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The Synthesis and Physical Properties of Some 1-Methyl and 2-Methyl Bridged Cycloheptapyrazolones

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THE SYNTHESIS AND PHYSICAL
PROPERTIES OF SOME
1-METHYL AND 2-METHYL BRIDGED
CYCLOHEPTAPYRAZOLONES

by

Gary R. Larson

A Thesis
Submitted to the
Faculty of The Graduate College
in partial fulfillment
of the
Degree of Master of Arts

Western Michigan University
Kalamazoo, Michigan
April, 1977

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Gary R. Larson

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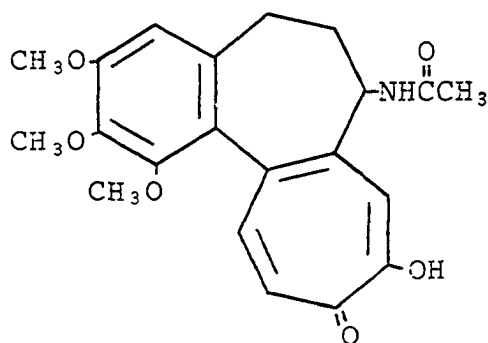
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INTRODUCTION

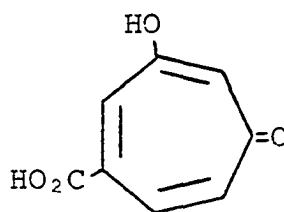
The problem of aromaticity in non-benzoid aromatic compounds has stimulated the synthesis of a variety of tropones and related compounds. Recently the preparation and physical properties of a series of 2,7-polymethylene-4,5-benzotropones have been reported. It was determined from the infrared and nuclear magnetic resonance spectra that the tropone ring was more planar if the methylene bridge was seven or more units long. The purpose of this work is to investigate the preparation and physical properties of a new series of bridged 1 and 2-methyl-cycloheptapyrazolones. The nuclear magnetic resonance and ultraviolet spectra are discussed in detail.

HISTORICAL

In 1945 Dewar proposed the 2-hydroxy-2,4,6-cycloheptatrien-1-one skeleton for colchicine (1) and stipitatic acid ^{1,2} (2). Hückel, in 1931, had discussed the theoretical similarity between the $C_7H_7^+$ ion and the benzene ring³. Dewar's proposal combined the theoretical studies of Hückel with the known experimental data for colchicine and stipitatic acid. It was Dewar's



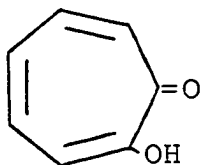
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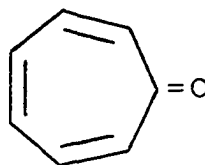
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proposal that formed the basis for future studies on the seven-membered aromatic system. The parent 2-hydroxy-2,4,6-cycloheptatrien-1-one, called tropolone (3) by Dewar, was first synthesized in 1950⁴ and the synthesis of tropone (4) was reported the following year⁵. In recent years there has been much discussion about the structure

and properties of these non-benzoid aromatic compounds. The problem of the aromaticity of these compounds has greatly stimulated the synthesis and investigation of a variety of related compounds. X-Ray crystallographic

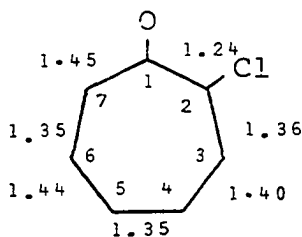


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analysis^{6,7} of 2-chlorotropone (5) shows that the seven-membered ring is planar. The chlorine atom lies close to the plane of the ring and the carbonyl oxygen is displaced out of the plane of the ring. The bond lengths indicate that the C(1)-C(2), C(3)-C(4) and C(5)-C(6) bonds are all slightly shorter than a C(sp²)-C(sp²) single bond (1.43-1.50Å)⁸ while the C(2)-C(3), C(4)-C(5) and C(6)-C(7) bond lengths are all slightly longer than a pure carbon-

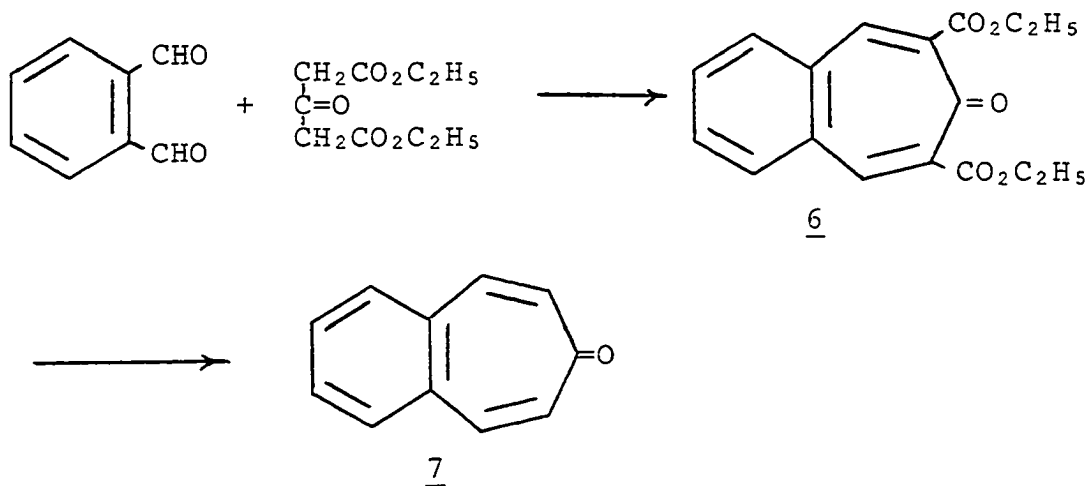


carbon double bond (1.33\AA)⁹. This data indicates only partial π -electron delocalization between C(2) extending to the oxygen and that a cyclically delocalized system is not present in 2-chlorotropone⁷.

The use of nuclear magnetic resonance spectroscopy has been gaining acceptance as a criteria for establishing the degree of aromatic character in a molecule. The nuclear magnetic resonance spectrum of a variety of tropones and related compounds has been studied^{10,11}. Veracini and Pietra found when they compared the experimentally observed spectrum of tropone with the spectrum calculated on the basis of a planar model, that only slight bond alteration occurred in the seven-membered ring. These results are consistent with the X-ray crystallographic data and rules out the regular heptagonal structure for tropone. While the pmr spectrum of tropone shows only slight delocalization, the spectrum of the corresponding tropylium ion shows a signal at a low field position (9.33 ppm) consistent with the complete delocalization of the positive charge¹².

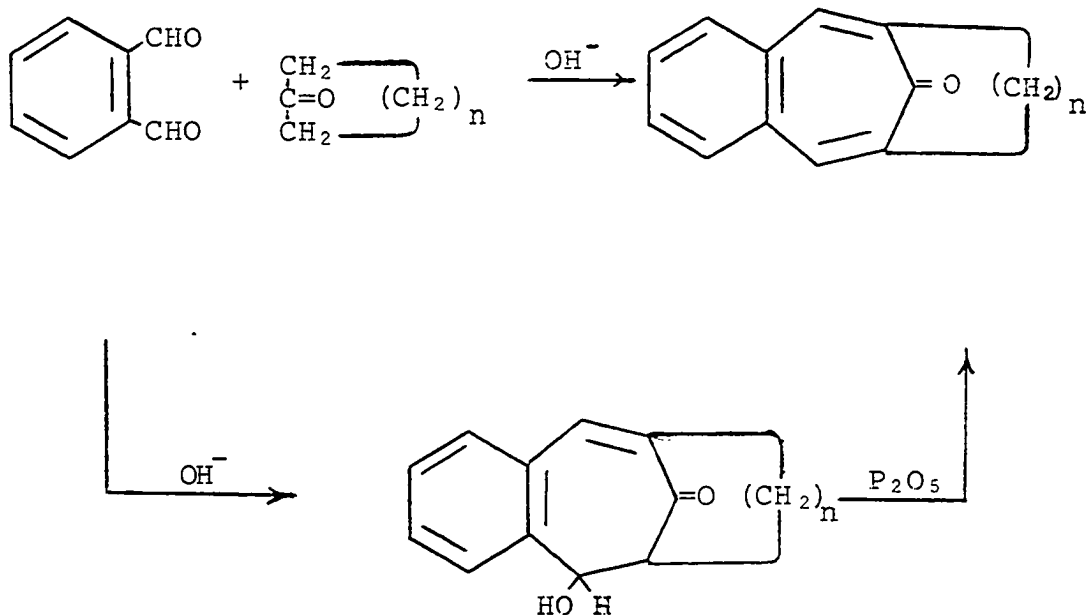
Adol-type cyclizations have been utilized to give a broad range of fused ring derivatives. The condensation of phthalaldehyde with diethyl acetonedicarboxylate (Scheme 1) gave the ester of 2,6-dicarboxy-4,5-benzotropone (6); which was hydrolyzed and decar-

boxylated to give 4,5-benzotropone¹³ (7). A series of 2,7-polymethylene-4,5-benzotropones has been synthesized by



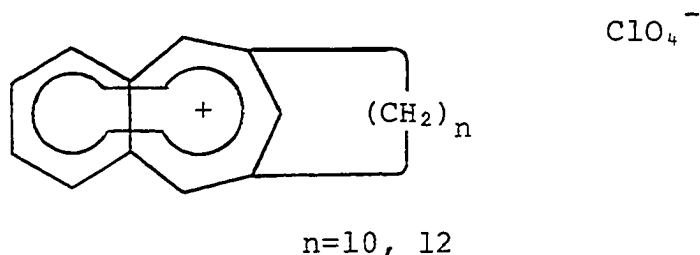
Scheme 1

condensation of phthalaldehyde with cyclic ketones¹⁴ (Scheme 2). It was found that the product was obtained



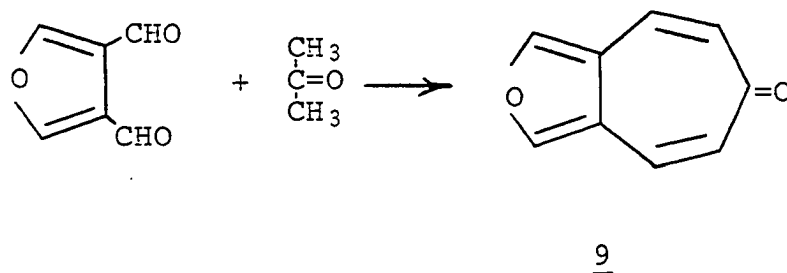
Scheme 2

directly when $n=7, 9, 12$ or 13 , but when $n=4, 5, 6$ or 8 the intermediate had to be dehydrated with phosphorous pent-oxide. Kloster-Jensen, Torkoy, Eschenmoser and Heilbronner determined from the infrared spectrum that the tropone ring was planar if n is seven or larger. The observed carbonyl frequency shifted from 1679 cm^{-1} for $n=5$, to 1609 cm^{-1} when $n=7$ indicating increasing single bond character in the carbonyl group. Harmon, Suder and Gupta substantiated these findings using nuclear magnetic resonance spectroscopy¹⁵. They observed that when $n=7$, the tropone protons resonated at 7.48 ppm . When $n=5$, however, the tropone protons resonated at 6.78 ppm . The downfield shift of these protons in the benzotropone system is attributed to an increase in the planarity of the system. Reduction of the carbonyl function with lithium aluminum hydride followed by treatment with perchloric acid gave the 6,8-poly-methylenebenzotropylum perchlorates¹⁷ (9). The observed



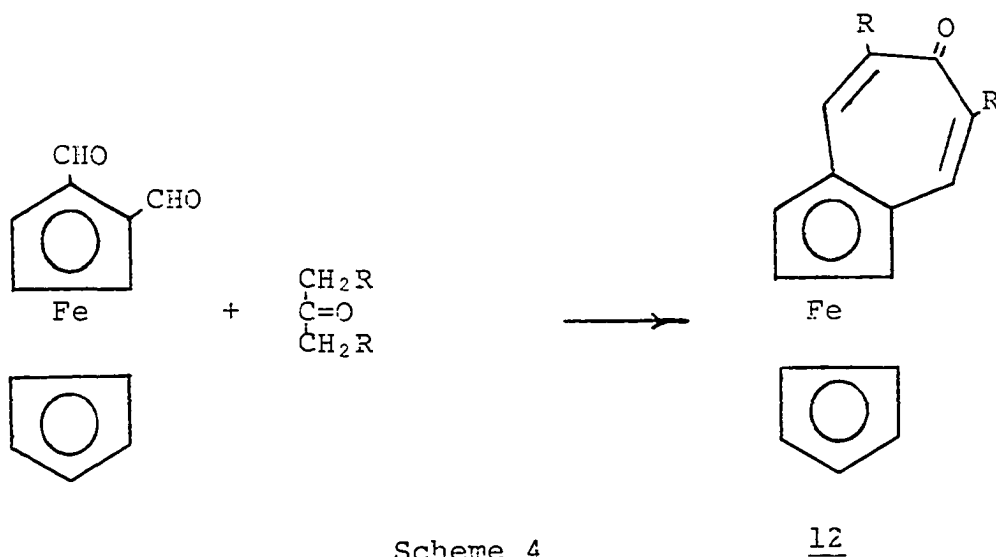
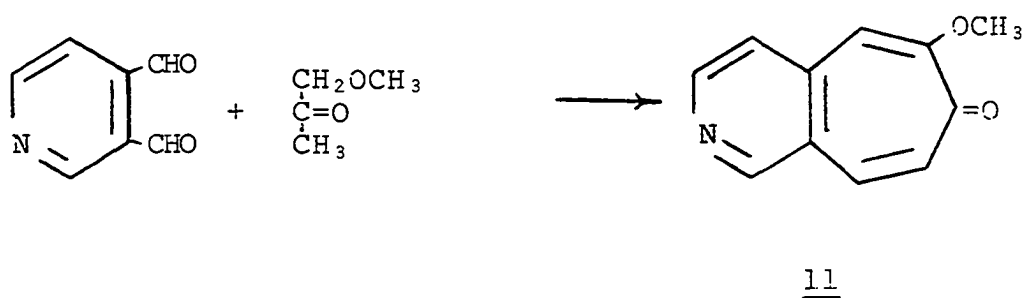
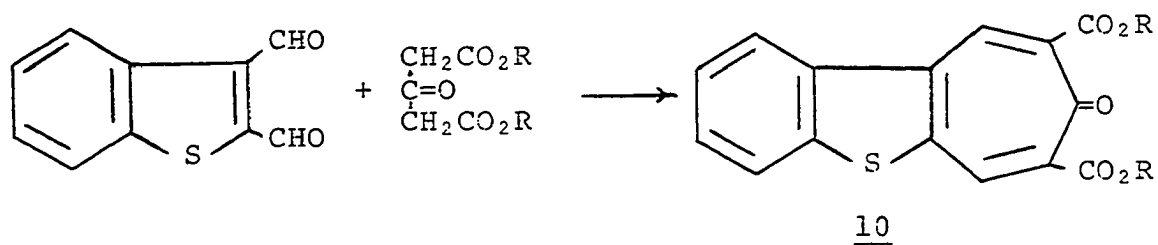
position of the tropone ring protons indicated an even further downfield shift (9.2 ppm)¹⁷ that is attributed to complete delocalization of the positive charge throughout the fused ring system.

Recently, the preparation of a series of heterocyclic analogs has been reported. Cook and Forbes synthesized (4,5-c) furotropone by the condensation of 3,4-furandicarboxaldehyde with acetone¹⁸ (Scheme 3). This was the only reported example of a dialdehyde being directly



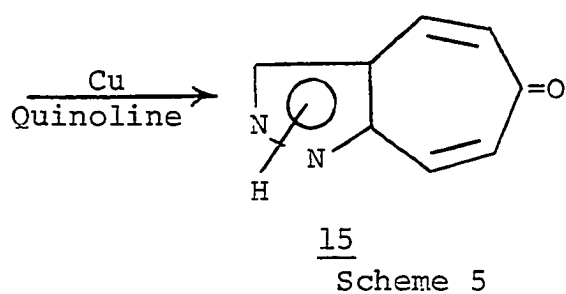
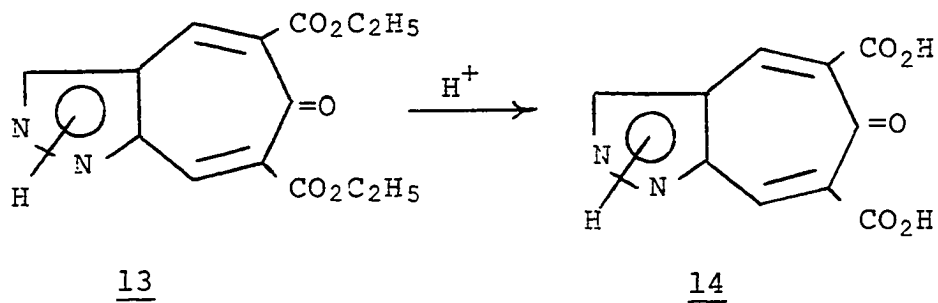
Scheme 3

condensed with acetone in the presence of base to give a seven-membered ring. Adol-type condensations using 2,3-diformyl benzothiophene¹⁹, 2,3-diformylpyridine²⁰ and the ferrocene derivative gave, respectively compounds 10, 11 and 12. Greco and Pesce reported the preparation of a new member in this series by condensation of pyrazole-3(5), 4-dicarboxaldehyde with diethyl acetonedicarboxylate.

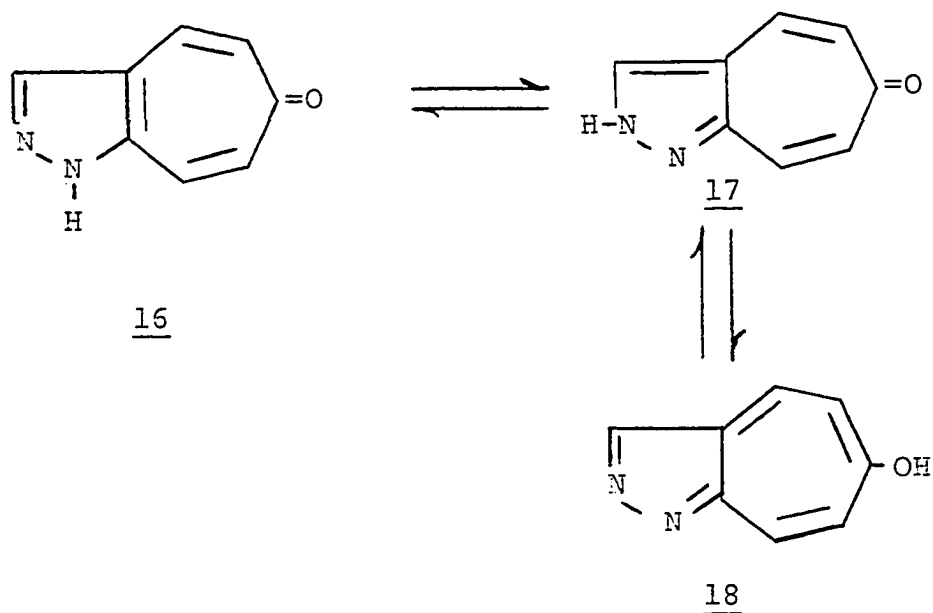


Scheme 4

Hydrolysis of 13 with aqueous sulfuric acid followed by decarboxylation gave cycloheptapyrazolone (15). The extent of aromaticity of 15 was estimated by comparison of some spectral characteristics with known data on (4,5-c)



benzotropones (7) and (4,5-c) furotropone (9)²¹. The nmr spectra indicates that the three bicyclic structures (7, 9 and 15) can sustain an induced ring current. When

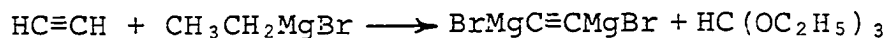


the three bicyclic tropones were compared to tropone, they appeared to be less aromatic. The ultraviolet absorption spectra showed the relative order of aromaticity to be benzotropone>pyrazolotropone (cycloheptapyrazolone)>furotropone. Greco and Pesce were also able to show from the spectroscopic data that the pyrazolotropone exists as the keto tautomers 16 and 17 and not the hydroxy form 18.

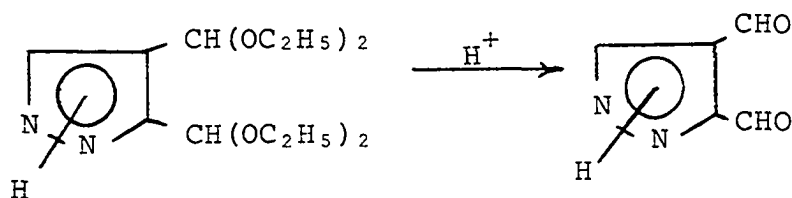
With the recent revision of the systematic nomenclature outlined in Chemical Abstracts Vol. 75 (1972), the name of pyrazolotropone was changed to cycloheptapyrazolone. The nomenclature used in the rest of this thesis will be consistent with this change.

DISCUSSION

The preparation of pyrazole-3(5),4-dicarboxaldehyde (20) is shown in Scheme 6. The acetylene dialdehyde bis-(diethyl acetal) (19) was prepared from acetylene gas by the method described by Wohl²². Treatment of acetylene dialdehyde bis(diethyl acetal) with diazomethane, prepared from N-methyl-N-nitroso-p-tolunesulfonamide²³, followed by acid hydrolysis affords pyrazole-3(5),4-dicarboxaldehyde²⁴. When pyrazole-3(5),4-dicarbox-



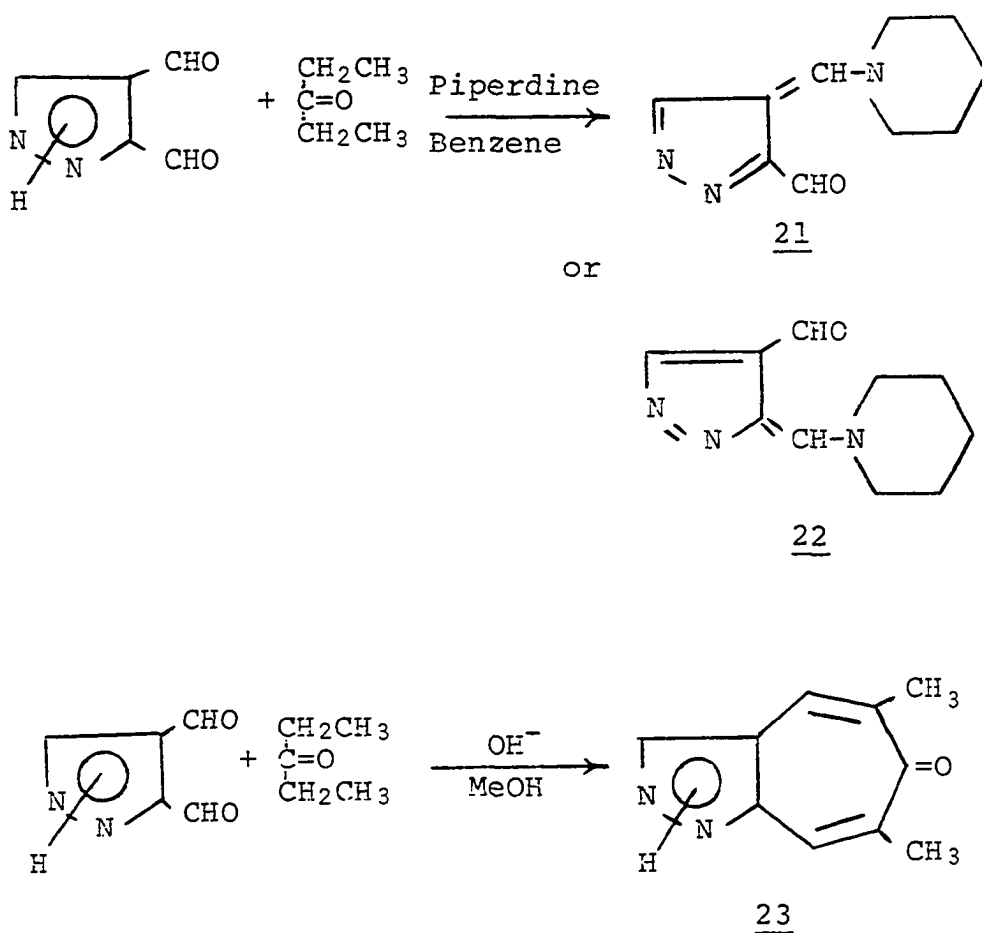
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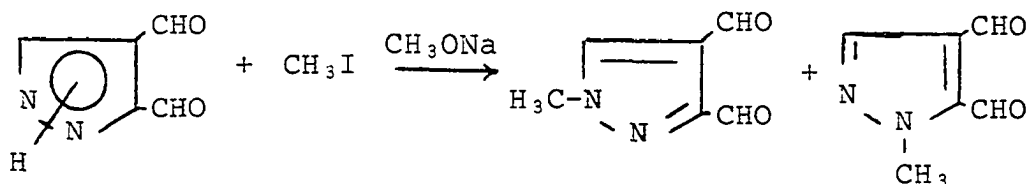
Scheme 6

aldehyde (20) was treated with 3-pentanone in benzene with a catalytic amount of piperidine²¹, the only isolated product was a small amount of an enamine (Scheme 7). The desired product 23 was obtained when the condensation was carried out in alcoholic sodium hydroxide. However, cyclic ketones failed to react under these conditions.



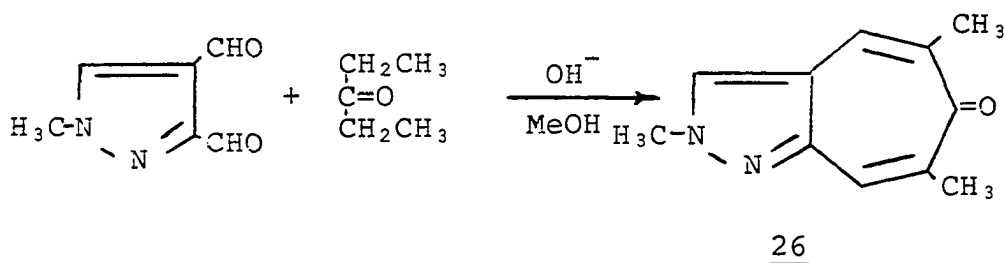
Scheme 7

Treatment of pyrazole-3(5),4-dicarboxaldehyde with iodomethane affords the two isomers 24 and 25 in 46% and 7% yield, respectively²⁵ (Scheme 8). Condensation of 2-methylpyrazole-3,4-dicarboxaldehyde (24) with 3-



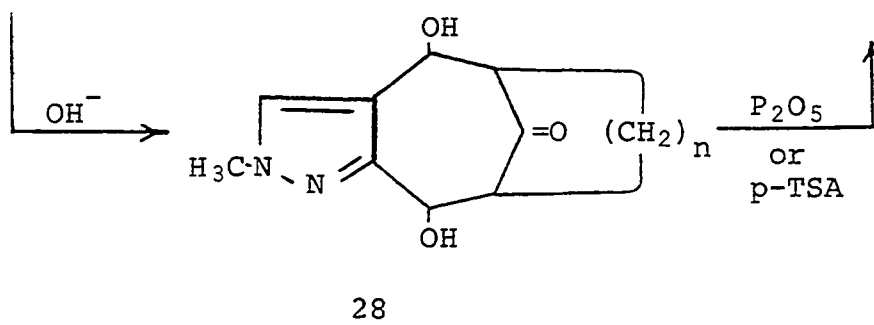
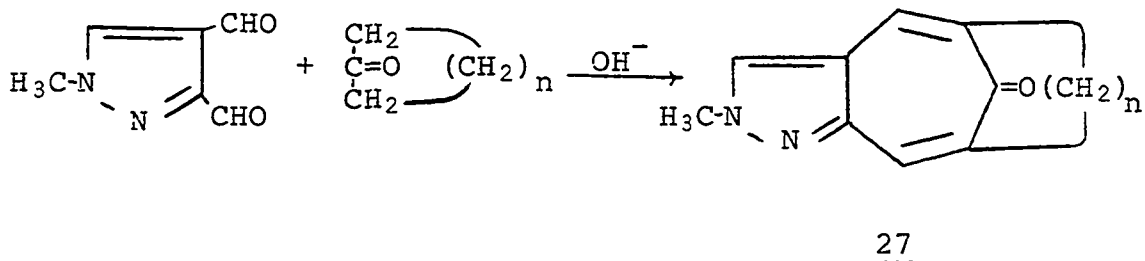
Scheme 8

pentanone gives 2,5,7-trimethyl-6(2H)-cyclohepta-pyrazolone (Scheme 9). A series of bridged 1-methyl-6(2H)-cycloheptapyrazoles has been synthesized by con-



Scheme 9

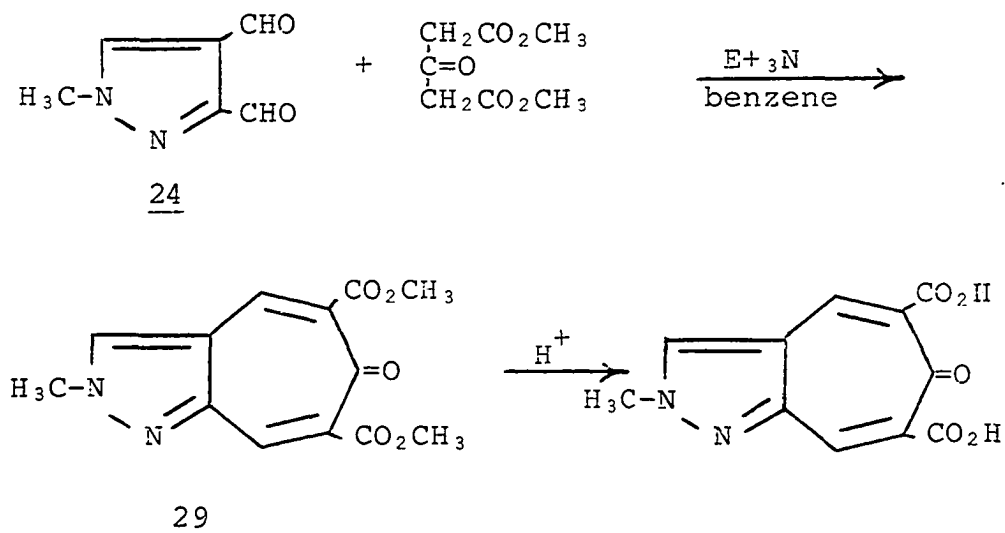
condensation of 1-methylpyrazole-3,4-dicarboxaldehyde with cyclic ketones (Scheme 10). In the case where $n=7$ or 12



Scheme 10

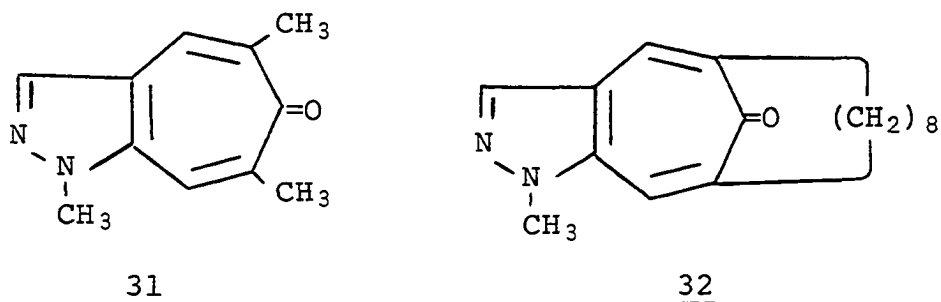
the product 27 was obtained in one step, but when $n=8$ or 9 the result of the adol-type condensation is the dihydroxyketone 28. It was shown in the case of the 6,8-polymethylene-7H-benzocyclohepten-7-ones (Scheme 2) that the intermediate was not the dihydroxyketone but rather the monohydroxyketone. While the isolation of the monohydroxyketone intermediates were shown to be

dependent upon ring size, the isolation of the dihydroxyketone intermediate was due to their low solubility in methanol. This is the only known example where dihydroxyketone intermediates have been isolated. The dihydroxyketones were dehydrated to give the product 27. Condensation of 1-methylpyrazole-3,4-dicarboxaldehyde with dimethyl acetonedicarboxylate affords 2,6-dihydro-2-methyl-6-oxo-5,7-cycloheptapyrazole-dicarboxylic acid, dimethyl ester, which upon hydrolysis with aqueous sulfuric acid gave 2,6-dihydro-2-methyl-6-oxo-5,7-cycloheptapyrazoledicarboxylic acid (Scheme 11).



Scheme 11

Two 1-methylcycloheptapyrazolones were prepared by condensation of 1-methylpyrazole-4,5-dicarboxaldehyde (25) with 3-pentanone and cycloundecanone to give 1,5,7-trimethyl-6(1H)-cycloheptapyrazolone (31) and 1-methyl-2,7-octano-6(2H)-cycloheptapyrazolone (32), respectively. While 2-methyl-2,7-octano-6(2H)-cycloheptapyrazolone (Scheme 10, n=8) was obtained in two steps through the



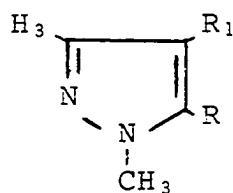
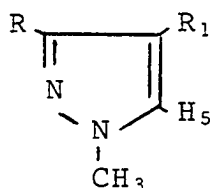
dihydroxyketone, 1-methyl-2,7-octano-6(2H)-cycloheptapyrazolone (32) was obtained in a single step.

Spectral Properties

The extent of aromaticity of 6H-cyclohepta-[c]-furan-6-one (furotropone, 9), 7H-benzocyclohepten-7-one (benzotropone, 7) and cycloheptatrienone (tropone, 4) was estimated by comparison of the frequency of the carbonyl group vibration in the infrared spectra²⁶. Greco and Pesce found in the case of cycloheptapyrazolone (16) that they were unable to compare the infrared

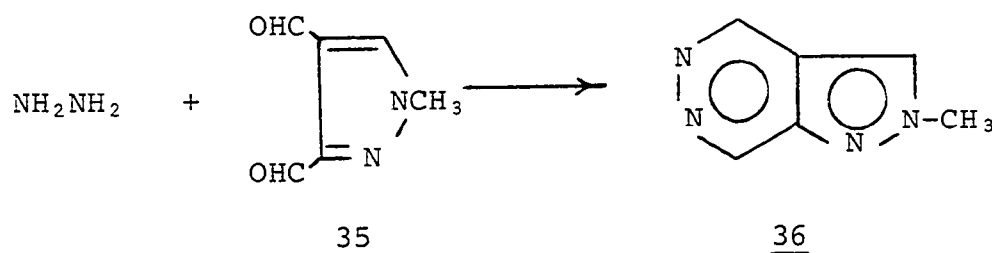
absorptions at $1620\text{--}1590\text{ cm}^{-1}$ with those of the other unsubstituted ring systems²¹. It was observed for compounds 26 through 32 that the carbonyl vibrations could not be distinguished from the pyrazole ring vibrations and thus were not useful as a means of estimating the extent of aromaticity.

The proton magnetic resonance spectra of 1-methyl-3,4 and 4,5-substituted pyrazoles have been extensively studied^{25,27,28,29}. Bastide and Lematre observed that the chemical shift of the remaining aromatic proton H_3 of isomer 33 and H_5 of isomer 34 was solvent dependent²⁷.

3334

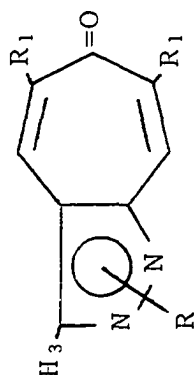
While the protons H_3 and H_5 both displayed a displacement when the solvent was changed from $\text{d}_6\text{-DMSO}$ to CDCl_3 , the degree of the displacement varied. The displacement of the chemical shift for H_3 of compounds of type 33 was between 0.1 and 0.2 ppm. However, the displacement of the chemical shift H_5 of compounds of type 34 was

0.5 to 0.7 ppm. This difference in the degree of the displacement with change of solvents allows for the unambiguous assignment of the structure when two isomers are possible. For example, when pyrazole-3(5), 4-dicarboxaldehyde was treated with iodomethane the two isomers 24 and 25 resulted (Scheme 8). Upon separation the two isomers could be identified and assigned using this technique. The aromatic proton H₅ of isomer 24 shifted 0.42 ppm with change in solvent (CDCl₃ to d₆-DMSO) while proton H₃ of isomer 25 was shifted 0.11 ppm. When 24 was condensed with hydrazine the resulting pyrazolo-{3,4-d}-pyridazine (Scheme 12) displayed the same displacement of the aromatic proton H₃ with change in solvent as the starting pyrazole. This property was shown to hold



throughout a series of 1- and 2-methyl pyrazolopyridazines substituted in the 4 and 7 positions²⁷. The chemical shift of the H₃ proton for the N-methylcyclohepta-pyrazolones is listed in Table I. The relative displacement of the chemical shift for the H₃ proton, with

TABLE I
CHEMICAL SHIFT OF THE H₃ PROTON

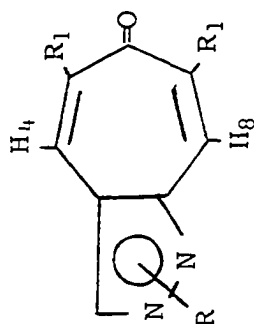


	R	R ₁	CDCl ₃ (ppm)	d ₆ -DMSO (ppm)	Δδ (ppm)
<u>23</u>	H	CH ₃	--	8.13	--
<u>24</u>	2-Methyl	CH ₃	7.72	8.27	0.55
<u>27a</u>	2-Methyl	-(CH ₂) ₁₂ -	7.70	8.23	0.53
<u>27b</u>	2-Methyl	-(CH ₂) ₉ -	7.65	8.08	0.73
<u>27c</u>	2-Methyl	-(CH ₂) ₈ -	7.59	8.14	0.73
<u>27d</u>	2-Methyl	-(CH ₂) ₇ -	7.50	8.05	0.55
<u>29</u>	2-Methyl	CO ₂ CH ₃	7.98	8.57	0.59
<u>30</u>	2-Methyl	CO ₂ H	--	7.85	--
<u>31</u>	1-Methyl	-(CH ₂) ₈ -	7.66	7.81	0.15
<u>32</u>	1-Methyl	CH ₃	7.81	7.95	0.14

change of solvent, was of the same order of magnitude as the pyrazoles. For instance, the displacement of the H₃ proton of 2,5,7-trimethyl-6(2H)-cycloheptapyrazolone was 0.77 ppm while the displacement for the 1,5,7-trimethyl-6(1H)-cycloheptapyrazolone was 0.14 ppm. The displacement of the H₃ proton with change in solvent allows for positive assignment of the N-methyl group.

The chemical shifts of the H₃ protons show a definite dependence upon the size of the methylene bridge (Table I). In the case where n=7 the H₃ proton resonates at 7.50 ppm (CDCl₃) and is shifted downfield to 7.70 ppm (CDCl₃) when n=12. The downfield shift of the H₃ proton as n is increased can be attributed to an increase in the planarity of the ring system. When the H₃ proton of 27a (n=12) is compared to the position of the H₃ proton of the non-bridged 2,5,7-trimethyl-6(2H)-cycloheptapyrazolone (26), it can be seen that the influence of the methylene bridge has diminished to only 0.02 ppm (CDCl₃). This means that size of the methylene bridge is large enough that its effect is no longer observed on the pyrazole ring proton. Similar results can be seen for the H₄ and H₈ protons (Table II). In the case of the bridged cycloheptapyrazolones (27a-d) there is a downfield shift of both the H₄ and H₈ protons as the size of n is increased. When n=7 H₄ resonates at 6.94 ppm and H₈ resonates at

TABLE II
CHEMICAL SHIFT OF H₁₄ AND H₈ PROTONS



	R	R ₁	H ₁₄ (ppm)		H ₈ (ppm)	
			CDCl ₃	d ₆ -DMSO	CDCl ₃	d ₆ -DMSO
<u>23</u>	H	CH ₃	--	7.82	--	7.82
<u>26</u>	2-Methyl	CH ₃	7.50	7.70	7.72	7.70
<u>27a</u>	2-Methyl	-(CH ₂) ₁₂ -	7.33	7.55	7.55	7.55
<u>27b</u>	2-Methyl	-(CH ₂) ₉ -	7.21	7.37	7.40	7.37
<u>27c</u>	2-Methyl	-(CH ₂) ₈ -	7.06	7.34	7.23	7.34
<u>27d</u>	2-Methyl	-(CH ₂) ₇ -	6.94	7.15	7.12	7.15
<u>29</u>	2-Methyl	CO ₂ CH ₃	8.07	7.97	8.10	8.18
<u>30</u>	2-Methyl	CO ₂ H	--	7.30	--	7.70
<u>31</u>	1-Methyl	-(CH ₂) ₈ -	7.09	7.36	7.21	7.50
<u>32</u>	1-Methyl	CH ₃	7.55	7.77	7.62	7.95

7.12 ppm (CDCl₃). Both protons shift downfield to 7.33 ppm (H₄) and 7.55 ppm (H₈) when n is increased to 12. The downfield shift shows that the size of the bridge is influencing the chemical shift of these protons. When n=12 the influence of the methylene bridge upon the H₃ proton could no longer be observed. However, when the chemical shifts of the H₄ and H₈ protons of 27a were compared to the position of the H₄ and H₈ protons of 26, it can be seen that the H₄ and H₈ protons of 26 are still 0.17 ppm further downfield. This means that although the influence of the methylene bridge, when n=12, is no longer observed for the H₃ proton, it is still influencing the H₄ and H₈ protons. The methylene bridge is applying enough strain on the seven-membered ring to shift the H₄ and H₈ protons 0.17 ppm upfield. While the influence of changing the size of n effects all three ring protons, the magnitude of the influence is greater for H₄ and H₈. The $\Delta\delta_{n=12-7}$ for H₃ is only 0.20 ppm (CDCl₃), while the $\Delta\delta_{n=12-7}$ for H₄ and H₈ is 0.39 ppm and 0.43 ppm (CDCl₃). This is another indication that the methylene bridge is applying more strain on the seven-membered ring than on the pyrazole ring.

Although the chemical shift of the H₃, H₄ and H₈ protons are influenced by the size of the methylene bridge, they are also dependent upon solvent. When

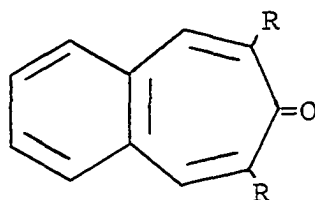
the nmr solvent is changed from CDCl_3 to d_6 -DMSO the H_3 proton of compounds 27a-d is shifted between 0.53 and 0.73 ppm downfield. The downfield shift of this proton with change in solvent was observed in the parent 1-methylpyrazole-3,4-dicarboxaldehyde and in a series of derivatives²⁷. The shift of the H_3 proton in compounds 27a-d can be attributed to this characteristic of N-alkyl pyrazoles. This was demonstrated in the case of the pyrazolopyridazines (36). As was seen earlier with CDCl_3 , there is a downfield shift of the H_3 proton as the size of the bridge is increased. For example, when $n=7$, H_3 resonates at 8.05 ppm and is shifted downfield to 8.23 ppm when $n=12$ in d_6 -DMSO. Similarly, the H_3 protons of 26 and 27a resonate only 0.04 ppm (d_6 -DMSO) apart, which indicates the influence of the bridge is insignificant. The effect of changing the solvent from CDCl_3 to d_6 -DMSO on the H_4 and H_8 protons is listed in Table II. The H_4 proton shifts downfield between 0.16 and 0.28 ppm and the H_8 proton shifts between -0.02 and 0.11 ppm. The shift of these protons is of the same order of magnitude observed for substituents in the 3 and 4 positions of N-methylpyrazoles when the solvent is changed from CDCl_3 to d_6 -DMSO^{25,26,27}. This means that the solvent dependency of these protons is caused by the effect of the solvent on the pyrazole ring and cannot be attributed to an

effect of the solvent on the cycloheptenone ring.

The ultraviolet, nuclear magnetic resonance and infrared spectra for a series of bridged 7H-benzocyclohepten-7-ones (Scheme 2) have been reported by several workers. Kloster-Jensen and coworkers postulated that the cycloheptenone ring system is planar if n is seven or larger¹⁴. They found that the carbonyl frequency in the infrared shifted from 1679 cm^{-1} when $n=5$ to 1609 cm^{-1} when $n=7$. The shift of the carbonyl frequency was attributed to an increase in single bond character of the carbonyl function as the ring system becomes planar. The nuclear magnetic resonance spectra provided further substantiating evidence¹⁷. When $n=5$ the cycloheptenone protons resonate at 6.78 ppm and shifted downfield to 7.31 ppm as n was increased to 9. This evidence was consistent with the infrared analysis and with an increase in the conjugation of the ring system. However, when $n=12$ the protons shifted even further downfield to 7.52 ppm. This indicates that the methylene bridge is still applying some strain upon the cycloheptenone ring and is consistent with the results observed for the cycloheptapyrazolones. The ultraviolet spectra of the benzocycloheptenone ring system has three major bands at ~ 230 , ~ 280 and $\sim 305\text{ nm}$. The band at $\sim 280\text{ nm}$ was found to decrease in intensity when the size of n was decreased

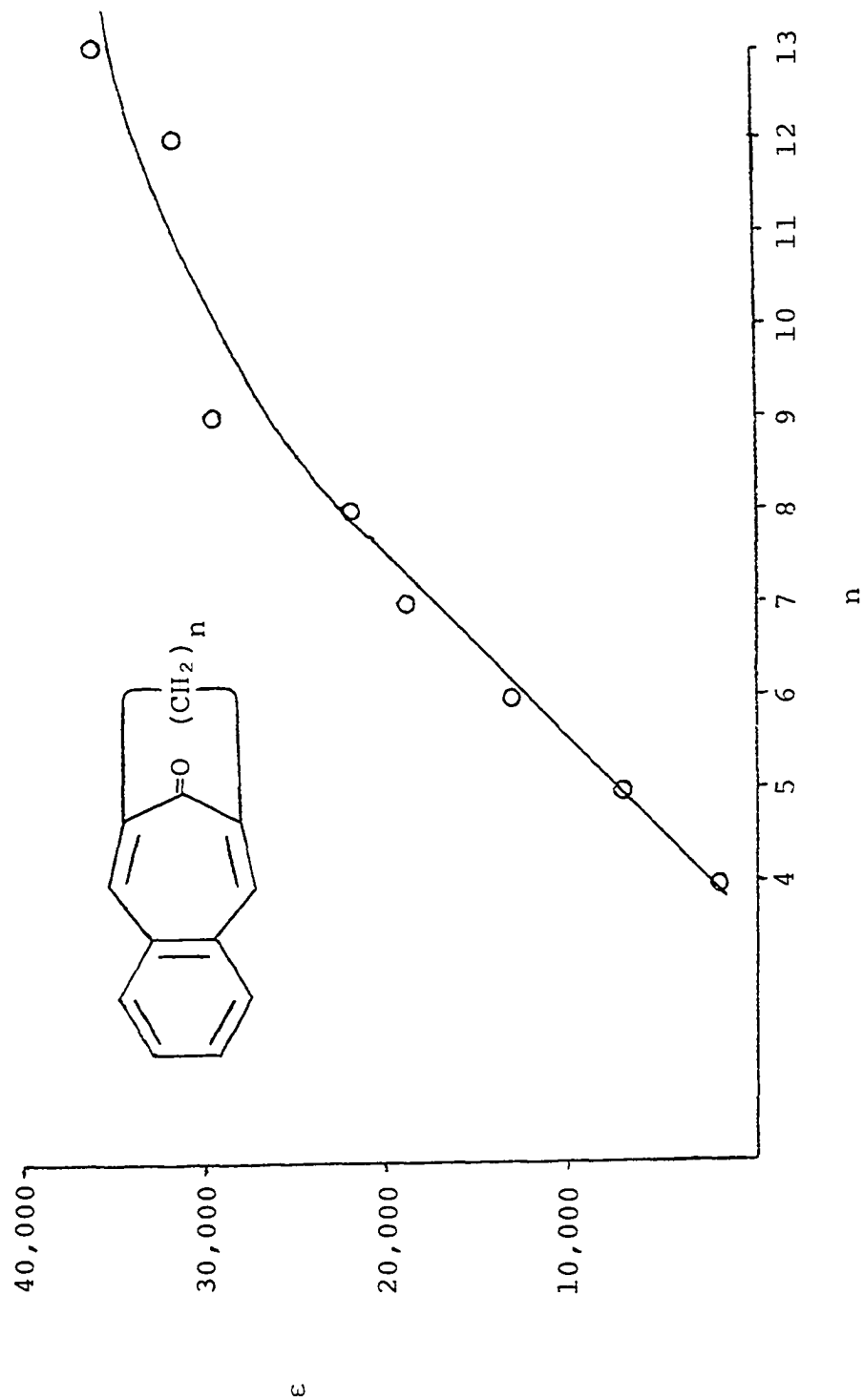
(Table III). For example, when $n=5$, $\epsilon=7,240$ and increases to 19,000 when $n=7$. The value of ϵ increases to 36,300 when $n=13$ and increases further to 41,700 in the case of the unsubstituted 7H-benzocyclohepten-7-one. The relationship between the size of n and the intensity of the

TABLE III
INTENSITY OF THE ~ 280 nm BAND
FOR 7H-BENZOCYCLOHEPTEN-7-ONES¹⁴



R	λ max. (nm) (MeOH)	ϵ ($l \cdot \text{mole}^{-1} \cdot \text{cm}^{-1}$)
$-(\text{CH}_2)_5-$	278	7,240
$-(\text{CH}_2)_6-$	280	13,200
$-(\text{CH}_2)_7-$	278	19,000
$-(\text{CH}_2)_8-$	274	21,900
$-(\text{CH}_2)_9-$	276	29,500
$-(\text{CH}_2)_{10}-$	276	31,600
$-(\text{CH}_2)_{13}-$	274	36,300
CH_3	272	40,700
H	270	41,700

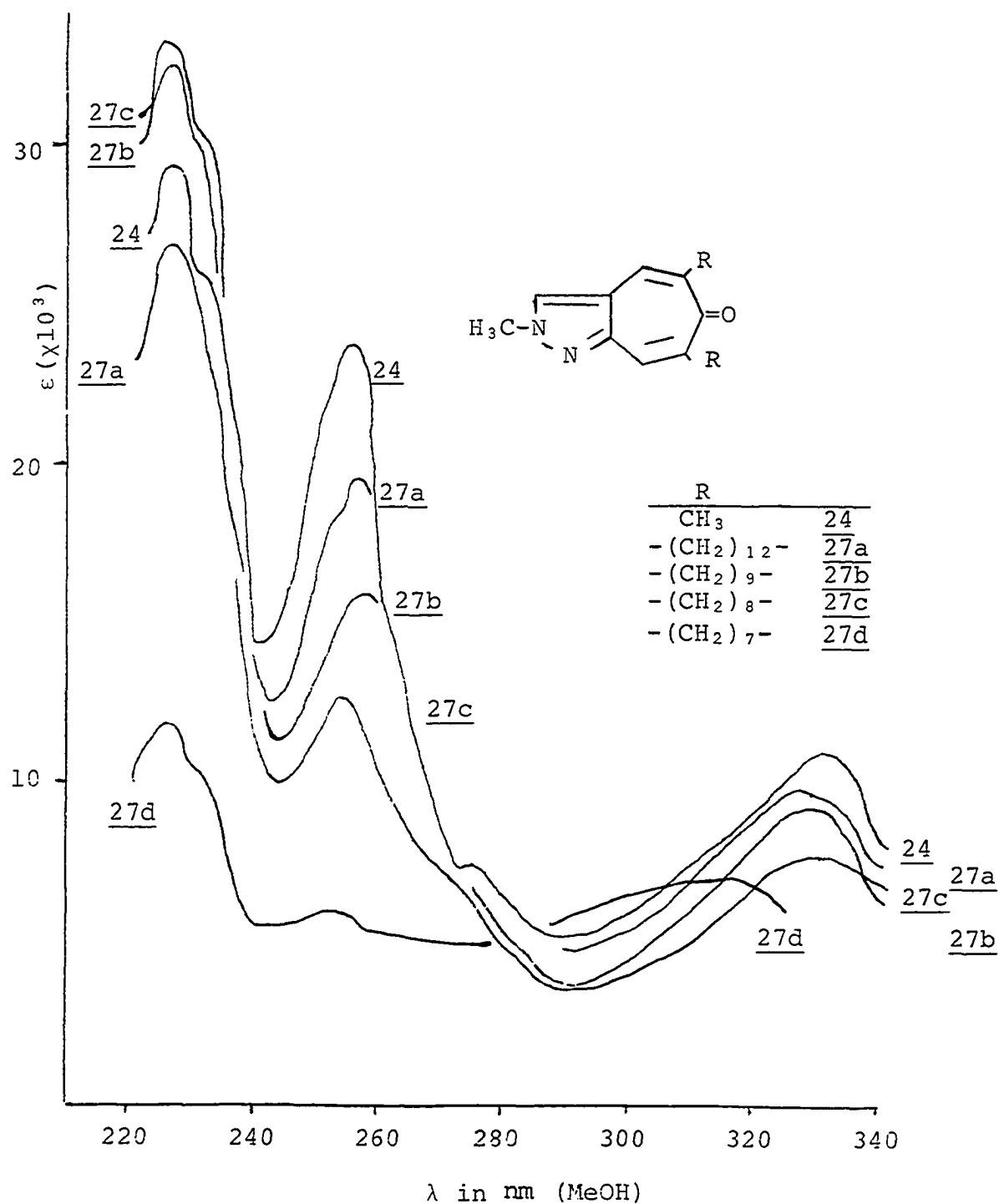
FIGURE I
INTENSITY OF THE ~280 nm BAND AS A FUNCTION OF n



280 nm band is further illustrated in Figure I. This again clearly illustrates that the methylene bridge is still applying strain upon the chromophore when $n=13$ and shows that the ultraviolet absorption is a more sensitive tool for detecting the strain than the infrared or nuclear magnetic resonance spectra. The ultraviolet spectra for the 2-methylcycloheptapyrazolones are shown in Figure II. While the chromophores of benzocycloheptenone and cycloheptapyrazole cannot be directly compared, the methylene bridge should exert a similar influence upon the cycloheptapyrazolone chromophore as it did upon the benzocycloheptenone chromophore. The influence of the methylene bridge can be seen in the band at ~ 255 nm. The 255 nm band of 2,5,7-trimethyl-6(2H)-cycloheptapyrazolone has an ϵ of 23,800 which decreases to 19,500 when $n=12$ and is further decreased to 6,100 when $n=7$. This clearly shows the effect of the methylene bridge upon the chromophore and indicates that the bridge is still applying strain upon the ring system when $n=12$. In the cases where $n=12$, 9 and 8 the two bands at ~ 227 and 330 nm only show minor changes as n is decreased; however, when $n=7$ both of these bands show marked alteration. The band at 227 nm is depressed from 26,800 ($n=12$) to 12,000 ($n=7$) while the 331 nm band is shifted to 313 nm and is depressed from 10,000

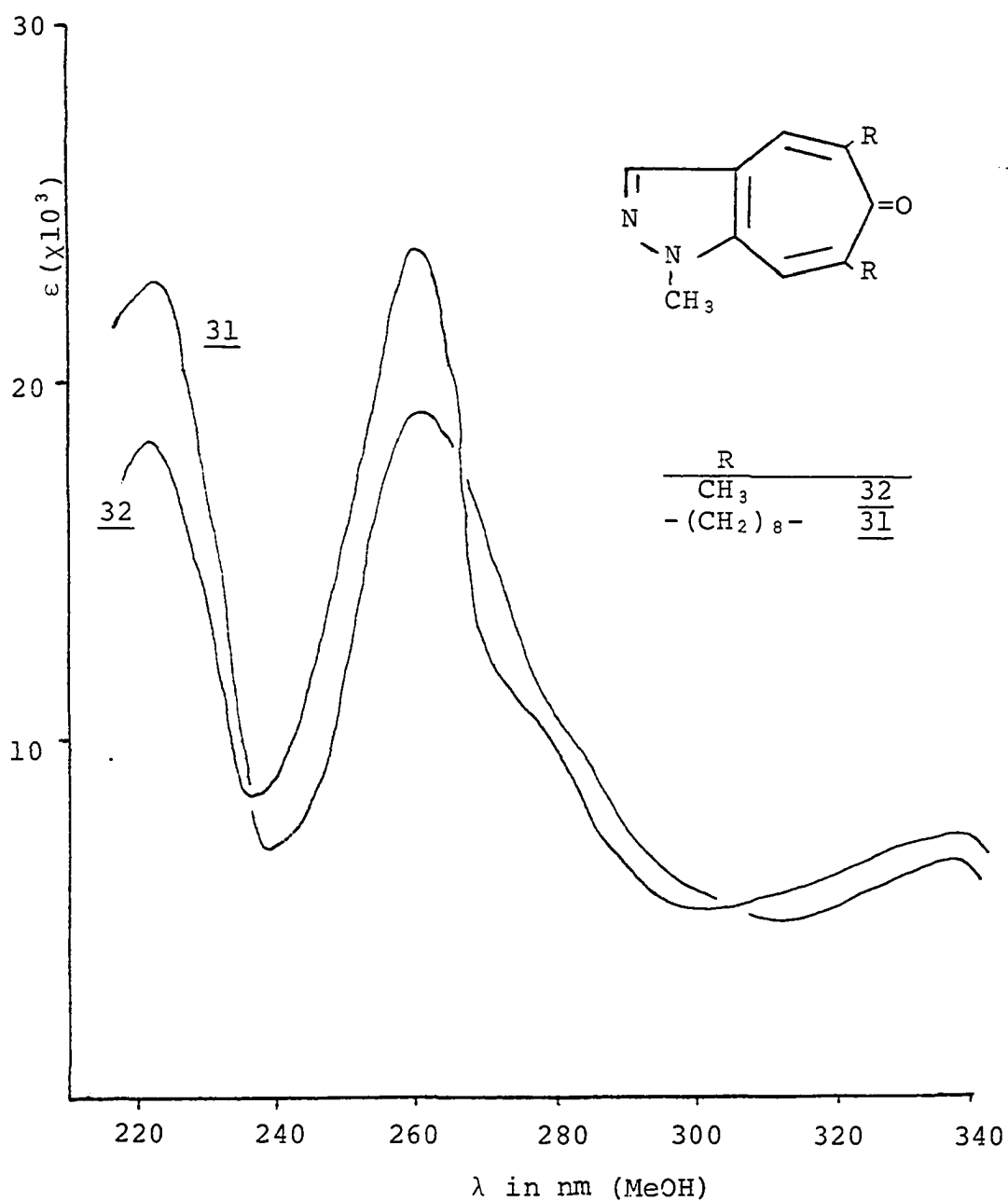
FIGURE II

ULTRAVIOLET SPECTRA OF 2-METHYL
CYCLOHEPTAPYRAZOLONES



to 7,200. The complete alteration of the ultraviolet spectrum indicates that the methylene bridge, when $n=7$, is applying an extreme amount of strain upon the ring system. These results are consistent with those observed in the nmr spectra and are similar to those observed in the case of the benzocycloheptenone when $n=4$. The ultraviolet spectra of the 1-methylcycloheptenones is shown in Figure III. The two short wavelength bands are shifted slightly from the positions of the corresponding bands of the 2-methylcycloheptenones and have reversed their relative intensities. While only two members of this series have been prepared, Figure III shows that the same trend observed for the 2-methylcycloheptapyrazolones is being observed for the 1-methylcycloheptapyrazolones. The intensity of the 261 nm band is decreased from 23,700 to 19,000 when R is changed from CH_3 to $-(\text{CH}_2)_8-$.

FIGURE III
 ULTRAVIOLET SPECTRA OF 1-METHYL
 CYCLOHEPTAPYRAZOLONES



EXPERIMENTAL

General Information

Melting points, reported in degree celcius, were determined using a Thomas-Hoover Unimelt instrument and are corrected. The nuclear magnetic resonance spectra were obtained using a Varian A-60 or a Bruker WH-90 spectrometer and are reported in ppm downfield from tetramethylsilane as an internal reference. Infrared spectra were recorded with a Digilab FTS-14 spectrometer (reported in cm^{-1}). The cycloundecanone was purchased from Aldrich Chemical Company and the cyclopentadecanone was obtained from Story Chemical. Both ketones were used without further purification. The cyclodecanone was prepared according to the procedure of Brannock, Burpitt, Goodlett and Thweatt³⁰.

Synthetic Procedures

Preparation of 5,7-dimethyl-6(1H)-cycloheptapyrazolone

A solution of 2.0 g (1.6×10^{-2} mole) of pyrazole-3(5), 4-dicarboxaldehyde, 1.4 g (1.6×10^{-2} mole) of 3-pentanone and 0.5 g of potassium hydroxide in 50 ml of methanol was heated under reflux for 3 hr. The solution was poured into 50 ml of water and extracted with chloroform. The chloroform extracts were dried over sodium sulfate and concentrated on a rotary evaporator. The resulting oil was dissolved in acetone and upon addition

of hydrogen chloride in 2-propanol gave a white precipitate. Recrystallization from acetone gave 1.0 g (31%), mp 187-188^o and a second crop of 0.5 g (15%), mp 184-185^o.

Anal. Calcd for C₁₀H₁₀N₂O•0.8 HCl; C, 59.06; H, 5.35; N, 13.78; Cl, 13.95.

Found: C, 58.84; H, 5.32; N, 13.83; Cl, 13.99.

Spectra

IR (KBr, CHCl₃)

Major peaks: 3150, 1605, 1550, 1515, 1400,
1370, 1275, 1020, 940 (KBr);
3400, 3010, 1595, 1560 (CHCl₃) cm⁻¹.

NMR (d₆-DMSO)

δ=12.40 (1.8 H, broad); 8.13 (1 H, s, H₃);
7.82 (2 H, m, H₈, H₄); 2.25 (3 H, s);
2.18 (3 H, s).

Preparation of 2,5,7-trimethyl-6(2H)-cycloheptapyrazolone

A solution of 0.5 g (3.6×10^{-3} mole) of 1-methylpyrazole-3,4-dicarboxaldehyde, 0.4 g (4.3×10^{-3} mole) of 3-pentanone and 0.2 g of potassium hydroxide in 30 ml of methanol was heated under reflux for 2.5 hr. The solution was then poured into water and extracted with ether. The ether extracts were dried over sodium sulfate and concentrated to yield a pale yellow solid. Recrystallization from acetone-ether yielded 0.4 g (63%), mp 157-158^o.

Anal. Calcd for $C_{11}N_2O$: C, 70.18; H, 6.43; N, 14.89.

Found: C, 69.95; H, 6.59; N, 14.93.

Spectra

IR (KBr)

Major peaks: 3110, 2950, 1615, 1560, 1525,
1165, 1140, 1030, 920 cm^{-1} .

NMR (CDCl_3)

$\delta=7.72$ (2 H, broad s, H_3, H_8); 7.50
(1 H, s, H_4); 4.07 (3 H, s, NCH_3);
2.30 (3 H, d, $J=1.0$, CH_3); 2.23
(1 H, d, $J=1.0$, CH_3).

(d_6 -DMSO)

$\delta=8.27$ (1 H, broad s, H_3); 7.70 (2 H, m,
 H_4, H_8); 4.05 (3 H, s, NCH_3); 2.17
(3 H, d, $J=1.0$, CH_3); 2.12 (3 H, d, $J=$
1.0, CH_3); 2.12 (3 H, d, $J=1.0$, CH_3).

Preparation of 2-methyl-5,7-dodecano-6(2H)-cyclohepta- pyrazolone

A solution of 0.5 g of (3.6×10^{-3} mole) of 1-methyl-3,4-pyrazoledicarboxyaldehyde, 0.97 g (4.3×10^{-3} mole) of cyclopentadecanone and 0.2 g of potassium hydroxide in 30 ml of methanol was heated under reflux for 6 hr. The solution was poured into water and extracted with chloroform. The combined chloroform ex-

tracts were dried over sodium sulfate and concentrated on a rotary evaporator. The residue was dissolved in 25 ml of ether and treated with hydrogen chloride in 2-propanol. The precipitate was collected and upon drying yielded 0.6 g (50%), decomposes at 40°.

Anal. Calcd for $C_{21}H_{30}N_2 \cdot 0.4 HCl$: C, 73.95; H, 8.98; N, 8.22; Cl, 4.16.

Found: C, 73.70; H, 9.15; N, 8.20; Cl, 3.81.

Spectra

IR (LF)

Major peaks: 2940, 2860, 1620, 1585, 1540, 1460, 1420, 1160 cm^{-1} .

NMR ($CDCl_3$)

δ =7.77 (1 H, broad s, H_3); 7.57 (1 H, s, H_8); 7.32 (1 H, s, H_4); 4.12 (3 H, s, CH_3); 1.40-1.10 (24 H, broad).

($CDCl_3$ + NaOD/ D_2O)

δ =7.70 (1 H, s, H_3); 7.55 (1 H, s, H_8); 7.33 (1 H, s, H_4); 4.05 (3 H, s, CH_3); 1.40-1.10 (24 H, broad).

(d_6 -DMSO-NaOD/ D_2O)

δ =8.23 (1 H, s, H_3); 7.55 (2 H, broad s); 4.03 (3 H, s, CH_3); 1.35-1.10 (24 H, broad).

Preparation of 4,8-dihydroxy-2-methyl-4,5,7,8-tetrahydro-5,7-nonano-6(2H)-cycloheptapyrazolone

A solution of 0.5 g (3.6×10^{-3} mole) of 1-methyl-pyrazole-3,4-dicarboxyaldehyde, 0.80 g (4.3×10^{-3} mole) of cyclododecanone and 0.2 g of potassium hydroxide in 50 ml of methanol was heated under reflux for 1 hr. The precipitate was collected and dried to give 1.23 g (95.3%), mp 192-196°.

Spectra

IR (KBr)

Major peaks: 3300, 2920, 2845, 1705, 1470, 1370, 1170, 1070, 1050, 1025 cm^{-1} .

NMR (d_6 -DMSO)

δ =7.31 (1 H, s, H_3); 5.40 (2 H, broad, OH); 4.91 (1 H, d, $J=8$); 4.08 (1 H, d, $J=8$); 3.71 (3 H, s, CH_3N); 2.10-0.90 (18 H, broad).

Preparation of 2-methyl-5,7-nonano-6(2H)-cycloheptapyrazolone

A suspension of 0.9 g (2.5×10^{-3} mole) of 4,8-dihydroxy-2-methyl-4,5,7,8-tetrahydro-5,7-nonano-6(2H)-cycloheptapyrazolone and 0.1 g of p-toluenesulfonic acid in 50 ml of toluene was heated under reflux for 3 hr.

The reaction mixture was poured into water and extracted with ether. The ether extracts were washed with water and dried over sodium sulfate. The ether was concentrated on a rotary evaporator and the residue was dissolved in 10 ml ether. Upon treatment with hydrogen chloride in 2-propanol a precipitate formed and was collected. Recrystallization from 2-propanol yielded 0.53 g (65%), mp 143-146^o.

Anal. Calcd for $C_{18}H_{24}N_2O \cdot HCl \cdot 0.1 H_2O$: C, 67.00;
H, 7.87; Cl, 10.99; N, 8.68; H_2O ,
0.56.

Found: C, 66.54; H, 7.67; Cl, 11.17; N, 8.60;
 H_2O , 0.76.

Spectra

IR (KBr)

Major peaks: 2920, 2420, 1600, 1575, 1465,
1265, 1170 cm^{-1} .

($CHCl_3$)

Major peaks: 2940, 1610, 1540, 1460 cm^{-1} .

NMR ($CDCl_3$)

δ =11.57 (1 H, s); 8.07 (1 H, s, H_3);
7.57 (1 H, s, H_8); 7.33 (1 H, s, H_4);
4.23 (3 H, s, CH_3); 2.57-0.96 (18 H,
broad).

($CDCl_3$ + NaOD/ D_2O)

δ =7.65 (1 H, s, H_3); 7.40 (1 H, broad s,

H₈); 7.21 (1 H, s, H₄); 4.00 (3 H, s, CH₃N); 2.40-1.00 (18 H, broad).
 (d₆-DMSO + NaOD/D₂O)
 δ=8.08 (1 H, s, H₃); 7.37 (2 H, m, H₈, H₄); 4.02 (3 H, s, CH₃); 2.30-0.90 (18 H, broad).

Preparation of 4,8-dihydroxy-2-methyl-5,7-octono-4,5,7,8-tetrahydro-6(2H)-cycloheptapyrazolone

A solution of 1.35 g (8.0×10^{-3} mole) of cyclo-undecanone, 1.0 g (7.2×10^{-3} mole) of 1-methyl-3,4-pyrazoledicarboxaldehyde and 0.3 g of sodium hydroxide in 30 ml of methanol was heated under reflux for 2 hr. The solution was cooled and the precipitate was collected and washed with methanol to give 1.7 g (69%), mp 225-233° (dec).

Anal. Calcd for C₁₇H₂₆N₂O: C, 66.64; H, 8.55; N, 9.14.

Found: C, 66.61; H, 8.35; N, 9.32.

Spectra

IR (KBr)

Major peaks: 3300, 2940, 1705, 1370, 1165, 1060, 1025 cm⁻¹.

NMR (d₆-DMSO)

δ=7.39 (1 H, s, H₃); 5.42 (2 H, m, H₈, H₄); 4.89 (1 H, broad t); 4.01 (1 H,

broad t); 3.69 (3 H, s, CH₃); 3.33-3.00 (2 H, broad); 2.22-1.11 (14 H, broad).

Preparation of 2-methyl-2,7-octano-6(2H)-cycloheptapyrazolone

A suspension of 0.5 g (1.6×10^{-3} mole) of 4,8-dihydroxy-2-methyl-5,7-octano-4,5,7,8-tetrahydro-6(2H)-cycloheptapyrazolone in 40 ml of benzene was heated under reflux for 2 hr over phosphorous pentoxide. The benzene was washed once with 0.1 N sodium hydroxide and dried over potassium carbonate. The benzene solution was concentrated on a rotary evaporator and the residue was recrystallized from chloroform-n-heptane and then cyclohexane to give 0.3 g (63%), mp 106-108°.

Anal. Calcd for C₁₇H₂₂N₂O: C, 75.52; H, 8.20; N, 10.36.

Found: C, 74.55; H, 8.01; N, 9.97.

Spectra

IR (KBr)

Major peaks: 2930, 1600, 1535, 1470, 1160 cm⁻¹.

NMR (CDCl₃)

δ=7.59 (1 H, s, H₃); 7.23 (1 H, s, H₈);
7.06 (1 H, s, H₄); 4.00 (3 H, s, NCH₃);
3.31 (2 H, broad); 2.53-1.00 (14 H, broad).

(d₆-DMSO)

δ=8.14 (1 H, s, H₃); 7.34 (2 H, broad s, H₄, H₈); 5.99 (3 H, s, NCH₃); 3.90-0.90 (16 H, broad).

Preparation of 2-methyl-5,7-heptano-6(2H)-cycloheptapyrazolone

A solution of 1.2 g (8.0×10^{-3} mole) of cyclo-decanone, 1.0 g (7.2×10^{-3} mole) of 1-methylpyrazole-3,4-dicarboxyaldehyde and 0.2 g of potassium hydroxide in 30 ml of methanol was heated under reflux for 24 hr. The solution was poured into 50 ml of water and extracted with methylene chloride. The combined methylene chloride layers were washed twice with water, dried over sodium sulfate and concentrated on a rotary evaporator. Recrystallization from chloroform-cyclohexane and then heptane gave 0.3 (17%), mp 104-106°.

Anal. Calcd for C₁₆H₂₀N₂O: C, 74.96; H, 7.86; N, 10.93.

Found: C, 74.98; H, 8.02; N, 10.72.

Spectra

IR (KBr)

Major peaks: 2830, 1615, 1535, 1470, 1445, 1160 cm⁻¹.

NMR (d₆-DMSO)

δ=8.05 (1 H, s, H₃); 7.15 (2 H, m, H₄,

H₈); 3.95 (3 H, s, CH₃); 3.70-1.10
(14 H, broad).

(CDCl₃)

δ=7.50 (1 H, s, H₃); 7.12 (1 H, broad
s, H₈); 6.94 (1 H, s, H₄); 3.98 (3 H, s,
CH₃); 3.50-1.10 (14 H, broad).

Preparation of 2,6-dihydro-2-methyl-6-oxo-5,7-cyclo-
heptapyrazolonedicarboxylic acid, dimethyl ester

A solution of 1.0 g (7.2×10^{-3} mole) of 1-methyl-
pyrazole-3,4-dicarboxyaldehyde, 1.5 g (8.7×10^{-3} mole)
of dimethylacetone dicarboxylate and 1 ml of triethylamine
in 35 ml of benzene was heated under reflux for 3 hr.
The white precipitate which formed was collected and
dried in vacuo. Recrystallization from chloroform-
cyclohexane gave 0.6 g (30%), mp 183-185°.

Anal. Calcd for C₁₃H₁₂N₂O₅: C, 56.52; H, 4.38;
N, 10.14.

Found: C, 55.97; H, 4.39; N, 10.02.

Spectra

IR (KBr)

Major peaks: 3115, 2960, 1740, 1620, 1600,
1535, 1435, 1400, 1230, 1065,
1000, 790 cm⁻¹.

NMR (CDCl₃)

δ=8.10 (1 H, s, H₈); 8.07 (1 H, s, H₄);

7.98 (1 H, broad s, H₃); 4.12 (3 H, s, CH₃N); 3.92 (3 H, s, CO₂CH₃); 3.88 (3 H, s, CO₂CH₃).

(d₆-DMSO)

δ=8.57 (1 H, broad s, H₃); 8.18 (1 H, s, H₈); 7.97 (1 H, s, H₄); 4.10 (3 H, s, CH₃N); 3.82 (3 H, s); 3.80 (3 H, s).

Preparation of 2,6-dihydro-2-methyl-6-oxo-5,7-cycloheptapyrazoledicarboxylic acid

A suspension of 1.0 g (3.6×10^{-3} mole) of 2,6-dihydro-2-methyl-6-oxo-5,7-cycloheptapyrazoledicarboxylic acid, dimethyl ester in 20% sulfuric acid was heated under reflux for 1.5 hr and then stirred at room temperature for 2 hr. The solid was collected, washed with water and dried to give 0.8 g (90%), mp 245-246°.

Anal. Calcd for C₁₁N₈N₂O₅: C, 53.23; H, 3.25; N, 11.29.

Found: C, 53.28; H, 3.35; N, 11.26.

Spectra

IR (KBr)

Major peaks: 1735, 1605, 1520, 1150, 820 cm⁻¹.

NMR (d₆-DMSO)

δ=7.85 (1 H, s); 7.70 (1 H, s); 7.30 (1 H, s); 4.16 (3 H, s).

Preparation of 1-methyl-2,7-octano-6(1H)-cyclohepta-pyrazolone

A solution of 1.0 g (7.2×10^{-3} mole) of 1-methyl-4,5-pyrazoledicarboxaldehyde, 1.35 g (8.0×10^{-3} mole) of cycloundecanone and 0.3 g of sodium hydroxide in 30 ml of methanol was heated under reflux for 6 hr. The solution was poured into water and extracted with methylene chloride. The combined methylene chloride layers were washed with water, dried over sodium sulfate and concentrated on a rotary evaporator. The residue was chromatographed (silica 280 g; 98% CH_2Cl_2 , 2% MeOH). Fractions were identified on the basis of thin layer chromatography ($R_F=0.80$) and concentrated on a rotary evaporator. The residue was recrystallized from n-heptane to give 0.4 g (20%), mp 165-167°.

Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}$: C, 75.52; H, 8.20;
N, 10.36.

Found: C, 75.28; H, 8.27; N, 10.14.

Spectra

IR (KBr)

Major peaks: 2930; 1595, 1545 cm^{-1} .

NMR (CDCl_3)

$\delta=7.66$ (1 H, d, $J=1$, H_3); 7.21 (1 H, d, $J=1$, H_8); 7.09 (1 H, d, $J=1$, H_4); 4.00 (3 H, s, CH_3); 3.62-3.13 (2 H, m);

2.60-2.15 (2 H, m); 1.96-0.69 (12 H, broad).

(d₆-DMSO)

δ=7.81 (1 H, s, H₃); 7.50 (1 H, s, H₈);
7.36 (1 H, s, H₄); 4.00 (3 H, s, CH₃);
3.38-2.95 (2 H, m); 2.63-2.13 (2 H, m);
1.78-0.66 (12 H, broad).

Preparation of 1,5,7-trimethyl-6(1H)-cycloheptapyrazolone

A solution of 0.5 g (3.6×10^{-3} mole) of 1-methyl-4,5-pyrazoledicarboxaldehyde, 0.4 g (4.3×10^{-3} mole) of 3-pentanone and 0.20 g of sodium hydroxide in 30 ml of methanol was heated under reflux for 3 hr. The solution was poured into water and extracted with ether. The combined ether layers were washed with water, dried over sodium sulfate and concentrated on a rotary evaporator. Recrystallization of the residue from cyclohexane gave 0.45 g (71%), mp 134-137°.

Anal. Calcd for C₁₁H₁₂N₂O: C, 70.18; H, 6.43; N, 14.89.

Found: C, 69.83; H, 6.46; N, 14.97.

Spectra

IR (KBr)

Major peaks: 1580, 1550, 1185, 990, 905,
835 cm⁻¹.

NMR (CDCl_3)

$\delta=7.81$ (1 H, broad s, H_3); 7.62 (1 H, d, $J=1$, H_8); 7.55 (1 H, d, $J=1$, H_4); 4.09 (3 H, s, NCH_3); 2.37 (3 H, d, $J=1$, CH_3); 2.28 (3 H, d, $J=1$, CH_3).

(d_6 -DMSO)

$\delta=7.95$ (2 H, m, H_3 , H_8); 7.77 (1 H, d, $J=1$, H_4); 4.11 (3 H, s, CH_3); 2.28 (3 H, s); 2.17 (3 H, s).

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SUMMARY

It was found that methylation of pyrazole-3(5),4-dicarboxaldehyde increased the reactivity of the molecule toward aldol condensation. When 1-methylpyrazole-3,4-dicarboxaldehyde was treated with cycloalkanones, the product was isolated in one step when $n=7$ or 12. However, when $n=8$ or 9 the dihydroxyketone intermediate was isolated and was dehydrated to give the desired product. The nuclear magnetic resonance spectra of these compounds show pronounced shifts of the ring protons with change in solvent and change in the size of the methylene bridge. It was observed that the shift of the H_3 proton, with change in solvent, allows for unambiguous assignment of the N-methyl group. While all of the three ring protons show the effect of decreasing the size of the methylene bridge, the effect is more pronounced for the two protons on the cycloheptenone ring. It was demonstrated that the bridge applied strain upon the ring system even when n was increased to 12. The 255 nm band in the ultraviolet spectra was found to be dependent upon the size of n and proved to be more sensitive to the effect of the methylene bridge than either the infrared or the nuclear magnetic resonance spectra.

VITA

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