[A CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

Alkylation of 2-Aminothiazoles

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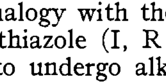
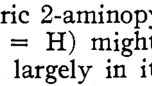
N,N-Disubstituted-2-aminothiazoles were prepared in good yield by the alkylation of N-substituted 2-aminothiazoles in the presence of lithium amide. This method was found to be unsatisfactory for the preparation of secondary amines from 2-aminothiazole. In the absence of a condensing agent, nuclear N-alkylated products were isolated.

In a previous communication from this Laboratory two methods for the preparation of 2-mono- and disubstituted aminothiazoles (I) were described, namely, the interaction of N-substituted thioureas with dimethyl chloroacetal and of amines with 2-bromothiazole.[2] The alkylation of 2-aminothiazole has since been studied as a more direct route to these compounds and constitutes the subject of this report.

By analogy with the isosteric 2-aminopyridine,[3] 2-aminothiazole (I, $R = R' = H$) might be expected to undergo alkylation largely in its imine form (II, $R = R' = H$) yielding, for the most part, 2-imino-3-substituted-thiazolines (II). Most compounds obtained by alkylating 2-aminothiazole have been presumed to have this imine structure (II),[4-9] although a few exceptions have been noted (I).[10-13] Rarely has the configuration been substantiated.[14] We have now established that, in the presence of a condensing agent, the reaction proceeds in such fashion as to yield compounds of type I; in its absence, N-substituted thiazolines were the only substances isolated.[14]



I



II

From the reaction of 2-aminothiazole with benzyl chloride there was obtained a substance whose properties differed from those of 2-benzylaminothiazole[2] but which appeared to be identical with the 2-imino-3-benzylthiazoline (II, $R = H$, $R' =$ benzyl) prepared by Druey[6] and Jensen and Thorsteinsson.[8] It seems likely, therefore, that the 2-*o*-chlorobenzylaminothiazole obtained by Karimullah[11] in a similar reaction has the imine configuration (II, $R = H$, $R' =$ *o*-chlorobenzyl). Since further benzylation of 2-benzylaminothiazole yielded the same compound (II, $R = R' =$ benzyl) as was isolated from the reaction of benzyl chloride and 2-imino-3-benzylthiazoline, it would appear that the secondary amine (I, $R' = H$, $R =$ benzyl) is better represented by formula II ($R' = H$, $R =$ benzyl).

Recently, Fox and Wenner[12] obtained a compound, designated as N,N-diethyl-N′-(2-thiazolyl)-ethylenediamine (III), by adding an aqueous solution of 2-diethylaminoethyl chloride hydrochloride to a refluxing mixture of 2-aminothiazole and sodium acetate in water. We have found that the dihydrochloride of this product is identical with that of the diamine (III) prepared previously from 2-bromothiazole and 2-diethylaminoethylamine.[2] By refluxing an alcoholic solution of 2-aminothiazole and 2-diethylaminoethyl chloride hydrochloride, there was obtained a dihydrochloride (IV) which differed from III·2HCl thus corroborating the 2-imino-3-(2-diethylaminoethyl)-thiazoline structure postulated by Druey (for IV).[6]

When 2-aminothiazole was treated with methylmagnesium iodide[15] followed by benzyl chloride, 2-benzylaminothiazole was formed, albeit in 6% yield. The same yield was obtained by the reaction of lithiated 2-aminothiazole with the aralkyl halide or by simply refluxing a mixture of 2-aminothiazole, benzyl chloride and lithium amide.[16] It was rather unexpected, therefore, to find that the latter procedure afforded good to excellent yields of N,N-disubstituted 2-aminothiazoles (I) from secondary 2-thiazolylamines. This represents a decided improvement over the previous methods which have been described for the preparation of these tertiary amines.[2]

Experimental[17]

Lithium amide,[18a] dimethyl chloroacetal,[18b] benzylamine,[18c] ethylamine,[18d] 2-dimethylaminoethyl chloride hydrochloride[19] and 2-diethylaminoethyl chloride hydrochloride[19] were obtained from commercial sources. N,N′-

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[1] From a thesis submitted by C. L. Parris to the Graduate Faculty of Brooklyn College, June, 1951, in partial fulfillment of the requirements for the Master of Arts degree.

[2] I. A. Kaye and C. L. Parris, THIS JOURNAL, **74**, 2271 (1952).

[3] (a) E. A. Steck and G. W. Ewing, *ibid.*, **70**, 3397 (1948); (b) N. Campbell and E. B. McCall, *J. Chem. Soc.*, 2411 (1951).

[4] R. Dahlbom and T. Ekstrand, *Svensk. Kem. Tid.*, **55**, 122 (1943); *C. A.*, **38**, 5208 (1944).

[5] E. Näf, *Ann.*, **265**, 108 (1892).

[6] J. Druey, *Helv. Chim. Acta*, **24**, 226E (1941).

[7] Y. Garreau, *Compt. rend.*, **226**, 814 (1948).

[8] K. A. Jensen and T. Thorsteinsson, *Dansk. Tids. Farm.*, **15**, 41 (1941); *C. A.*, **35**, 5109 (1941).

[9] G. Young and S. I. Crookes, *J. Chem. Soc.*, **89**, 59 (1906).

[10] P. Das-Gupta and P. Gupta, *J. Indian Chem. Soc.*, **22**, 364 (1945).

[11] Karimullah, *J. Chem. Soc.*, 961 (1937).

[12] H. H. Fox and W. Wenner, *J. Org. Chem.*, **16**, 225 (1951).

[13] R. Dahlbom and T. Ekstrand, *Svensk. Kem. Tid.*, **56**, 304 (1944); *C. A.*, **40**, 3415 (1946).

[14] Recently, I. A. Kaye, I. C. Kogon and C. L. Parris, THIS JOURNAL, **74**, 403 (1952), have proved that the product obtained from 2 aminothiazole and benzohydryl chloride, in the absence of a condensing agent, is the extranuclear alkylated product (I, $R =$ benzohydryl, $R' = H$). Although this is at variance with the findings in this investigation, a similar discrepancy has been noted in the alkylation of 2-aminopyridine.

[15] From 2-benzylaminopyridine, ethylmagnesium bromide and 2-bromoethylphthalimide, J. H. Gardner and J. R. Stevens, *ibid.*, **71**, 1868 (1949), isolated N-benzyl-N-(2-pyridylaminoethyl)-phthalimide in low yield.

[16] I. A. Kaye and I. C. Kogon, *ibid.*, **73**, 5891 (1951).

[17] Melting points are corrected; boiling points are not.

[18] Samples of these compounds were generously donated by (a) Metalloy Corp., (b) General Aniline and Film Corp., (c) Heyden Chemical Corp., and (d) Sharples Chemicals, Inc. The lithium amide was of 98% purity and the ethylamine was supplied as a 70% aqueous solution.

[19] Michigan Chemical Corp.

Dibenzylthiourea[20] was prepared in 79% yield from benzyl isothiocyanate[2] and benzylamine. N,N-Diethyl-N′-(2-thiazolyl)-ethylenediamine (III), b.p. 123–127° (0.4 mm.), was obtained in 48% yield by the method of Fox and Wenner.[12] The dihydrochloride melted at 181–183° after recrystallization from isopropyl alcohol and showed no depression in melting point on admixture with an authentic sample.[2] 2-Imino-3-ethylthiazoline hydroiodide,[6] m.p. 108.5–110.5° after recrystallization from isopropyl alcohol, was prepared by method B (*vide infra*) in 77% yield.

Anal. Calcd. for $C_5H_8N_2S{\cdot}HI$: N, 10.94. Found: N, 10.59.

2-Imino-3-(2-diethylaminoethyl)-thiazoline dihydrochloride,[6] m.p. 244–245° after recrystallization from isopropyl alcohol, was obtained in 86% yield (method B). The free base distilled at 97–98° (0.1 mm.).

Anal. Calcd. for $C_9H_{17}N_3S{\cdot}2HCl$: Cl, 26.05. Found: Cl, 25.88.

2-Imino-3-benzylthiazoline hydrochloride,[6,8] m.p. 182–183° after recrystallization from ethanol, was prepared similarly in 99% yield.

Anal. Calcd. for $C_{10}H_{10}N_2S{\cdot}HCl$: N, 12.25. Found: N, 12.25.

The free base, after three recrystallizations from hexane, melted at 52–53.5°.

Anal. Calcd. for $C_{10}H_{10}N_2S$: N, 14.72. Found: N, 14.65.

2-Benzylimino-3-benzylthiazoline Hydrochloride. By Method A.—A mixture of 25.6 g. (0.1 mole) of N,N′-dibenzylthiourea, 15.0 g. (0.12 mole) of dimethyl chloroacetal and 75 ml. of water was heated on a steam-bath for 16 hours. Upon cooling, the crystalline precipitate was separated and washed sparingly with water. The air-dried product weighed 26.0 g. (82%) and melted at 217.5–218° after three recrystallizations from isopropyl alcohol.

Anal. Calcd. for $C_{17}H_{16}N_2S{\cdot}HCl$: N, 8.85. Found: N, 8.73.

Method B.—A solution of 3.85 g. (0.02 mole) of 2-benzylaminothiazole[2] and 3.2 g. (0.025 mole) of benzyl chloride in 50 ml. of isopropyl alcohol was refluxed for 24 hours. The solvent was removed by distillation and the gummy residue, after suspension in hot benzene, was filtered, washed with the hot solvent and recrystallized from isopropyl alcohol. Four grams of the salt (63%), m.p. 217–219°, was obtained.

Method C.—A mixture of 11.4 g. (0.05 mole) of 2-imino-3-benzylthiazoline hydrochloride, 7.6 g. (0.06 mole) of benzyl chloride, 20.0 g. of anhydrous potassium carbonate and 110 ml. of 90% isopropyl alcohol was refluxed 24 hours. After cooling, the mixture was filtered and the residue washed several times with isopropyl alcohol. The solvent was removed by distillation and the residue distilled *in vacuo*. The yellow oil, b.p. 168–170° (0.03 mm.), weighed 9.0 g. (64%).

Anal. Calcd. for $C_{17}H_{16}N_2S$: N, 9.99. Found: N, 9.84.

The hydrochloride, prepared in ether and recrystallized from isopropyl alcohol, melted at 216–218° and showed no depression in melting point on admixture with product obtained by either of the foregoing methods.

2-Benzylimino-3-ethylthiazoline.—Prepared by method C from 2-imino-3-ethylthiazoline hydroiodide and benzyl chloride, the base, b.p. 120–124° (0.06 mm.), was obtained in 71% yield.

Anal. Calcd. for $C_{12}H_{14}N_2S$: N, 12.84. Found: N, 12.59.

The oxalate melted at 144–145° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{12}H_{14}N_2S{\cdot}H_2C_2O_4$: N, 9.08. Found: N, 8.95.

2-Ethylimino-3-benzylthiazoline.—Prepared by method C from 2-imino-3-benzylthiazoline hydrochloride and ethyl iodide, the base, b.p. 113–114° (0.07 mm.), was obtained in 75% yield.

Anal. Calcd. for $C_{12}H_{14}N_2S$: N, 12.84. Found: N, 12.56.

The oxalate melted at 147–149° after recrystallization from isopropyl alcohol. A mixture with the oxalate of 2-benzylimino-3-ethylthiazoline melted at 125–130°.

Anal. Calcd. for $C_{12}H_{14}N_2S{\cdot}H_2C_2O_4$: N, 9.08. Found: N, 9.05.

2-Dibenzylaminothiazole.[2]—A mixture of 9.6 g. (0.05 mole) of 2-benzylaminothiazole,[2] 7.6 g. (0.06 mole) of benzyl chloride and 1.4 g. (0.06 mole) of lithium amide in 100 ml. of dry benzene was refluxed for 24 hours and then filtered. The insoluble material was washed several times with hot benzene, the solvent removed from the filtrate, and the residue distilled *in vacuo*. The pale yellow oil, b.p. 148–154° (0.04 mm.), weighed 8.6 g. (61%). The hydrochloride melted at 166–167°. The following compounds were prepared similarly: 2-benzylaminothiazole (6%, from 2-aminothiazole), m.p. 126–127°; 2-N-benzyl-N-ethylaminothiazole (72%, from 2-ethylaminothiazole), b.p. 109–113° (0.04 mm.), picrate m.p. 152–153.5°; N,N-dimethyl-N′-benzyl-N′-(2-thiazolyl)-ethylenediamine (89%, from 2-benzylaminothiazole), b.p. 119–121° (0.05 mm.), oxalate m.p. 157–158°; N,N-diethyl-N′-benzyl-N′-(2-thiazolyl)-ethylenediamine (89%, from 2-benzylaminothiazole), b.p. 134–135° (0.06 mm.), oxalate m.p. 149–150°. 2-Benzylaminothiazole, which was also obtained in 6% yield by a modification of the method of Gardner and Stevens,[15] and the salts of the tertiary amines were recrystallized from isopropyl alcohol and showed no depression in melting point on admixture with authentic samples.[2]

The picrate of N,N-dimethyl-N′-benzyl-N′-(2-thiazolyl)-ethylenediamine has been described[21] as melting at 138–141°. The picrate of our product melted at 121.5–123° after three recrystallizations from isopropyl alcohol.

Anal. Calcd. for $C_{14}H_{19}N_3S{\cdot}C_6H_3N_3O_7$: N, 17.49. Found: N, 17.16.

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(20) E. A. Werner, *J. Chem. Soc.*, **59**, 396 (1891). H. Salkowski, *Ber.*, **24**, 2724 (1891).

(21) C. W. Sondern and P. J. Breivogel, U. S. Patent 2,440,703, May 4, 1948.