Proof of Structure of III and IV.—The structures of III and IV were proved by decarboxylation and comparison of the resulting ketones with authentic samples.[20] Because both 3-methyl-1-naphthyl *m*-tolyl ketone and 3-methyl-1-naphthyl *o*-tolyl ketone were liquids, comparison was effected by means of the 2,4-dinitrophenylhydrazones. The 2,4-DNPH derivative of the *m*-tolyl isomer, prepared by reaction of 3-methyl-1-naphthylmagnesium bromide with *m*-tolunitrile, melted (alone and mixed with the 2,4-DNPH derivative of the ketone formed by decarboxylation of III) at 234–236° dec., after recrystallization from benzene–isopropyl alcohol. The infrared spectra of the two samples were also identical. Similarly the 2,4-DNPH derivative of the *o*-tolyl isomer, prepared by reaction of 3-methyl-1-naphthylmagnesium bromide with *o*-tolunitrile, melted (alone and mixed with the ketone formed by decarboxylation of IV) at 246–248° dec., after recrystallization from benzene–isopropyl alcohol. The infrared spectra of the two samples were also identical.

Anal. Calcd. for $C_{25}H_{20}N_4O_4$: C, 68.2; H, 4.5; N, 12.7. Found (for *m*-isomer): C, 68.1; H, 4.5; N, 12.8. Found (for *o*-isomer): C, 68.1; H, 4.5; N, 12.9.

2-(3-Methyl-1-naphthyl)methyl-6 methylbenzoic Acid (V).—A mixture of 50 g. of zinc dust activated with copper sulfate, 29.1 g. of III, and 700 ml. of 10% sodium hydroxide solution was refluxed and stirred for 36 hr. The acid fraction, isolated by the usual means, was crystallized from toluene to yield 27.4 g. (99%) of V, m.p. 162–163°.

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.8; H, 6.2. Found: C, 82.8; H, 6.2.

When a similar mixture was heated for 20 hr., a 32% yield of the lactone of 2-(3-methyl-1-naphthyl)hydroxymethyl-6-methylbenzoic acid, m.p. 178–179°, was obtained in addition to 57% of V.

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.4; H, 5.6. Found: C, 83.2; H, 5.7.

4,5-Dimethyl-9,10-dihydro-10-keto-1,2-benzanthracene (VI).—A solution of 25.0 g. of V in 200 ml. of anhydrous hydrogen fluoride was left to evaporate overnight in a plastic narrow-mouth bottle. After isolation in the usual way (which included a washing with 10% sodium carbonate) there was obtained 19.7 g. (87%) of VI, m.p. 103–106°. Recrystallization from benzene and methanol afforded a pure sample, m.p. 107–108°, with little loss. The infrared spectrum showed no hydroxyl absorption and a strong ketonic band at 6.02 μ (1660 cm.$^{-1}$).

Anal. Calcd. for $C_{20}H_{16}O$: C, 88.2; H, 5.9. Found: C, 88.2; H, 6.0.

4,5-Dimethyl-1,2-benzanthracene (VII).—A well-stirred mixture of 10 g. of zinc activated with copper sulfate solution, 3.0 g. of VI, m.p. 103–106°, 20 ml. of toluene, and 50 ml. of 10% sodium hydroxide solution was heated at reflux for 36 hr. The yellow color of the initial mixture faded towards the end. After the usual work-up, the crude product was purified by chromatography over alumina using petroleum ether–benzene as developing solvent. Finally, recrystallization from benzene and ethanol afforded 2.2 g. (78%) of colorless needles, m.p. 138–139°.

Anal. Calcd. for $C_{20}H_{16}$: C, 93.7; H, 6.3. Found: C, 93.7; H, 6.3.

The trinitrofluorenone derivative,[21] m.p. 227–228°, was prepared in benzene and recrystallized from xylene.

Anal. Calcd. for $C_{33}H_{21}N_3O_7$: C, 69.4; H, 3.7; N, 7.4. Found: C, 69.0; H, 3.7; N, 7.7.

4,5,10-Trimethyl-1,2-benzanthracene (VIII).—Methyllithium prepared from 23 g. of methyl iodide and excess lithium in 75 ml. of ether was forced under nitrogen into a solution of 3.2 g. of VI in 75 ml. of pure dry benzene. After refluxing for 10 hr. the mixture was poured on dilute hydrochloric acid and the organic product was isolated as usual. After chromatography over alumina as for VII there was isolated a pale yellow oil which afforded 1.2 g. (38%) of VIII on crystallization from ethanol. When first obtained a form, m.p. 87–88°, was isolated. This proved to be a low-melting polymorphic form, as a form of VIII, m.p. 105–106°, was later obtained.

Anal. Calcd. for $C_{21}H_{18}$: C, 93.3; H, 6.7. Found: C, 93.4; H, 6.8.

The trinitrofluorenone derivative, m.p. 232–234°, was obtained in and recrystallized from benzene containing about 2% excess VIII.

Anal. Calcd. for $C_{34}H_{23}N_3O_7$: C, 69.8; H, 3.9; N, 7.2. Found: C, 69.5; H, 3.8; N, 7.2.

(20) The decarboxylations and the syntheses of ketones were carried out as described for similar cases by M. S. Newman and P. G. Schiavelli, *J. Am. Chem. Soc.*, **78**, 5004 (1956).

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Synthesis of N^6,N^6-Bis(2-chloroethyl)-DL-lysine

G. VITA, L. MONTI, AND R. ANGELUCCI

Carlo Erba Therapeutic Research Institute, Milan, Italy

Received January 27, 1964

The synthesis of N^6,N^6-bis(2-chloroethyl)-DL-lysine, using classical procedures, is described. The starting material, 5-(4-hydroxybutyl)-3-benzylhydantoin, was converted to the 5-(4-bromobutyl) derivative. By reaction of this with diethanolamine, hydrolytic ring opening, N^2-benzoylation, esterification, chlorination, and hydrolysis, N^6,N^6-bis(2-chloroethyl)-DL-lysine was obtained as the hydrochloride. The free base was obtained from this. A method has been studied (which could be extended to other amino acids) for the purification of the intermediate and final products through their precipitation as reineckates. The free intermediates and amino acids were obtained from their reineckates by use of a cation-exchange resin.

As a result of the studies by Larionov[1] and Bergel[2] the investigation of amino acids as precursors of possible antitumor agents, has attracted the attention of numerous research workers.[3–5] A number of N-substituted bis(2-chloroethyl)amino acids were synthesized and subjected to biological testing. In particular, the synthesis of N^6,N^6-bis(2-chloroethyl)-DL-lysine was suggested,[6] and a first hint on the preparation of this compound was given by Ishidate.[7] From Ishidate's work it appears that the lysine derivative was isolated as an impure double salt of picrylsulfonic and hydrochloric acids. Larionov[8] then reported on the antitumor

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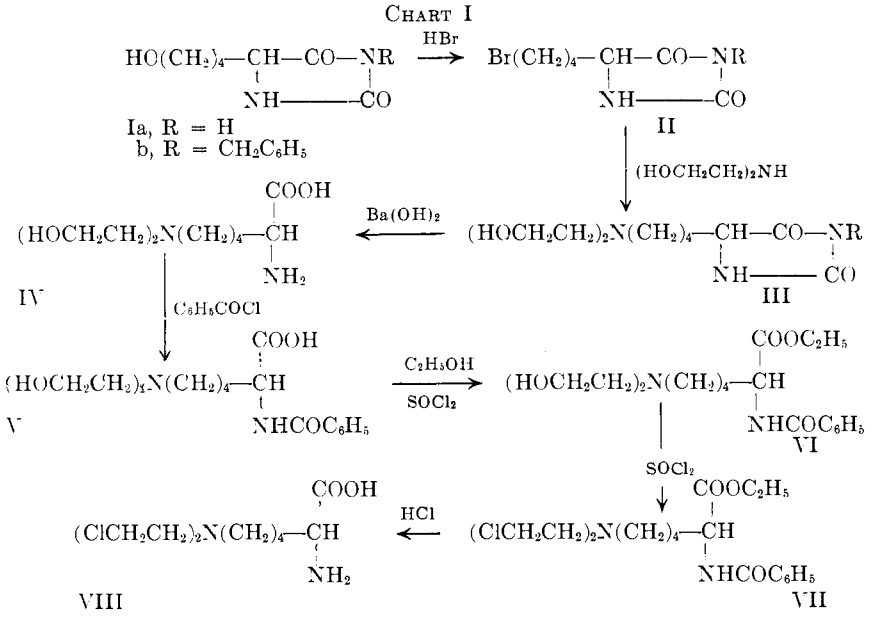
CHART I



activity of a mixture of α- and ϵ-bis(2-chloroethyl) derivatives of lysine, prepared by Ginzburg.

Further work by Ginzburg[9] dealt with the synthesis of N^6,N^6-bis(2-chloroethyl)-L-lysine. This was prepared by allowing N^2-acetyl-L-lysine to react with ethylene oxide in an alkaline medium, followed by direct chlorination of the hydroxyethyl groups produced. Attempts to reproduce this method in our laboratories did not give the desired products.

It therefore seemed interesting to us to study a new synthesis of N^6,N^6-bis(2-chloroethyl)-DL-lysine based on classical methods of amino acid preparation. The synthesis was to be carried out so as to preclude formation of the α-isomer in the first stage. We started on the basis of Rogers' synthesis[10] of lysine from 5-(4-hydroxybutyl)hydantoin. The nitrogen in position 3 on the hydantoin ring was protected by benzylation before the amination step. This was done to avoid undesired side reactions.

The hydroxyl group was substituted by bromine (II), and in turn this was substituted by diethanolamine (III) which, in excess, also acted as an acceptor of hydrogen bromide during the reaction. The hydantoin ring was hydrolyzed in an alkaline medium according to the method of Gaudry[11] in his synthesis of DL-α-amino-ϵ-hydroxycaproic acid. An oily product, N^6,N^6-bis(2-hydroxyethyl)-DL-lysine (IV) was obtained. It was purified by forming the reineckate using the method of Panouse[12] applied to nicotine and pyridine.

The reineckate of IV was benzoylated in alkaline solution, and the reineckate of N^6,N^6-bis(2-chloroethyl)-N^2-benzoyl-DL-lysine (V) was precipitated on acidification. Benzoylation was also performed directly on IV without recourse to its reineckate. Subsequent chlorination and hydrolysis led to N^6,N^6-bis(2-chloroethyl)-DL-lysine (VIII) which was purified as its reineckate. The product could be separated from this salt by absorption of the amino acid on a cation-exchange resin, followed by elution (as the dihydrochloride).

The free base VIII was prepared by a procedure which prevented loss of bound chlorine from the labile 2-chloroethyl position; the dihydrochloride of VIII has been shown to be extremely susceptible to such loss. All the intermediates and final products were subjected to thin layer chromatography. Different adsorbents and solvents were used as and where suitable.

The use of cation-exchange resins for conversion of the reineckates to the hydrochlorides has also been applied to the following amino acids: aspartic acid, phenylalanine, valine, and hydroxyproline. Its scope should be broad.

Test of the Antitumor Activity on Cells Cultured *in Vitro*.—The activity of N^6,N^6-bis(2-chloroethyl)-DL-lysine was tested on KB cells maintained *in vitro* in Eagle's medium[13] supplemented with 10% of human blood serum. The cells, obtained as a suspension by trypsinization of the stock cultures, were seeded in a suitable number of tubes. For these experiments 1 ml. of cell suspension containing approximately 10^5 cells was placed in each tube. When the cellular sheet had developed, the tubes were divided into four groups (I, II, III, and IV). The medium was removed and substituted with fresh media containing, respectively, 5γ (I), 10γ (II), and 20 γ (III) of the compound per ml; group IV was kept as control. In each group the multiplication of cells was followed over a period of 144 hr. by enumeration of cell nuclei according to Sanford's method.[14] The counts were taken every 48 hr. In the cultures the media containing the products under investigation in the doses stated were renewed every 48 hr. The culture media in the control group were similarly renewed.

Every count was taken on three tubes per group and three samples of cellular suspension were counted from each tube. The cytological changes were recorded at the same time by microscopic examination of slides placed in Leighton's tubes seeded with cells and treated

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as described above. The slides were fixed and stained with hematoxylin. The experiments carried out showed a significant reduction in cellular multiplication in the tubes treated with 10 (30%) and 20 γ (47%) of the compound per ml. (Table I). The reduction observed with 5 γ of product per ml. was within the limits of experimental accuracy. Morphologically, there was an increase on mitosis number in metaphase.

TABLE I

GROWTH OF CELLS TREATED WITH THE PRODUCT

Tube, γ/ml.	Time, hr. 48	96	144
0 (control)	266.000	391.000	495.000
10	136.000	266.000	347.000
20	166.000	236.000	266.000

Experimental[15]

3-Benzyl-5-(4-hydroxybutyl)hydantoin (Ib).—5-(4-Hydroxybutyl)hydantoin (Ia, 10 g., 0.038 mole) and potassium carbonate (9.63 g., 0.07 mole) were dissolved in 46.4 ml. of water and 23.2 ml. of acetone. Benzyl bromide (12.0 g., 0.07 mole), dissolved in 23.2 ml. of acetone,[16] was added dropwise. The solution was refluxed for 8–10 hr. with constant stirring and the acetone was evaporated. Ib was precipitated in the aqueous phase; recrystallization from ethanol gave pure Ib (12.3 g., 77%), m.p. 122–123°.

Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.1; H, 6.91; N, 10.7. Found: C, 64.0; H, 6.94; N, 10.6.

3-Benzyl-5-(4-bromobutyl)hydantoin (II).—A suspension of Ib (25 g.) in 300 ml. of 48% hydrobromic acid was warmed to 100° and stirred continuously for 2–3 hr. The compound dissolved completely during the reaction. The solution was left to cool, and the crystalline product (30.5 g.) was filtered and recrystallized from 170 ml. of 95% ethanol giving II (23.45 g., 85%), m.p. 136–137°.

Anal. Calcd. for $C_{14}H_{17}BrN_2O_2$: C, 51.6[5]; H, 5.26; Br, 24.56; N, 8.61. Found: C, 51.63; H, 5.28; Br, 24.56; N, 8.6.

3-Benzyl-5-[4-bis(2-hydroxyethyl)aminobutyl]hydantoin (III).—A solution of II (10 g., 0.03 mole) and diethanolamine (12.6 g., 0.12 mole) in 130 ml. of anhydrous dioxane was heated to 90° and stirred continuously for 48 hr. The two phases which had formed were separated and the lower, oily layer of diethanolamine hydrobromide and unreacted diethanolamine was washed with about 10 ml. of anhydrous dioxane. The combined dioxane solutions were then evaporated to dryness under reduced pressure at 50°. The crystalline residue was redissolved in about 10 ml. of boiling water and the constantly stirred solution was left to cool to room temperature. After 1.5 hr. the product was filtered and dried (10.2 g., m.p. 89–90°). It was dissolved in 15 ml. of warm 2-propanol, charcoal was added, and the whole filtered. Boiling ligroin (20 ml.) was added to the filtrate, the mixture was vigorously stirred, the temperature was reduced to −5°, and III (8.9 g., 83%, m.p. 95–96°) was filtered.

Anal. Calcd. for $C_{18}H_{27}N_3O_4$: C, 61.8; H, 7.7; N, 12.05. Found: C, 61.26; H, 7.74; N, 11.94.

N^6,N^6-Bis(2-hydroxyethyl)-DL-lysine (IV).—A mixture of III (25 g., 0.07 mole) and $Ba(OH)_2 \cdot 8H_2O$ (56.5 g., 0.18 mole) was placed in an autoclave with 200 ml. of water. The temperature was brought to 160° and maintained there for 1.5 hr. The suspension was cooled and placed in a current of carbon dioxide until the excess barium was precipitated as carbonate. The filtered solution was steam distilled to remove benzylamine formed by hydantoin ring opening. A dried sample of residue IV was analyzed.

Anal. Calcd. for $C_{10}H_{22}N_2O_4$: C, 51.27; H, 9.4; N, 11.98. Found: C, 50.63; H, 9.77; N, 11.65.

The solution containing IV, concentrated to 50 ml., was acidified to pH 1–2 with hydrochloric acid and decolorized with carbon. A solution of ammonium reineckate (52 g., 0.15 mole) in 1 l. of water was added with stirring; pink crystals of the reineckate of N^6,N^6-bis(2-hydroxyethyl)-DL-lysine were precipitated (58.8 g., 90%); they soften at 139°, m.p. 193° dec.

Anal. Calcd. for $C_{18}H_{36}Cr_2N_{10}O_4S_8 \cdot 2H_2O$: C, 23.79; H, 4.44; Cr, 11.44; N, 21.57; S, 28.22. Found: C, 23.78; H, 4.48; Cr, 12.75; N, 21.54; S, 27.94.

Thin layer chromatography was carried out using cellulose powder as adsorbent and a mixture of 1-butanol–acetic acid–water (60:20:20) as the mobile phase. The chromatogram, developed with 2% solution of ninhydrin in acetone, showed a single violet-tinged spot, R_f 0.36.

N^2-Benzoyl-N^6,N^6-bis(2-hydroxyethyl)-DL-lysine (V).—Finely powdered reineckate of IV (100 g., 0.11 mole) was dissolved, with stirring, in a solution of sodium hydroxide (17.6 g., 0.44 mole) in 1.5 l. of water; benzoyl chloride (15.58 g., 0.11 mole) was added slowly dropwise. Vigorous stirring was continued for 3 hr. at 20–25°. The mixture was then acidified to pH 1 with 10% hydrochloric acid and cooled to 10°. The reineckate of V was precipitated, filtered, and washed with water, then benzene; m.p. 86–88°.

Anal. Calcd. for $C_{29}H_{33}CrN_8O_8S_4 \cdot H_2O$: C, 37.34; H, 5.22; Cr, 7.69; N, 16.58; S, 18.99. Found: C, 37.2; H, 5.24; Cr, 7.73; N, 16.55; S, 18.93.

The product, without previous drying, was dissolved in acetone (270 ml.) and diluted with 1 *N* hydrochloric acid (270 ml.). The solution was extracted with ether until the red color passed completely into the ether phase. The aqueous layer was stirred at 10° and the theoretical quantity of silver carbonate was added. The silver chloride was filtered and the aqueous solution evaporated under reduced pressure. The residue (V) was an oily product (33.5 g., 90%).

Ethyl Ester of N^2-Benzoyl-N^6,N^6-bis(2-hydroxyethyl)-DL-lysine (VI).—A solution of V (11.1 g., 0.016 mole) in anhydrous ethanol (150 ml.) was stirred in a dry round-bottom flask cooled to −10° (protection from moisture). Then thionyl chloride (11.1 ml.) was added slowly dropwise, and stirring was continued for 4 hr. The solution was allowed to warm to room temperature, treated with charcoal, and evaporated under reduced pressure. An oily residue of VI hydrochloride remained. The yield was quantitative.

Ethyl Ester of N^2-Benzoyl-N^6,N^6-bis(2-chloroethyl)-DL-lysine (VII).—The hydrochloride of VI (5.0 g., 0.012 mole), dissolved in anhydrous methylene chloride (50 ml.), was stirred at 0° in a dried flask (protection from moisture). Thionyl chloride (7 ml., 0.11 mole) was added slowly, dropwise. The internal temperature was brought to 35° and maintained there for 1.5 hr. The solution was evaporated to dryness, and the oily residue was dissolved in water (25 ml.) and buffered to pH 5 with a saturated solution of sodium acetate. The oily product which separated was extracted with three 30-ml. portions of chloroform. The dried chloroform solution was evaporated to dryness to give 4.25 g. (84%) of VII as an oil.

Anal. Calcd. for $C_{19}H_{28}Cl_2N_2O_4$: C, 56.6; H, 7.21; Cl, 17.58; N, 6.94. Found: C, 56.45; H, 7.38; Cl, 17.6; N, 6.91.

N^6,N^6-Bis(2-chloroethyl)-DL-lysine (VIII).—A solution of VII (40 g.) in 37% hydrochloric acid (400 ml.) was refluxed for 10 hr., then cooled and washed with ether to remove benzoic acid (95–100% of theory) obtained by hydrolysis. It was treated with decolorizing carbon, filtered, and evaporated to dryness under reduced pressure. The residue was dissolved in 300 ml. of water and treated with the theoretical amount of 5% aqueous ammonium reineckate. The reineckate of VIII was filtered and washed with water, redissolved in acetone, and again precipitated by dilution with water (80.7 g., 85%); it softened at 138°, m.p. 183° dec.

Anal. Calcd. for $C_{18}H_{34}Cl_2Cr_2N_{10}O_2S_8 \cdot 2H_2O$: C, 22.87; H, 4.01; Cl, 7.51; Cr, 11.0; N, 20.72; S, 27.11. Found: C, 22.99; H, 4.13; Cl, 7.5; Cr, 11.35; N, 20.5; S, 27.32.

A solution of VIII reineckate (10 g.) in acetone (70 ml.) was diluted with water (150 ml.). The solution was percolated through Amberlite IR 120 (100–200 mesh). The resin was washed thoroughly with water and eluted with 7–10% hydrochloric acid. The eluate was evaporated to dryness under reduced pressure and the residue dried under high vacuum in the presence of P_2O_5 for at least 48 hr. (yield 90%).

The **dihydrochloride** was a solid, foamy, extremely hygroscopic mass, with a slightly greenish color.

Anal. Calcd. for $C_{19}H_{28}Cl_2N_2O_2 \cdot 2HCl$: C, 34.88; H, 6.63; Cl, 41.28; N, 8.14. Found: C, 34.42; H, 6.72; Cl, 40.5; N, 8.02.

(15) Melting points were obtained on a Kofler hot stage and are uncorrected. This work was completed before the announcement of the requirements for corrected melting points by journals of the American Chemical Society.

(16) W. J. Close, U. S. Patent 2,759,002 (Aug. 14, 1956).

This dihydrochloride (1 g.) was dissolved with 20 ml. of anhydrous methanol, and the theoretical amount of silver carbonate was added slowly with stirring and cooling. Stirring was continued for 15 min., and the silver chloride was filtered. The methanol solution was evaporated under reduced pressure. The residue (VIII) was a white crystalline powder (0.75 g., 95%).

Anal. Calcd. for $C_{10}H_{10}Cl_2N_2O_2$: C, 44.29; H, 7.43; Cl, 26.15; N, 10.32. Found: C, 44.2; H, 7.6; Cl, 26.2; N, 10.21.

VIII dihydrochloride was thin layer chromatographed with cellulose powder, using 1-butanol–acetic acid–water (60:20:20) as a solvent. The chromatogram, developed with a 2% solution of ninhydrin, showed a single orange-red spot (R_f 0.67). The base showed a single violet spot (R_f 0.64).

Precipitation of the Reineckates of Valine, Phenylalanine, Ornithine, Hydroxyproline, and Aspartic Acid. Isolation of the Amino Acids from their Respective Salts Using a Cation-Exchange Resin.—These amino acids were precipitated as their reineckates from their respective aqueous solutions, acidified with HCl (pH 1–2), by the addition of the theoretical amount of 5% aqueous ammonium reineckate solution. These salts were all crystalline but without definite melting points.

The amino acids were isolated from their salts almost quantitatively. First, the salts were dissolved in acetone and diluted with a double volume of water. Then these solutions were percolated through 1.5 equiv. of Amberlite IR 120 (100–200 mesh). The resin was washed by percolation with water until the red color due to reinecke acid disappeared. The amino acid adsorbed by the resin was eluted with 5–10% hydrochloric acid recovered as the pure hydrochloride salt by concentration of the eluate.

Acknowledgment.—The writers are indebted to Dr. E. Pella for the microanalyses, to Dr. G. Tosolini for the chromatographic data, and to Mr. A Cantaluppi for technical collaboration.

Further Investigations of Heterocyclic Alkylating Agents[1]

ROBERT K. PRESTON, RICHARD M. PECK, EVELYN R. BREUNINGER, ANN J. MILLER, AND HUGH J. CREECH

The Institute for Cancer Research, Philadelphia 11, Pennsylvania

Received December 20, 1963

The exceptional antitumor and mutagenic activities displayed by a quinacrine derivative of a monofunctional nitrogen mustard, 2-methoxy-6-chloro-9-[3-(ethyl-2-chloroethyl)aminopropylamino]acridine, led to the synthesis of 50 additional mono- and difunctional analogs of acridine, quinoline, and quinazoline. The acridine nucleus was found to exert a pronounced activating influence on the nitrogen mustard moiety. On a molar basis, the "half-mustard" 2-methoxy-9-[3-(ethyl-2-chloroethyl)aminopropylamino]acridine dihydrochloride was considerably more effective against the Ehrlich ascites tumor than methylbis(2-chloroethyl)amine hydrochloride; the corresponding bis analog was even more potent. Substitution of a 6-chloro group into 2-methoxyacridine decreased the molar activities of the mono and bis mustards. Several monofunctional nitrogen mustards of quinazoline and quinoline displayed moderate antitumor activity, but only at high molar dosages; other closely related analogs were inactive. The relationships between the chemical structures and antitumor activities of the compounds are presented.

From our earlier work[2–4] it was evident that the unusual antitumor activity of certain monofunctional nitrogen mustards was determined by the chemical structure of the heterocyclic nucleus that was attached through a side chain to the mono-2-chloroethylamino group. The first nitrogen "half-mustard" that displayed pronounced activity in prolonging the survival time of mice bearing several varieties of ascites tumors[2] and exhibited an extraordinary mutagenic capability in *Drosophila*[5] was 2-methoxy-6-chloro-9-[3-(ethyl-2-chloroethyl)aminopropylamino]acridine dihydrochloride.[4] On the other hand, the partial acridine structures, 7-chloro- and 6-methoxy-4-[3-(ethyl-2-chloroethyl)aminopropylamino]quinoline dihydrochloride,[2] and the secondary amine, 2-methoxy-6-chloro-9-[2-(2-chloroethyl)aminoethylamino]acridine dihydrochloride, showed no antitumor activity. Since their corresponding bis mustards were highly effective, it is apparent that both the heterocyclic nucleus and the presence of an alkyl group on the nitrogen containing the 2-chloroethyl group are of critical importance in activating the monofunctional mustard grouping.

It appeared worthwhile to determine whether the 2-methoxy or the 6-chloro group on the acridine nucleus played a significant role in this activation and whether any modifications of simpler heterocyclic nuclei, such as quinoline and quinazoline, would impart enhanced physiological activity to the "half-mustards." The effects of attachment of the nitrogen-mustard moiety at the 4-position of variously substituted quinolines, at the 2-position of quinoline and lepidine, at the 4-position of quinazoline and 6-chloroquinazoline, and at the 8-position of 6-methoxyquinoline, as well as the presence of an N-alkyl substituent on the 4-quinolyl nitrogen, were investigated both in the mono and bis forms, as shown in Table I. The letters A to X in the first column of Tables I and II represent the heterocyclic group Ar in the formula Ar-( )-$N\langle^{R}_{CH_2CH_2X}$ at the top of Table I. The heterocyclic structures corresponding to these letters are as follows.

Most of the tertiary amino side chains were added stepwise to the nucleus by condensing 4-chloroquinoline with an alkylaminoethanol, chlorinating, and condensing with diethanolamine, or an analog, to give the mustard precursor. However, when the readily crystallized nitrate salts[6] of the first hydroxy intermediate,

(1) Supported by research Grants CA 02975 and CA 06927 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

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