of acetyl chloride. The reaction mixture was heated at reflux for 2 hr., cooled to about 100°, and poured into 4 l. of 0° water. The almost white product which separated was collected on a Buchner funnel and washed with 10 l. of 0° water. The yield of air-dried products was 1756 g. (91%), m.p. 151–154°.

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.1; H, 5.72; N, 7.25. Found: C, 62.25; H, 5.70; N, 7.19.

3-Nitrodiacetyl-p-aminophenol To 218 g. (1.9 moles) of fuming nitric acid (sp. gr. 1.45–1.50) cooled to 18° in a Dry Ice–acetone bath was added 148 g. (0.76 mole) of diacetyl-*p*-aminophenol in small increments over a period of 1 hr. with continuous stirring. The tan to red colored reaction mixture was decanted into 1 l. of 0° water. The yellow solid which separated was collected on a Buchner funnel and washed free of acid with 0° water.

Five similar runs were made yielding 760 g. (83%) of crude product, m.p. 136–139°. The combined batches were recrystallized from 2 l. of 50% ethanol to yield 638 g. (68%) of pure product, m.p. 145–146°.

Anal. Calcd. for $C_{10}H_{10}N_2O_5$: C, 50.5; H, 4.20; N, 11.77. Found: C, 51.08; H, 4.35; N, 10.4.

3-Nitro-4-acetyl-p-aminophenol. Seven hundred and forty grams (3.776 moles) of 3-nitrodiacetyl-*p*-aminophenol was suspended in 1.5 l. of 15° water in a 2-l. beaker cooled by a Dry Ice–acetone bath. Forty per cent sodium hydroxide solution was added in small portions with stirring until a solution was obtained. The addition required 30 min. Concentrated hydrochloric acid was added to the black solution until the mixture was acid to the Congo red paper. The bright orange solid which separated was collected on a Buchner funnel and washed with three 2-l. portions of 0° water. The product was recrystallized from 50% ethanol; yield, 158 g. (26%) m.p. 218–220°.

Anal. Calcd. for $C_8H_8N_2O_4$: C, 48.9; H, 4.08. Found: C, 50.13; H, 4.61.

2,3-Dinitro-4-acetylaminophenol. To 78 g. of concd. nitric acid (sq. gr. 1.42) cooled to 0° in a Dry Ice–acetone bath was added slowly with constant stirring 11 g. (0.056 mole) of 3-nitro-4-acetyl-*p*-aminophenol. The temperature was held below 10° during the 30-min. reaction interval. Orange crystals began separating after 15 min. and the mixture became quite viscous at the end of the reaction. The mixture was transferred to a beaker containing 200 ml. of 0° water. The yellow crystals which separated were collected on a Buchner funnel, washed with three 200-ml. portions of 0° water, and air dried.

Fourteen 0.056-mole batches were processed as described above to yield 102 g. of crude product. The combined material was dissolved in 500 ml. of hot 95% ethanol, treated with 10 g. of Nuchar, and filtered through Dicalite. To the filtrate was added 500 ml. of cold water which resulted in the separation of the product as yellow needles; yield 98 g. (41%), m.p. 196–198.5°.

Anal. Calcd. for $C_8H_7N_3O_6$: C, 39.8; H, 2.89; N, 17.36. Found: C, 39.58; H, 3.02; N, 16.9.

5-Hydroxy-8-acetylaminoquinoxaline. Thirty-five grams (0.145 mole) of 2,3-dinitro-4-acetylaminophenol was dissolved in 600 ml. of dimethyl formamide and reduced with hydrogen in the presence of 24.37 g. of 5% palladium-on-charcoal catalyst. The reduction was carried out at room temperature under a pressure of 2.04 atm. The theoretical amount of hydrogen was absorbed in 30 min. The mixture was filtered from catalyst directly into a solution of 56.8 g. (0.20 mole) of sodium glyoxal bisulfite in 200 ml. of 60° water. The filtrate was heated on the steam cone for 6 hr. at 558 mm. to remove most of the solvent. One liter of hot acetone was added to the 100 ml. of residue and the precipitate which formed removed *via* filtration and discarded. The filtrate was evaporated to dryness at 10 mm. without application of heat. The golden solid which remained was transferred to a Buchner funnel with the aid of 100 ml. of cold water, washed with three 20-ml. portions of water; yield 12 g. (41%), m.p. 246–247°.

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.1; H, 4.43; N, 21.6; OH, 8.37. Found: C, 59.91, H. 4.40; N, 20.8; OH, 7.92.

Cupric salt of 5-hydroxy-8-acetylaminoquinoxaline. A solution of 1 g. (0.005 mole) of cupric acetate in 50 ml. of water was added with stirring to a solution of 2 g. (0.01 mole) of 5-hydroxy-8-acetylaminoquinoxaline in 200 ml. of 80° ethanol. A blood red precipitate formed immediately. The product was removed by filtration on a Buchner funnel, washed with ten 50-ml. portions of water; yield 2 g. (89%).

Anal. Calcd. for $C_{20}H_{16}N_6O_4Cu$: Cu, 13.5. Found: Cu, 13.2.

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The Structure of 2-Substituted Amino-1,3,4-thiadiazoles

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2-Substituted amino-1,3,4-thiadiazoles are well known, generally being prepared by the reaction of a 4-substituted thiosemicarbazide and anhydrous formic acid,[1,2] from benzoylated thiosemicarbazides with acetylchloride,[3] or from 4-substituted thiosemicarbazones with ferric chloride.[4] The parent compound, 2-amino-1,3,4-thiadiazole (I, R=H), was recently prepared by the reaction of thiosemicarbazide with triethyl orthoformate.[5]

2-Substituted amino-1,3,4-thiadiazoles, which can be formulated as tautomers, are on the basis

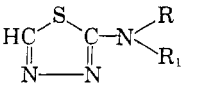
I II

of degradation evidence preferentially formulated as II.[6,7] We have applied the reaction with triethyl orthoformate to 4-substituted thiosemicarbazides and found it advantageous for the preparation of substituted 2-amino-1,3,4-thiadiazoles (Table I). Among other substances we have pre-

(1) G. Pulvermacher, *Ber.*, **27**, 613 (1894).
(2) M. Freund, *Ber.*, **29**, 2483 (1896).
(3) W. Marckwald and A. Both, *Ber.*, **29**, 2914 (1896).
(4) G. Young and W. Eyre, *J. Chem. Soc.*, **79**, 54 (1901).
(5) C. Ainsworth, *J. Am. Chem. Soc.*, **78**, 1973 (1956).
(6) L. L. Bambas, *Five-membered Heterocyclic Compounds with Nitrogen and Sulfur or Nitrogen, Sulfur, and Oxygen (except Thiazole)*, Interscience Publ., Inc., New York, 1952, p. 104.
(7) When this work was already completed, we noticed that G. A. Reynolds and J. A. Van Allan, *J. Org. Chem.*, **24**, 1478 (1959), prepared 2-phenylamino-1,3,4-thiadiazole from 4-phenylthiosemicarbazide and triethyl orthoformate and they formulated it as II (R = C_6H_5—).

TABLE I

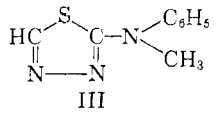
2-Substituted Amino-1,3,4-thiadiazoles



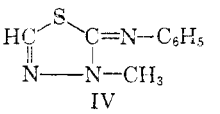
Compound No.	R	R_1	M.P.	Formula	Analyses, %N Calcd.	Found
1	Phenyl-	H	174[a]	$C_8H_7N_3S$	23.72	23.78
2	*m*-Methylphenyl-	H	103.5	$C_9H_9N_3S$	21.98	22.08
3	*p*-Methylphenyl-	H	162.5	$C_9H_9N_3S$	21.98	21.89
4	*o*-Methoxyphenyl-	H	119.5	$C_9H_9ON_3S$	20.28	20.41
5	*p*-Methoxyphenyl-	H	152.5	$C_9H_9ON_3S$	20.28	20.24
6[b]	*p*-Chlorophenyl-	H	204	$C_8H_6N_3SCl$	19.86	19.71
7	*m*-Chlorophenyl-	H	164	$C_8H_6N_3SCl$	19.86	19.76
8	*p*-Bromophenyl-	H	219	$C_8H_6N_3SBr$	16.40	16.67
9	Benzyl-	H	109	$C_9H_9N_3S$	21.98	21.88
10	α-Naphthyl-	H	136	$C_{12}H_9N_3S$	18.49	18.53
11	Cyclohexyl-	H	167[b]	$C_8H_{13}N_3S$	22.94	22.99
12	Phenyl-	Methyl-	70	$C_9H_9N_3S$	21.98	21.94

[a] Lit.,[1] m.p. 173° and lit.[12] m.p. 170°. [b] Lit.,[13] m.p. 165°.

pared 2-methylphenylamino-1,3,4-thiadiazole (III) and 2-phenylimino-3-methyl-1,3,4-thiadiazoline (IV) using the above mentioned procedure. The ultraviolet spectra of both substances, when compared with the spectrum of the unmethylated compound, revealed a close similarity in the case of III and 2-phenylamino-1,3,4-thiadiazole (I, R = C_6H_5—)(Fig. 1). On the basis of chemical and



III



IV

spectral evidence, the structure I should be the correct one for 2-substituted amino-1,3,4-thiadiazoles.

Compound IV was prepared by Pulvermacher[1] from I (R = C_6H_5—) and methyl iodide. When repeating this procedure, we found that this substance was identical with our compound, prepared from 2-methyl-4-phenylthiosemicarbazide and triethyl orthoformate.

EXPERIMENTAL[8]

2-Methyl-4-phenylthiosemicarbazide was prepared from methylhydrazine and phenylisothiocyanate.[9,10]

4-Methyl-4-phenylthiosemicarbazide. This compound was prepared from carboxymethyl *N*-methyl-*N*-phenyl dithiocarbamate[11] (8.8 g.), which was heated on a water bath with excess hydrazine hydrate (15 ml. of 80%) for 10 min. After cooling to room temperature the mixture was diluted with an equal volume of water and the precipitate collected.

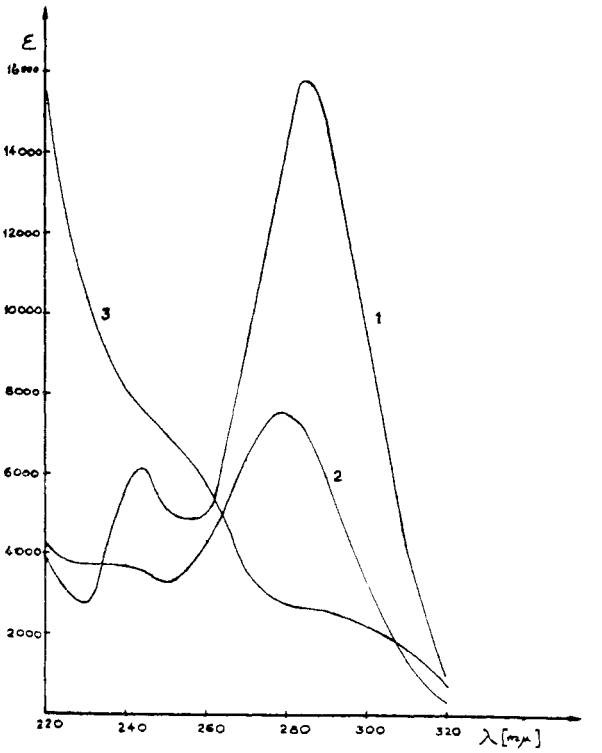


Fig. 1. Ultraviolet absorption spectra (in ethanol): (1) 2-Phenylamino-1,3,4-thiadiazole [λ_{max} 244 mμ (ε 6160), 284 mμ (ε 15,790)]. (2) 2-Methylphenylamino-1,3,4-thiadiazole [λ_{max} 278 mμ (ε 7570), inflection point 235 mμ (ε 3730)]. (3) 2-Phenylimino-3-methyl-1,3,4-thiadiazoline [Inflection point 286 mμ (ε 2730)]

Crystallization from ethanol gave 2.6 g. (39.5% yield), m.p. 125°.

Anal. Calcd. for $C_8H_{11}N_3S$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.15; H, 6.25; N, 23.39.

Benzylidene derivative, m.p. 183°.

Anal. Calcd. for $C_{15}H_{15}N_3S$: C, 66.90; H, 5.61; N, 15.61. Found: C, 66.85; H, 5.76; N, 15.64.

General procedure (Table I). A 0.01-mole sample of the corresponding 4-substituted thiosemicarbazide was heated on an oil bath at 120° with 5–10 ml. of triethyl orthoformate for 1

(8) The melting-points were determined with Koflers heating microscope.

(9) G. Brüning, *Ann.*, **253**, 11 (1889).

(10) M. Busch, E. Opfermann, and H. Walther, *Ber.*, **37**, 2318 (1904).

(11) B. Holmberg and B. Psilanderhielm, *J. prakt. Chem.*, **82**, 440 (1910).

(12) E. T. Fromm, *Ann.*, **433**, 1 (1923).

(13) C. W. Whitehead and J. J. Traverso, *J. Am. Chem. Soc.*, **77**, 5872 (1955).

hr. On cooling, in most cases the cyclization product was obtained crystalline, otherwise the solvent was evaporated *in vacuo* and the residue left for crystallization. The products were recrystallized from ethanol and the yields were usually in the range of 50–80%; only in the case of compounds No. 9, 10 and 12 were they 10–15%.

2-Phenylimino-3-methyl-1,3,4-thiadiazoline was prepared by the above procedure from 2-methyl-4-phenylthiosemicarbazide and by methylation of 2-phenylamino-1,3,4-thiadiazole with methyl iodide.[1] Crystallization from ethanol afforded the pure substance with m.p. and mixed m.p. 260° (lit.[1] m.p. 258°).

Anal. Calcd. for $C_9H_9N_3S$: N, 21.98. Found: N, 21.80.

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2-Imidazolone- and 2-Imidazolidonepropionic Acids

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The importance of oxygenated imidazoles in the metabolism of histidine[1] has led us to synthesize 2-imidazolonepropionic acid and the corresponding imidazolidone for metabolic studies. The method was analogous to that of Dittmer, *et al.*[2] involving the synthesis of 5-aminolevulinic acid and its condensation with potassium cyanate. The overall yield of imidazolone from methyl 5-chlorolevulinate was 50%. High pressure reduction of the imidazolone[2] was unnecessary; the solubility of the imidazolidone in acetic acid facilitated smooth reduction with Adam's catalyst at atmospheric pressure.

EXPERIMENTAL[3]

Methyl 5-chlorolevulinate was prepared from methyl 4-chloro-4-oxobutyrate by the method described by Neuberger and Scott,[4] b.p. 92–94° (2 mm.), 99–101° (3 mm.), 128–131° (23 mm.) and n_D^{25} 1.4536. Infrared peaks in cm.$^{-1}$ ($CHCl_3$) follow: strong—1733, 1437, 1399, 1356, 1325, 1240–1200, 1172–1168; moderate—2924, 1087, 1021–1017, 992, 966–962; weak—3520–2420, 3229–3150, 1620, 889–881, 867–866, 842–837.

The *2,4-dinitrophenylhydrazone*, after several recrystallizations from methanol, was obtained as yellow-orange flat elongated plates, m.p. 109–112°.

Anal. Calcd. for $C_{12}H_{13}N_4O_6Cl$: C, 41.81; H, 3.80; Cl, 10.29. Found: C, 41.79; H, 3.95; Cl, 10.19.

Methyl 5-phthalimidolevulinate, although reported,[4] was prepared by the method of Dittmer[2] in 60–75% yields. Recrystallization from alcohol was far more convenient than from water.

2-Imidazolone-4(5)-propionic acid. Crude methyl 5-phthalimidolevulinate (29.15 g., 0.106 mole) was refluxed with 300 ml. of 6*N* hydrochloric acid for 8 hr., cooled, and filtered from phthalic acid.[5] The filtrate was concentrated *in vacuo* and again three times from water, finally on the oil pump, to yield 20.36 g. of gummy crystals. The crude amino acid hydrochloride was added to 40 ml. of water and filtered from 0.95 g. of 5-phthalimidolevulinic acid. To the solution potassium cyanate (15.0 g., 0.185 mole, in 25 ml. of water) was added as rapidly as possible without allowing the solution to warm up, maintaining the *p*H around 5 by the addition of acetic acid. The precipitating solution was shaken intermittently until gas evolution ceased and was then warmed over steam for an hour. After chilling, the light tan product was collected: 12.74 g. (77%), m.p. 251–253° dec. The product was combined with 1.0 g. of product from a previous run, dissolved in 70 ml. of hot sodium bicarbonate solution, filtered, and acidified while hot with 6*N* hydrochloric acid until precipitation ceased (*p*H 3). After chilling, filtration provided 11.50 g. of nearly white crystals, which began to decompose (black) at 253–255° and melted from 255–257°. This sample was used for analysis, but recrystallization from 30% alcohol provided a whiter product, though in poorer yield and no better melting point. Acetic acid provided white crystals dec. (black) 263–263.5° but recovery was moderate.

Anal. Calcd. for $C_6H_8N_2O_3$: C, 46.15; H, 5.16; N, 17.95. Found: C, 46.24; H, 5.27; N, 17.81.

Infrared bands in cm.$^{-1}$ (Nujol) follow: strong—1699–1691, 1625–1598; moderate—3369, 3280, 3165, 1414, 1350, 1303, 1242, 775; mod. to weak—1221, 1194, 1020, 794, 753–742, 735–732; weak—1960–1909, 1085, 1058, 1003, 919, 910.

Ultraviolet (water): end absorption, 220 mμ, log ϵ 3.77[6]; in acid, λ_{max} 310 mμ, log ϵ 2.33, plus end absorption, 220 mμ, log ϵ 3.29; in base, λ_{max} 296 mμ, log ϵ 2.66, plus end absorption, 230 mμ, log ϵ 3.28.

2-Imidazolidone-4(5)-propionic acid. 2-Imidazolone-4(5)-propionic acid (11.50 g.) as a slurry in 280 ml. of acetic acid was added to 1.50 g. of Adam's catalyst (prereduced in 20 ml. of acetic acid) and stirred under hydrogen at atmospheric pressure for 16 hr. when uptake ceased at the theoretical amount. Solution had occurred when about 80% reduced. The solution was filtered and concentrated *in vacuo* to a solid, which was dissolved in about 10 ml. of hot water. Chilling afforded 9.38 g. of hard, tiny, colorless crystals, insoluble in acetone, m.p. 159–160°. Recrystallization did not raise the melting point. Recrystallization proceeds well from acetic acid, in which it is less soluble. Concentration of the mother liquor to 3 ml. yielded another 0.65 g., m.p. 152–156°.

Anal. Calcd. for $C_6H_{10}N_2O_3$: C, 45.56; H, 6.37; N, 17.72. Found: C, 45.74; H, 6.20; N, 17.69.

Infrared in cm.$^{-1}$ (Nujol): strong—1709, 1652, 1290–1269, 1197; moderate—3335, 3251, 2658, 2565–2512, 1497, 1408, 1345, 1306, 1167, 1107, 904, 764; weak—1886–1873, 1033, 964, 877, 806.

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(1) D. D. Brown and M. W. Kies, *J. Am. Chem. Soc.*, **80**, 6147 (1958); D. D. Brown and M. W. Kies, *J. Biol. Chem.*, **234**, 3182 (1959); H. Tabor, *Pharmacol. Revs.*, **6**, 229 (1954).

(2) K. Dittmer, M. F. Ferger, and V. du Vigneaud, *J. Biol. Chem.*, **164**, 19–28 (1946).

(3) Analyses were performed by W. C. Alford, Analytical Laboratory, National Institutes of Health, Bethesda, Md. Infrared spectra were run by O. Silva, NIMH, National Institutes of Health, on a Perkin-Elmer Double Beam Model 21. Ultraviolet spectra were run by L. S. Pijanowski, Department of Chemistry, University of Florida, Gainesville, Fla. Melting points were determined under a microscope on a Fisher-Johns Melting Point Apparatus and are uncorrected.

(4) A. Neuberger and J. J. Scott, *J. Chem. Soc.*, 1820–1825 (1954).

(5) Reflux time should be increased; work-up of such precipitates afforded 5-phthalimidolevulinic acid, m.p. 160–161°, from 5–20%.

(6) Ref. 2 reports almost identical spectra for the homologous valeric, caproic and octanoic acids.