Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08; N-(CH_3), 7.02. Found: C, 72.65; H, 6.71; N, 13.45; N-(CH_3), 6.84.

The **oxime** of **8** was prepared with methanolic hydroxylamine acetate and crystallized from aqueous methanol as pale yellow prisms: m.p. 160–162° dec.; n.m.r. 2.00 (s, 3), 3.07 (s, 3), 3.70 (s, 2), 7.35 (m, 5), 7.87 (s, 1), and 8.03 (s, 1—exchanged by D_2O) p.p.m.

Anal. Calcd. for $C_{13}H_{15}N_3O$: N, 18.33. Found: N, 18.47.

The **semicarbazone** was prepared from 88 mg. of **8** with methanolic semicarbazide acetate. After standing for 30 min. the solution was diluted with water, giving 131 mg. of colorless prisms, m.p. 184° dec. Recrystallization from methanol–water and ethanol–ether gave prisms: m.p. 184–185° dec.; n.m.r. 2.05 (s, 3), 3.05 (s, 3), 3.70 (s, 2), 7.30 (m, 5), 7.43 (s, 1), and 8.00 (s, 3—exchanged by D_2O) p.p.m.

Anal. Calcd. for $C_{14}H_{17}N_5O$: C, 61.97; H, 6.32; N, 25.81. Found: C, 61.82; H, 6.40; N, 26.45.

1,4-Dimethyl-3-formyl-5-phenylpyridazinium Bromide (10).—To a solution of 144 mg. (0.67 mmole) of the dihydropyridazine aldehyde **8** in 3 ml. of methylene chloride was added a solution of 104 mg. (0.65 mmole) of bromine in 2 ml. of methylene chloride. A yellow oil immediately separated from the pale yellow solution; evaporation gave a glass: softening point 74–75°; n.m.r. (in D_2O) 1.67 (s, 3), 4.78 (s, 3), 6.63 (s, 1), 7.80 (m, 5), and 9.75 (s, 1) p.p.m.[16]

Semicarbazone of 1,4-Dimethyl-3-formyl-5-phenylpyridazinium Perchlorate.—A solution of 124 mg. (0.46 mmole) of the semicarbazone of **4** in methylene chloride was treated with 0.46 mmole of bromine and the resulting suspension was evaporated to an orange glass containing the quaternary bromide: n.m.r. (in D_2O) 2.82 (s, 3), 4.73 (s, 3), 7.69 (m, 5), 8.50 (s, 1), and 9.68 (s, 1) p.p.m.[16]

To a solution of 88 mg. of the bromide in 2 ml. of water at 0° was added 0.03 ml. of 70% aqueous perchloric acid. The resulting yellow precipitate, m.p. 212–213°, was recrystallized from ethanol to give colorless needles, m.p. 215–216°.

(16) The n.m.r. spectrum was measured at 60 Mc. with internal standard of 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt.

Anal. Calcd. for $C_{14}H_{16}ClN_5O_5$: C, 45.47; H, 4.36; N, 18.94. Found: C, 45.37; H, 4.54; N, 19.03.

3-Hydroxy-4-methyl-6-methylamino-5-phenylpyridine (13b).—To a solution of 250 mg. of the diazepinone **4** in 2 ml. of methanol was added 1 ml. of 5% aqueous NaOH. After refluxing 3 hr. under a nitrogen atmosphere, the solution was chilled and neutralized to pH 8 with hydrochloric acid. The resulting brown precipitate was collected and washed with water, giving 248 mg. of tan solid, softening at 80°, complete melting at 150°. The material was sublimed at 0.1 mm. to give 157 mg. of long, pale yellow crystals of **13b**, m.p. 155–156°, λ_{max}^{MeOH} 327 mμ (ε 5180), $\lambda_{max}^{MeOH + HCl}$ 219 mμ (ε 20,000) and 332 mμ (ε 7300), $\lambda_{max}^{MeOH + KOH}$ 228 mμ (ε 14,600) and 339 mμ (ε 4900), pK_A' 5.9 and 10.1. Satisfactory analytical values for carbon could not be obtained.

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.24; H, 6.63; N, 13.05.

3-Hydroxy-4-methyl-6-(N-methyl)benzamido-5-phenylpyridine.—To a solution of 118 mg. of the pyridine **13b** in 5 ml. of 5% aqueous KOH solution was added 0.3 ml. of benzoyl chloride. After shaking until all of the benzoyl chloride had reacted, water was added and the mixture was extracted with methylene chloride. Evaporation of the washed and dried methylene chloride solution gave 205 mg. of the **O,N-dibenzoyl derivative**, $\lambda_{C=O}^{KBr}$ 5.72 and 6.03 μ, as a colorless glass which could not be crystallized.

The amorphous dibenzoyl compound was hydrolyzed for 30 min. in methanolic KOH solution, the methanol was then removed, water was added, and the solution was neutralized by addition of acid and then $NaHCO_3$. Extraction with methylene chloride gave 79 mg. of a crystalline powder, m.p. 110°. Recrystallization from ether–hexane gave colorless prisms of the N-benzoyl-3-hydroxypyridine, m.p. 150–151°, λ^{KBr} 3.20 and 6.10 μ, λ_{max}^{MeOH} 290 mμ (ε 5200).

Anal. Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.10; H, 5.86; N, 8.72.

Acknowledgment.—We thank Dr. J. M. Vandenbelt and Mrs. Carola H. Spurlock, Parke, Davis and Company, for the ultraviolet data.

Heterocyclic Studies. XV. 5-Methyl-4-phenylpyrazole-1-acetic Acid. An Oxidation Product of 2,3-Dihydro-5-methyl-6-phenyl-4H-1,2-diazepin-4-one*,[1]

JAMES A. MOORE AND CLARISSE L. HABRAKEN[2]

Department of Chemistry, University of Delaware, Newark, Delaware, and the Organic Chemistry Laboratory, University of Leiden, Netherlands

Received April 7, 1964

Oxidation of the diazepinone (**1**) with hydrogen peroxide gives 5-methyl-4-phenylpyrazole-1-acetic acid (**2**). Condensation of 1-ethoxymethylene-1-phenylacetone (**7**) with ethyl hydrazinoacetate and alkylation of 5-methyl-4-phenylpyrazole (**5**) with ethyl bromoacetate gives both **2** and the 3-methyl isomer **9**. The structures of these pyrazoles are assigned on the basis of the formation of **2** from **1**.

During studies on the chemistry of the diazepinone **1**, it was found that treatment of this orange ketone with alkaline hydrogen peroxide gave a colorless acid containing one additional oxygen atom. This product was of interest originally as a source of structural information for the parent ketone and later in revealing another pathway for rearrangement of **1**. The acid has been shown to be 5-methyl-4-phenylpyrazole-1-acetic acid (**2**); the evidence for this structure, independent synthesis, and the formation of **2** from **1** are discussed in this paper.

Initial consideration of the formula and standard transformations to the ester **3** and carbinol **6** suggested a pyrazoleacetic acid structure for the oxidation product, and the rather low pK_A value (3.6) indicated an N-acetic acid. A neutral by-product was later obtained in another oxidation of **1** under more vigorous conditions and was identified as 5-methyl-4-phenylpyrazole (**5**).[3] This compound was shown to arise from **2** under the conditions of the oxidation, supporting the methylphenylpyrazole-N-acetic acid formula. Earlier attempts to remove the suspected N-acetic acid group by a Barbier–Wieland degradation of **3** or direct oxidation of **2** with permanganate were unsuccessful. Treatment of

* To Professor Louis F. Fieser.

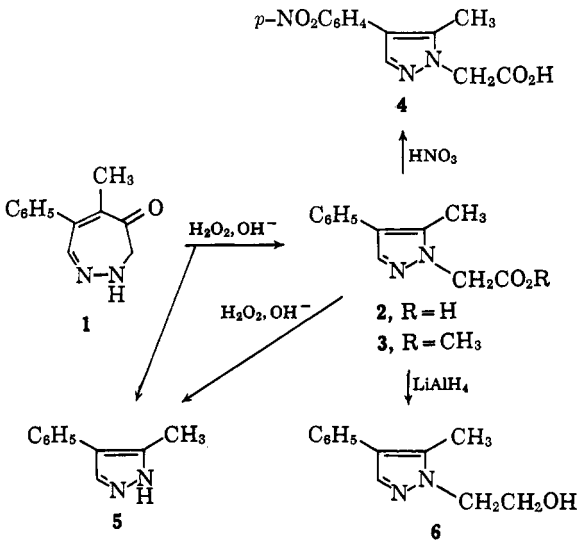
(1) (a) Supported in part by Grant DA-CML-18-108-61-G-24 from the Army Chemical Corps. (b) Part XIV: J. A. Moore and W. J. Theuer, *J. Org. Chem.*, **30**, 1887 (1965).

(2) Visiting Land Grant Assistant Professor, 1961–1962, on leave of absence from the University of Leiden.

(3) G. N. Walker and B. N. Weaver, *J. Org. Chem.*, **26**, 4441 (1961); the tautomeric structure **5** for this pyrazole has been defined by n.m.r. studies presented in the following paper.[4]

(4) C. L. Habraken and J. A. Moore, *ibid.*, **30**, 1892 (1965).

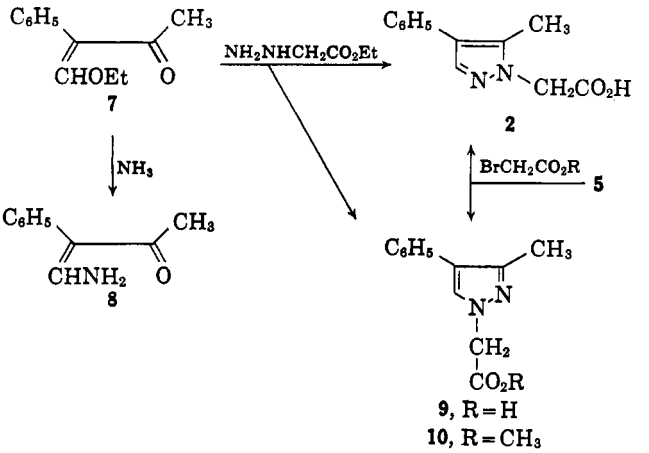
2 with hot 1:1 nitric acid, in an effort to completely oxidize the alkyl chains, led unexpectedly to a nitro derivative of 2 in 40% yield. The pK_A value of this acid indicated that nitration had not occurred in the pyrazole ring, and the ultraviolet spectrum was consistent only with the *p*-nitrophenylpyrazole structure **4**. Very little is known concerning substitution reactions of 4-phenylpyrazoles, but the formation of **4** under such relatively mild nitration conditions indicates that the 4-(1-substituted)-pyrazolyl group is a rather effective activating substituent for electrophilic substitution in a benzene ring. This point was further brought out when n.m.r. spectra of 2 and 5 were determined in 100% sulfuric acid. After the solution had stood for 12 hr. at room temperature, the aryl proton peak developed a characteristic four-line A_2B_2 pattern (J = 8.5 c.p.s.) of a *para*-disubstituted benzene, indicating sulfonation of the phenyl group.



The presence of a methylene group adjacent to the carboxyl was eventually demonstrated directly by the change in the n.m.r. spectrum on going from the methyl ester **3** (two-proton peak for $-NCH_2CO_2CH_3$ at δ = 4.89 p.p.m.) to the carbinol **6** (four-proton A_2B_2 multiplet centered at δ = 4.09 p.p.m.). The other signals in the n.m.r. spectra were consistent with the methylphenylpyrazole structure. At this point synthetic studies were undertaken to provide additional structure evidence. Two synthetic methods were examined: the condensation of α-formylphenylacetone with ethyl hydrazinoacetate, and the alkylation of **5** with ethyl bromoacetate.

The formation of 1,4-diphenyl-5-methylpyrazole from α-formylphenylacetone and phenylhydrazine has been reported by Walker and Weaver[5]; this structure is consistent with the usual orientation observed in the condensation of β-ketoaldehydes and arylhydrazines.[6] In our hands the hydroxymethylene ketone proved difficult to isolate and purify, and a more satisfactory derivative for condensations was the ethyl ether **7** which was obtained by the conventional reaction of phenylacetone with ethyl orthoformate in the presence of acetic anhydride and zinc chloride.[7] The initially formed acetal was converted to the enol ether by thermal elimination of alcohol. Condensation of **7** with hydrazine and phenylhydrazine in the presence of sulfuric acid gave excellent yields of 5-methyl-4-phenylpyrazole (**5**) and 1,4-diphenyl-5-methylpyrazole, respectively. With ammonia the amino ketone **8**[8] was obtained, confirming the expected[9] reactivity of the ethoxymethylene group in **7**.

The condensation of **7** with ethyl hydrazinoacetate gave both pyrazoles. When the reaction was carried out in the presence of acid, as in the preparation of **5**, a water-soluble compound was obtained which was not characterized. On refluxing in neutral aqueous ethanolic solution followed by saponification, low yields of an acid identical with the oxidation product **2** obtained from **1** were obtained in two experiments; on one occasion a small amount of the other acid was isolated. No attempt was made to develop optimum conditions for the synthesis of **2** or to separate the two pyrazoles quantitatively, but **2** was clearly present in larger amounts. The alternative synthetic route to the acids **2** and **9**, alkylation of pyrazole **5** with methyl



bromoacetate, likewise gave both acids, but in this case **2** was the minor product. The physical properties of the two compounds were very similar; the melting points were identical, although there was a substantial depression on mixture. The identity of the major product from the hydrazino ester condensation (minor alkylation product) and the oxidation product of **1** was established by comparison of infrared spectra of the acids and methyl esters.

These syntheses confirmed a 3(5)-methyl-4-phenylpyrazole-1-acetic acid structure for the oxidation product of **1**, but did not provide a basis for choice between the isomers **2** and **9**. In the reaction of ethyl hydrazinoacetate with **7** the major course of condensation might be better rationalized as leading to **2**, but the balance of electronic and steric factors in the four reactive centers in such condensations, especially the two nucleophilic positions in the hydrazine, is difficult to evaluate. On purely steric grounds the alkylation reaction would be expected to give mainly **9**. In neither case, how-

(5) In ref. 3 this pyrazole is incorrectly named as the 1,4-diphenyl-3-methyl isomer.

(6) T. L. Jacobs in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p. 50.

(7) O. Bayer, in Houben–Weyl, "Methoden der organische Chemie," Vol. 7/1, 4th Ed., Georg Thieme Verlag, Stuttgart, 1954, p. 49.

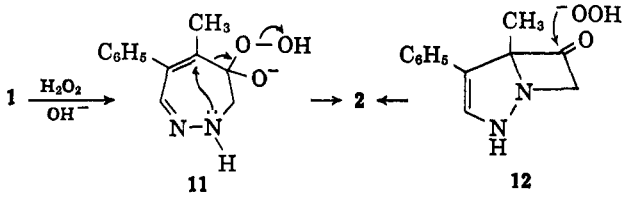
(8) J. A. Moore, F. J. Marascia, R. W. Medeiros, and E. Wyss, *J. Am. Chem. Soc.*, **84**, 3022 (1962).

(9) W. Franke, R. Kraft, and K. Kosswig, "Neuere Methoden der praparativen organischen Chemie," Vol. II, W. Foerst, Ed., Verlag Chemie, Weinheim, Bergstrasse, 1960, p. 6.

ever, was the ratio of products sufficiently large or the mechanistic argument compelling enough to support a structural assignment.

Evidence supporting the indicated assignment of the 5-methyl isomer **2** as the major product from the condensation of **7** with the hydrazino ester, and **9** as the major alkylation product of **5**, is provided by n.m.r. data presented in the following paper.[4] This conclusion actually follows most directly, however, from the formation of **2** in the diazepinone oxidation. This reaction involves loss of the C-4–C-5 bond in **1** and formation of an N–C-5 bond. Regardless of the timing of these stages, there seems to be no reasonable basis for formulating an additional rearrangement of the two-carbon chain from N-2 to N-1 leading to structure **9**.

The cleavage of unsaturated and saturated ketones with hydroperoxide has been observed on a number of occasions and has been studied in some detail by House and Wasson[10]; the reaction can be formulated essentially as an anionic counterpart of the Baeyer–Villiger oxidation.[10,11] In the case of **1**, transannular attack of N-2 at C-5 (**11**) could accompany the displacement of the C-4–C-5 bond to the electron-deficient oxygen, with fragmentation similar to the base-induced cleavage of α-phenethyl *t*-butyl peroxide.[12] Similar nucleophilic N-2–C-5 participation has been observed in other reactions of the diazepinone **1** leading to the 1,2-diazabicyclo[3.2.0]heptane system[9]; a strong driving force in the present reaction is the gain of the pyrazole resonance. The oxidation of **1** may alternatively be pictured as attack of hydroperoxide on a bicyclic species such as **12**, but at present there is no direct evidence that bicyclic tautomers of **1** play a role as intermediates in transformations of **1** to bicyclic products.



Experimental

Melting points were determined on a Fisher-Johns apparatus with a calibrated thermometer. Infrared spectra were obtained in KBr pellets. N.m.r. data are presented in the following paper.[1] Ether and methylene chloride extracts were dried with Na_2SO_4 or $MgSO_4$ prior to evaporation.

5-Methyl-4-phenylpyrazole-1-acetic Acid 2 by Oxidation of Diazepinone 1.—A solution of 1.0 g. of **1** in 15 ml. of methanol and 30 ml. of 5% aqueous KOH was treated with 5 ml. of 30% H_2O_2. The solution was kept at 25° and four additional 5-ml. portions of 30% H_2O_2 were added over a period of 3 days until the solution was pale yellow. After neutralization with HCl the white precipitate was filtered and the filtrate was extracted with ether to give a total of 540 mg. (50%) of colorless acid **2**, m.p. 204–208°. Recrystallization from methanol–water gave white needles, m.p. 212–213°, λ_{max}^{EtOH} 244 mμ (14,400), pK_A' = 3.6 (50% MeOH).

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 67.16; H, 6.07; N, 12.92.

This acid was freely soluble in 5% HCl or Na_2CO_3 solution. It sublimed at atmospheric pressure (bath 230°) with slight decomposition. It did not reduce alkaline $KMnO_4$ solution on heating for 1 min. at 90°.

In another oxidation, a solution of 5.2 g. of **1** in 300 ml. of 10% KOH was treated with 25 ml. of 30% H_2O_2 in one portion. The temperature rose to 55°, with vigorous evolution of oxygen and a strong odor of ammonia. An additional 10 ml. of H_2O_2 was then added; after standing for 16 hr. at 25° the pale yellow solution had deposited 180 mg. of white crystalline solid. This material was recrystallized from methanol–water and sublimed to give colorless prisms of 5-methyl-4-phenylpyrazole (**5**), m.p. 142–143°, λ_{max}^{EtOH} 244 mμ (ϵ 12,600).

Anal. Calcd. for $C_{10}H_{11}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 76.08; H, 6.68; N, 17.42.

The filtrate from the pyrazole was acidified to give 1.57 g. of the acetic acid **2**, m.p. 210–211°.

A sample of the above pyrazole **5** was warmed with acetic anhydride and the 1-acetyl-3-methyl-4-phenylpyrazole[13] was isolated in the usual manner, recrystallized from ether–pentane, and sublimed; m.p. 67–68°, λ^{KBr} 5.75 μ.

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 71.97; H, 6.04. Found: C, 72.54; H, 5.82.

On standing, this acetyl derivative slowly reverts to **5**; better analytical data could not be obtained even with freshly sublimed material.

Oxidation of 2 to 5.—A solution of 300 mg. of the acid **2** in 10 ml. of 10% KOH was treated with 2 ml. of 30% H_2O_2 and the solution was heated at 60° for 2 hr. After cooling the solution was extracted with CH_2Cl_2 and the extract was evaporated to give about 10 mg. of crystalline residue which was recrystallized from ethanol–water to give **5**, m.p. 141–142°, infrared curve identical with authentic pyrazole.

Methyl 5-Methyl-4-phenylpyrazole-1-acetate (3).—A solution of 540 mg. of the acid **2** in methanol was treated with diazomethane and then evaporated to give 513 mg. of colorless needles which were recrystallized from methanol–water; m.p. 90–91°, λ_{max}^{EtOH} 243 mμ (ϵ 14,800), λ_{max}^{KBr} 5.70 μ.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 68.04; H, 6.13; N, 12.05.

The **picrate** of the ester crytallized from ethanol–alcohol–acetone mixtures as yellow rods, m.p. 170–171°.

Anal. Calcd. for $C_{10}H_{17}N_5O_9$: C, 49.67; H, 3.73; N, 15.25. Found: C, 49.57; H, 3.95; N, 15.37.

2-(5-Methyl-4-phenylpyrazole)-1-ethanol (6).—A solution of 456 mg. of the above methyl ester in ether was treated with 300 mg. of $LiAlH_4$. After 30 min., water and then KOH solution were added and the ether solution was evaporated (no acid wash) to give 295 mg. of the carbinol, which was recrystallized from acetone–pentane to give shiny plates, m.p. 98°, λ_{max}^{EtOH} 243 mμ (ϵ 14,400).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.66; H, 7.28; N, 14.18.

The **picrate** crystallized from aqueous ethanol, m.p. 122–123°.

5-Methyl-4-*p*-nitrophenylpyrazole-1-acetic Acid (4).[14]—A solution of 530 mg. of the pyrazoleacetic acid **2** in 5 ml. of water and 5 ml. of concentrated HNO_3 was heated 30 min. on the steam bath. After cooling and neutralization with $NaHCO_3$ to pH 3 the solution was extracted with ether. The solid residue obtained after evaporation of the ether was recrystallized from ethanol to give 250 mg. of colorless needles, m.p. 218–222°. Further recrystallization from methanol gave prisms, m.p. 227–229°, pK_A' = 4.0 (50% MeOH), λ_{max}^{EtOH} 222 mμ (ϵ 12,000) and 325 mμ (ϵ 13,200).

Anal. Calcd. for $C_{12}H_{11}N_3O_4$: C, 55.17; H, 4.24; N, 16.09. Found: C, 55.05; H, 4.14; N, 16.21.

The **methyl ester** was obtained with diazomethane, m.p. 163–164°.

1-Ethoxy-2-phenyl-1-buten-3-one (7).—A mixture of 90 g. of phenylacetone, 170 g. of acetic anhydride, 174 g. of ethyl orthoformate, and 0.5 g. of anhydrous $ZnCl_2$ was maintained at 120–130° for 20 hr.; ethyl acetate slowly distilled. After cooling and filtration of some black solid, excess acetic anhydride and orthoformate were distilled at aspirator pressure. Distillation at 0.8 mm. gave 48 g. of unreacted phenylacetone and then 34 g. of liquid, b.p. 102–103°, which from the n.m.r. spectrum appeared to be largely the diethyl acetal. After heating this material at 280° until no further ethanol distilled, the residue was fractionally distilled to give 24.9 g. of **10** (44% corrected for recovered phenyl-

(10) H. O. House and R. L. Wasson, *J. Org. Chem.*, **22**, 1157 (1957).

(11) P. A. S. Smith in "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p. 457.

(12) N. Kornblum and H. E. de la Mare, *J. Am. Chem. Soc.*, **73**, 880 (1951).

(13) This structure is based on n.m.r. evidence.[4]

(14) This experiment was performed by Mr. Michael Fletcher.

acetone), b.p. 118–120° (0.4 mm.), λ_{max}^{EtOH} 227 mμ (ε 9700) and 260 mμ (ε 10,000); on prolonged standing the compound crystallized, m.p. 38°.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.8; H, 7.4. Found: C, 75.7, 75.9; H, 7.4, 7.5.

1-Amino-2-phenyl-1-buten-3-one (8).[5]—A solution of 1 g. of the enol ether and 2 ml. of 37% NH_4OH in 10 ml. of methanol was stored at 25° for 20 hr. and then evaporated. The residue crystallized on addition of ether and a total of 0.75 g. (89%) of white crystals of **8**, m.p. 93–99°, was obtained. Sublimation gave material with m.p. 99–101°,[16] λ_{max}^{EtOH} 289 mμ (ε 14,300).

1-Benzamido-2-phenyl-1-butene-3-one was prepared by treatment of 1.0 g. of the above enamine in 7 ml. of pyridine with 1 ml. of benzoyl chloride. After addition of water and extraction with ether, 0.7 g. (45%) of pale cream crystals, m.p. 102–103°, was obtained; λ^{KBr} 5.94 and 6.08 μ.

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 77.03; H, 5.69. Found: C, 76.76; H, 5.85.

5-Methyl-4-phenylpyrazole (5).—To a solution of 5 g. of the enol ether in 20 ml. of ethanol was added 20 ml. of 2 *N* H_2SO_4 and 1.5 g. of hydrazine. After heating for 30 min. the solution was cooled and the pH was adjusted to 8 with NaOH. The precipitate which separated on chilling and addition of water was recrystallized to give 4.0 g. (96%) of **5**, m.p. 143–144° (lit. m.p. 142–144°).

5-Methyl-4-phenylpyrazole-1-acetic Acid (2) from 7.—A solution of 1.8 g. (0.015 mole) of ethyl hydrazinoacetate hydrochloride (Aldrich Chemical Co.) in 30 ml. of water was neutralized (pH 7) with NaOH and then added to a solution of 2 g. (0.0105 mole) of the enol ether **7** in 16 ml. of ethanol. After heating on the steam bath for 1 hr. the solution was made strongly basic with NaOH and refluxed for 30 min. to saponify the ester. The ethanol was then evaporated and the solution was acidified with acetic acid. The resulting precipitate was recrystallized twice from methanol–water to give 650 mg. (30%) of the acid **2**, m.p. 210°, mixture melting point with material from oxidation of 1 210–212°; infrared spectra were identical. The methyl ester, prepared by treatment with diazomethane, had m.p. 89°, undepressed on mixture with sample from **1**.

3-Methyl-4-phenylpyrazole-1-acetic Acid (9).—To a solution of 0.80 g. (0.035 g.-atom) of sodium in 40 ml. of absolute ethanol was added 4.0 g. (0.027 mole) of pyrazole **5** and then 8 g. (0.052 mole) of methyl bromoacetate. After standing for 24 hr. at 30° (NaBr precipitated) the solution was diluted with 200 ml. of water, made strongly alkaline, and refluxed for 30 min. On cooling, 0.95 g. of unreacted **5** precipitated. After filtration the solution was acidified with acetic acid until crystallization just began. The first crop of crystals, 1.50 g., had m.p. 193–194°. Three recrystallizations from methanol–water gave 900 mg. of the acid **9**, m.p. 210–212°, mixture melting point with **2** 182°, λ_{max} 245 mμ (ε 13,800).

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.60; H, 5.74; N, 12.83.

After standing for 1 week, the aqueous mother liquor from the 1.50-g. first crop above deposited a further crop of crystals which was recrystallized from methanol and methanol–water to give 400 mg. of 5-methyl-4-phenylpyrazole-1-acetic acid (**2**), m.p. 209–211°, mixture melting point with acid from the first crop 183°.

Methyl 3-Methyl-4-phenylpyrazole-1-acetate (10).—The methyl ester of **9** was prepared by treatment of the acid with diazomethane; recrystallization from methanol–water gave colorless prisms, m.p. 73°, mixture melting point with methyl ester **3** 58–60°.

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 68.03; H, 6.35; N, 12.04.

Acknowledgment.—The authors wish to thank Dr. J. M. Vandenbelt and Mrs. Carola H. Spurlock, Parke, Davis and Company, for the ultraviolet and titration data.

(15) This experiment was performed by L. D. Kornreich [M.S. Thesis, University of Delaware, 1963].

(16) H. Rupe, A. Metzger, and H. Vogler [*Helv. Chim. Acta*, **8**, 848 (1925)] report m.p. 96°.

Heterocyclic Studies. XVI. The Assignment of Isomeric and Tautomeric Structures of Pyrazoles by Nuclear Magnetic Resonance*[1a,b]

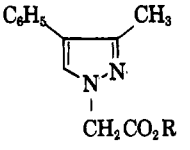
CLARISSE L. HABRAKEN[1c] AND JAMES A. MOORE[1d]

Organic Chemistry Laboratory, University of Leiden, Netherlands, and the Department of Chemistry, University of Delaware, Newark, Delaware

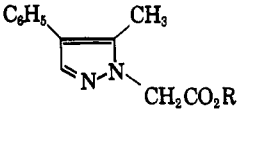
Received October 22, 1964

Authentic samples of 1,3-dimethylpyrazole (**8a**) and 1,3-dimethyl-4-phenylpyrazole (**8b**) were prepared by hydrogenolysis of the respective 5-chloropyrazoles, which were obtained from the pyrazolones. The properties of **8a** agreed with those of the isomer originally assigned this structure rather than a more recent reverse assignment. The n.m.r. spectra of three pairs of 1-alkyl-3(5)-methylpyrazoles showed in each case a lower field peak for the C-3 ring proton and a higher field peak for the 5-methyl protons in the 5-methyl isomer than the corresponding C-5 ring proton and 3-methyl peaks in the 3-methyl isomer. By comparison of the different spacings of the peaks of the 1-alkyl isomers with those of 3(5)-methylpyrazole and 3(5)-methyl-4-phenylpyrazole the 5-methyl structures **11** and **12** were assigned as the predominant tautomeric forms of these two pyrazoles.

The assignment of structures to N-alkyl derivatives of unsymmetrical pyrazoles is a problem for which no general solution is available. Syntheses by either ring closure or alkylation methods are usually ambiguous with respect to the location of the N-substituent and the 3- or 5-position, and the properties of isomeric pairs of N-alkylpyrazoles do not clearly reveal the respective structures. This situation was encountered in the 3- and 5-methyl-4-phenylpyrazole-1-acetic acids **1** and **2** discussed in the preceding paper[2]; structural assignment was possible in this case by reference to the formation of the 5-methyl isomer **2a** in an oxidation reaction.



1a, R = H
b, R = CH_3



2a, R = H
b, R = CH_3

Another case of this uncertainty in pyrazole isomerism is found in the simplest members of the series,

* To Professor Louis F. Fieser.

(1) (a) Supported in part by Grant DA-CML-18-108-61-G-24 from the Army Chemical Corps. (b) Part of this work was described in a preliminary communication: J. A. Moore and C. L. Habraken, *J. Am. Chem. Soc.*, **86**, 1456 (1964). (c) Visiting Land Grant Assistant Professor at the University of Delaware, 1961–1962, on leave from the University of Leiden. (d) To whom inquiries should be addressed.

(2) J. A. Moore and C. L. Habraken, *J. Org. Chem.*, **30**, 1889 (1965).