37. CPK model and phosphorescence emission spectrum of 2-(4-oxopentyl)-3-methylindole in EPA (1.00 x 10^-2 M). Excitation at 320 nm, photomultiplier x 0.001.
Figure 38. CPK model and phosphorescence emission spectrum of yohimban-17-one in chloroform/methanol (1.00 x 10^{-2} M). Excitation at 320 nm, photomultiplier x 0.003.

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Figure 39. Phosphorescence emission spectrum of 2,3-dimethylindole in EPA (1.00 x 10^-2 M). Excitation at 320 nm, photomultiplier x 0.003.
Figure 40. Phosphorescence emission spectrum of 1,2,3,4-tetrahydrocarbazole in EPA (1.00 x 10^{-2} M). Excitation at 320 nm, photomultiplier x 0.003.
Figure 41. Phosphorescence emission spectrum of yohimbine in chloroform/methanol (1.00 x 10^-2 M). Excitation at 320 nm, photomultiplier x 0.003.
Figure 42. Phosphorescence emission spectrum of acetone in EPA (1.00 M). Excitation at 290 nm, photomultiplier x 0.003
Table 3. Wavelengths of phosphorescence emission peaks of several indole compounds upon excitation at 290 nm at 77°C in EPA (yohimbine in chloroform/methanol).

<table>
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<tr>
<th>Compound</th>
<th>Emission</th>
</tr>
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<tr>
<td>Indole</td>
<td>405 nm</td>
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<tr>
<td></td>
<td>432</td>
</tr>
<tr>
<td></td>
<td>445</td>
</tr>
<tr>
<td>2-Methylindole</td>
<td>407</td>
</tr>
<tr>
<td></td>
<td>431</td>
</tr>
<tr>
<td></td>
<td>452</td>
</tr>
<tr>
<td>3-Methylindole</td>
<td>417</td>
</tr>
<tr>
<td></td>
<td>440</td>
</tr>
<tr>
<td></td>
<td>458</td>
</tr>
<tr>
<td>2,3-Dimethylindole</td>
<td>420</td>
</tr>
<tr>
<td></td>
<td>445</td>
</tr>
<tr>
<td></td>
<td>466</td>
</tr>
<tr>
<td>1,2,3,4-Tetrahydrocarbazole</td>
<td>415</td>
</tr>
<tr>
<td></td>
<td>442</td>
</tr>
<tr>
<td></td>
<td>462</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>413</td>
</tr>
<tr>
<td></td>
<td>438</td>
</tr>
<tr>
<td></td>
<td>463</td>
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Table 4. Quantum efficiencies of phosphorescence ($\Phi_p$) of indole compounds upon excitation at 320 nm, lifetimes of phosphorescence when excited at 290 and 320 nm, and distances between van der Waals radii of the carbonyl group and indole chromophores from CPK models.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\Phi_p$</th>
<th>Lifetimes</th>
<th>Distances between chromophores</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Indolylacetone</td>
<td>0.0998</td>
<td>3.1 sec</td>
<td>2.6 sec</td>
</tr>
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<td>4-(3'-Indolyl)-2-butanone</td>
<td>0.0471</td>
<td>5.9</td>
<td>4.0</td>
</tr>
<tr>
<td>5-(3'-Indolyl)-2-pentanone</td>
<td>0.0235</td>
<td>4.6</td>
<td>4.5</td>
</tr>
<tr>
<td>2-Oxo-1,2,3,4-tetrahydrocarbazole</td>
<td>0.0655</td>
<td>4.7</td>
<td>4.1</td>
</tr>
<tr>
<td>3-Oxo-1,2,3,4-tetrahydrocarbazole</td>
<td>0.116</td>
<td>5.0</td>
<td>5.6</td>
</tr>
<tr>
<td>3-(3'-Indolyl)cyclohexanone</td>
<td>0.0286</td>
<td>3.6</td>
<td>3.1</td>
</tr>
<tr>
<td>2-(4'-Oxopentyl)-3-methyllindole</td>
<td>0.0120</td>
<td>4.5</td>
<td>4.4</td>
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<td>Yohimban-17-one</td>
<td>0.00742</td>
<td>5.5</td>
<td></td>
</tr>
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<td>Indole</td>
<td></td>
<td>6.0</td>
<td></td>
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<tr>
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<td>5.4</td>
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Table 4. Continued

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<tr>
<th>Compound</th>
<th>$\bar{\Phi}$</th>
<th>Lifetimes Excitation at</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>290 nm 320 nm</td>
</tr>
<tr>
<td>3-Methylindole</td>
<td></td>
<td>5.4 sec</td>
</tr>
<tr>
<td>2,3-Dimethylindole</td>
<td>0.0287</td>
<td>5.9</td>
</tr>
<tr>
<td>1,2,3,4-Tetrahydrocarbazole</td>
<td>0.0469</td>
<td>6.2 6.2</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>0.0245</td>
<td>5.7</td>
</tr>
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Discussion of Spectroscopic Results

Intermolecular triplet-triplet energy transfer

Equimolar mixtures of indole and acetone at concentrations of $1.00 \times 10^{-2}$ M each under excitation at 320 nm showed no evidence of triplet-triplet transfer from acetone to indole. In fact, no emission was seen. A calculation assuming uniform distribution of the molecules shows that the average distances between molecules is $4.4 \text{ Å}$. This is well beyond the 12-15 Å limit for triplet-triplet energy transfer to occur. From measurements of molecular models of indole and acetone the distances between the van der Waals radii of the molecules would be around 35 Å. When concentrations are increased to 0.25 M for each component there appears to be some emission characteristic of indole indicating that triplet-triplet energy transfer is occurring.

The lack of transfer at concentrations of $1.00 \times 10^{-2}$ M insures that intermolecular transfer will not take place at the concentrations employed for intramolecular studies. With only one component present in solution at $10^{-2}$ M, the distance between centers of molecules under the assumption above is calculated to be 55 Å.

In one run 1.00 M concentrations of each component were used. The frozen solution formed a cracked glass at 77°K. However, upon excitation at 320 nm, an emission characteristic of indole was seen distinctly and was fairly

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intense. The lifetime (4.4 sec) was the same as upon excitation at 290 nm where indole is being directly excited. Distances between centers of molecules at these concentrations are around 9.5 Å. Many molecules would be in contact or near contact, certainly good conditions for intermolecular triplet-triplet energy transfer.

Absorption spectra

The absorption spectra of the various indolylketones displayed a range of ε values at 320 nm, all considerably more than for acetone or cyclohexanone at the same concentrations. For acetone ε_{320} = 3.5 and for 3-indolylacetone, ε_{320} = 157 (see Figure 15, p 89). At 320 nm the tailoff of the n→π* transition of the carbonyl group is being observed in all of the indolylketones. Presumably, the indole moiety is exerting some perturbation on the n→π* transition at 320 nm. Any perturbation of the carbonyl absorption at the wavelength of maximum absorption (for acetone λ_{max} = 279 nm) will be hidden by the indole absorption band and consequently could not be seen. This perturbation may be due to an inductive type effect. The possibility of a highly absorbing impurity at 320 nm is doubtful since a similar impurity would need to be present in all the samples. The compounds were all prepared by different schemes.

1,2,3,4-Tetrahydrocarbazole gave an unexpected absorption at 320 nm (ε_{320} = 12, see Figure 27, p 95) unlike indole or 3-methylindole whose cutoff was around 300 nm. The
absorption intensity remained nearly constant throughout three recrystallizations of the material. The absorption was assumed to be inherent to tetrahydrocarbazole itself. To our knowledge, no one has reported the uv absorption of indoles at relatively high concentrations in this wavelength region. A literature spectrum\textsuperscript{70} of tetrahydrocarbazole in the concentration range $10^{-4}$ M exhibits no absorption at 320 nm. It is identical to our spectrum at that concentration.

Confirmation of the absorption of tetrahydrocarbazole at 320 nm comes from the emission spectrum (Figure 40, p 111). When excited at 320 nm, tetrahydrocarbazole exhibited a weak emission characteristic of indole. The lifetime was identical to that obtained under excitation at 290 nm (4.4 sec). The corrected emission spectrum was used to revise the spectra of 2-oxo- and 3-oxo-1,2,3,4-tetrahydrocarbazole discussed below.

2,3-Dimethylindole gave an absorption at 320 nm at $10^{-2}$ M in EPA ($\epsilon_{320} = 10$, see Figure 26, p 94). However, the absorption may be due to impurities since the emission under excitation at 320 nm (Figure 39, p 110) is more efficient than that of 2-(4'-oxopentyl)-3-methylindole (Figure 37, p 108), a compound which should show enhanced emission from triplet-triplet energy transfer. In fact, the efficiency is less ($\Phi_p = 0.0120$) than for 2,3-dimethylindole ($\Phi_p = 0.0287$).
Phosphorescence emission studies

On the basis of the phosphorescence spectra of the indolylketones studied in this work, triplet energy is being transferred from the carbonyl group to the indole chromophore. However, the efficiency of the transfer varies for the individual compounds.

The series of indolylketones with the chromophores being held apart by one, two, or three methylene groups seems to provide a useful confirmation of the distance requirements for the transfer. From an examination of CPK models of the compounds (photographs reproduced with the emission spectra, Figures 31-38, pp 102-109), the more likely conformations place the chromophores at nearly maximum distances apart. There are conformations, of course, that place the chromophores in near van der Waals contact, but these conformations require more steric crowding of methylene groups, etc. Most conformations seem to keep the chromophores apart except for 3-indolylacetone, in which the carbonyl group oxygen nearly lies on the indole ring. These compounds suffer the same deficiency as those studied by other workers, i.e., nonrigidity. However, the carbonyl group affords a size advantage that their compounds lack, i.e., its small size. The transfer efficiencies of our compounds decrease from $\Phi_p = 0.0998$ to $0.0471$ to $0.0235$ as the number of methylene groups increases. This decrease seems to parallel the increase in the distance between
chromophores and is consistent with the exchange mechanism. On the basis of the experimental efficiencies, the extended model for these compounds appears justified.

The transfer efficiency for 2-(4'-oxopentyl)-3-methylindole ($\Phi_p = 0.0120$) also justifies the critical distance requirements for efficient transfer. The efficiency is lower than for the analogous compound above, 5-(3'-indolyl)-2-pentanone. The efficiency was lower than that expected on the basis of the emission from the model indole, 2,3-dimethylindole ($\Phi_p = 0.0287$). The fact that $\Phi_p$ for the indolylketone is lower indicates that 2,3-dimethylindole is not a suitable compound for comparison or that our model indole contained an impurity absorbing at 320 nm. On this basis no revision is made on the $\Phi_p = 0.0120$ to correct for emission due solely to 2,3-dimethylindole. In addition, $\Phi_p$ for 2-(4'-oxopentyl)-3-methylindole is in the range for the analogous compound, 5-(3'-indolyl)-2-pentanone.

Among the compounds prepared having a structure assuring separation of the chromophores, 2-oxo- and 3-oxo-1,2,3,4-tetrahydrocarbazole offer an interesting comparison. Both exhibited fairly high $\varepsilon_{320}$ values (for 3-oxo, $\varepsilon_{320} = 125$ and for 2-oxo, $\varepsilon_{320} = 640$). The phosphorescence emission spectra of these compounds (Figures 34 and 35, pp 105, 106) indicate that triplet-triplet energy transfer is occurring in both of these compounds despite the lack of overlap of the van der Waals radii of the two chromophores. The
transfer efficiencies are $\Phi_p = 0.0655$ for 2-oxotetrahydrocarbazole and 0.116 for the 3-oxo isomer. Since the distances between the chromophores are nearly the same in both compounds (ca. 0.5 Å), it might be expected that the $\Phi_p$'s should be nearly the same. As mentioned previously, tetrahydrocarbazole itself shows an absorption at 320 nm. Therefore, a portion of the absorbance at 320 nm and the resulting emission in these two indolylketones is also due to direct excitation of the tetrahydrocarbazole moiety. This alters the energy level scheme to allow direct excitation of the indole chromophore, at least in these two compounds. This complicates the interpretation of the emission results. The energy level scheme would approximate that in Figure 43 with a lower level for the $S_1$ state of

![Figure 43. Schematic energy level diagram for lower singlet and triplet states of tetrahydrocarbazole and an aliphatic ketone.](image)

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indole (compare to Figure 12, p 83). Excitation with 320 nm wavelength energy would populate the indole $S_1$ state partially in addition to the $S_1$ of the carbonyl group. This could allow singlet-singlet energy transfer to occur from the $S_1$ state of indole to the $S_1$ state of the ketone or vice versa. Intersystem crossing to $T_1$ of the ketone would be followed by triplet-triplet transfer back to $T_1$ of indole. Conversely, intersystem crossing of $S_1$ of indole to the $T_1$ state would be followed by direct phosphorescence. These pathways do not seem to be used, as the following evidence shows.

A comparison of the absorbances of the oxo compounds reveals that the 2-oxo compound absorbs 50 times as much 320 nm light as tetrahydrocarbazole. Similarly, the 3-oxo compound absorbs 10 times as much. If the tetrahydrocarbazole moiety absorbs in these two compounds, the 3-oxo isomer will have 5 times more light exciting the indole moiety as 2-oxotetrahydrocarbazole. A part of the emission efficiency for these two compounds can be considered, therefore, to be due to the tetrahydrocarbazole structure, and a correction can be made. For the 3-oxo isomer, $\Phi_p = 0.116$ and since the efficiency for tetrahydrocarbazole phosphorescence under the same conditions is 0.0469, the corrected $\Phi_p$ for 3-oxotetrahydrocarbazole would be $\Phi_p = 0.069$. Because of the difference in relative absorption of the two indolylketones with respect to tetrahydrocarbazole, the correction
\[ \Phi_p = 0.0655 - 0.0047 = 0.060 \] appears to be justified. This would give efficiencies of triplet transfer of the same order and place them in the range of the \( \Phi_p \)'s of the other indolylketones. On the basis of the distances between the carbonyl group and the indole moiety in 2-oxo- and 3-oxotetrahydrocarbazole (0.5 \( \AA \)), the \( \Phi_p \)'s seem reasonable. The separation distance is similar to that of indolylacetone (\( \Phi_p = 0.0998 \)).

3-(3'-Indolyl)cyclohexanone exhibited an efficiency of 0.0286, comparable to that of 4-(3'-indolyl)-2-butanone. The distance between chromophores for the two compounds is similar. The cyclohexanone has a structure which does not permit van der Waals contact between the chromophores. Although there is free rotation about the bond connecting C-3 of indole and C-3 of cyclohexanone, this does not alter the separation distance substantially. Presumably, the efficiency should be less for this compound. However, the difference in efficiencies with respect to the other compounds is not significant, and the fact that the efficiency is within the range seems to be the most important aspect.

The final indolylketone examined, yohimban-17-one, contained the indole and carbonyl group chromophores at the greatest separation distance of those studied in this work. The distance between the closest extremities of the two chromophores was 6.5 \( \AA \), over twice that of any of the other indolylketones. From a study of CPK models of the
compound, yohimban-17-one (Figure 38, p 109) is rigid and does not allow close approach of the two groups. The compound exhibited the lowest triplet-triplet transfer efficiency ($\phi_p = 0.00742$), nearly half that of 2-(4'-oxopentyl)-3-methylindole. Yohimbine, the model indole for this compound, had $\phi_p = 0.0245$, three times that of yohimban-17-one. This does not make sense since yohimban-17-one should have shown an enhanced efficiency above this or at least the same amount if yohimbine is indeed a justifiable model for this system. A better model would appear to be indole itself.

Summary

Triplet-triplet energy transfer in the indolylketones studied in this work seems to be taking place from the carbonyl group to the indole chromophore. While no orientation dependence for the transfer could be obtained from these compounds because of their inherent structures, a distance requirement did seem to be present. On the basis of the efficiency of transfer in yohimban-17-one, triplet-triplet transfer would seem to be efficient only for distances less than $6.5 \hat{R}$, the separation distance in this compound. Its efficiency is on the order of only 10% of that for 3-indolylacetone and near the limit of detection with the equipment employed although the comparison is for different solvents and a cracked versus a clear rigid glass.
Although the efficiencies fall off with increasing separation, the decrease should have been considerably more on the basis of the exchange mechanism. The transfer efficiencies of the indolylketones are plotted versus the separation distance in Figure 44. No apparent relationship seems to exist for all of the compounds. For the indolylketones with methylene groups separating the chromophores (compounds XXXV, XXXVI, XXXVII), the falloff of efficiency with increasing distance follows an approximately linear order. For the more rigid structures the curved plot in Figure 44 approximates an exponential curve (exp \(-0.5R\), where \(R\) is the separation distance). Dexter's work\(^\text{11}\) predicts an exponential type falloff of transfer efficiency with increasing distance if a true exchange mechanism occurs. The chromophore separation term appears in Dexter's equations as \(\exp \frac{-2R}{L}\), where \(L\) is an effective average Bohr radius for the excited donor and unexcited acceptor. For agreement with the experimental curve in Figure 44, \(L = 4 \AA\). If \(L\) is close to the van der Waals radii of the two chromophores, the agreement seems to be fairly close.

It is also possible that a different route other than the exchange mechanism is being followed for the triplet-triplet energy transfer. A participation of the sigma bond "bridge" separating the chromophores is a distinct possibility. Zimmerman\(^\text{24}\) found that triplet transfer via the sigma bond "bridge" may very likely occur for
the compound mentioned in the introduction (XXXIII). If this is true in his work and ours, many of the previous studies require a reinterpretation.

Because of the transfer efficiency results, the usefulness of studies of this type for determining an efficiency-distance relationship for adaptation to phosphorescent probes will be minimal. Apparently, the introduction of a sigma-bonded separating framework changes the characteristics of the chromophores significantly. In the enzyme-phosphorescent probe complex, the two chromophores are separated mainly by space. The interconnecting peptide backbone may be many peptide units long, but yet a close approach of the chromophores is permitted.

Further work in this area to determine a distance-transfer efficiency relationship seems to require the preparation of compounds with the chromophores being held at fixed distances apart in the range 0–15 Å, but with a relatively long interconnecting framework between the chromophores. Chromophores could be attached to two points of a polypeptide. The amino acid residues would provide a long interconnecting framework, while the conformation of the polypeptide would provide a close (0–15 Å) approach of the two chromophores. Knowledge of the distance separation could be obtained from models or the actual structure as determined by X-ray diffraction.
Figure 44. Plot of distance between chromophores in the indolylketones versus transfer efficiency. Straight line: for nonrigid structures. Dashed line: for rigid structures. Curved, full line: plot of exp \(-0.5R\), where R is the distance between chromophores.
EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared (ir) spectra were determined in chloroform or as Nujol mulls with a Beckman IR-8 instrument. Ultraviolet spectra (uv) were obtained in EPA solution with a Cary 14 recording spectrophotometer. Nmr spectra were determined with a Varian A-60 instrument in CDCl₃ using TMS as an internal standard. Solutions of ether and other solvents were dried with anhydrous magnesium sulfate. Microanalyses were performed by Midwest Laboratories, Indianapolis, Indiana.

N-Methylindole (LXXI).—To liquid ammonia (400 ml) containing ferric nitrate (0.1 g) at ca. -50° was added sodium (20.0 g, 0.854 g-atom) as small pieces over 5 min. After stirring for 1 hr, indole (50.0 g, 0.427 mole) in anhydrous ether (50 ml) was added over 15 min. Stirring was continued for another 0.5 hr after which methyl iodide (121.2 g, 0.854 mole) in ether (100 ml) was added over 15 min. The solution was stirred for 1 hr, and the ether and ammonia allowed to evaporate. The residue was shaken with ether (200 ml) and water (200 ml). The aqueous layer was extracted with ether (3 x 50 ml), the ether extracts combined, dried, and taken to dryness leaving a yellow-green oil. A distillation gave a clear oil (49.4 g, 89%), bp 98-100° (1.8 mm). The liquid was heated over sodium at 220°.
for 22 hr and redistilled affording an N-H free (by ir) oil (12.7 g, 23%), bp 56-57° (0.2 mm) [lit.46 bp 133° (26 mm)].

1-2'-(1'-Methylindolyl) cyclohexanol (LXXII).---To a solution of N-methylindole (1.00 g, 0.00763 mole) in sodium-dry ether (25 ml) was added at room temperature under a dry nitrogen atmosphere, n-butyllithium in hexane (12.2 ml, 0.0305 mole). The resulting solution was refluxed and stirred for 22 hrs. A solution of cyclohexanone (0.75 g, 0.00763 mole) in ether (5 ml) was added dropwise over 2 min, and the resulting solution refluxed for 5 hr. The solution was poured into water (25 ml), the ether solution separated, and the aqueous layer extracted with ether (3 x 20 ml). The ether extracts were combined, dried, and the solvent evaporated leaving a light brown oil (1.96 g) which partially crystallized upon standing. A recrystallization of the oily solid from aqueous ethanol gave nearly colorless crystals (0.19 g, 11%), mp 126-128°. A further recrystallization from ethanol-water gave material of analytical purity, mp 125-126.5°. ir (Nujol) 2.86-2.93 (0-H), 3.29, 3.43, 6.56, 6.78 μ; nmr (CDCl₃) δ 7.25 (m, 7 aryl protons), 6.25 (s, H-3), 3.93 (s, 1-CH₃), 1.8 (m, broad, 10 methylene protons and 0-H). Anal. Calcd for C₁₅H₂₀N₀ (229.31): C, 78.51; H, 8.35; N, 6.11. Found: C, 78.70; H, 8.19; N, 5.94.

3,3'-Ethylenedioxy-bis-(5,5-dimethyl-2-cyclohexen-1-one

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To a solution of \(5,5\)-dimethyl-1,3-cyclohexanedione (5.00 g, 0.0357 mole) in anhydrous benzene (100 ml) was added ethylene glycol (2.21 g, 0.0357 mole) and p-toluenesulfonic acid monohydrate (50 mg). The mixture was refluxed and stirred for 4.5 hr while the water produced was collected in a Dean-Stark trap. The benzene solution was washed with a 5% aqueous solution of sodium bicarbonate (1 x 25 ml) and water (1 x 25 ml), dried, and taken to dryness leaving a clear oil (5.09 g, 78%). Dissolving the oil in hot ethanol and allowing the resulting solution to stand for 3 days afforded long needles (3.45 g, 53%), mp 130-134.5°. A further recrystallization from ethanol raised the mp to 136.5-137° (lit. 50 mp 139-140°). Nmr (CDCl\(_3\)) \(\delta\) 1.08 (s, 12 H), 2.22 (s, 4 H), 2.33 (s, 4 H), 4.15 (s, 4 H), 5.37 (s, 2 vinyl H). This is identical to that reported. 50

4-(3'-Indoyl)-2-butanone (XXXVI).—Indole (2.34 g, 0.02 mole) was dissolved in glacial acetic acid (12 ml) and methyl vinyl ketone (4.7 g, 0.06 mole) added. The solution was allowed to stand at room temperature for 5 min and then heated on a steam bath for 25 min. The dark brown reaction mixture was cooled in ice, and water (100 ml) added with stirring. After setting for 10 min, a tan precipitate formed. A recrystallization from benzene-petroleum ether (30-60°) gave a slightly yellow powder (1.10 g, 30%), mp 90.5-92°, lit. 51 mp 93-94°. A further recrystallization gave colorless needles (Norit), mp 92-93°.
\( \text{uv } \lambda_{\text{max}} 292 \text{ nm (6400), 283 (7400), 277 (6800)}. \)

**5-(3'-Indolyl)-2-pentanone (XXXVII).**---To a stirred solution of 3-indolebutyric acid (1.00 g, 0.00492 mole) in sodium-dry ether (10 ml) was added dropwise at \( 0^\circ \) under a dry nitrogen atmosphere, methyllithium in ether (6.92 ml, 0.0152 mole). A gummy precipitate formed immediately, and the mixture was stirred at room temperature for 8 hr. The suspension and gummy precipitate were withdrawn and stirred into water (15 ml). The aqueous layer was extracted with ether (3 x 10 ml) and the combined ether extracts dried and taken to dryness leaving a tan oil (0.62 g). The oil was chromatogrammed on a silica gel column (CC-7, 200-325 mesh, 25 x 300 mm). The first fraction off the column was taken to dryness leaving a light orange oil which slowly crystallized (0.11 g). A recrystallization from ethanol-water gave slightly orange plates (0.090 g, 9%), mp 76.5-85°. A further recrystallization gave a powder from benzene-petroleum ether (30-60°) (0.059 g, 6%), mp 81-84.5°. \( \text{ir (Nujol mull)} 3.00 (\text{N-H}), 5.86 (\text{C=O}), 6.86 \mu. \text{ uv } \lambda_{\text{max}} 292 \text{ nm (5100), 283 (6100), 276 (7400)}. \) Anal. Calcd for C13 H15 NO (201.26): C, 77.58; H, 7.51. Found: C, 77.85; H, 7.80.

**3-Bromo-4-hydroxybiphenyl (XCIX).**---To a warm solution of 4-hydroxybiphenyl (100.0 g, 0.588 mole) in chloroform (1.1 l) was added dropwise with stirring a solution of bromine (94.2 g, 0.588 mole) in chloroform (125 ml). After the addition was complete (ca. 1 hr), the clear, light yellow solution was reduced in volume to 300 ml and petroleum

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ether (30-60°) added. After standing a few hours, white needles were obtained (130.0 g, 89%), mp 94-94.5° (lit.56 mp 96°). A second crop of needles (12.3 g, 8%), mp 91-92.5° was obtained from the mother liquor.

3-Bromo-4-methoxybiphenyl (C).—A solution of dimethyl sulfate (71.2 g, 0.565 mole) was added dropwise rapidly to a 10% aqueous sodium hydroxide (22.6 g in 200 ml of water) containing 3-bromo-4-hydroxybiphenyl (XCIX) (127.5 g, 0.513 mole). A thick, white precipitate formed which was suspended by addition of water (200 ml). After stirring an addition 0.5 hr, and heating on a steam bath for 15 min, the reaction mixture was cooled affording a granular solid (137.0 g, 101%). A recrystallization from ethanol yielded needles (115.0 g, 85%), mp 73.5-74.5° (lit.57 mp 76-77°).

2-Amino-4-methoxybiphenyl (G).—Sodium amide (prepared from 4.63 g, 0.201 mole of sodium cut in small pieces and 0.5 l of ammonia) and ferric chloride (0.8 g) were stirred while finely powdered 3-bromo-4-methoxybiphenyl (C) (25.0 g, 0.101 mole) was added gradually. The reaction mixture was stirred for 5 hr and dry ammonium chloride (16.0 g) was added followed by ether (100 ml) and benzene (100 ml). The excess ammonia was allowed to evaporate. The resulting mixture was extracted with 5% hydrochloric acid (7 x 500 ml), the combined acidic extracts neutralized with concentrated ammonium hydroxide and the precipitate extracted with methylene chloride (6 x 75 ml). The combined organic extracts
were dried, filtered, and taken to dryness leaving a brown oil (6.7 g, 33%). The oil was washed over a silica gel column (CC-7, 60-200 mesh, 75 g) with chloroform. Taking the fractions to dryness left a tan oil (6.62 g, 31%).

2-Methoxycarbazole (CII).—A solution of 2-amino-4-methoxybiphenyl (CI) (3.3 g, 0.0165 mole) in a warm (40-50°) solution of sulfuric acid (3 ml of concentrated sulfuric acid in 25 ml of water) was cooled in an ice bath causing a precipitate to form. To this was added a solution of sodium nitrite (1.38 g, 0.02 mole) in water (15 ml). Urea was added to remove excess nitrous acid and then Norit (0.25 g) added. After stirring for 0.5 hr, the Norit was filtered off and a solution of sodium azide (1.8 g) in water (10 ml) added dropwise to the cold solution. After allowing the reaction mixture to stand overnight, a red oil was extracted with ether (3 x 25 ml). The combined ether extracts were dried and taken to dryness leaving a red oil which was dissolved in hot (180-190°) kerosine (25 ml). This was poured into additional hot kerosine (100 ml, 180-190°). The solution was allowed to cool slowly to room temperature affording tan plates (1.75 g, 53%), mp 225-230°. A further recrystallization from ethanol (Norit) gave fine plates, mp 234-235°. lit. mp 235-236°.

2-Methoxy-1,4-dihydrocarbazole (CIII).—Finely powdered 2-methoxycarbazole (CII) (1.00 g, 0.00508 mole) was added to a stirred solution of ammonia (50 ml) and sodium-dry
ether (50 ml). Lithium metal (0.35 g, 0.05 mole) was added in small pieces. After stirring for 1.5 hr, ethanol was added dropwise until the blue color was discharged. The solution was left to stir while the ammonia evaporated. Water (50 ml) was added and the aqueous layer extracted with ether (2 x 20 ml). The combined ethereal extracts were washed with water (2 x 15 ml), dried and taken to dryness leaving a white powder (0.91 g, 91%), mp 175-179° lit. 54 mp 178-179°. A recrystallization from ethanol gave plates (0.68 g, 68%), mp 181-184.5°.

2-Oxo-1,2,3,4-tetrahydrocarbazole (XLI).—2-Methoxy-1,4-dihydrocarbazole (CIII) (0.25 g, 0.00125 mole) was dissolved in sodium-dry ether (20 ml) and hydrochloric acid (0.08 ml) added to the rapidly stirred solution. After stirring for 1 hr, the reaction mixture was shaken with a saturated sodium bicarbonate solution (10 ml) and the organic phase collected. The aqueous layer was extracted with ether (2 x 10 ml), the combined organic extracts shaken with water (10 ml), dried, and the solvent evaporated affording a fine powder (0.29 g), mp 124.5-128°. A recrystallization from ethanol-water gave a fine powder (0.12 g, 52%), mp 125-128° lit. 54 mp 131-133° (from cyclohexane). A further recrystallization gave material of analytical purity, mp 125-128°. ir (CHCl₃) 2.88 (N-H), 5.83 nm (C=O). uv λ_max 292 nm (5700), 283 (7400), 276 (7400). nmr (CDCl₃) δ7.83 (m broad, N-H), 6.97-7.60 (m, 4 H), 3.56
(s, 2H), 3.07 (m, 2 H), 2.68 (m, 2 H). Anal. Calcd for 
C12H11NO (185.21): C, 77.81; H, 5.99; N, 7.56. Found: 
C, 77.62; H, 6.06; N, 7.27.

1,4-Diacetoxy cyclohexane (CXX).—A mixture of 1,4-di-
hydroxy cyclohexane (156.6 g, 1.35 mole) and acetic anhy-
dride (550 ml) was refluxed for 1.5 hr and allowed to 
cool to 50°. The mixture was poured into water (3 l) at 
50° and the resulting solution allowed to stand overnight. 
The crystals were collected, dried, and recrystallized 
from ethanol as long needles (114.3 g, 43%), mp 100-102° 
(lit. 62 mp 98-101°).

4-Acetoxy cyclohexanol (CXXI).—To a stirred solution of 
1,4-diacetoxy cyclohexanone (CXX) (71.8 g, 0.359 mole) in 
ethanol (290 ml) and water (190 ml) at 45° was added over 
7 min a solution of potassium hydroxide (18.7 g) in ethanol 
(37 ml) and water (37 ml). Stirring was continued for an 
additional 15 min keeping the temperature at 47±2°. The 
volume was reduced on a rotary evaporator until crystals 
precipitated. These were collected and discarded 
(7.8 g of diacetate, 11% recovery). The filtrate was ex-
tracted with chloroform (5 x 25 ml) and the extracts taken 
to dryness separately affording clear oils that did not 
solidify. A portion of the first extract was distilled 
as a clear oil, bp 79-90° (0.2 mm). The distillate crys-
tallized upon cooling and crystals were used to seed the 
remaining extracts. The white solids were combined (mp 
70°) and recrystallized from ether:petroleum ether (30-60°)
as fine, white needles (24.5 g, 43%), mp 65-68.5° lit.62 mp 67-71.5°.

4-Acetoxycyclohexanone (CXXII).—Jone's reagent (39.2 ml, prepared from 13.4 g of chromic oxide and 12.5 ml of concentrated sulfuric acid diluted to 50 ml with water) was added to an ice-cooled solution of monoacetate CXXI (24.5 g, 0.155 mole) in acetone (510 ml) over 7 min. Stirring was continued for an additional 3 min, and then the acetone removed in vacuo. The residue was shaken with water (25 ml) and ether (100 ml). The organic layer was washed with water (1 x 25 ml), dried, and taken to dryness leaving a clear oil (22.5 g, 93%). The residue was distilled giving 18.6 g of CXXII, (77%) bp 64-66° (0.2 mm) lit.62 bp 71-73° (0.4 mm).

4-Hydroxycyclohexanone (CXV).—A solution of 4-acetoxycyclohexanone (CXXII) (18.6 g, 0.119 mole) and sodium bicarbonate (9.9 g) in methanol (95 ml) was stirred at reflux for 17 hr. The solvent was removed in vacuo and the residue suspended in ether. The mixture was filtered, the solid washed well with ether, and the filtrates combined, dried, and taken to dryness giving a clear, viscous oil which was distilled (19.0 g, 90%), bp 89-90° (0.5 mm) lit.62 bp 71-76° (0.2 mm).

3-Hydroxy-1,2,3,4-tetrahydrocarbazole (CXVI).—To a solution of 4-hydroxycyclohexanone (CXV) (5.00 g, 0.0439 mole) in hot acetic acid (25 ml) was added dropwise phenylhydrazine (4.75 g, 0.0439 mole) and the mixture refluxed

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for 10 min. Water (5 ml) was added and the mixture allowed to cool and stand overnight. The small grayish needles (6.76 g, 81%), mp 129-138° were recrystallized from aqueous ethanol (5.64 g, 69%), mp 147-148° lit. 62 mp 152-154°. 3-Oxo-1,2,3,4-tetrahydrocarbazole (XL).---To a solution of 3-hydroxy-1,2,3,4-tetrahydrocarbazole (CXVI) (1.00 g, 0.00534 mole) in DMSO (6.5 ml, dried over 4 A Molecular Sieves) and dicyclohexylcarbodiimide (3.30 g, 0.0160 mole) and benzene (3.5 ml, dried over sodium) was added crystalline ortho phosphoric acid (0.27 g, 0.00267 mole). The reaction was carried out in a nitrogen-filled dry box. After standing at room temperature for 3 hr with occasional shaking, oxalic acid (2.02 g, 0.0160 mole) was added followed by water (10 ml) and ether (25 ml). After stirring the mixture was filtered, and the organic layer extracted with water (4 x 10 ml), the ether layer dried and taken to dryness affording a yellow solid (0.83 g, 84%), mp 116-153°. A recrystallization from aqueous ethanol gave crystals (0.07 g, 7%), mp 149-152° lit. 61 148-150°. uv λmax 291 nm (6300), 284 (8100), 277 (8000).

3-(3'-Indolylcyclohexanone (XXXIX).---Indole (1.22 g, 0.0104 mole) was dissolved in glacial acetic acid (3 ml) and then 2-cyclohexen-1-one (1.00 g, 0.0104 mole) added. The yellow solution was heated on a steam bath for 3.0 hr. The dark purple solution was cooled in ice and water (20 ml) added. A black semisolid precipitate formed. The acid

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was neutralized by the addition of small amounts of solid sodium bicarbonate, and the mixture extracted with ether (3 x 20 ml). The combined ether extracts were dried and taken to dryness leaving a dark solid (2.00 g). The material was washed with chloroform over a silica gel column (CC-7, 60-200 mesh, 50 mm i.d., 100 g). Early fractions off the column containing unreacted indole and 2-cyclohexen-1-one were discarded. The third fraction was taken to dryness leaving a yellow oil which solidified upon standing (0.30 g). A recrystallization from benzene-petroleum ether (30-60°) gave crystals of analytical purity (121 g, 6%), mp 99-100.5°. ir (melted film) 5.87 (C=O). uv \( \lambda_{\text{max}} \) 292 nm (5700), 283 (6800), 277 (6400). Anal. Calcd for \( \text{C}\text{\textsubscript{14}}\text{H}\text{\textsubscript{15}}\text{NO} \): C, 78.84; H, 7.09; N, 6.57. Found: C, 79.04; H, 6.99; N, 6.30.

6-Oxo-6,7,8,9-tetrahydro-10-methylpyrido[1,2-\( \text{a} \)]indole (CXXXII).---To 2-methyl-1,3-cyclohexanedione (2.5 g, 0.02 mole) suspended in benzene (50 ml) was added freshly distilled phenylhydrazine (2.5 g, 0.023 mole) in 40% aqueous sulfuric acid (20 ml) and the mixture refluxed for 2 hr. After cooling, the two layers were separated and the aqueous phase extracted with benzene (2 x 10 ml). The combined organic extracts were washed with water (1 x 10 ml) and water again (1 x 10 ml). After drying and taking to dryness, an off-white solid was obtained (2.57 g, 65%), mp 77-77.5°. A recrystallization from methanol gave fine
needles (2.24 g, 56%), mp 79-79.5°. lit. 66 mp 81°. uv 
$\lambda_{\text{max}}$ 267 nm (12900), 295 (5400), 303 (5100).

2-(4'-Oxopentyl)-3-methylindole (XXXVIII).---Methyl mag-
nesium iodide was prepared by the addition of methyl iodide
(2.84 g, 0.020 mole) in sodium-dry ether (30 ml) to mag-
nesium turnings (0.49 g) under ether (10 ml). After dis-
solution of the magnesium the pyrido[1,2-\text{a}]indole CXXXII
(2.00 g, 0.010 mole) in ether (25 ml) was added dropwise
over 0.5 hr. After stirring at room temperature overnight,
the ice-cooled mixture was poured into ice-water (50 ml)
containing 38% hydrochloric acid (2 ml). The aqueous layer
was extracted with ether (3 x 10 ml) and the combined ether
extracts washed with a saturated sodium bicarbonate solu-
tion (1 x 10 ml), water (1 x 10 ml), and dried. Evapora-
tion of the solvent gave a yellow oil which slowly crystal-
lized (2.02 g, 93%). The solid was extracted several times
with hot petroleum ether (60-110°) (10 ml portions) con-
taining 2 drops of methanol. The solution yielded needles
upon cooling (0.80 g, 38%), mp 76-76.5° lit. 66 mp 86°.

A further recrystallization from petroleum ether (60-110°)
and finally ethanol gave fine white needles, mp 82-84°.

uv $\lambda_{\text{max}}$ 292 nm (7300), 284 (8300), 277 (7500).

Yohimbine (CXXVI).---Yohimbine hydrochloride (10.00 g,
0.0256 mole) was dissolved in aqueous ethanol (ca. 600 ml
of a 1:1 mixture by volume). Concentrated ammonium hydrox-
ide was added until the pH = 11. The solution was cooled.
in the freezer affording a precipitate which was extracted with chloroform (4 x 50 ml). The combined extracts were taken to dryness affording a white powder (8.56 g, 95%), mp 235-236° lit. mp 235-236°. \( \lambda_{\text{max}} \) 292 (6400), 283 (7700), 276 (7300).

Yohimbinone (CXXVII).—To a solution of yohimbine (CXXVI) (7.09 g, 0.02 mole) and dicyclohexylcarbodiimide (12.38 g, 0.06 mole) in dry DMSO (30 ml, dried over 4 A type Molecular Sieves) was added crystalline ortho phosphoric acid (3.00 g, 0.03 mole). The DMSO and phosphoric acid were added in a dry box. The mixture was shaken and cooled when it became hot. It was allowed to stand at room temperature for 17.5 hr, and methylene chloride added to the heterogeneous mixture. The precipitate was collected and after partially drying, it was mixed with hot acetic acid-water (1:2 by volume) in portions (4 x 50 ml). The extracts were combined, cooled, and neutralized with concentrated ammonium hydroxide. The precipitate was filtered, dried, triturated with ethanol and refiltered giving pale yellow crystals (2.76 g, 40%), mp 245-246.5° lit. \( \lambda_{\text{max}} \) 246.5-248.5°. \( \lambda_{\text{max}} \) 292 (6800), 283 (8000), 276 (7600).

Yohimbane-17-one (XLII).—A mixture of yohimbinone (CXXVII) (1.90 g, 0.00054 mole), 3 N hydrochloric acid (100 ml) and glacial acetic acid (25 ml) was refluxed for 5 hr. After 2 hr the solid was completely dissolved. The reaction mixture was cooled and poured into a mixture of ice (50 g)
and concentrated ammonium hydroxide (75 ml). After cooling in the freezer overnight, the fine precipitate was collected, dried, dissolved in ethanol-dichloromethane and concentrated in vacuo. The residue was triturated with methanol and filtered affording a fine powder (0.80 g, 50%), mp 293-296°. A recrystallization from hot methanol-dichloromethane gave fine needles, mp 300-302° lit. A recrystallization from hot methanol-dichloromethane gave fine needles, mp 300-302° lit. A recrystallization from hot methanol-dichloromethane gave fine needles, mp 300-302° lit.64 mp 298-303°. uv $\lambda_{\text{max}}$ 291 nm (6400), 284 (7700), 276 (7400).
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