[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BROOKLYN COLLEGE]

6-METHOXY-2-BENZOTHIAZOLYLAMINES. AN EXTRANUCLEAR N-ALKYLATION OF A 2-AMINOBENZOTHIAZOLE

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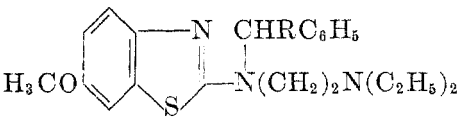
As part of a program involving the preparation of N-(1,2-diphenylethyl)-N-heterocyclic amines as potential antimitotic agents (1) and of N,N,dialkyl-N′-aralkyl-N′-heterocyclic ethylenediamines as histamine antagonists (2), the synthesis of the 6-methoxy-2-benzothiazolyl tertiary amines represented by formula I was projected (3).



A; R = H
B; R = $CH_2C_6H_5$

I

Some of the relatively few N,N-disubstituted 2-aminobenzothiazoles described in the literature have recently been made by heating a mixture of a 2-chlorobenzothiazole and a secondary amine (4–7). While yields are generally good, the method suffers from the disadvantage that the 2-chlorobenzothiazoles are generally prepared in low yield from the corresponding 2-aminobenzothiazoles by a diazotization process which is best adapted to the preparation of small amounts of material (6, 7).

Direct alkylation of the amino group, a method used so successfully in the preparation of basically substituted 2-pyridylamines (2), has enjoyed but limited success in this heterocyclic system. When the aryl ring is either unsubstituted (8, 9) or contains alkyl (4, 10), bromo (4), or chloro (4) substituents, 2-benzothiazolyl primary amines are alkylated only on the nuclear nitrogen (in the absence of a condensing agent). This and other reactions of the 2-aminobenzothiazoles have led previous investigators to assume that these compounds, as well as their extranuclear N-monosubstituted derivatives, exist chiefly as the tautomeric 2-iminobenzothiazolines (9, 10). The presence of a nitro group in the aromatic nucleus alters the direction of alkylation. In this case there is obtained a mixture in which the nuclear N-substituted product predominates somewhat (4). When sodium ethoxide is employed as the condensing agent, extranuclear N-alkylation is favored. Nitro-2-aminobenzothiazoles are alkylated exclusively in the 2-position. With other substituents, mixtures result, 65–88% of which are non-nuclear-substituted products (4). Alkylation of 2-acylaminobenzothiazoles, in the presence of sodium ethoxide, proceeds solely on the amide nitrogen (8, 9). Since an acyl group is easily introduced and removed, this appears to offer a good route for the preparation of 2-monoalkylaminobenzothiazoles. The prepa-

ration of 2-arylaminobenzothiazoles by fusion of a 2-aminobenzothiazole with a primary aromatic amine (10) has not been shown to be generally applicable.

Very little information has been recorded concerning the further alkylation of these compounds. Although Brewster and Dains (10) were unable to effect dialkylation of substituted 2-aminobenzothiazoles by prolonged heating at elevated temperatures, Wagner-Jauregg and Helmert (9) have described the ring N-ethylation of 2-ethylaminobenzothiazole.

Previous work in this laboratory (11) has shown that when 2-aminothiazole is lithiated with lithium amide and then brought into reaction with an alkyl halide, only a small amount of the desired 2-alkylaminothiazole is formed (two-step reaction). Treatment of a 2-alkylaminothiazole in the same manner yields none of the expected 2-dialkylamino product. The latter, however, is prepared in excellent yield simply by refluxing a mixture of all three reactants; *i.e.*, a non-nuclear N-substituted 2-aminothiazole, lithium amide, and an alkyl halide. (This method offered no improvement in yield over the two-step procedure for the preparation of monoalkylated 2-aminothiazoles.) Application of this technique, in the present investigation, to a 2-substituted aminobenzothiazole, was equally successful. The reaction between 2-benzylamino-6-methoxybenzothiazole (II) and β-diethylaminoethyl chloride hydrochloride, in the presence of lithium amide, gave an almost quantitative yield of N,N-diethyl-N′-benzyl-N′-(6-methoxy-2-benzothiazolyl)ethylenediamine (I A).

The secondary amine (II) was prepared by bromination of N-benzyl-N′-anisylthiourea. This method, employed by others (10, 12) for the preparation of extranuclear N-mono- and di-substituted 2-aminobenzothiazoles, was also used for the preparation of our tertiary amines (I A and B). One of the products (I A) was identical with that obtained by alkylating 2-benzylamino-6-methoxybenzothiazole (II).

$$C_6H_5RC{=}O + H_2N(CH_2)_2N(C_2H_5)_2 \rightarrow C_6H_5RC{=}N(CH_2)_2N(C_2H_5)_2$$

$$\downarrow H_2$$

$$4\text{-}(CH_3O)C_6H_4NHCSNR'CHRC_6H_5 \xleftarrow{4\text{-}(CH_3O)C_6H_4N{=}C{=}S} C_6H_5RCHNH(CH_2)_2N(C_2H_5)_2$$

IV

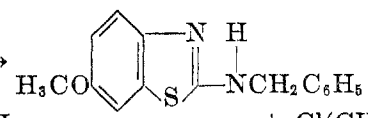
R′ = $(CH_2)_2N(C_2H_5)_2$

III A; R = H

III B; R = $CH_2C_6H_5$

$\downarrow Br_2$

I (A and B)

III C $\xrightarrow{Br_2}$ 

II

R = R′ = H + $Cl(CH_2)_2N(C_2H_5)\cdot HCl + LiNH_2 \rightarrow$ I A

Both the alkylation and ring-closure methods are convenient procedures for preparing tertiary amines of this type (I) in good yield. The latter method is limited mainly by the availability or ease of preparation of the requisite secondary amine (IV). In the alkylation procedure, it would appear that intermediate secondary amines (similar to II) might be more conveniently prepared by lithium aluminum hydride reduction of 2-acylaminobenzothiazoles or by reductive alkylation of 2-aralkylideneaminobenzothiazoles with Grignard reagents, methods successfully employed in the preparation of analogous thiazole derivatives (11, 13a, b).

One of the compounds (I A) has shown only 0.1% of the antihistaminic activity of Pyribenzamine in preliminary *in vitro* studies on the isolated guinea pig ileum strip. Against acetylcholine it had 0.1% of the activity of atropine. A more detailed account of further results of the pharmacological screening of these compounds will be described elsewhere.

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EXPERIMENTAL

All melting points are corrected; boiling points are not. The preparation of 1,2-diphenylethylamine was described in a previous publication (13b). The β-diethylaminoethylamine, diethylaminoethyl chloride hydrochloride, 10% palladium-charcoal, and lithium amide were obtained from commercial sources.

N,N-Diethyl-N'-benzylethylenediamine (IV A). After 64 g. (0.55 mole) of β-diethylaminoethylamine was added in small portions, with stirring and cooling, to 53.0 g. (0.5 mole) of benzaldehyde the cloudy mixture was heated on a steam bath for 1.5 hours and then dissolved in 150 ml. of absolute ethanol. The solution, hydrogenated at an initial pressure of 58 lbs. in the presence of 5 g. of 10% palladium-charcoal catalyst, absorbed the theoretical amount of hydrogen in 35 minutes. After removal of the catalyst and solvent, vacuum-distillation of the residue yielded 94.9 g. (92%) of product boiling at 118–121° (3 mm.). This represents an improvement over the procedure of Villani and co-workers who obtained this compound in 56% yield by another method (14).

N,N-Diethyl-N'-(1,2-diphenylethyl)ethylenediamine (IV B). A solution of 23.2 g. (0.2 mole) of β-diethylaminoethylamine and 39.2 g. (0.2 mole) of desoxybenzoin in 100 ml. of thiophene-free benzene was refluxed for 2.5 hours, the water liberated in the reaction being collected in a moisture trap. The solvent was removed by distillation and replaced by 100 ml. of propanol-2. The solution was hydrogenated at an initial pressure of 58 lbs. in the presence of 2 g. of 10% palladium-charcoal catalyst, the theoretical amount of hydrogen being absorbed in about 1.5 hours. After removing the catalyst and solvent and vacuum-distilling the residue, 53.9 g. (91%) of a light-yellow oil, distilling at 158–160° (0.3 mm.), was obtained.

Anal. Calc'd for $C_{20}H_{28}N_2$: N, 9.45. Found: N, 8.78.

The analysis of the re-distilled product deviated even more from the theoretical value (Found: N, 8.25). Despite the poor analysis, the diamine formed the thiourea III B in good yield. It is interesting to note that the N,N-diethyl-N'-benzylethylenediamine prepared by Villani, *et al.* (14) similarly analyzed too low for nitrogen even after re-distillation.

p-Anisyl isothiocyanate. Although this compound has been prepared in better yield by others (15), it was made more conveniently by an adaptation of the method described in Organic Syntheses (16) for the preparation of methyl isothiocyanate.

To a stirred mixture of 24.0 g. (0.6 mole) of sodium hydroxide dissolved in 300 ml. of water and 45.6 g. (0.6 mole) of carbon disulfide, solid *p*-anisidine was added in small portions while maintaining the reaction temperature below 15°. The thick suspension was heated, with stirring, on a steam-bath for 1.5 hours. After adding 65.2 g. (0.6 mole) of ethyl chlorocarbonate and heating, with stirring, for an additional one-half hour, the mixture was filtered and the residue washed well with both ether and water. The residue (43.2 g.) probably consisted of *sym*-di-*p*-anisylthiourea but was not investigated further. The ether layer was separated from the aqueous part of the filtrate. The latter was extracted several times and the combined ether extracts were dried over potassium carbonate. The ether was removed by distillation. The residue, on distillation *in vacuo*, yielded 47.1 g. (47%) of a light yellow liquid, b.p. 93–96° (0.4 mm.).

N-Benzyl-N-(β-diethylaminoethyl)-N'-(p-anisyl)thiourea (III A). A solution of 20.6 g. (0.1 mole) of N,N-diethyl-N'-benzylethylenediamine in 50 ml. of acetone was added cautiously to a cold solution of 16.5 g. (0.1 mole) of *p*-anisyl isothiocyanate in 50 ml. of acetone. The mixture was refluxed for 15 minutes, then poured into ice-water. After standing *ca.* 0.5 hour, the bulky precipitate was separated, washed with water, and air-dried. The white crystalline solid weighed 33.8 g. (91%), m.p. 120–125°. After one recrystallization from propanol-2, the compound melted at 128.5–129°. Further recrystallization from this solvent did not change the melting point.

Anal. Calc'd for $C_{21}H_{29}N_3OS$: N, 11.31. Found: N, 11.31.

N-(1,2-Diphenylethyl)-N-(β-diethylaminoethyl)-N'-(p-anisyl)thiourea (III B). Prepared by the same procedure used in synthesizing III A, the crude product was obtained in 97% yield, m.p. 133–136°. After 3 recrystallizations from propanol-2, the analytical sample melted at 136–137°.

Anal. Calc'd for $C_{28}H_{35}N_3OS$: N, 9.11. Found: N, 9.11.

N-Benzyl-N'-(p-anisyl)thiourea (III C). A solution of 14.9 g. (0.1 mole) of benzyl isothiocyanate, prepared by the method described in Organic Syntheses (16), and 12.3 g. (0.1 mole) of *p*-anisidine in 50 ml. of benzene was refluxed for 3 hours. On removing the solvent and chilling, the residue crystallized. The crude product, after washing with cold propanol-2 and air-drying, weighed 26.0 g. (96%), m.p. 100–107°. After three recrystallizations from propanol-2, the compound melted at 108–109°.

This compound has previously been prepared by the reaction of benzylamine with *p*-anisyl isothiocyanate, m.p. 109° (17).

N,N-Diethyl-N'-benzyl-N'-(6-methoxy-2-benzothiazolyl)ethylenediamine (I A). A solution of 9.3 g. (0.058 mole) of bromine in 25 ml. of chloroform was added dropwise to a stirred solution of 18.4 g. (0.0495 mole) of N-benzyl-N-(β-diethylaminoethyl)-N'-(*p*-anisyl)thiourea (III A) dissolved in 100 ml. of the same solvent while keeping the reaction temperature below 30°. The mixture was then refluxed with stirring for 6 hours during which time hydrogen bromide was evolved. After removal of the chloroform by distillation, the crude hydrobromide was dissolved in 600 ml. of hot water. Ammonia water was added until the mixture was alkaline and the product was then extracted several times with ether. After the combined ether extracts were dried over potassium carbonate and the solvent removed, distillation of the residue *in vacuo* yielded 15.3 g. (84%) of a yellow oil, b.p. 195–197° (0.08 mm.). The *oxalate*, prepared in ether, melted at 163–164° after three recrystallizations from propanol-2.

Anal. Calc'd for $C_{21}H_{27}N_3OS \cdot H_2C_2O_4$: N, 9.14. Found: N, 9.15.

N,N-Diethyl-N'-(1,2-diphenylethyl)-N'-(6-methoxy-2-benzothiazolyl)ethylenediamine (I *B*). Using the procedure described above (for I A), 18.0 g. (0.039 mole) of the thiourea (III B) gave 14.9 g. (83%) of a very viscous, dark red oil, b.p. 230–238° (0.1 mm.).

Anal. Calc'd for $C_{28}H_{33}N_3OS$: N, 9.14. Found: N, 9.08.

The *oxalate*, prepared in ether, melted at 145.5–147° after four recrystallizations from propanol-2.

Anal. Calc'd for $C_{28}H_{33}N_3OS \cdot H_2C_2O_4$: N, 7.64. Found: N, 7.61.

2-Benzylamino-6-methoxybenzothiazole (II). The directions for the preparation of I A and I B were followed. The base [from 48.7 g. (0.179 mole) of N-benzyl-N'-anisylthiourea]

crystallized on treatment of an aqueous suspension of the intermediate hydrobromide with ammonia water. It was removed, washed with water, and air-dried. The crude product weighed 45.6 g. (94%), m.p. 132–135°. After two recrystallizations from propanol-2 the melting point remained constant at 136–136.5°.

Anal. Calc'd for $C_{15}H_{14}N_2OS$: N, 10.35. Found: N, 10.25.

N,N-Diethyl-N'-benzyl-N'-(6-methoxy-2-benzothiazolyl)ethylenediamine (I A) by alkylation of 2-benzylamino-6-methoxybenzothiazole. A mixture of 13.5 g. (0.05 mole) of 2-benzylamino-6-methoxybenzothiazole (II), 10.3 g. (0.06 mole) of diethylaminoethyl chloride hydrochloride, and 2.8 g. (0.12 mole) of 98% lithium amide in 100 ml. of dry benzene was refluxed for 23 hours. The mixture was filtered, the residue washed with benzene, and the solvent removed from the filtrate by distillation. Vacuum-distillation of the residual oil yielded 17.8 g. (96%) of a yellow oil, b.p. 208–215° (0.09 mm.).

Anal. Calc'd for $C_{21}H_{27}N_3OS$: N, 11.37. Found: N, 11.20.

The *oxalate*, m.p. 163.5–165° after one recrystallization from propanol-2, on admixture with product obtained by ring synthesis, melted at 163–165°.

SUMMARY

N,N-Diethyl-N'-(benzyl and 1,2-diphenylethyl)-N'-(6-methoxy-2-benzothiazolyl)ethylenediamines (I A and B), as well as 2-benzylamino-6-methoxybenzothiazole (II), were prepared by ring closure of the corresponding N,N,N'-tri- and N,N'-di-substituted thioureas with bromine. One of the products (I A) was also prepared by the alkylation of II with diethylaminoethyl chloride hydrochloride in the presence of lithium amide. This is apparently the first recorded instance of the preparation of a 2-disubstituted aminobenzothiazole by the N-alkylation of a 2-monosubstituted aminobenzothiazole. The product (I A) showed little activity against histamine or acetylcholine.

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