Recovery of I from Solutions in Concentrated Sulfuric Acid.—2,4-Dinitrobenzenesulfenyl chloride (I), 0.10 g., m.p. 96–97° was finely-ground and added to 20 ml. of 96% sulfuric acid. The mixture was let stand, and stirred occasionally, for one hr. This was filtered through a sintered-glass funnel, the filtrate poured on 50 g. of crushed ice, and the latter mixture was extracted with 50 ml. of carbon tetrachloride. Evaporation of the solvent, from the extract, gave 5 mg. of unchanged I (m.p. and m.m.p. with authentic I, 95–96°).

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NOTES

5-Thiol-7-hydroxy-1-γ-triazolo[d]pyrimidine[1,2]

BY CARL TABB BAHNER AND DOROTHY ELLIS BILANCIO

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5-Thiol-7-amino-1-γ-triazolo[d]pyrimidine has been reported to be a strong inhibitor of the growth of *Streptococcus faecalis* R.[3] but not of *Adenocarcinoma* 755.[4] The closely related compound having an hydroxy group in place of the 7-amino group has been prepared as described below. It produces a 65% reduction in the growth of *L. casei* at a concentration of 0.005 mg./ml.[5] The effect can be reversed by pteroylglutamic acid or adenine. The results of screening against various tumors are to be published elsewhere.

A solution of 7.0 g. of sodium nitrite in the minimum volume of water was added slowly to a solution of 15.0 g. of 2-thiol-4,5-diamino-6-hydroxypyrimidine[6,7] in one liter of 2 *N* H_2SO_4 at 40°. Stirring was continued 15 minutes after all the sodium nitrite had been added. The solution was chilled for two hours and the solid product was recovered by filtration. It was suspended in boiling water and dissolved by addition of ammonia. The resulting solution was chilled and the crystals which formed were dissolved in boiling water. The hot solution was treated with activated charcoal, filtered hot, acidified with acetic acid and chilled. The crystals which formed were recrystallized from acetone; they then decomposed sharply at 265°. In sodium bicarbonate-buffered solution, the product reacted with iodine in the ratio of 4 atoms of iodine to 1 molecule of product. Grynberg[8] reported similar results with xanthine and guanine. However 8-azaguanine does not behave in the same way. Ultraviolet absorption data for this compound are shown in Table I. The sample for carbon and hydrogen analysis was dried at 110° and 0.1 mm. before analysis, but the analysis indicated the presence of one molecule of water. Roblin,[9] *et al.*, observed that the corresponding dihydroxy compound also was obtained as the monohydrate in spite of careful drying. *Anal.* Calcd. for $C_4H_5N_5O_2S$: C, 25.64; H, 2.69. Found: C, 25.85; H, 2.60.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA

*p*H	$\lambda_{max.}$	$\lambda_{min.}$
1	242	255
	270	278
	294	
6.5	238	219
	288	253
10	232	252
	276	
11	277	250

We are indebted to Gertrude Elion and George H. Hitchings of the Wellcome Research Laboratories and Lee Bennett, Jr., of the Southern Research Institute for ultraviolet absorption data and to Galbraith Analytical Laboratories for carbon and hydrogen determination.

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(2) Presented in part at the Southeastern Regional Meeting of the American Chemical Society, Auburn, Ala., October 24, 1952.

(3) C. T. Bahner, H. A. Rutter, Jr., and J. R. Totter, *J. Tenn. Acad. Sci.*, **27**, 179 (1952).

(4) G. W. Kidder, V. C. Dewey, R. E. Parks, Jr., and G. L. Woodside, *Cancer Research*, **11**, 204 (1951).

(5) Gertrude Elion and George H. Hitchings, private communication.

(6) W. Traube, *Ann.*, **331**, 71 (1904).

(7) A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

(8) M. Z. Grynberg, *Biochem. Z.*, **253**, 143 (1932).

(9) R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole and J. R. Vaughan, Jr., THIS JOURNAL, **67**, 290 (1945).

On Competition between the Clarke–Eschweiler and Pictet–Spengler Reactions

BY RICHARD BALTZLY

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Some years ago in these laboratories Dr. J. S. Buck and the author observed that the attempt to produce dimethylhomoveratrylamine from homoveratrylamine or N-methylhomoveratrylamine by the Clarke–Eschweiler reaction[1] gave mainly 2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. Similar results were obtained with N-benzylhomoveratrylamine[2] and an attempt to methylate β-(2,5-dimethoxyphenyl)-propylamine by this procedure afforded a compound that was not the corresponding dimethylamine and whose hydrochloride gave analyses consistent with the composition $C_{13}H_{20}ClNO_2$.[3] In this latter case the authors were reluctant to ascribe to this substance the structure of a tetrahydroisoquinoline since there was no activating group in the parent phenethylamine para to the point of prospective ring closure.

More recently Castrillon[4] has reported the cycli-

(1) H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

(2) J. S. Buck and R. Baltzly, *ibid.*, **64**, 2263 (1942).

(3) R. Baltzly and J. S. Buck, *ibid.*, **62**, 161 (1940).

(4) J. C. Castrillon, *ibid.*, **74**, 558 (1952).

zation of mescaline to 2-methyl-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline as a result of attempts to prepare N,N-dimethylmescaline by the Clarke–Eschweiler procedure.

While the Pictet–Spengler[5,6] method of cyclization of phenethylamines to tetrahydroisoquinolines usually employs mineral acid, the conditions of acidity are not far removed from those in the usual Clarke–Eschweiler, especially if, as is often convenient with small quantities, the excess of formic acid is not minimized.

Since up to the present, the Pictet–Spengler had not been observed in the absence of strong acid except with phenolic amines[7] and a recent study of the Wallach reaction (of which the Clarke–Eschweiler is a special case) has shown that acidity is not required for it[8] the probability seemed high that homoveratrylamine could be methylated by formalin and formic acid if acidity were avoided.

In an application of the above argument homoveratrylamine was heated with formalin while the *p*H was kept close to 7 by addition of formic acid. Toward the end of the operation enough acid was admitted to give a *p*H of 5. Despite these precautions, the yield of N,N-dimethylhomoveratrylamine was only 44%. In addition there was obtained a 14% yield of 2-methyl-6,7-dimethoxytetrahydroisoquinoline and a small amount of a substance apparently isomeric with the latter.

It appears consequently that the Pictet–Spengler cyclization is considerably more facile than has previously been supposed and that when the structural peculiarities of a phenethylamine are favorable for this cyclization the Clarke–Eschweiler reaction cannot be manipulated to avoid the cyclization completely. To some extent this can be rationalized if one assumes that both reactions proceed through an alkylolamine intermediate which must become cationic for either reaction to proceed. Such an assumption is generally made for the Pictet–Spengler reaction and is not unreasonable for the Wallach reaction.

$$RNHCH_2OH \xrightarrow[H_3O^+]{} RNH_2^+CH_2OH \rightleftharpoons \underset{I}{RNH_2^+CH_2OH} \rightleftharpoons \underset{II}{RNH{=}CH_2^+} \longleftrightarrow RNH{-}CH_2^+$$

Two obvious cationic forms, I and the resonance hybrid II, can be written and the equilibrium between them might well be *p*H dependent. Thus, in the present instances, the essentially neutral medium may have minimized the tendency of I to pass into II without preventing it completely.

Experimental

Ten cc. of formalin was added to 9.1 g. (50 mmoles) of homoveratrylamine in a 3-necked conical flask set in a steam-bath and equipped with a stirrer, thermometer and dropping funnel. After the admission of 2.4 cc. of 90% formic acid the stirrer was started and the flask was heated to about 87°. The evolution of gas commenced at about 50°. Further quantities of 90% formic acid were added to maintain a *p*H of about 7. After three hours a total of 5 cc. of formic acid had been added. Five cc. more formalin was then run in and the reaction continued, 3 cc. more formic acid being added in the next 1.5 hour. The *p*H was then 5 and was unaltered by 1.5 hours further heating. The solution was evaporated *in vacuo*, 7 cc. of concentrated hydrochloric acid was added (change of color from brown to green) and the mixture was again taken down *in vacuo*. The residue was dissolved in absolute ethanol, ethyl acetate was added and the solution was seeded with N,N-dimethylhomoveratrylamine hydrochloride. The solid obtained, however, was not this expected salt since it melted at 204–208°. On recrystallization the melting point rose to 213–215° and was not depressed by admixture of authentic 2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride. The weight of this pure fraction was 1.7 g. (7 mmoles).

The mother liquors were evaporated and the bases were liberated and distilled *in vacuo* (below 1 mm.). The more volatile material (boiling below 120°) afforded, after crystallization of the hydrochlorides, 22 mmoles of pure N,N-dimethylhomoveratrylamine hydrochloride. The undistilled bases (*ca.* 3 g.) were dissolved in hot hexane, a small amount of tar was removed, and attempts were made to crystallize the bases. As these were unsuccessful the material was reconverted to the hydrochlorides and 0.8 g. of a solid melting at 224–225° was obtained. Recrystallization from ethanol–ether mixture raised this melting point to 229–230° dec. Higher decomposition points could be obtained if the bath was heated rapidly (242°, 239°), but all these were decomposition points and none were so high as those reported for 6,7-dimethoxytetrahydroisoquinoline hydrochloride (253°, 262°)[9] which is said to melt without obvious decomposition.

Anal. Calcd. for $C_{12}H_{18}ClNO_2$: C, 59.1; H, 7.4. Found: C, 59.3; H, 7.4.

The composition is thus consistent with this substance being a dimethoxy-N-methyltetrahydroisoquinoline hydrochloride. Permanganate oxidation yielded an acid whose identity is as yet uncertain.

(5) *Cf.* "Organic Reactions." Edited by Roger Adams. Vol. VI, John Wiley and Sons. Inc., New York, N. Y., 1951. p. 151.

(6) J. S. Buck, THIS JOURNAL, **56**, 1769 (1934).

(7) C. Schöpf and H. Bayerle, *Ann.*, **513**, 190 (1934). Actually a considerable gap exists between the conditions of Schöpf (dilute neutral solution and room temperature) and those customary in the synthetic reaction (high acidity, relatively high concentration and steam-bath temperatures). So far as the cyclization is concerned, concentration should affect only the formation of the methylolamine intermediate.

(8) E. Staple and E. C. Wagner, *J. Org. Chem.*, **14**, 559 (1949).

(9) J. S. Buck, THIS JOURNAL, **56**, 1769 (1934); R. Forsyth, C. I. Kelly and F. L. Pyman, *J. Chem. Soc.*, **127**, 1659 (1925).

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Identification Derivatives of 2-Aminofluorene and of 2-Aminofluorenone

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The following new derivatives of 2-aminofluorene have been prepared and characterized.

2-Fluorenyl Phenyl Thiourea.—A solution of 1 g. of 2-aminofluorene in 50 ml. of ethanol and 2 g. of phenyl isothiocyanate was heated to boiling. Upon cooling, white needles separated. After recrystallization from ethanol, the m.p. was 179–180° uncor.

Calcd.[2] for $C_{20}H_{16}SN_2$: N, 8.86. Found: N, 9.40.

N-(2-Fluorenyl)-3-nitrophthalimide.—A mixture of 1 g. of 2-aminofluorene, 1.5 g. of 3-nitrophthalic anhydride and 15 ml. of dimethylaniline (solvent) was refluxed for 2 hours at the b.p. While still hot, 100 ml. of 95% ethanol was added. Shiny, golden flakes amounting to 0.4 g. when recrystallized from benzene of m.p. of 255.6° uncor. were obtained.

Calcd. for $C_{21}H_{12}O_4N_2$: N, 7.86. Found: N, 7.94.

New Derivatives of 2-Amino-9-fluorenone. N-2-(9-Oxo)-fluorenyl-4-nitrobenzamide.—A mixture of 0.5 g. of 2-aminofluorenone, 0.5 g. of *p*-nitrobenzoyl chloride and 10 ml. of pyridine was brought to the boiling point. While still hot, the mixture was filtered, diluted with 50 ml. of

(1) Abstracted from the M.S. thesis of W. W. Muelder.

(2) Analyses were performed by Dr. Carl Tiedcke of Teaneck, N. J.