distilled, no other product was detected. The yellow oil (42 g., 52%) was presumed to be 1,1-diethylpyrrolinium chloride, and this was confirmed by conversion to a *picrate* that melted at 247–248° after recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.45; H, 5.12; N, 15.81. Found: C, 47.28; H, 5.19; N, 15.71.

3-Pyrroline (IV). *cis*-1,4-Dichloro-2-butene (62.5 g., 0.5 mole) dissolved in 150 ml. of ethanol was added slowly and with cooling to 667 ml. (10 moles) of 28% aqueous ammonia. Enough additional ethanol was added to produce one phase. After the mixture had been standing at room temperature for 3 days, air was passed through it to remove the excess ammonia. The mixture was neutralized with concd. hydrochloric acid, with cooling, and evaporated to dryness under vacuum. The solid was dissolved in the minimum amount of water, which was then made strongly basic with sodium hydroxide and extracted with ether. The extract was washed with saturated aqueous sodium chloride, dried over potassium hydroxide, and distilled to yield 4.8 g. (14%) of 3-pyrroline boiling at 91° (reported[8] b.p. 90–91°). A *picrate* was prepared which melted at 155.6–157° (reported[9] m.p. 156°).

5-Azaspiro[4.4]nona-2,7-dienium chloride (V). Freshly distilled *cis*-1,4-dichloro-2-butene (30 g., 0.24 mole) was added to 100 ml. of absolute ethanol which had previously been saturated with anhydrous ammonia at 25°. After about 30 min., a white precipitate began to form. After 36 hr. at 5°, the ammonium chloride (14 g., 73%) was filtered. The filtrate was shaken for 1 hr. with 25 g. of Amberlite IRA-400 (basic form, dried overnight with Drierite under vacuum) to transform the remaining ammonium chloride to ammonia. The resin was filtered and the solvent was removed *in vacuo* at 40° to give 15.2 g. of a semicrystalline, yellow material. This material was triturated with four successive portions of dry acetone and filtered to yield 13.6 g. (72%) of slightly yellow,[10] slightly hygroscopic product, m.p. 259–260°. A portion was decolorized by recrystallization from absolute ethanol (dissolved warm and cooled in Dry Ice-acetone) and dried over phosphorus pentoxide under vacuum at 80°, m.p. 260–261°.

Anal. Calcd. for $C_8H_{12}ClN$: C, 60.99; H, 7.67; Cl, 22.55; N, 8.88. Found: C, 60.90; H, 7.77; Cl, 22.61; N, 8.97.

A *picrate* was prepared in ethanol and recrystallized from the same solvent, m.p. 218–219°.

Anal. Calcd. for $C_{14}H_{14}N_4O_7$: C, 48.00; H, 4.03; N, 16.00. Found: C, 48.26; H, 4.11; N, 16.07.

A *styphnate* was prepared in absolute ethanol and recrystallized from the same solvent, m.p. 140.5–141°.

Anal. Calcd. for $C_{14}H_{14}N_4O_8$: C, 45.90; H, 3.85; N, 15.30. Found: C, 45.87; H, 3.97; N, 15.50.

5-Azaspiro[4.4]nonanium chloride (VI). Pyrrolidine and 1,4-dichlorobutane were condensed in the presence of sodium hydroxide by the general procedure of Blicke and Hotelling[2] to give a low yield (8%) of hygroscopic product, m.p. 289–295°[11] (reported[2] m.p. 277–279°). The *chloroaurate*[2] melted at 254–256° (reported[2] m.p. 254–256°). A *picrate* was prepared in absolute ethanol and recrystallized from the same solvent, m.p. 263–264°.

Anal. Calcd. for $C_{14}H_{18}N_4O_7$: C, 47.45; H, 5.12; N, 15.81. Found: C, 47.63; H, 5.19; N, 15.76.

Reduction of 5-azaspiro[4.4]nona-2,7-dienium chloride (V). A mixture of 3 g. of 5-azaspiro[4.4]nona-2,7-dienium chloride, 0.25 g. of 5% palladium on charcoal and 75 ml. of absolute ethanol was hydrogenated at 33 p.s.i. Hydrogenation was complete in about 11 min.; after filtration, the solvent was removed under reduced pressure. After the addition of 100 ml. of dry benzene, the crystalline product was filtered in the absence of air and dried at 80° under reduced pressure; yield 2.4 g. (79%) of 5-azaspiro[4.4]nonanium chloride; m.p. 286–289°.[11] The *picrate* melted at 264–265° and the *chloroaurate* melted at 256–262°. In each case, mixture melting points with the synthetic specimens described above were undepressed.

(8) G. L. Ciamician and M. Dennstedt, *Ber.*, **15**, 1831 (1882).

(9) F. Anderlini, *Ber.*, **22**, 2512 (1889).

(10) The amount of color varied directly with the time elapsing between distillation and use of the dichloride.

(11) The extreme hygroscopic nature of this substance causes its melting point to depend upon how it is taken. This sample was baked on a Kofler block at 250° before the measurement was taken.

Acknowledgment. This work was supported in part by Grants No. CY-3437 and CY-3905 of the National Cancer Institute of the National Institutes of Health.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CONNECTICUT
STORRS, CONN.

Heterocyclic Compounds from Dinitriles[1]

ALBERT I. MEYERS

Received March 18, 1960

As part of a general study on the preparation of heterocyclic nitrogen compounds form nitriles[2–5] in cold concentrated sulfuric acid, a logical extension of this reaction was pursued which led to α,ω-bis(heterocyclyl)alkanes, I, Ia. The addition of 2,5-dimethyl-2,5-hexanediol, 2-methyl-2,4-pentanediol, and 4-mercapto-2-methyl-2-butanol to a cold solution of a dinitrile in concentrated sulfuric acid yielded *N*-heterocyclic bases of the type, II, III, and IV, respectively. This reaction is considered to occur in a manner completely analogous to that which affords the corresponding monocyclic derivatives.[5]

The ring closure may be limited to the formation of a monocyclic product by utilizing equimolar quantities of the dinitrile and the alcohol derivative. Under the conditions of the reaction, no appreciable hydrolysis of the remaining nitrile group occurs. This fact was demonstrated when 2-methyl-2,4-pentanediol was added to an excess of succinonitrile in sulfuric acid. When the reaction mixture was quenched in ice and water and subsequently neutralized, only the 2-(2-cyanoethyl)dihydro-1,3-oxazine (V) was isolated and no amide (VI) was found to be present. There was obtained, however, a considerable quantity of succinamide derived from the excess succinonitrile employed in the reaction. This reaction was previously performed in connection with another study and details are given elsewhere.[4] This behavior has been

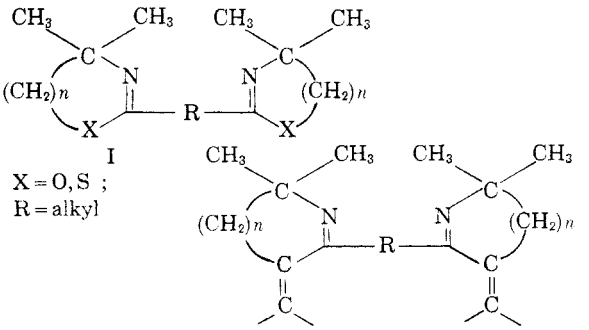
(1) This investigation was supported by funds granted by the United States Public Health Service, National Institutes of Health (RG-6248).

(2) A. I. Meyers and J. J. Ritter, *J. Org. Chem.*, **23**, 1918 (1958).

(3) A. I. Meyers, *J. Org. Chem.*, **24**, 1233 (1959).

(4) A. I. Meyers, *J. Org. Chem.*, **25**, 145 (1960).

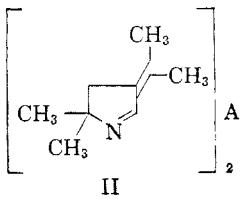
(5) A. I. Meyers, *J. Org. Chem.*, **25**, 1147 (1960).



I

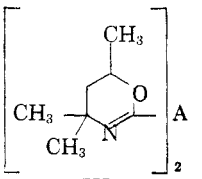
X = O, S ;
R = alkyl

Ia



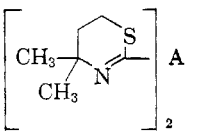
II

IIa, A = -$(CH_2)_2$-
IIb, A = -$(CH_2)_3$-
IIc, A = -$(CH_2)_4$-
IId, A = -$(CH_2)_2O(CH_2)_2$-



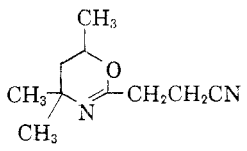
III

IIIa, A = -$(CH_2)_2$-
IIIb, A = -$(CH_2)_4$-

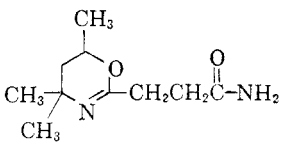


IV, A = -$(CH_2)_2$-

previously observed in the Ritter *N*-alkylamide synthesis[6] where succinonitrile condensed with isobutene in sulfuric–acetic acid to yield only the



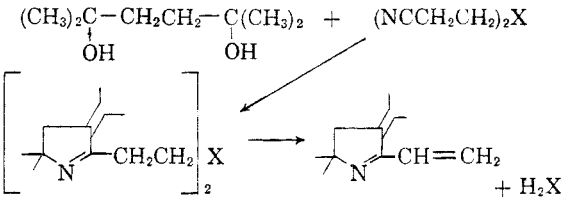
V



VI

monosubstituted succinamide. Repeated attempts by these workers to obtain the *N*,*N*′-di-*t*-butylsuccinamide were fruitless. In this study, however, succinonitrile was successfully employed to yield the 1,2-bis(1-pyrrolinyl)ethane (IIa).

When 3,3′-thiodipropionitrile and 3,3′-oxydipropionitrile were treated with 2,5-dimethyl-2,5-hexanediol in cold concentrated sulfuric acid, the reaction took its expected course. However, distillation of the crude product resulted in carbon-oxygen bond cleavage in the nitrile moiety and the 2-vinyl-1-pyrroline (IX) was the only product obtained. A considerable quantity of polymeric material, resulting from the thermal instability of the vinyl compound, was also formed during the distillation. In the case of the reaction between dimethylhexanediol and 3,3′-oxydipropionitrile, which yielded VII, only the fact that this product was solid permitted its pure isolation. When this compound was heated above 90° at reduced pressure, it easily decomposed into the 2-vinyl-1-pyrroline and its polymer. Since the sulfur analog (VIII) was a viscous oil, all attempts to purify it by methods other than distillation, were unsuccessful. Distillation of VIII gave only the 2-vinyl-1-pyrroline, its polymers, and hydrogen sulfide. The physical constants of the 2-vinyl-1-pyrroline, were compared with those of the product obtained[2] from acrylonitrile and 2,5-dimethyl-2,5-hexanediol and shown to be identical. The cleavage of cyanoethylated products on being heated in the presence of a



VII, X = O
VIII, X = S

IX

base, in this case the heterocyclic compound, have been observed previously.[7]

Further studies on this ring closure were undertaken using malononitrile. In the reaction with all three alcohol derivatives mentioned herein, only viscous undistillable oils resulted. It may be of interest to mention that the infrared spectra of these viscous oils (in chloroform) exhibited a strong band in the 6.0–6.10 μ region which is consistent with previous studies[3,8] on the cyclic C=N link in heterocyclic compounds.

EXPERIMENTAL[9,10]

Materials. 4-Mercapto-2-methyl-2-butanol[5] was prepared by treating 3-mercaptopropionic acid (Evans Chemetics, Inc., New York) with butanol to form the *n*-butylester and then allowing it to react with excess methylmagnesium bromide in tetrahydrofuran, b.p. 52.0–53.5° (1.5 mm.), n_D^{20} 1.4750. 2,5-Dimethyl-2,5-hexanediol was obtained from the Air Reduction Chemical Co., Murray Hill, N. J.

Preparation of α,ω-bis(heterocyclyl)alkanes, II–IV. All the compounds reported were prepared using the procedure outlined below.

To a cold solution of 0.05 mole of the dinitrile in 50 ml. of concd. sulfuric acid was added dropwise or in portions, if solid, 0.10 mole of the glycol or mercaptoalcohol. Efficient stirring was maintained and the temperature of the solution kept below 10° during the addition. After all the glycol had been added, the resulting clear solution (usually golden yellow to orange in color) was stirred at 3–5° for an hour and then poured over approximately 250–300 g. of chipped ice. The aqueous acid solution, after being treated several

(6) F. R. Benson and J. J. Ritter, *J. Am. Chem. Soc.*, **71**, 4128 (1949).

(7) J. H. MacGregor and C. Pugh, *J. Chem. Soc.*, 535 (1945).

(8) A study has recently been completed on the spectral position of the cyclic C=N link in dihydro-1,3-oxazines and dihydro-1,3-thiazines which indicates that these compounds containing identical 2-substituents exhibit a strong band in the 6.0 and 6.1 μ regions, respectively. This work will be submitted for publication shortly.

(9) All melting points and boiling points are uncorrected.

(10) Microanalyses were performed by A. Bernhardt, Max-Planck Institute, Mulheim (Ruhr), West Germany.

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.

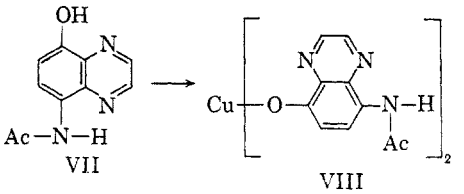
5-Hydroxy-8-acetylaminoquinoxaline

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

Received January 25, 1960

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).