TABLE I

PHYSICAL CONSTANTS OF α,ω-BIS(HETEROCYCLYL)ALKANES

Compound	Yield, %	Formula	B.P./Mm.	M.P.	n_D^{30}	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
IIa	72	$C_{24}H_{32}N_2$[a]		151–152		80.00	79.89	10.66	10.81		
IIb	76	$C_{21}H_{34}N_2$[b]	148–150/1.3			80.25	79.74	10.82	10.62		
IIc	74	$C_{22}H_{36}N_2$[c]		103–104		80.48	80.20	10.97	10.84		
IId	64	$C_{22}H_{36}N_2O$[d]		59–60		76.74	76.75	10.46	10.37		
IIIa	53	$C_{17}H_{30}N_2O_2$	110–113/1.3		1.4700					9.52	9.49
IIIb	47	$C_{18}H_{32}N_2O_2$	150–153/4		1.4676					9.09	8.94
IV	45	$C_{14}H_{24}N_2S_2$		80–81						9.85	9.70

[a] Picrate, m.p., 180° (with decomposition). [b] Picrate, m.p. 175–176°. [c] Picrate, darkens above 200°. [d] Picrate, m.p. 140–142°.

times with 75-ml. portions of chloroform to extract polymeric material, was cautiously neutralized with 30% sodium hydroxide solution. The heterocyclic base, which then appeared, was taken up in ether and dried overnight with potassium carbonate. After the ether had been removed at atmospheric pressure, the residual oil was distilled *in vacuo*.

If the heterocyclic base upon neutralization appeared as a solid, it was collected on a suction filter, washed several times with cold water, and then recrystallized from 50% aqueous ethanol.

Reaction of 3,3'-dithiopropionitrile with 2,5-dimethyl-2,5-hexanediol. To a cold solution of 14.0 g. (0.10 mole) of 3,3'-dithiopropionitrile in 100.0 ml. of concd. sulfuric acid, was added with stirring, 29.6 g. (0.20 mole) of 2,5-dimethyl-2,5-hexanediol. The temperature of the reaction was kept below 10° by employing an ice bath. After the glycol addition had been completed, the mixture was stirred for an additional hour at 4–6° and then slowly poured over 300 g. of chipped ice. The above procedure was followed to isolate the crude product in an ether solution. Distillation of the ether residue yielded a light yellow oil, b.p., 86–87° (1.25 mm.); n_D^{30} × 1.5019. This was identified as the 2-vinyl-1-pyrroline prepared previously,[2] b.p., 91–93° (2 mm.); n_D^{30} 1.5012.

DEPARTMENT OF CHEMISTRY
LOUISIANA STATE UNIVERSITY IN NEW ORLEANS
NEW ORLEANS 22, LA.

5-Hydroxy-8-acetylaminoquinoxaline

MARGARET H. BROYLES[1,2] AND WILLIAM K. EASLEY[3]

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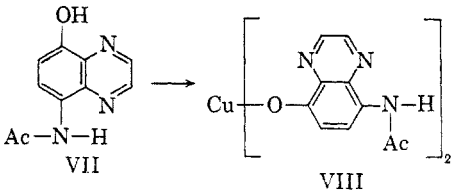
The historical review of quinoxaline compounds having carbocyclic substituents revealed members with fungistatic and medicinal characteristics. It seemed to us of interest to undertake the preparation of 5-hydroxy-8-acetylaminoquinoxaline and its copper salt. In this publication we wish to report the synthesis of 5-hydroxy-8-acetylaminoquinoxaline (VII) and the cupric salt of 5-hydroxy-8-acetylaminoquinoxaline (VIII). Also, we wish to report improved procedures for the preparation of diacetyl-*p*-aminophenol,[4] 3-nitro-diacetyl-*p*-aminophenol,[5,6] 3-nitro-4-acetyl-*p*-aminophenol,[7] and 2,3-dinitro-4-acetylaminophenol.[8] This synthesis was accomplished by the following sequence: *p*-aminophenol (I) was converted by acetylation with equimolar quantities of acetic anhydride and acetyl chloride to diacetyl-*p*-aminophenol (II); nitration of II yielded 3-nitro-diacetyl-*p*-aminophenol (III); partial deacetylation of III by 40% sodium hydroxide yielded 3-nitro-*N*-acetyl-*p*-aminophenol (IV), and nitration of IV yielded 2,3-dinitro-*N*-acetylaminophenol (V).

The following reactions involve catalytic reduction of 2,3-dinitro-4-acetylaminophenol with hydrogen in the presence of 5% palladium-on-charcoal catalyst to the intermediate 2,3-diamino-4-acetylaminophenol (VI), which was not isolated but allowed to react with sodium glyoxal bisulfite to form 5-hydroxy-8-acetylaminoquinoxaline (VII). An alcoholic solution of 5-hydroxy-8-acetylaminoquinoxaline was treated with aqueous solution of cupric acetate which yielded a reddish precipitate (VIII) of the copper chelate. Both VII and VIII have been found to produce only slight inhibition of the standard organism, *Aspergillus niger*, in 250 parts per million concentrations. Results of the fungistatic evaluation of these compounds will be published elsewhere.



EXPERIMENTAL

Diacetyl-p-aminophenol. To 981 g. (9.0 moles) of *p*-aminophenol was added slowly 1020 g. (10.0 moles) of acetic anhydride with stirring. The reaction was exothermic and cooling with an ice bath was employed to lower the temperature to 75° prior to the rapid addition of 785 g. (10.0 moles)

(1) From a thesis submitted by Margaret H. Broyles as partial fulfillment of the requirements for the degree of Master of Arts, East Tennessee State College, 1959.

(2) Tenite Development Department, Tennessee Eastman Company, Kingsport, Tenn.

(3) Northeast Louisiana State College, Monroe, La.

(4) F. Reverdin and A. Bucky, *Ber.*, **39**, 2678 (1906).

(5) F. Reverdin and A. Dresel, *Ber.*, **38**, 1593 (1905).

(6) O. Hinsberg, *Ber.*, **19**, 483 (1886).

(7) O. Fischer and F. Romer, *Ber.*, **41**, 2350 (1908).

(8) O. Hinsberg, *Ber.*, **18**, 1228 (1884).

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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EAST TENNESSEE STATE COLLEGE
JOHNSON CITY, TENN.

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

B. STANOVNIK AND M. TIŠLER

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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-

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(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—).