minimal amount of hot water and cooling gave 0.5 g. or *p*-aminophenylacetamide; m.p., 160–162° (lit.[9] m.p. 161–162°).

1-Ethyl-1-methyl-1-*n*-butyl-2-(3,5-dinitrobenzoyl)hydrazonium *p*-Toluenesulfonate.—A solution of the hydrazine (5.92 g.) and methyl *p*-to'uenesulfonate (3.54 g.) in acetonitrile (100 ml.) was refluxed for 48 hr. Removal of the solvent under reduced pressure gave a solid which was recrystallized from a mixture of ethanol and ether; yield, 9.4 g.; m.p., 174–175°.

Anal. Calcd. for $C_{21}H_{28}N_4O_8S$: C, 50.79; H, 5.68; N, 11.28. Found: C, 51.26; H, 5.85; N, 11.47.

(9) I. Heilbron and H. H. Bunburg, "Dictionary of Organic Compounds," Vol. I, Eyre and Spottisworde, London, 1953, p. 123.

Acknowledgment.—Support of this research by the National Science Foundation is gratefully acknowledged.

Imidazoimidazoles. I. The Reaction of Ureas With Glyoxal. Tetrahydroimidazo[4,5-*d*]imidazole-2,5-diones[1,2]

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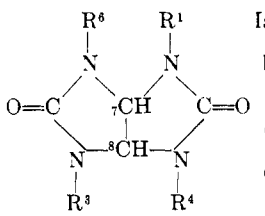
Received January 14, 1963

The acid-catalyzed condensations of a variety of substituted ureas with glyoxal have been shown to yield tetrahydroimidazo[4,5-*d*]imidazole-2,5-diones. With aryl substituted ureas, 1-arylhydantoins were obtained as side products.

Earlier investigations of the urea–glyoxal condensation to give tetrahydroimidazo[4,5-*d*]imidazole-2,5-diones[4–8] (I) left several questions unanswered. Identities of isomeric products Ib,c obtained from methylurea and glyoxal[6,7] have not been established. No condensations with arylureas have been reported. That the reactions of urea,[9] methylurea, and 1,3-dimethylurea all lead to the same carbon–nitrogen skeleton has not been established and the existence of the fused bicyclic system is open to some objection on the basis of strain.[10] Finally, if the structure is correct, it could conceivably have either the *cis* or the *trans* configuration.



Ia, $R^1 = R^3 = R^4 = R^6 = H$
b, $R^1 = R^4 = CH_3$, $R^3 = R^6 = H$
c, $R^1 = R^6 = CH_3$, $R^3 = R^4 = H$
d, $R^1 = R^3 = R^4 = R^6 = CH_3$
e, $R^1 = R^4 = C_6H_5$, $R^3 = R^6 = H$
f, $R^1 = R^4 = CH_3$, $R^3 = R^6 = C_6H_5$
g, $R^1 = R^6 = CH_3$, $R^3 = R^4 = C_6H_5$

Repetition of the condensations of urea[4,5] and 1,3-dimethylurea[8] confirmed the earlier reports. The urea product Ia was converted by exhaustive methylation to the same tetramethyl derivative Id as obtained by condensation of 1,3-dimethylurea with glyoxal, thus indicating that these substances have a common carbon–nitrogen skeleton. Neither the urea nor the 1,3-dimethylurea–glyoxal condensation product show significant ultraviolet absorption above 210 mμ.[11,12] The n.m.r. spectrum of the urea condensation product shows only one sharp peak and that of the tetramethyl

(1) This work was supported, in part, by a grant from the National Institutes of Health (training grant 2 G-728 Cl) and an American Cancer Society Institutional grant IN 33D, no. 3. The nuclear magnetic resonance spectrometer used in this work was provided by a grant (NSF G 21268) from the National Science Foundation.

(2) The nomenclature requires comment. *Chemical Abstracts* uses either glycoluril, the trivial name, or tetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-dione. The systematic name seems preferable, but raises two questions. The (1*H*,3*H*) part of the name appears unnecessary. The propriety of considering the dione rather than imidazo[4,5-*d*]imidazole as the parent system seems questionable. The *Chemical Abstracts* systematic name with omission of the (1*H*,3*H*) portion is used throughout this paper.

(3) To whom inquiries should be directed.

(4) (a) H. Schiff, *Ann.*, **189**, 157 (1877); (b) U. Schiff, *Gazz. chim. ital.*, **7**, 351 (1877); (c) L. Siemonsen, *Ann.*, **333**, 101 (1904); (d) R. Behrend, E. Meyer and F. Rusche, *ibid.*, **339**, 4 (1905); (e) H. Biltz, *ibid.*, **368**, 243 (1909); (f) C. Böttinger, *Ber.*, **10**, 1923 (1877).

(5) (a) F. B. Slezak, H. Bluestone, T. A. Magee, and J. H. Wotiz, *J. Org. Chem.*, **27**, 2181 (1962); (b) F. B. Slezak, A. Hirsch, and I. Rosen, *ibid.*, **25** 660 (1960).

(6) A. P. N. Franchimont and E. A. Klobbie, *Rec. trav. chim.*, **7**, 12 (1887).

(7) E. Weitzner, *Ann.*, **362**, 125 (1908).

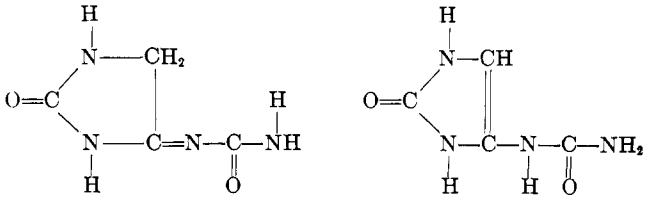
(8) A. P. N. Franchimont and E. A. Klobbie, *Rec. trav. chim.*, **7**, 236 (1887).

(9) Unsubstituted tetrahydroimidazo[4,5-*d*]imidazole-2,5-dione had been obtained earlier by reduction of allantoin with sodium amalgam. H. Rheineck, *Ann.*, **134**, 219 (1865).

(10) J. W. Barrett and R. P. Linstead, *J. Chem. Soc.*, 436, 612 (1935).

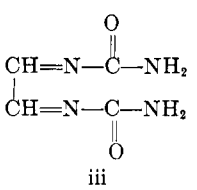
(11) We are indebted to Mr. Harold D. Aylor of Beckman Instruments, Inc., for extending our measurements to the far-ultraviolet. The 1,3,4,6-tetramethyl derivative shows a shoulder at 187 mμ, but the 1,4-dimethyl derivative and the unsubstituted condensation product show only end absorption above 185 mμ. These spectra were determined on a Beckman far-ultraviolet DK-2A spectrophotometer.

(12) The only alternate isomeric structures which were considered are the two monocyclic structures, i and ii, and the open chain system, iii.



i

ii



iii

Of these, only ii could have been converted to a tetramethyl derivative identical with the 1,3-dimethylurea-glyoxal condensation product. However, it should have produced a pentamethyl derivative on exhaustive methylation.

These structures contain chromophoric systems which should absorb above 210 mμ. The amidine system present in i exhibits an ultraviolet maximum at about 230 mμ.[13] 2,3-Dihydro-2-oxo-4-imidazolecarboxylic acid, a model compound for structure ii, has an absorption maximum at 250 mμ.[14] Glyoxime, a model compound for structure iii, absorbs at 329 mμ.[15] However, the relative complexity of these structures and the presence of cross conjugated systems renders conclusions based on the simple model systems subject to some doubt.

(13) (a) J. C. Gage, *J. Chem. Soc.*, 221 (1949); (b) S. F. Mason, *ibid.*, 2071 (1954).

(14) K. Ditmar, M. F. Ferger, and V. du Vigneaud, *J. Biol. Chem.*, **164**, 19 (1946).

(15) H. Schmid and W. Bencze, *Helv. Chim. Acta*, **36**, 205 (1953).

compound shows two sharp peaks, the ratio of whose intensities (6:1) is consistent with the presence of twelve identical methyl hydrogens and two identical hydrogens on tertiary carbons.

The greater strain involved in *trans* compared to *cis* fusion[10] of two five-membered rings leads to the prediction that these compounds should have the *cis* configuration. In order to confirm this, the dipole moment of the tetramethyl derivative was determined in benzene according to the method of Halverstadt and Kumler.[16] The *trans* structure should have no dipole moment since the various bond moments cancel, whereas the *cis* structure should have a high dipole moment. The observed dipole moment was 4.05 D., thereby proving that these compounds have the expected *cis* geometry.

The condensation of glyoxal and 1-methylurea has been reported to afford both 1,4- and 1,6-dimethyl derivatives,[6,7] melting at 285–287° and 230–232°, but no attempt was made to assign the two possible structures Ib,c to the products obtained. The integrated n.m.r. spectrum of the reaction product mixture indicated that the ratio of 1,4- to 1,6-dimethyl isomers was 7:4. Pure products were obtained only after extensive fractional crystallization. The melting points of the purified products were 298–300° and 268–270°, thus indicating that the early workers did not have pure samples.

The major product was the more symmetrical 1,4-dimethyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (Ib), but, contrary to expectations, it proved to have the lower melting point, 268–270°. Its n.m.r. spectrum showed two sharp peaks with a ratio of 1:3, consistent with six identical methyl hydrogens and two identical tertiary hydrogens. The minor, higher melting isomer was 1,6-dimethyltetrahydroimidazo-[4,5-*d*]imidazole-2,5-dione (Ic). Its n.m.r. spectrum showed a peak for methyl hydrogens and a four-line resonance pattern ascribed to spin–spin splitting of the two adjacent, nonidentical, tertiary hydrogens at positions 7 and 8.

The reaction of 1-phenylurea with glyoxal afforded only one bicyclic product, shown by its n.m.r. spectrum to be 1,4-diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (Ie) consistent with the two sharp peaks observed. No evidence for any of the 1,6-diphenyl isomer was obtained.

A side product in the 1-phenylurea–glyoxal condensation was shown to be 1-phenylhydantoin by its identity with an authentic sample[17] synthesized from N-phenylglycine and nitrourea according to a method[18] used previously to prepare methylurea. No 3-phenylhydantoin was obtained.

The reaction between 1-methyl-3-phenylurea and glyoxal afforded a mixture of 1,4-dimethyl-3,6-diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (If), 1,6-dimethyl-3,4-diphenyltetrahydroimidazo[4,5-*d*]-imidazole-2,5-dione (Ig), and 1-phenyl-3-methylhydantoin. The structure of the hydantoin was proved by its identity with an authentic sample[19] prepared by methylation (methyl iodide) of 1-phenylhydantoin. None of the isomeric 1-methyl-3-phenylhydantoin was obtained.

The higher melting product (266–269°) in this instance was shown to be the more symmetrical product. If by its n.m.r. spectrum which contained three sharp peaks whose relative intensities (5:3:1) are consistent with a structure having two identical phenyl groups, six identical methyl hydrogens, and two identical tertiary hydrogens. Ie was converted to If by alkylation with methyl sulfate.

The lower melting product (225–226°) was Ig as indicated by its n.m.r. spectrum which, in addition to peaks assigned to methyl and phenyl hydrogens, contained a four-line resonance pattern ascribed to spin–spin splitting between the two nonidentical, adjacent, tertiary hydrogens at 7 and 8.

Analysis of the integrated n.m.r. spectrum of the crude product showed that the ratio of bicyclic products to hydantoin was about 2:1, and that there were equal amounts of the two bicyclic compounds. This is particularly surprising in view of the fact that none of the 1,6-diphenyl product was observed in the 1-phenylurea condensation. A small doublet near the main phenyl peak in the n.m.r. spectrum of Ig might be attributed to nonequivalence of the two closely placed phenyl groups caused by steric hindrance.

Attempts to obtain a bicyclic product from 1,3-diphenylurea all failed. The only product isolated in high yield was 1,3-diphenylhydantoin, identical with an authentic sample prepared from N-phenylglycine and phenyl isocyanate.[20] In those cases in which the hydantoin was observed as a minor side product, its yield can be increased slightly by raising the acidity of the reaction mixture. Preparations of 1-aryl-, 1,3-diaryl-, and 1-aryl-3-alkylhydantoins from glyoxal and the appropriately substituted urea thus constitute a convenient one-step synthesis from inexpensive reagents.

When these tetrahydroimidazo[4,5-*d*]imidazole-2,5-diones were refluxed with acid, there was no significant conversion to hydantoin. Also, when the hydantoins are refluxed with an excess of the corresponding urea, no bicyclic products are obtained. This indicates that neither product is intermediate in the formation of the other.

Experimental[21]

Tetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (Ia).—This material was prepared from 30% glyoxal and urea according to the method of Slezak[5] in 78% yield; m.p. above 300° dec. (lit.[5] m.p. above 300° dec.); ν_{max}^{KBr} 1680, 3200 cm.$^{-1}$; n.m.r., δ 5.45 (CH). It is insoluble in most solvents, including dimethylformamide, N-methyl-2-pyrrolidone, and dimethyl sulfoxide. It is sparingly soluble in hot water from which it can be crystallized.

1,3,4,6-Tetramethyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (Id). A. From Tetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (Ia).—To 71 g. (0.5 mole) of Ia in 800 ml. of 13% sodium hydroxide was added, dropwise, 100 ml. (1.05 moles) of methyl sulfate at 90–95°. The reaction mixture, after standing at 90–95° for 15 min., was made alkaline with 80 g. of sodium hydroxide followed by dropwise addition of 100 ml. of methyl sulfate at 90–95°. This addition of sodium hydroxide and methyl sulfate was repeated once. The solvent was removed and the residue extracted in a Soxhlet apparatus with benzene.

(16) I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, **64**, 2988 (1942).

(17) A. Lumiere, L. Lumiere, and H. Barbier, *Bull. soc. chim. France*, [3] **35**, 124 (1906).

(18) T. L. Davis and K. C. Blanchard, *J. Am. Chem. Soc.*, **51**, 1790 (1929).

(19) G. Frerichs and G. Breustedt, *J. prakt. Chem.*, [2] **66**, 235 (1902).

(20) H. L. Wheeler and C. Hoffman, *Am. Chem. J.*, **45**, 368 (1911).

(21) Melting points are uncorrected. Analyses are by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley, Calif.

The benzene was evaporated and the solid residue crystallized twice from dioxane to give 20 g. (20%); m.p. 225–227° (lit.[8] m.p. 217°); ν_{max}^{KBr} 1715 cm.$^{-1}$; n.m.r., δ 4.98 (CH), 2.73 (CH_3). The molecular weight by the Rast method was 230 (calcd. 198). When determined in water by the method of Goyan and Johnson,[22] it was found to be 260 and 232 at 0.50 and 0.25 molar concentrations, respectively.

B. From Glyoxal and 1,3-Dimethylurea.—To 0.725 g. (0.01 mole) of 80% crystalline glyoxal[23] in 100 ml. of 70% aqueous methanol and 0.5 ml. of concentrated hydrochloric acid was added 1.8 g. (0.02 mole) of 1,3-dimethylurea in 100 ml. of methanol. The solution was heated for 30 min. on a steam bath, then allowed to stand 4 hr. at room temperature. The solvent was removed and the residue crystallized from dioxane to give 1.2 g. (61%), m.p. 225–227°, identical with the product obtained by method A.

Dipole Moment of 1,3,4,6-Tetramethyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (Id).—The dielectric constant was measured with the Dipolmeter DM01 and the dipole moment was calculated by the Halverstadt–Kumler equation.[16]

$$p_{2_0} = \frac{3\alpha\nu_1}{(\epsilon_1 + 2)^2} + (\nu_1 + \beta)\frac{(\epsilon_1 - 1)}{(\epsilon_1 + 2)}$$

$$P_{2_0} = p_{2_0}M \qquad M = 198.2$$

$$\mu = 0.01281\sqrt{(P_{2_0} - P_E)T}$$

The data obtained are shown in Table I following.

TABLE I[a]

ω_2	ϵ_{12}	ν_{12}
0.000000	2.276892	1.143985
4.686405	2.319520	1.142456
4.915584	2.319606	1.142456
6.434033	2.337068	1.141693
10.639269	2.375760	1.140170
12.622612	2.389113	1.139714

ϵ_1 = 2.27674 α = 9.17121 ν_1 = 1.14403 β = −3.45403
P_{2_0} = 1.95933 P_E = 52.22 μ = 4.055 ± 0.015 D.

[a] Calculations were made with an IBM 1620 computer.

1,4- and 1,6-Dimethyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (Ib and Ic).—To 14.8 g. (0.2 mole) of 1-methylurea in 200 ml. of water was added 7.2 g. (0.1 mole) of 80% crystalline glyoxal[23] and 1.5 ml. of concentrated hydrochloric acid, and the reaction mixture was heated on a steam bath for 8 hr. The solvent was removed and the residue crystallized from methanol to afford 10.5 g. (62%), m.p. 215–260°, of a mixture of Ib and Ic. The integrated n.m.r. spectrum indicated that this mixture was 64% Ib and 36% Ic.

Separation of this mixture proved to be extremely difficult. Recrystallization from water, followed by several crystallizations from methanol gave Ic, m.p. 298–300°; ν_{max}^{KBr} 1685, 3250 cm.$^{-1}$; n.m.r., δ 2.75 (CH_3), 5.41 (C_8H), 5.09 (C_7H); $J_{7,8}$ = 8.5 c.p.s.

Anal. Calcd. for $C_6H_{10}N_4O_2$: C, 42.35: H, 5.92; N, 32.93. Found: C, 41.99; H, 5.93; N, 32.74.

The other isomer Ib was purified by concentrating the aqueous mother liquor and recrystallizing the residue first from dioxane–absolute ethanol and then from methanol to give crystals, m.p. 268–270°; ν_{max}^{KBr} 1705, 3200 cm.$^{-1}$; n.m.r., δ 2.58 (CH_3), 5.25 (CH).

Anal. Calcd. for $C_6H_{10}N_4O_2$: C, 42.35; H, 5.92; N, 32.93. Found: C, 42.18; H, 5.75; N, 32.66.

1,4-Diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (Ie).—A solution containing 13.6 g. (0.1 mole) of 1-phenylurea, 3.6 g. (0.05 mole) of 80% crystalline glyoxal[23] and 1.5 ml. of concentrated hydrochloric acid in ethanol was heated under reflux. Crystals began to separate after 45 min. and the solid was collected after 2 hr. The filtrate was boiled for an additional 4 hr. and the solid again collected. Further heating did not furnish more product. After crystallization from cyclohexanone, there was obtained 3.25 g. (22%), m.p. 375–380°; ν_{max}^{KBr} 1710 cm.$^{-1}$; n.m.r., δ 5.72 (CH), 7.03 (C_6H_5).

Anal. Calcd. for $C_{16}H_{14}N_4O_2$: C, 65.29; H, 4.80; N, 19.04. Found: C, 65.19; H, 4.65; N, 19.48.

The ethanol filtrate was evaporated and the residue crystallized from methanol to give 3.0 g. (17%) of 1-phenylhydantoin, m.p. 190–192°. This was identical with an authentic sample[17] prepared in 18% yield by refluxing equimolar amounts of nitrourea and N-phenylglycine in water for 2.5 hr.,[18] m.p. 193–195° (lit.[17] m.p. 191–194°); ν_{max}^{KBr} 1725, 3210 cm.$^{-1}$; n.m.r., δ 7.05 (C_6H_5), 4.13 (CH_2).

When this condensation was carried out using 50 ml. of concentrated hydrochloric acid for 8 hr., the yield of bicyclic product dropped to 12.5% and the hydantoin was 24%.

1,4-Dimethyl-3,6-diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (If) and 1,6-Dimethyl-3,4-diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (Ig).—A solution of 15 g. (0.1 mole) of 1-phenyl-3-methylurea, 3.6 g. (0.05 mole) of 80% crystalline glyoxal[23] and 1.5 ml. of concentrated hydrochloric acid in ethanol was heated under reflux for 6 hr. The solvent was evaporated to afford 10 g. of crystalline product which was a mixture of If, Ig, and 1-phenyl-3-methylhydantoin. Recrystallization of the mixture from methanol gave 2.0 g. (22.8%) of the hydantoin, m.p. 182–184°, identical (infrared, melting point, and mixture melting point comparisons) with an authentic sample[19] prepared from 1-phenylhydantoin with methyl iodide in the presence of sodium methoxide. The least soluble portion was 8.0 g. (50%) of If and Ig, 25% of which was If as determined from the integrated n.m.r. spectrum of the mixture. Some If, m.p. 266–269°, was obtained by crystallization from methanol. Evaporation of the filtrate gave crystals, m.p. 200–235°. This mixture was separated by chromatography on Florisil. The sample was put on the column in methylene chloride–benzene (1:1) and developed by gradually adding 1% of methanol to the original solvent mixture. The first fraction, 1-phenyl-3-methylhydantoin, was followed by If and finally Ig. The If obtained from the column was crystallized from ethanol to give the analytical sample, m.p. 225–226°; ν_{max}^{KBr} 1700; n.m.r., δ 2.81 (CH_3), 6.62 (C_6H_5), 5.17 (C_8H), 6.05 (C_7H); $J_{7,8}$ = 9.0 c.p.s.

Anal. Calcd. for $C_{18}H_{18}N_4O_2$: C, 67.06; H, 5.63; N, 17.38. Found: C, 67.39; H, 5.51; N, 17.43.

When the procedure was modified by increasing the concentrated hydrochloric acid to 50 ml., the yield of hydantoin was increased to 28%; m.p. 183–185° (lit.[19] m.p. 185°); ν_{max}^{KBr} 1710 cm.$^{-1}$; n.m.r., δ 7.04 (C_6H_5), 4.15 (CH_2), and 2.81 (CH_3).

1,4-Dimethyl-3,6-diphenyltetrahydroimidazo[4,5-*d*]imidazole-2,5-dione (If) from 1,4-Diphenyltetrahydroimidazo[4,5-*d*]-imidazole-2,5-dione (Ie).—To 5.5 g. (0.02 mole) of Ie and 5 g. of sodium hydroxide in 150 ml. of N-methyl-2-pyrrolidone was added dropwise 10 ml. (0.1 mole) of methyl sulfate at 120–150°. Two further treatments, each with 3 g. of sodium hydroxide and 10 ml. of methyl sulfate, completed the alkylation. The solvent was removed and the residue extracted with benzene in a Soxhlet apparatus. Evaporation of the benzene followed by crystallization from ethanol gave 1.4 g. (23%), m.p. 260–265°; ν_{max}^{KBr} 1695; n.m.r., δ 5.65 (CH), 2.30 (CH_3), 7.05 (C_6H_5).

Anal. Calcd. for $C_{18}H_{18}N_4O_2$: C, 67.06; H, 5.63; N, 17.38. Found: C, 66.80; H, 5.54; N, 17.24.

1,3-Diphenylhydantoin.—A solution of 10.6 g. (0.05 mole) of 1,3-diphenylurea, 3.6 g. (0.05 mole) of 80% crystalline glyoxal,[23] and 10 ml. of concentrated hydrochloric acid in 400 ml. of 95% ethanol was heated under reflux for 60 hr. The solvent was removed and the residue crystallized from methanol to afford 16 g. (71%) of 1,3-diphenylhydantoin, m.p. 134–136° (lit.[20] m.p. 137–139°); ν_{max}^{KBr} 1710, 1775 cm.$^{-1}$; n.m.r. δ 7.06 (C_6H_5), 4.27 (CH_2). This material was identical with an authentic sample[20] prepared from N-phenylglycine and phenylisocyanate.

N.m.r. Spectra—All spectra were determined in trifluoroacetic acid on a Varian Associates Model A-60 n.m.r. spectrometer at room temperature. Chemical shifts are reported in parts per million δ, downfield from tetramethylsilane.

Acknowledgment.—The authors wish to express their appreciation for many helpful discussions with Dr. L. D. Tuck and for the assistance of Mr. Thomas Simpson in determination of the dipole moment.

(22) F. M. Goyan and R. D. Johnson, *J. Pharm. Sci.*, **52**, 390 (1963).

(23) Obtained from F. Jonas Co., New York, N. Y. The 30% aqueous glyoxal often failed to give condensation products with substituted ureas.