[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, QUEEN'S UNIVERSITY]

SYNTHESES OF SUBSTITUTED β,β'-DICHLORODIETHYLAMINES

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Received November 28, 1949

The nitrogen mustards, as chemotherapeutic agents for cancer, have attracted considerable attention, since their action on living cells closely resembles that of x-rays (1). It has been emphasized by Gilman and Philips (1) that the effects of the nitrogen mustards rival those of short-wave radiation, and that no other class of chemical agents has been found to exhibit the same specificity of action on chromosomal structures.

At the present time only *bis*-(β-chloroethyl)methylamine and *tris*-(β-chloroethyl)amine have been subjected to extensive clinical examination. Both these compounds, administered as the hydrochlorides, have given promising results in the treatment of several neoplastic diseases including Hodgkin's disease and lymphatic leukemia (2). Furthermore, they have been shown to be of value in inducing temporary symptomatic remissions in Hodgkin's disease where x-ray treatment no longer seemed feasible or effective (3). One disadvantage in the use of nitrogen mustards is that they have a general cytotoxic effect. All rapidly proliferating tissue is especially subject to this action. Thus one of the undesirable side reactions of these compounds is their cytotoxic effect on normal hematopoietic tissue (3).

Of particular interest in the selection of specific nitrogen mustards to be synthesized for future testing are those having groups already known to possess special biological properties. The resulting substituted nitrogen mustards might be expected to retain in part some of the biological properties associated with these groups, or perhaps by virtue of these structures to exert a more selective toxic action. It was with these considerations in view that the present work was undertaken.

It was decided to prepare substituted nitrogen mustards containing the phenanthrene nucleus and the diphenylethane structure. This decision was based on the findings of Turner (4) who tested 75 phenanthrene derivatives on transplanted sarcomas in mice. He found tumor regression rates ranging from none to 50%. Phenanthrene itself, when applied to the skin of mice in conjunction with either of the carcinogens 3,4-benzopyrene or 1,2,5,6-dibenzanthracene, reduced the rate of tumor induction (5). On the other hand some mitotic poisons, *e.g.*, α,β-di-(*p*-methoxyphenyl)ethylamine, which warrant the attention of those seeking a chemotherapeutic agent to combat a disease characterized by uncontrolled cell division, possess the diphenylethane structure. The specific compounds prepared were the hydrochlorides of N,N-*bis*-(β-chloroethyl)-9-aminomethylphenanthrene, N,N-*bis*-(β-chloroethyl)-β,γ-diphenyl-*n*-propylamine, and N,N-*bis*-(β-chloroethyl)-β,γ-di-*p*-anisyl-*n*-propylamine.

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In order to compare the two methods available for the preparation of *bis*-(β-hydroxyethyl)amines, *n*-butylamine was treated with ethylene oxide, and *n*-butyl bromide was treated with diethanolamine. Although the yields (85%) of *bis*-(β-hydroxyethyl)-*n*-butylamine by these two methods were the same, the more convenient ethylene oxide method was adopted for subsequent preparations. *Bis*-(β-hydroxyethyl)-*n*-butylamine hydrochloride was chlorinated with thionyl chloride giving a 53% yield of *bis*-(β-chloroethyl)-*n*-butylamine hydrochloride.

9-Bromophenanthrene (6, 7), was converted to 9-cyanophenanthrene (8) in 70% yield as described by Mosettig and van de Kamp (9). Hydrolysis of 9-cyanophenanthrene resulted in a 97% yield of phenanthrene-9-carboxylic acid, while reduction in glacial acetic acid with Adams' catalyst gave an 83% yield of 9-aminomethylphenanthrene (10). 9-Aminomethylphenanthrene on treatment with ethylene oxide and isolation of the product as the hydrochloride gave N,N-*bis*-(β-hydroxyethyl)-9-aminomethylphenanthrene (94% yield) which was finally chlorinated with thionyl chloride to give a quantitative yield of N,N-*bis*-(β-chloroethyl)-9-aminomethylphenanthrene hydrochloride.

β,γ-Diphenylpropylamine was prepared from α-phenylcinnamonitrile [obtained in 95% yield by condensation of benzaldehyde with benzylcyanide according to Frost (11)] by catalytic reduction in glacial acetic acid with Adams' catalyst. The product was obtained in 46% yield. Unchanged α-phenylcinnamonitrile and some secondary amine were also isolated. The reduction of the nitrile to the amine in 14% yield by use of sodium in ethanol had been reported by Freund and Remse (12), catalytically with nickel in 60% yield by Braun, Bayer, and Cassel (13), and with Raney nickel in ethanol and liquid ammonia in 88% yield by Freeman, Ringk, and Spoerri (14). The amine was readily converted with ethylene oxide to the N,N-*bis*-(β-hydroxyethyl)amine from which N,N-*bis*-(β-chloroethyl)-β,γ-diphenyl-*n*-propylamine hydrochloride was obtained in good yield by treatment with thionyl chloride.

The condensation of anisaldehyde with *p*-methoxybenzyl cyanide to give *p*,*p*′-dimethoxy-α-cyanostilbene as described by Niederl and Ziering (15) was affected in 85% yield. The reduction of *p*,*p*′-dimethoxy-α-cyanostilbene in glacial acetic acid with Adams' catalyst gave the desired β,γ-di-(*p*-methoxyphenyl)-*n*-propylamine (40% yield) along with some unchanged *p*,*p*′-dimethoxy-α-cyanostilbene. β,γ-Di-(*p*-methoxyphenyl)-*n*-propylamine was treated next with ethylene oxide and the product, N,N-*bis*-(β-hydroxyethyl)-β,γ-di-*p*-anisyl-*n*-propylamine, as the hydrochloride was chlorinated with thionyl chloride. The over-all yield of N,N-*bis*-(β-chloroethyl)-β,γ-di-*p*-anisyl-*n*-propylamine hydrochloride from β,γ-di-(*p*-methoxyphenyl)-*n*-propylamine was 92%.

The pharmacological properties of the substituted *bis*-(β-chloroethyl)amines reported in this paper are under investigation at the Massachusetts General Hospital, Boston. The results of these studies will be published elsewhere.

Acknowledgement. The authors wish to thank the National Cancer Institute of Canada for full support of this work and a grant-in-aid to one of them (H. H. B.)

EXPERIMENTAL[2]

Bis-(β-chloroethyl)-n-butylamine hydrochloride. Method A. Into a mechanically-stirred solution of 38.5 g. (0.526 mole) of *n*-butylamine in 115 cc. of water was bubbled 53.4 g. (1.21 moles) of ethylene oxide over a period of 6½ hours. The reaction product was then fractionated *in vacuo* and 72 g. (85%) of *bis-(β*-hydroxyethyl)-*n*-butylamine (b.p.$_3$ 112–117°) was obtained. The hydrochloride of this amine in 100 cc. of toluene was treated drop-wise with 140 g. (1.18 mole) of thionyl chloride under stirring over a period of 1¼ hours. The solution was then refluxed for two hours, and the toluene and excess thionyl chloride were removed *in vacuo*. The residue was dissolved in acetone and toluene was added to turbidity. On cooling at −20° for several days, a crystalline product (m.p. 67–74°) separated, yield 42.8 g. (52%). Four wasteful crystallizations from acetone-toluene raised the melting point to 95–96°.

Anal. Calc'd for $C_8H_{18}Cl_3N$: C, 40.9; H, 7.73; Cl, 45.3; N, 5.9.
Found: C, 41.0; H, 7.69; Cl, 45.2; N, 6.0.

Method B. A mixture of 43 g. (0.314 mole) of *n*-butyl bromide, 20 g. (0.190 mole) of diethanolamine, and 19.7 g. (0.143 mole) of potassium carbonate was refluxed for eight hours. To facilitate filtration 50 cc. of ethanol was added. The potassium bromide and unchanged potassium carbonate were removed and washed with ethanol (3 × 15 cc.). Vacuum-distillation of the filtrate gave 26.1 g. (85%) of *bis-(β*-hydroxyethyl)-*n*-butylamine. This latter compound was converted to *bis-(β*-chloroethyl)-*n*-butylamine hydrochloride (m.p. 75.5–76.5°) in 53% yield by the above procedure. The pure product melted at 95–96° alone and on admixture with a sample prepared by Method A.

9-Bromophenanthrene (m.p. 63.8–64.8°) was prepared in 52% yield as previously described (7).

9-Cyanophenanthrene was obtained in a purified yield of 70% (m.p. 111.0–111.3°) by heating 9-bromophenanthrene with cuprous cyanide (8, 9).

9-Phenanthroic acid. 9-Cyanophenanthrene was converted to 9-phenanthroic acid (m.p. 256.5–257.5°) in a manner similar to that reported by Goldberg, Ordas, and Carsch (16). They reported m.p. 252–253°.

9-Aminomethylphenanthrene (m.p. 108.2–108.8°) was prepared in 83% yield by the method of van de Kamp, Burger, and Mosettig (10).

N,N-Bis-(β-hydroxyethyl)-9-aminomethylphenanthrene hydrochloride. A solution of 6.9 g. (0.033 mole) of 9-aminomethylphenanthrene in 26 cc. of methanol was held at 56–57° and 3.2 g. (0.073 mole) of ethylene oxide was allowed to slowly bubble into the solution over a period of 2¼ hours. After the addition was complete, the reaction mixture was aged for a further period of one hour at 57° and then left at room temperature for 5½ hours. The methanol and excess ethylene oxide were removed *in vacuo* and the residual viscous oil was treated with 5.5 cc. of conc'd hydrochloric acid. On standing overnight, the solution deposited 10.4 g. (94%) of N,N-*bis-(β*-hydroxyethyl)-9-aminomethylphenanthrene hydrochloride melting at 173.5–174.7°. Three crystallizations from ethanol gave a good yield of product melting at 176.2–176.8°.

The hydrochloride is soluble in methanol and hot ethanol. It is less soluble in cold ethanol and very slightly soluble in acetone and benzene.

Anal. Calc'd for $C_{19}H_{22}ClNO_2$: C, 68.7; H, 6.68; Cl, 10.70; N, 4.2.
Found: C, 68.9; H, 6.42; Cl, 10.65; N, 4.2.

N,N-Bis-(β-chloroethyl)-9-aminomethylphenanthrene hydrochloride. A mixture of 6.32 g. (0.019 mole) of N,N-*bis-(β*-hydroxyethyl)-9-aminomethylphenanthrene hydrochloride and 35 cc. of benzene under a reflux condenser was treated with 6.12 g. (0.0514 mole) of thionyl chloride. When the mixture was warmed to approximately 40°, a vigorous reaction ensued. Heating was then discontinued and after 15 minutes the reaction subsided. On further warming crystals formed and the flask was gently shaken during the crystallization period.

[2] All melting points have been corrected against reliable standards.

After refluxing for a period of one hour, the mixture was kept at room temperature overnight. The crystals were washed with benzene (10 cc.). In this way, 7.03 g. (100%) of N,N-*bis*-(β-chloroethyl)-9-aminomethylphenanthrene hydrochloride (m.p. 182–183.3°) was obtained. One crystallization from ethanol (7.15 cc./g.) failed to raise the melting point, which was found to be somewhat dependent on the rate of heating. The hydrochloride is soluble in hot methanol and hot ethanol but insoluble or slightly soluble in acetone and benzene.

Anal. Calc'd for $C_{19}H_{20}Cl_3N$: C, 61.9; H, 5.47; Cl, 28.8; N, 3.8.
Found: C, 62.2; H, 5.21; Cl, 28.6; N, 4.0.

α-Phenylcinnamonitrile (m.p. 86.0–86.3°) was prepared in 95% yield from benzyl cyanide and benzaldehyde by a procedure similar to that employed by Frost (11).

β,γ-Diphenyl-n-propylamine hydrochloride and di-(β,γ-diphenyl-n-propyl)amine hydrochloride. Seven grams (0.034 mole) of α-phenylcinnamonitrile was dissolved in 100 cc. of glacial acetic acid (distilled over potassium permanganate) and 200 mg. of Adams' catalyst added. The mixture was shaken for 65 hours in a low pressure (55 p.s.i) hydrogenation apparatus. The catalyst was filtered off and the filtrate evaporated *in vacuo* to a viscous oil which was separated into its components through their hydrochlorides. By triturating the hydrochlorides with ether (25 cc.), the unreacted α-phenylcinnamonitrile was extracted. The undissolved material was filtered off and washed with ether (2 × 10 cc.). This left 6.90 g. of a mixture of β,γ-diphenyl-*n*-propylamine hydrochloride, di-(β,γ-diphenyl-*n*-propyl)amine hydrochloride, and ammonium chloride.

The ammonium chloride and the primary amine hydrochloride were extracted from the mixture by stirring with water (2 × 40 cc.) and filtration. The combined filtrates on evaporation *in vacuo* gave 4.6 g. of solid. This mixture was crystallized from 25 cc. of conc'd hydrochloric acid. In this way 3.90 g. (46%) of β,γ-diphenyl-*n*-propylamine hydrochloride (m.p. 194–194.5°) was obtained. Another crystallization from conc'd hydrochloric acid gave 3.66 g. (43%) of pure material melting at 194.7–195.2°.

The crude secondary amine hydrochloride residue, obtained from the above water extraction, melted at 150–198°. One crystallization from ethanol (4 cc.) gave 2.07 g. (27%) melting at 181–204°. A sample of this material was purified by extraction with acetone, and crystallization of the residue from ethanol. Di-(β,γ-diphenyl-*n*-propyl)amine hydrochloride melting at 222.5–225° was thus obtained.

Anal. Calc'd for $C_{30}H_{32}ClN$: Cl, 8.06. Found: Cl, 8.20.

N,N-Bis-(β-chloroethyl)-β,γ-diphenyl-n-propylamine hydrochloride. β,γ-Diphenyl-*n*-propylamine was liberated from a solution of 3.66 g. (0.0147 mole) of the hydrochloride in 40 cc. of water by adding a solution of 1.20 g. (0.029 mole) of sodium hydroxide in 25 cc. of water. The free amine was extracted with ether (3 × 30 cc.) and the combined ethereal extracts were washed with water and evaporated to dryness. The residual yellow oil after solution in methanol (25 cc.) and treatment with ethylene oxide as described above, gave N,N-*bis*-(β-hydroxyethyl)-β,γ-diphenyl-*n*-propylamine. This amine was isolated as the hydrochloride in 97% yield.

A solution of 8.8 g. (0.074 mole) of thionyl chloride in 20 cc. of carbon tetrachloride was added to 4.81 g. (0.014 mole) of the hydrochloride. The reaction mixture was heated to 63° and within 25 minutes it became homogeneous. The resulting solution was held at 80–85° for 1½ hours. After standing overnight at room temperature, the solution was evaporated *in vacuo* at 60–65°, to a viscous yellow oil. This oil was crystallized by redissolving in 10 cc. of dry carbon tetrachloride, cooling to −20°, add seeding with N,N-*bis*-(β-chloroethyl)-β,γ-diphenyl-*n*-propylamine hydrochloride obtained in a previous run. After standing at −20° for five days crystallization appeared to be complete. On filtration 4 g. (75%) of product (m.p. 131.8–133°) was obtained. One crystallization from toluene (19 cc.) gave pure crystals melting at 135.3–137°, yield 3.52 g. (66%).

N,N-*Bis*-(β-chloroethyl)-β,γ-diphenyl-*n*-propylamine hydrochloride is very soluble in ethanol, dioxane, and chloroform and soluble in acetone, hot toluene, and hot benzene.

Anal. Calc'd for $C_{19}H_{24}Cl_3N$: C, 61.2; H, 6.49; Cl, 28.5; N, 3.7.

Found: C, 61.4; H, 6.51; Cl, 28.5; N, 3.9.

p-Methoxybenzyl chloride was obtained from *p*-methoxybenzyl alcohol in 94% yield by chlorination with thionyl chloride in benzene.

p-Methoxybenzyl cyanide was prepared in 88% yield by the method of Lee, *et al.* (17).

p,p'-Dimethoxy-α-cyanostilbene (m.p. 107.8–108.7°) was obtained in 85% yield from the condensation of *p*-methoxybenzyl chloride with *p*-methoxybenzyl cyanide. The procedure was the same as that followed in the preparation of α-phenylcinnamonitrile. Niederl and Ziering (15) reported m.p. 108°.

β,γ-Di-(p-methoxyphenyl)-n-propylamine. Adams' catalyst (300 mg.) was added to 10.1 g. (0.038 mole) of *p,p'*-dimethoxy-α-cyanostilbene in 150 cc. of purified glacial acetic acid. This mixture was reduced in a Parr hydrogenator at an initial hydrogen pressure of 60 p.s.i. Shaking under pressure was continued for 42 hours. The solution was filtered and evaporated under reduced pressure, leaving a dark oil. Ether (100 cc.) was added and swirled with the oil. On standing overnight, β,γ-di-(*p*-methoxyphenyl)-*n*-propylamine acetate and di-[β,γ-di(*p*-methoxyphenyl-*n*-propyl)]amine acetate crystallized and were filtered from the ether solution. After washing with ether (50 cc.), the mixture of crystalline acetates was suspended in water (50 cc.), and treated with a solution of 2 g. of sodium hydroxide in water (20 cc.). The liberated amines were extracted with ether (3 × 30 cc.) and the ethereal solution was washed with water (2 × 15 cc.) and evaporated. The residual oil on distillation gave 4.12 g. (40%) of β,γ-di-(*p*-methoxyphenyl)-*n*-propylamine, b.p.$_1$ 204°. Three crystallizations from isopropyl ether (10 cc.) raised the melting point of this amine from 70–73° to 73–74°; yield 3.54 g. (34%).

Anal. Calc'd for $C_{17}H_{21}NO_2$: C, 75.2; H, 7.75; N, 5.1.

Found: C, 75.2; H, 7.65; N, 5.3.

N,N-Bis-(β-chloroethyl)-β,γ-di-(p-methoxyphenyl)-n-propylamine hydrochloride. Ethylene oxide was added to a solution of β,γ-di-(*p*-methoxyphenyl)-*n*-propylamine and the product converted to N,N-*bis*-(β-hydroxyethyl)-β,γ-di-(*p*-methoxyphenyl)-*n*-propylamine hydrochloride as described above for the preparation of N,N-*bis*-(β-hydroxyethyl)-β,γ-diphenyl-*n*-propylamine hydrochloride. In this case the product was also an oil.

When N,N-*bis*-(β-hydroxyethyl)-β,γ-dianisyl-*n*-propylamine hydrochloride in carbon tetrachloride was chlorinated with thionyl chloride as described above a 92% yield of product (m.p. 162–162.5°) was obtained. One crystallization from anisole (7.1 cc./g.) gave an 80% yield of pure material melting at 165–167°.

Anal. Calc'd for $C_{21}H_{28}Cl_3NO_2$: C, 58.2; H, 6.52; Cl, 24.5; N, 3.24.

Found: C, 57.8; H, 6.60; Cl, 24.4; N, 3.16.

SUMMARY

Four new substituted *bis*-(β-chloroethyl)amine hydrochlorides, of interest as possible chemotherapeutic agents for cancer, have been synthesized. They are: *bis*-(β-chloroethyl)-*n*-butylamine hydrochloride, N,N-*bis*-(-β-chloroethyl)-9-aminomethylphenanthrene hydrochloride, N,N-*bis*-(β-chloroethyl)-β,γ-diphenyl-*n*-propylamine hydrochloride, and N,N-*bis*-(β-chloroethyl)-β,γ-dianisyl-*n*-propylamine hydrochloride.

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