Summary

The preparation and properties of 1-methyl-4-chloro(and bromo)-4-phenylpiperidines, 1-methyl-3,4-dibromo(and dihydroxy)-4-phenylpiperidines and 1-methyl-3-bromo(and hydroxy)-4-phenyl-1,2,3,6-tetrahydropyridines are described.

Some observations on the preparation of 1-methyl-4-phenyl-4-hydroxypiperidine (I) from the reaction of phenylmagnesium bromide with 1-methyl-4-piperidone are reported. An improved method for the preparation of I from this piperidone and phenyllithium is described.

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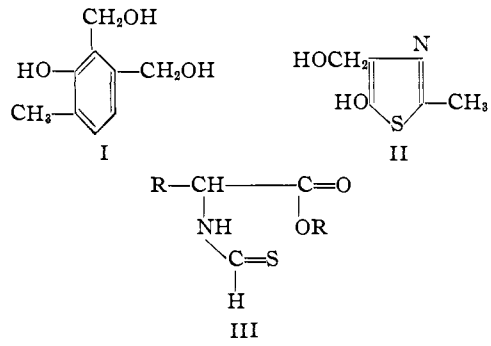
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

2-Methyl-5-ethoxythiazole and Related Compounds[1]

BY D. S. TARBELL, H. P. HIRSCHLER AND R. B. CARLIN

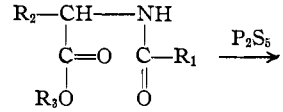
The possibility that analogs of pyridoxine (I) might have antimalarial activity was suggested by some observations of Seeler,[2] and the synthesis of pyridimidine[3] and thiazole[4] analogs of



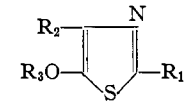
I II III

pyridoxine was therefore undertaken. The 5-hydroxythiazoles were virtually an unknown class of compounds when this work was started, and it therefore seemed of chemical, as well as of antimalarial, interest to investigate the preparation of 2-methyl-4-hydroxymethyl-5-hydroxythiazole II.[5]

One approach to the 5-hydroxythiazole structure would be the treatment of α-amino esters with dithioformic acid[6] followed by cyclization of the α-thioformylamino ester III. However, the reported cyclization[7] of α-acylaminoesters with phosphorus pentasulfide to yield 5-alkoxythiazoles offered an alternative approach. The present paper deals with a study of this cyclization reaction and with the properties of 2-methyl-5-ethoxythiazole.



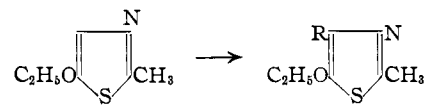
IV, $R_1 = CH_3$, $R_2 = H$, $R_3 = C_2H_5$
V, $R_1 = H$, $R_2 = CH_3$, $R_3 = CH_3$
VI, $R_1 = H$, $R_2 = CH_2OCH_3$, $R_3 = CH_3$



VII, $R_1 = CH_3$, $R_2 = CH_2OCH_3$, $R_3 = CH_3$
VIII, $R_1 = CH_3$, $R_2 = H$, $R_3 = C_2H_5$
IX, $R_1 = H$, $R_2 = CH_3$, $R_3 = CH_3$

It was found that 2-methyl-5-ethoxythiazole VIII could be isolated (as the picrate) in 65% yield from the cyclization of N-acetylglycine ethyl ester IV with phosphorus pentasulfide; the free base was readily obtained from the picrate by the convenient lithium hydroxide method.[8] The cyclization of N-formylalanine methyl ester (V), however, gave only a 22% yield of 4-methyl-5-methoxythiazole IX, and attempted cyclization of N-formyl- and N-acetylserine methyl ether methyl ester (VI and VII) under a variety of conditions gave only decomposition. This behavior was probably caused by the loss of methanol from the serine methyl ether derivatives, followed by polymerization of the acrylate, $CH_2{=}C(NHCOR)COOCH_3$, which would be formed.

2-Methyl-5-ethoxythiazole was found to be a liquid of pyridine-like odor, when pure; it was stable to aqueous alkali, but was decomposed by



VIII X, R = Br XI, R = NO_2

mineral acids when attempts were made to cleave the ether linkage. It formed a picrate,

(1) Part of this work was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Rochester.

(2) Seeler, *Proc. Soc. Exp. Biol. Med.*, **57**, 113 (1944).

(3) (a) McCasland, Tarbell, Carlin and Shakespeare, THIS JOURNAL, **68**, 2390 (1946); McCasland and Tarbell, *ibid.*, **68**, 2393 (1946).

(4) Conover and Tarbell, THIS JOURNAL, in press.

(5) More recently numerous cyclization reactions leading to 5-thiazolone (or 5-hydroxythiazoles) have been studied by Heilbron, A. H. Cook and co-workers (summarized by Heilbron, *J. Chem. Soc.*, 2099 (1949)). The preparation of 2-benzoyl-4-oxymethylene-5-thiazolone and some derivatives is described in "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, pp. 773, 847–848.

(6) *Cf.* Todd, *et al.*, *J. Chem. Soc.*, 361 (1937).

(7) Miyamichi, *J. Pharm. Soc. Japan*, No. 528, 103 (1926) [*C. A.*, **20**, 2679 (1926); *Chem. Zentr.*, **97**, I, 3402 (1926).

(8) Burger, THIS JOURNAL, **67**, 1615 (1945).

picrolonate, styphnate and a methiodide; the latter condensed with benzaldehyde to form a benzal derivative, the condensation doubtless occurring on the activated 2-methyl group.[9] Treatment with N-bromosuccinimide in the presence of benzoyl peroxide,[10] which was expected to yield the 2-bromomethyl compound,[11] formed instead the 4-bromo derivative X. The position of the bromine was indicated by its unreactive character, and by the fact that bromination of 2-methyl-5-ethoxythiazole with bromine in chloroform yielded the same product.

Nitration of VIII readily yielded 2-methyl-4-nitro-5-ethoxythiazole (XI). Neither the nitro compound nor the bromo compound formed a picrate, picrolonate or styphnate, although both derivatives gave hydrobromides; the basic character of the molecule seemed to be decreased by the negative group in the 4-position.

It should be noted that the presence of the electron-releasing ethoxyl group in the 5-position of the thiazole nucleus in VIII promotes electrophilic substitution at the 4-position; this position is ordinarily resistant to electrophilic attack, due to the effect of the ring nitrogen atom. The easy nitration of 3-ethoxypyridine, which is the pyridine analog of a 5-ethoxythiazole, to form 2-nitro-3-ethoxypyridine,[12] shows that the effect of an alkoxyl group in favoring electrophilic substitution is the same in both pyridine and thiazole rings.[13]

Experimental[14]

N-Formylalanine Methyl Ester (V).—An ether solution of diazomethane was prepared from 20 g. of nitrosomethylurea as described,[15] except that the ether solution was dried over potassium hydroxide pellets and used without distillation. This solution was added in portions consistent with a moderate reaction rate to a suspension of N-formylalanine[16] in 100 cc. of ether. When the reaction was nearly complete, the cooling bath was removed, and the mixture was permitted to stand overnight at room temperature. Glacial acetic acid was added dropwise until excess diazomethane was destroyed, the solution was filtered, the solvent was removed under reduced pressure, and the residual liquid was distilled. The principal fraction was a water-white liquid of the following properties: b. p. 92–94° (1 mm.); $n^{20}D$ 1.4515; weight 10.5 g. (94%).

Anal. Calcd. for $C_5H_9NO_3$: C, 45.80; H, 6.86. Found: C, 46.00; H, 7.11.

N-Formylserine Methyl Ether Methyl Ester (VI).—The methyl ester was prepared from the acid[17] with diazomethane. The ether solution of the product, obtained from 12 g. of acid and the diazomethane from 20 g. of nitrosomethylurea, was boiled, filtered and concentrated to 100 cc. On cooling in ice, the solution deposited 4.5 g. of glistening white needles, m.p. 47–48°. Concentration of the filtrate to 25 cc. and cooling caused another 2 g. of the product, m. p. 44–45°, to crystallize. The ether was removed from the filtrate, and the residual oil, on distillation, yielded a fraction, b. p. 125° (4 mm.), weight 3.0 g. This fraction solidified after seeding, making the total yield 9.5 g. (68%). A sample, after three recrystallizations from ether, had a m. p. of 48°.

Anal. Calcd. for $C_6H_{11}NO_4$: C, 44.71; H, 6.88. Found: C, 44.76; H, 6.97.

N-Acetylserine Methyl Ether (VII).—The following procedure is preferable to that of Synge.[18] Serine methyl ether[18] (17 g.) was dissolved in 30 cc. of water, and 22 cc. of acetic anhydride was added in one portion. The solution warmed up noticeably and, after the reaction was over, the mixture was evaporated *in vacuo* on the steam-bath as far as possible. Chloroform (50 cc.) was added to the residue and, after standing overnight, the suspended solid was collected. The product was taken up in acetone and concentrated on the steam-bath; the addition of 20 cc. of chloroform yielded, after standing overnight, 13.5 g. of product, m. p. 95–105°. It was best recrystallized from a mixture of nine volumes of chloroform to one of acetone (about 9 cc. per g.) and was obtained with the m. p. 110.5–111° (the reported value[18] is 108–109°). The product is very soluble in water, alcohol, acetone and dioxane.

4-Methyl-5-methoxythiazole (IX).—A suspension of 5 g. of crystalline phosphorus pentasulfide (obtained by extraction of crude Eastman Kodak Co. product with carbon disulfide in a Soxhlet apparatus) in a solution of 2.5 g. of N-formylalanine methyl ester in 50 cc. of chloroform was boiled for forty-eight hours, in an apparatus protected from moisture. The mixture was treated with two 50-cc. portions of 10% aqueous potassium hydroxide until the yellow gum present in the mixture disappeared, and the chloroform solution was washed twice with water. Most of the chloroform was removed, and 15 cc. of a saturated alcoholic solution of picric acid was added; the mixture was boiled until most of the remaining chloroform was removed. When the resulting dark solution was cooled, it deposited 1.3 g. of the crystalline picrate of 4-methyl-5-methoxythiazole, m. p. 146–147°. Concentration of the mother liquors yielded another 0.1 g. of product of the same m. p.: total yield was 22%.

Anal. Calcd. for $C_{11}H_{10}N_4O_8S$: C, 36.87; H, 2.82. Found: C, 36.88; H, 2.77.

Decomposition of a 3.4-g. sample of the picrate by lithium hydroxide solution, followed by extraction with chloroform and distillation of the product through a micro still at 20 mm., yielded 0.9 g. of the free base as a water-white liquid with a pronounced pyridine-like odor, with $n^{20}D$ 1.5170.

2-Methyl-5-ethoxythiazole (VIII).—Phosphorus pentasulfide was added in small portions to 20 g. of N-acetylglycine ethyl ester,[19] contained in a 3-neck flask fitted with a condenser and an efficient stirrer, while heating on a steam-bath with stirring. After about one-third of the amount required (40 g.) had been added, evolution of hydrogen sulfide commenced and the mixture turned dark red. The remainder of the pentasulfide was added at a rate sufficient to maintain the evolution of gas; a local excess of pentasulfide was avoided, because it tended to convert the creamy reaction mixture into lumps which caused the reaction to get out of control. When the mixture became too viscous to stir, 10 cc. of chloroform was added. Heating was continued for several hours after all of the pentasulfide had been added. The mixture was treated with 20% aqueous potassium hydroxide and the basic solution extracted several times with chloroform;

(9) *Cf.* Kondo and Nagasawa, *J. Pharm. Soc. Japan*, **57**, 249 (1937) [*C. A.*, **32**, 1699 (1938)]; Koelsch, THIS JOURNAL, **66**, 2126 (1944).

(10) Schmid and Karrer, *Helv. Chim. Acta*, **29**, 573 (1946).

(11) *Cf.* Duschinsky and Dolan, Emil Barell Jubilee Volume, p. 174, 1946.

(12) Koenigs, Gerdes and Sirot, *Ber.*, **61**, 1022 (1928); Schickh, Binz and Schulz, *ibid.*, **69**, 2593 (1936).

(13) The similarity of thiazoles and pyridines in substitution reactions has been frequently remarked (*e. g.*, Hantzsch, *Ann.*, **250**, 258 (1889); Ochiai and Nagasawa, *Ber.*, **72**, 1470 (1939); Wibaut, *ibid.*, p. 1708).

(14) Analyses by Mrs. G. Sauvage and Micro-Tech Laboratories.

(15) "Organic Syntheses," Coll. Vol. II, 1943, p. 165.

(16) Bilman, Jensen and Jensen, *Bull. soc. chim.*, [5] **1**, 1661 (1934).

(17) Schiltz and Carter, *J. Biol. Chem.*, **116**, 796 (1936); Carter and West, *Org. Syn.*, **20**, 81 (1940).

(18) Synge, *Biochem. J.*, **33**, 1931 (1939).

(19) Curtius, *J. prakt. Chem.*, **94**, 116 (1916).

the chloroform solution was washed with alkali, dried, the solvent was removed, and the residue was treated with alcoholic picric acid as described above. The resulting **picrate** (33.5 g., 65%) melted at 122° after recrystallization from alcohol. Miyamichi[5] also reported it to melt at 122°.

Anal. Calcd. for $C_{12}H_{12}N_4O_8S$: C, 38.71; H, 3.25. Found: C, 38.75; H, 3.27.

Decomposition of 22 g. of the picrate with lithium hydroxide, as described above, yielded 7 g. of the thiazole as an almost colorless liquid with b. p. 102–103° (38 mm.), $n^{20.5}D$ 1.5094.

Anal. Calcd. for C_6H_9NOS: C, 50.33; H, 6.33. Found: C, 50.00; H, 6.30.

The **styphnate** was prepared in alcohol solution, and melted at 128°.

Anal. Calcd. for $C_{12}H_{12}N_4O_9S$: C, 37.12; H, 3.19. Found: C, 37.53; H, 3.51.

In one run, the isolation of the thiazole by steam distillation of the alkaline solution was investigated. The distillate was saturated with salt and extracted with chloroform; the solution was then dried, the solvent removed and the residue fractionated *in vacuo*. The thiazole could not be obtained pure by fractionation, because there was a small amount of higher-boiling material, b. p. 87–93° (15 mm.), with a higher refractive index, from which the thiazole could not be separated. This material formed a *picrate*, m. p. 129–130°, which depressed the m. p. of the picrate of 2-methyl-5-ethoxythiazole.

Anal. Found: C, 37.5; H, 3.2.

The compound was not 2-methyl-5-ethoxyoxazole, because the picrate of that compound melts at 98°.[20] The styphnate melted at 124–125°, and gave a depression with the styphnate of 2-methyl-5-ethoxythiazole.

2-Styryl-5-ethoxythiazole Methiodide.—The methiodide of 2-methyl-5-ethoxythiazole was prepared by treating the thiazole with methyl iodide in ethanol; after several hours, the white precipitate which formed was collected and washed with cold ether; it melted at 109–110°. To 4.3 g. of this methiodide in 50 cc. of alcohol was added 1.6 g. of freshly distilled benzaldehyde and 0.5 cc. of piperidine. A red color developed rapidly and a yellow precipitate began to separate; after keeping at 60° for twenty hours, the precipitate was collected and recrystallized from alcohol; it weighed 1.7 g., and melted, with decomposition, above 170°. A solution of the styryl derivative in acetone reduced permanganate.

Anal. Calcd. for $C_{14}H_{16}INOS$: C, 45.05; H, 4.32. Found: C, 45.32; H, 4.41.

2-Methyl-4-bromo-5-ethoxythiazole (X). A. Using N-Bromosuccinimide.—To 15 g. (0.1 mole) of 2-methyl-5-ethoxythiazole in 50 cc. of dry carbon tetrachloride was added 18.80 g. (0.115 mole) of N-bromosuccinimide and 2.5 g. of benzoyl peroxide. The mixture became hot and, after the spontaneous reaction had subsided, it was refluxed for one hour, then cooled and filtered. The filtrate, a brown solution, was washed with cold dilute sodium hydroxide and was then diluted with petroleum ether. Purification was effected by passing the solution through a column of low grade alumina. Elution with benzene produced, after evaporation of the organic solvents, a yellow, mobile liquid which was fractionated several times. It yielded 18.5 g. (81%) of material boiling at 120° (11 mm.), $n^{19.5}D$ 1.5488.

Anal. Calcd. for C_6H_8BrNOS: C, 32.44; H, 3.63; Br, 36.3. Found: C, 32.72; H, 3.2; Br, 36.3.

B. **Using Bromine in Chloroform.**—The thiazole (1.0 g.) in 5 cc. of chloroform was treated with 1.3 g. of bromine in 5 cc. of chloroform. After standing overnight, the precipitate (1.6 g., m. p. 100–108°) was collected and recrystallized several times from absolute alcohol–ether; it formed light yellow rods, m. p. 137° (darkening at 127°), and was the hydrobromide of the above 4-bromo compound X as shown by the neutral equivalent (calcd., 303; found, 301). There was no depression on mixed m. p. with a sample of hydrobromide prepared from the N-bromosuccinimide bromination product.

The 4-bromo compound did not yield a picrate, styphnate or picrolonate; treatment with methyl iodide gave decomposition, with a strong odor of mercaptan, suggesting formation of an unstable sulfonium compound. The bromo compound was unchanged by treatment with hot aqueous or alcoholic alkali, with silver acetate in acetic acid, or with thiourea.

2-Methyl-4-nitro-5-ethoxythiazole (XI).—2-Methyl-5-ethoxythiazole (10 g.) was added slowly to 20 g. of concentrated sulfuric acid, which was cooled in an ice–salt mixture. When most of the thiazole had dissolved, 20 cc. of concentrated nitric acid (d. 1.5) was added dropwise. The mixture was allowed to stand in the ice-bath for several hours and was kept at room temperature overnight. The solution was poured into crushed ice, and the resulting precipitate collected and washed with a small amount of ice-water. The crude product (9 g., 68%) was recrystallized for analysis once from chloroform–petroleum ether and twice from absolute alcohol; it melted at 82°.

Anal. Calcd. for $C_6H_8N_2O_3S$: C, 38.30; H, 4.28. Found: C, 38.36; H, 4.23.

Summary

5-Alkoxythiazoles have been prepared by cyclization of α-acylaminoesters with phosphorus pentasulfide; the reaction fails with serine methyl ether derivatives. 2-Methyl-5-ethoxythiazole brominates readily in the 4-position, even with N-bromosuccinimide and benzoyl peroxide, and is easily nitrated to the 4-nitro compound. The 5-ethoxyl group promotes electrophilic attack in the 4-position, just as the ethoxyl group in 3-ethoxypyridine favors nitration of the normally resistant pyridine nucleus. Several new α-acylaminoesters are reported.

ROCHESTER, N. Y. RECEIVED DECEMBER 28, 1949

(20) Karrer and Gränacher, *Helv. Chim. Acta*, **1**, 776 (1924).