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]

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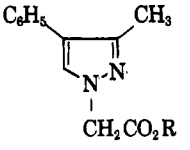
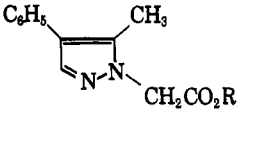
Received October 22, 1964

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

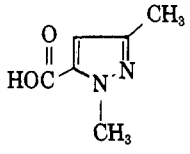
Another case of this uncertainty in pyrazole isomerism is found in the simplest members of the series,

* 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).

the 1,3- and 1,5-dimethylpyrazoles. In the earliest pyrazole literature the status of the two isomers was quite nebulous, but the situation was clarified by von Auwers and Hollmann,[3] who prepared the two isomers **3** and **4** of 1,3(5)-dimethylpyrazole-5(3)-carboxylic acid and the respective 4-bromo derivatives. Only one of



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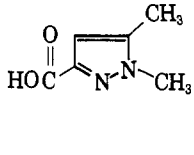

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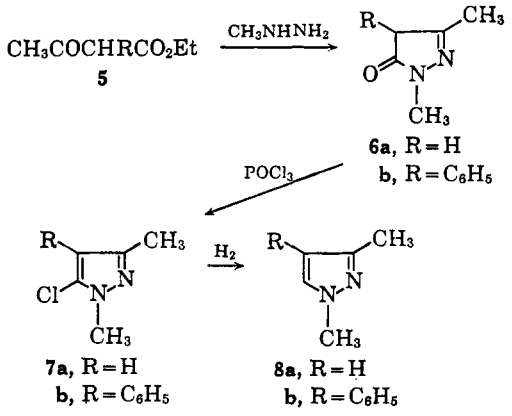
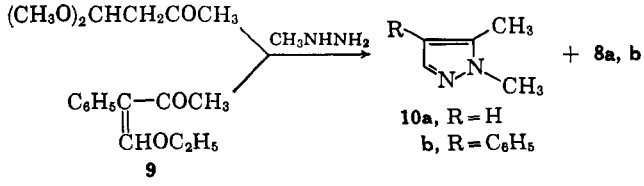
the bromo acids could be esterified; the parent acid of this isomer was therefore assigned structure **4** and the pyrazole (picrate m.p. 172°) obtained by decarboxylation of this acid was assigned the 1,5-dimethyl structure. The dimethylpyrazole derived from the other acid **3**, assigned the 1,3-dimethyl structure, gave a picrate with m.p. 136–138°. These conclusions were reached simultaneously by Rojahn[4] by another line of evidence and formed the basis for a number of subsequent structural assignments of 1-alkylpyrazoles. More recently, however, it has been suggested that the assignment of the 1,3- and 1,5-dimethylpyrazoles should be reversed.[5] This view was based on the assumption that the condensation of methyl hydrazine with β-ketobutyraldehyde acetal proceeds through an intermediate methylhydrazone.

To resolve the question of the 1,3(5)-dimethylpyrazole structures and confirm the assignment of the pyrazole-1-acetic acid isomers **1** and **2**,[2] authentic samples of 1,3-dimethylpyrazole (**8a**) and 1,3-dimethyl-4-phenylpyrazole (**8b**) were prepared by reduction of the respective 5-chloropyrazoles. The chloropyrazoles **7a** and **7b** were obtained from the pyrazolones with phosphorus oxychloride in the usual way.[6] The key point in the synthesis of **8a** and **8b** by this route, from the standpoint of the structural problem, lies in the pyrazolones. The reaction of methylhydrazine with a β-keto ester is potentially subject to the same ambiguity that renders the reaction with β-ketoaldehydes an unreliable basis for conclusions of pyrazole structure. It has been stated, however, that "almost any monosubstituted β-keto ester will react with almost any monosubstituted hydrazine to form a 2-pyrazoline-5-one,"[7] and this generalization applies to the limited number of condensations with methylhydrazine that have been examined.

There is very adequate evidence that the pyrazolone, m.p. 117–118°, obtained from acetoacetic ester and methylhydrazine[8] is the 1,3-dimethyl-5-pyrazolone **6a**. The preparation has been confirmed several times,[6,9,10] and a detailed study of the tautomeric structure has been made.[11] The alternative 1,5-dimethyl-3-pyrazolinine has been obtained by other routes[10,12] and is also well characterized.[13] The 4-phenylpyrazolone which was prepared for the first time in this work by the condensation of methylhydrazine and ethyl α-phenylacetoacetate is assigned the 1,3-dimethyl-5-one structure **6b** by analogy to **6a**.



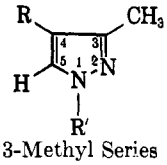
The reductive removal of α-halogen is a commonplace operation in many heterocyclic syntheses, but it has had relatively little use in the pyrazole series, and has apparently not been applied previously to 1-alkyl-5-chloropyrazoles. The direct reduction of 3-methyl-1,4-diphenyl-5-pyrazolone to the pyrazole with phosphorus and phosphorus tribromide has been carried out by Stoermer,[14] and this reduction was repeated in the present work, but the method failed with the 1-alkylpyrazolone **6b**. Attempted reductions of the chloropyrazoles **7a** and **7b** with lithium aluminum hydride, phosphorus–hydriodic acid, and zinc met with little success, but catalytic hydrogenolysis with Raney nickel was found to give quite satisfactory yields of the 5-unsubstituted pyrazoles. The 1,3-dimethylpyrazole formed from **7a** had b.p. 136–139°, picrate m.p. 133°, corresponding to the earlier assignment of von Auwers and Hollmann.[3] The isomer, b.p. 158° (picrate m.p. 172°), which is isolated from the condensation of sodio formylacetone[3] or β-ketobutyraldehyde dimethyl acetal[5] and methylhydrazine is thus 1,5-dimethylpyrazole **10a**. An isomer mixture is obtained in these condensations[3,5] and it is probable that most of the earlier preparations of **10a** were in fact mixtures.[15] A sample of the 1,5 isomer, b.p. 158°, was isolated in this work by fractional distillation on a spinning band column; the n.m.r. spectrum showed no impurity of the 1,3-dimethyl isomer, although the melting point of the picrate given in the previous literature could not be reproduced.



A mixture of pyrazoles was also obtained from the reaction of methylhydrazine and α-ethoxymethylene-α-phenylacetone (**9**). The mixture was not resolved

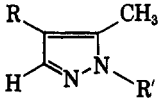
(3) K. von Auwers and H. Hollmann, *Ber.*, **59**, 601, 1282 (1926).
(4) C. A. Rojahn, *ibid.*, **59**, 607 (1926).
(5) D. M. Burness, *J. Org. Chem.*, **21**, 97 (1956).
(6) K. von Auwers and F. Niemyer, *J. prakt. Chem.*, [2] **110**, 153 (1925).
(7) R. H. Wiley and P. Wiley, "Pyrazolones, Pyrazolidines and Derivatives," Interscience Publishers, Inc., New York, N. Y., 1964, p. 14.
(8) L. Knorr, *Ann.*, **279**, 236 (1894).
(9) S. Veibel, K. Eggersen, and S. C. Linholt, *Acta Chem. Scand.*, **8**, 768 (1954).
(10) R. Kitamura, *J. Pharm. Soc. Japan*, **60**, 45 (1940); *Chem. Abstr.*, **34**, 3737 (1940).
(11) A. R. Katritzky and F. W. Maine, *Tetrahedron*, **20**, 299 (1964).
(12) W. Krohs, *Chem. Ber.*, **88**, 866 (1955).
(13) A. R. Katritzky and F. W. Maine, *Tetrahedron*, **20**, 315 (1964).
(14) Rr Stoermer and J. Martinsen, *Ann.*, **352**, 322 (1908).
(15) R. Huttell and M. E. Schon, *ibid.*, **625**, 55 (1959).

TABLE I
N.M.R. DATA FOR ISOMERIC 3(5)-METHYLPYRAZOLES



3-Methyl Series

Compd.	R	R′	Chemical shift (δ), p.p.m. 3-CH_3	4-R	5-H	Δ $\delta_{5\text{-H}} - \delta_{4\text{-R}}$	Δ $\delta_{5\text{-H}} - \delta_{3\text{-}CH_3}$
8a	H	CH_3	2.22	5.93[a]	7.13[a]	1.20	4.91
1b	C_6H_5	$CH_2CO_2CH_3$	2.40	7.37	7.49	0.12	5.09
8b	C_6H_5	CH_3	2.37	7.32	7.33 ± 0.03	0.1 ± 0.03	4.96 ± 0.03



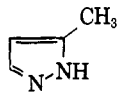
5-Methyl Series

Compd.	R	R′	Chemical shift (δ), p.p.m. 5-CH_3	4-R	3-H	Δ $\delta_{3\text{-H}} - \delta_{4\text{-R}}$	Δ $\delta_{3\text{-H}} - \delta_{5\text{-}CH_3}$
10a	H	CH_3	2.19	5.90[a]	7.27[a]	1.37	5.08
11	H	H	2.33	6.03[a]	7.45[a]	1.42	5.12
2b	C_6H_5	$CH_2CO_2CH_3$	2.30	7.33	7.62	0.29	5.32
10b	C_6H_5	CH_3	2.19	7.26	7.50	0.24	5.31
12	C_6H_5	H	2.46	7.34	7.70	0.36	5.24

[a] Doublet, $J \cong 2$ c.p.s.

in this case; the n.m.r. spectrum indicated a ratio of 1,5-dimethyl (**10b**) to 1,3-dimethyl (**8b**) isomers of about 1:2. Similar mixtures were also obtained by methylation of 5-methyl-4-phenylpyrazole and pyrolysis of 1,2,3-trimethyl-4-phenylpyrazolium iodide. These results are comparable to those observed in the preparation of the esters **1b** and **2b** discussed in the preceding paper.[2]

N.m.r. data for the pairs of pyrazole isomers **1** and **2**, **8a** and **10a**, and **8b** and **10b** and the unsubstituted pyrazoles **11** and **12** are given in Table I. Integrations were consistent with the peak assignments in all cases. The values for 1,5-dimethyl-4-phenylpyrazole (**10b**) were obtained from the spectrum of a mixture of **8b** and **10b**. The C-5 pyrazole proton peak was not completely separated from the phenyl resonance in the spectrum of **8b**; it was seen as a shoulder on the low field side, but there is an uncertainty of about 2–3 c.p.s. in the chemical shift. It has recently been noted that the resonance signals of the 2- and 3-protons in indoles are shifted to a higher field with increasing concentration in $CDCl_3$[16]; to examine this possibility in the pyrazoles the spectra of **1b**, **2b**, and the unsubstituted pyrazoles **11** and **12** were checked over a fourfold range of concentrations. With the exception of the –NH peaks of **11** and **12**, the chemical shifts for all other protons, including the α-protons in **11** and **12**, varied no more than ±1 c.p.s., which was the limit of reproducibility for spectra run at different times on different instruments.



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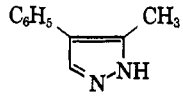

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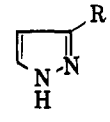
The chemical shift values for the three pairs of N-alkylpyrazoles in Table I show a uniform pattern, with a paramagnetic displacement of the pyrazole ring proton peak and a diamagnetic shift of the methyl peak in each case on going from the 3-methyl to the 5-methyl isomer. This correlation is consistent with the previous assignment of the structures of the N-acetic acids and esters **1** and **2**,[2] and should provide a reliable basis for the assignment of isomeric structure in other pairs of 1,3(5)-dialkylpyrazoles, which, as noted above, frequently are formed together.

This clear-cut distinction of isomeric pyrazoles suggested that n.m.r. data might permit assignment of the tautomeric structure of N-unsubstituted pyrazoles. The possibility of specifying the tautomeric structure, *viz.* **13** or **14**, of an unsymmetrical pyrazole has engendered some controversy. The failure of attempts to prepare and isolate the individual tautomers led early workers to the conclusion that the two forms are indistinguishable and that the 3- and 5-positions are equivalent. This view was amplified by Hunter[17,18] in the principle of "mesohydric tautomerism" which held that in pyrazoles and similar systems the mobile hydrogen atoms were completely delocalized in hydrogen-bridged aggregates such as **15** and that individual tautomers do not exist. Although the association of pyrazoles has been clearly demonstrated,[17,19,20] the complete equivalence of positions 1 and 2 and positions 3 and 5 expressed in **15** is not consistent with current views of the hydrogen bond, and the validity of con-



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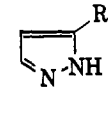

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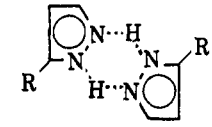

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(16) M. G. Reinecke, H. W. Johnson, Jr., and J. F. Sebastian, *Chem. Ind.* (London), 151 (1964).

(17) H. T. Hayes and L. Hunter, *J. Chem. Soc.*, 1 (1941).

(18) L. Hunter, *ibid.*, 806 (1945).

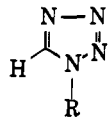
(19) W. Huckel, J. Datow, and E. Simmersbach, *Z. physik. Chem.*, **186A**, 129 (1940).

(20) D. M. W. Anderson, J. L. Duncan, and F. J. C. Rossotti, *J. Chem. Soc.*, 140 (1961).

sidering **13** and **14** as discrete substances (or the individual dimers) has been emphasized in the more recent literature.[21,22]

The predominance of one tautomeric form of unsymmetrical pyrazoles was first suggested by von Auwers[23] from comparison of the molecular refractions of several 3(5)-phenylpyrazoles with those of the 1-alkyl-3-phenyl and 1-alkyl-5-phenyl isomers. In several series the exaltation values for the N-substituted pyrazole corresponded closely to those of the 1-alkyl-3-phenyl compounds, and it was concluded that in these cases the compounds existed largely as the 3-phenyl tautomers. This method was applicable only to 3-arylpyrazoles and no further clear-cut evidence on pyrazole tautomerism from physical measurements has been presented.[24] Ultraviolet data, which have been of great value in resolving the structure of tautomeric heterocyclic compounds by comparisons with N-alkyl derivatives,[22] are of little utility for the diagnosis of tautomerism in the pyrazole series. The absorption maxima of N-alkyl 3- and 5-isomers differ by only 1–2 mμ,[2,25] which is a smaller amount than the difference between either N-alkyl isomer and the N-unsubstituted compound.

The application of n.m.r. data to the similar problem of tautomerism in the tetrazoles has been demonstrated by Moore and Whittaker.[26] In this series the difference in chemical shifts of the 5-proton in the 1-alkyl (**16**) and 2-alkyl (**17**) isomers is large enough (0.64–0.79 p.p.m.) to permit assignment of the tautomeric structure **16** (R = H) for the parent unsubstituted tetrazole by direct comparison of the 5-H chemical shift with those of the 1-alkyl isomers.



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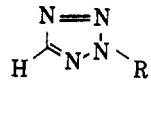

17

In the pairs of pyrazole isomers **1b** and **2b**, **8a** and **b**, and **10a** and **b** the difference in chemical shifts of the pyrazole 3- and 5-protons is only about one-fifth that in the tetrazoles, and would not be sufficient alone to permit assignment of the structures **11** and **12** for the unsubstituted compounds. This limitation is offset, however, by the additional signals available due to the 5(3)- and 4-substituents and the opposite direction of the displacement of the shifts in the two series. By comparing the spacings (Δ, Table I) of the 3(5)-H-proton peak of **12** from the phenyl and methyl peaks, 0.36 and 5.24 p.p.m., respectively, with those for the 3-methyl series (**1b**, 0.12 and 5.09; **8b**, 0.1 and 4.96 p.p.m.) and the 5-methyl series (**2b**, 0.29 and 5.32; **10b**, 0.24 and 5.31 p.p.m.), it is concluded that the tautomeric structure of **12** resembles that of the 5-methyl series more closely than that of the 3-methyl. A similar comparison for the 4-unsubstituted series leads to the same assignment of the 5-methyl structure **11** as the predominant component of the tautomeric equilibrium.

It must be emphasized that the assignment of **11** and **12** as the predominant tautomeric structures on the basis of these n.m.r. comparisons does not imply the absence of dimeric association or rapid interconversion of the two tautomeric forms. It has been found that the n.m.r. spectra of 2-aminopyrimidine and 2-pyrimidone[27] show apparent equivalence of the 4- and 6-protons due to rapid proton exchange. It has recently been pointed out[28] that the n.m.r. spectra of unsubstituted pyrazoles contain sharp peaks due to the rapid interconversion of the tautomers. This does indeed reflect the time averaging of the protons in the two tautomeric structures, but reference to the spectra of the two N-substituted isomers permits assignment of the predominant double-bond system in the equilibrium mixture.

Experimental[29]

1,3-Dimethyl-2-pyrazolin-5-one (6a), m.p. 118° (lit.[6] m.p. 117°), and **1,3-dimethyl-5-chloropyrazole (7a)**, b.p. 153–155° (lit.[6] m.p. 157°), were prepared as previously described.

1,3-Dimethylpyrazole (8a).—A solution of 16.5 g. (0.127 mole) of 1,3-dimethyl-5-chloropyrazole in 150 ml. of ethanol containing 5 g. of NaOH was stirred (Vibromix) under a hydrogen atmosphere with 6 ml. of Raney nickel.[30] After 24 hr., during which two additional 2-ml. portions of catalyst were added, a total of 2.8 l. (0.125 mole) of hydrogen was absorbed. After filtration from the catalyst the neutral solution was concentrated, the residue was dissolved in ether, and the sodium chloride was removed by filtration. The crude pyrazole was distilled and a 4.1-g. fraction with b.p. 98–136° was then redistilled to give 2.5 g. of colorless oil, b.p. 136–139°; the n.m.r. spectrum (Table I) showed no impurity peaks.

The **picrate** was prepared in aqueous solution. The melting point on a block or in an open tube was unsharp, but in an evacuated capillary the melting point was 133°.

Anal. Calcd. for $C_{11}H_{11}N_5O_7$: C, 40.62; H, 3.41; N, 21.53. Found: C, 40.69; H, 3.96; N, 21.11.

1,5-Dimethylpyrazole (10a).—The condensation of 100 g. of 1,1-dimethoxy-3-butanone methylhydrazine was carried out according to the procedure of Burness.[5] The product was distilled in a 20-cm. Vigreux column and the following fractions were collected: (1) 32 g., b.p. 96–139°; (2) 16.1 g., b.p. 139–141°; (3) 21 g., b.p. 141–147°; and (4) 8 g., b.p. 147–152°. The final fraction which still contained both isomers (n.m.r.) was distilled in a small spinning-band column and a fraction, b.p. 158°, was obtained; the n.m.r. spectrum contained no methyl peak corresponding to **8a**. The picrate of this material was prepared a number of times in different solvents and with varying amounts of picric acid, but the melting point was always unsharp, ranging from 145–165°. After several recrystallizations from water, m.p. 158–164° was obtained, but a melting point as high as 172°[5,6] was never observed. The sample used for analysis had m.p. 147–149°.

Anal. Calcd. for $C_{11}H_{11}N_7O_5$: C, 40.62; H, 3.41; N, 21.53. Found: C, 40.76; H, 3.53; N, 21.47.

1,3-Dimethyl-4-phenyl-2-pyrazolin-5-one (6b).—To 10 g. of ethyl α-phenylacetoacetate[31] which was chilled in an ice–salt bath was added 2.2 g. of methylhydrazine. After the initial vigorous

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

(22) A. R. Katritzky and J. M. Lagowski, *Advan. Heterocyclic Chem.* **1**, 316 (1963).

(23) K. von Auwers, *Ann.*, **508**, 51 (1933).

(24) Pyrazole tautomerism has recently been reviewed by A. R. Katritzky and J. M. Lagowski [*Advan. Heterocyclic Chem.*, **2**, 30 (1964)].

(25) R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson, and C. Carabateas, *J. Am. Chem. Soc.*, **83**, 1478 (1961).

(26) D. W. Moore and A. G. Whittaker, *ibid.*, **82**, 5007 (1960).

(27) S. Gronowitz and R. Hoffmann, *Arkiv Kemi*, **16**, 459 (1960).

(28) J. K. Williams, *J. Org. Chem.*, **29**, 1377 (1964); I. L. Finar and E. F. Mooney, *Spectrochim. Acta*, **20**, 1269 (1964).

(29) Melting points are corrected. Analyses were performed in the Microanalytical Department, University of Amsterdam, and by Mr. N. W. Louwrier, Laboratory of Organic Chemistry, University of Leiden.

(30) Prepared according to A. A. Pavlic and H. Adkins [*J. Am. Chem. Soc.*, **68**, 1471 (1946)] as modified by M. Brenner and H. R. Rickenbacker [*Helv. Chim. Acta*, **41**, 181 (1958)].

(31) R. H. Kimball, G. D. Jefferson, and A. B. Pike, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 284.

reaction, the solution was heated at 180–190° for 1 hr. The solid product was recrystallized from ethanol–water to give 7.5 g. of colorless crystals, m.p. 179–180°.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4; N, 14.9. Found: C, 70.1, 70.2; H, 6.6, 6.6; N, 15.0, 15.1.

5-Chloro-1,3-dimethyl-4-phenylpyrazole (7b).—A mixture of 6.5 g. of the pyrazolone **6b**, 5.4 g. of pyridine, and 9.5 g. of freshly distilled $POCl_3$ was heated for 40 hr. at 110–130° and was then poured onto ice. Twenty milliliters of 4 *N* NaOH was then added and the resulting oil was extracted with chloroform. After the chloroform extracts were washed with alkali and water and dryed over $MgSO_4$, the solvent was evaporated and the residue was distilled to give 3.0 g. (42%) of colorless oil, b.p. 100–104° (0.5 mm.) and 151–152° (15 mm.).

Anal. Calcd. for $C_{11}H_{11}ClN_2$: Cl 17.1. Found: C, 17.0, 17.1.

1,3-Dimethyl-4-phenylpyrazole (8b).—Hydrogenation of **7b** was carried in the same way described for **7a**. From 7.3 g. of **7b** was obtained 5.0 g. of crude pyrazole. Distillation gave a colorless oil, b.p. 150–152° (13 mm.). This material contained a trace of the chloropyrazole and was purified by conversion to the **picrate** which was recrystallized from ethanol, m.p. 148°.

Anal. Calcd. for $C_{17}H_{15}N_5O_7$: C, 50.87; H, 3.77; N, 17.45. Found: C, 50.42; H, 4.02; N, 16.80.

After decomposition of the picrate with warm NaOH solution, the base was extracted with ether; after standing over K_2CO_3 to remove traces of picric acid, the solution was evaporated and the pyrazole was distilled, b.p. 155–156° (15 mm.). The oil crystallized on standing, m.p. ~40°.

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 77.06; H, 7.29; N, 16.11.

Reaction of Methylhydrazine with 1-Ethoxymethylene-1-phenylacetone.—To a solution of 20 g. of the enol ether in 100 ml. of ethanol were added 10 g. of H_2SO_4 in 20 ml. of water and then a solution of 8.6 g. of methylhydrazine in 60 ml. of water. After refluxing for 1 hr. the ethanol was distilled and the residue was diluted with water. The solution was made alkaline and extracted with ether. The solution was dried and concentrated and the residue was distilled at 18 mm. to give 5 g. of yellow oil, b.p. 155–157°, and 8 g., b.p. 157–159°. Redistillation of the second fraction gave 7 g., b.p. 161–164° (19 mm.). This material contained about 65% of the 1,3-dimethyl isomer (**8b**) and 35% of the 1,5-dimethyl compound (**10b**) estimated from n.m.r. peak areas.

Methylation of 5-Methyl-4-phenylpyrazole.—To a solution of 5.5 g. of 5-methyl-4-phenyl-pyrazole[2] (**12**) in 50 ml. of ethanol was added a solution of 1 g. of sodium in 45 ml. of ethanol and 10 g. of methyl iodide. After standing for a day the solution was evaporated, water was added, and the pyrazole was extracted with ether. Distillation at 0.5 mm. gave 0.95 g. of material with b.p. 97–100° and 3.6 g. of colorless oil with b.p. 120–140°; the n.m.r. spectrum of the second fraction indicated a mixture of about 65% of **8b** and 35% of **10b**.

1,2,3-Trimethyl-4-phenylpyrazolium Iodide.—A solution of 3.4 g. of mixed 1,3- and 1,5-dimethyl-4-phenylpyrazole isomers from the enol ether condensation and 5.7 g. of methyl iodide in 1.5 ml. of methanol was heated in a Carius tube at 100° for 48 hr. The tube contents were dissolved in hot water and the solution was filtered to remove a small amount of amorphous solid. On cooling, an oil separated which crystallized on standing. Recrystallization from ethanol–water gave 9 g. of pale yellow needles, m.p. 149°.

Anal. Calcd. for $C_{12}H_{15}IN_2$: C, 45.87; H, 4.81; I, 40.40; N, 8.92. Found: 45.48; H, 4.90; I, 39.66; N, 8.83.

Thermal decomposition of the salt and distillation of the pyrazoles gave an isomer mixture of essentially the same composition as obtained in the condensation and methylation reactions.

The Protonation of Benzoylbenzoic Acids[1,2]

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The behavior of *o*-benzoylbenzoic acid (I) as a simple base in strong sulfuric acid has been examined spectrophotometrically. I is 50% converted to the conjugate acid in about 80% sulfuric acid. The nature of the spectral changes resulting on protonation and the sensitivity of the basicity to substitution both suggest that protonation occurs at the ketonic oxygen. The ionization ratios do not show exact 1:1 correspondence with the acidity function; slopes of log (BH^+/B) *vs.* H_0 are about 0.8.

There has been much recent interest in the protonation of weak bases in fairly concentrated mineral acids. Though the original development of the acidity scale by Hammett suggested that many different classes of compounds would respond similarly to the acid concentration of the medium, more recent investigations have shown that this is not invariably the case. A recent review by Arnett[4] summarizes much of the relevant information. Taft[5a] showed that the protonation equilibria of tertiary amines and primary amines are not parallel in 60–80% sulfuric acid. Recently, Arnett and Mach[5b] established an acidity scale using only tertiary aromatic amines. This scale (designated H_0''' by Arnett and Mach) differs from the original H_0 scale of Hammett and clearly points out that differences in solvation and of activity-coefficient behavior severely limit the general applicability of the H_0 scale. In re-evaluating the H_0 scale, Jorgenson and Hartter[6] used a set of primary amines (anilines). The fact that the acidity scale defined in this way showed some deviations above 60% sulfuric acid from the original scale of Hammett[7] implied that the protonation equilibria of primary amines and of oxygen bases are not invariably parallel.

As the original set of indicators used by Hammett included some ketones and tertiary amines, we also examined the acid–base behavior of benzalacetophenone[8] in more detail than had been done previously. It was found that extreme caution must be used in evaluating the data for chalcone, since the spectral changes with increasing sulfuric acid concentration included not only the formation of the conjugate acid, but also a very pronounced bathochromic shift and a further increase in molar absorbancy. When appropriate corrections were made, the behavior of chalcone as an acid–base indicator was satisfactory.

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(2) For previous paper, see D. S. Noyce, F. B. Miles, and D. R. Hartter, *J. Am. Chem. Soc.*, **86**, 3583 (1964).

(3) National Science Foundation Cooperative Fellow, 1961–1962; National Institutes of Health Predoctoral Fellow, 1962–1963.

(4) E. M. Arnett, *Progr. Phys. Org. Chem.*, **1**, 237 (1963).

(5) (a) R. W. Taft, Jr., *J. Am. Chem. Soc.*, **82**, 2965 (1960); (b) E. M. Arnett and G. W. Mach, *ibid.*, **86**, 2671 (1964).

(6) M. J. Jorgenson and D. R. Hartter, *ibid.*, **85**, 878 (1963).

(7) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).

(8) D. S. Noyce and M. J. Jorgenson, *J. Am. Chem. Soc.*, **84**, 4312 (1962).