hr. Removal of catalyst and solvent gave an oil from which no crystalline product could be obtained. Elution from a magnesium trisilicate (50/50) column with petroleum ether gave 0.905 g. of light colored oil which likewise could not be crystallized.

*Isolation of 17β-methyl-1,3,5(10)-estratrien-3-ol benzoate* (IVb). The above oil was treated with 25 cc. 10% aqueous KOH and 5 cc. benzoyl chloride. Work-up gave a light oil which crystallized from methanol as a good crop of jagged needles, m.p. 134–135°. Several crystallizations from acetone gave white rods, m.p. 160–161.5°, unchanged by an additional crystallization from methanol-benzene; $[\alpha]_D^{17°}$ +43.5°.

*Anal.* Calcd. for $C_{26}H_{30}O_2$: C, 83.38; H, 8.07. Found: C, 83.20; H, 8.01.

*17β-Methyl-1,3,5(10)-estratrien-3-ol* (IVa). The previous benzoate (IVb, 0.271 g.) was refluxed in 20 cc. of 5% alc. KOH for 1 hr. Work-up and crystallization to constant melting point from aqueous methanol gave micro needles, m.p. 133–135°, not raised by an additional crystallization from aqueous acetone: $[\alpha]_D^{17°}$ +92.5°. $\lambda_{max}$ 280 mμ ($E_{1\,cm.}^{1\%}$ 80).

*Anal.* Calcd. for $C_{19}H_{26}O$: C, 84.39; H, 9.68. Found: C, 84.20; H, 9.49.

*17β-Methyl-1,3,5(10)-estratrien-3-methyl ether* (IVc). The free phenol (IVa, 0.125 g.) was treated with 1 cc. of dimethyl sulfate and 20 cc. of 10% aqueous KOH. Work-up gave a colorless oil which could not be crystallized. Sublimation at 70° on a cold finger at $2.5 \times 10^{-3}$ mm. pressure gave a colorless oil; $[\alpha]_D^{18°}$ +53.1°. $\lambda_{max}$ 280 mμ.

*Anal.* Calcd. for $C_{20}H_{28}O$: C, 84.45; H, 9.92. Found: C, 84.36; H, 9.70.

Acetylation of IVa gave an oil which could not be crystallized and was not analyzed. Saponification of this oil gave IVa, m.p. 130°.

*Isolation of 17α-methyl-1,3,5(10)-estratrien-3-ol benzoate* (Vb). Following the removal of as much IVb as possible by crystallization from methanol, the mother liquor was freed of solvent, leaving an oily deposit. This was saponified, but the resulting oil could not be crystallized, even after chromatography on alumina. It was rebenzoylated (benzoyl chloride in aqueous alkali) and the crude product in methanol gave a small deposit which was filtered and discarded. The filtrate was free of solvent and the residue was dissolved in aqueous acetone. Eventually 0.243 g. of needles deposited. Crystallization to constant melting point from aqueous acetone-methanol gave brilliant needles, m.p. 118–120°; $[\alpha]_D^{17°}$ −50.7°.

*Anal.* Calcd. for $C_{26}H_{30}O_2$: C, 83.38; H, 8.07. Found: C, 83.37; H, 8.07.

*17α-Methyl-1,3,5(10)-estratrien-3-ol* (Va). Saponification of the benzoate Vb (0.130 g.) gave small, pearly scales. Crystallization to constant melting point gave white crystals, m.p. 129–129.5°; $[\alpha]_D^{17°}$ −79.1°. $\lambda_{max}$ 280 mμ ($E_{1\,cm.}^{1\%}$ 81).

*Anal.* Calcd. for $C_{19}H_{26}O$: C, 84.39; H, 9.68. Found: C, 84.49; H, 9.51.

*17α-Methyl-1,3,5(10)-estratrien-3-methyl ether* (Vc). The free phenol Va (0.020 g.) was treated with 20 cc. 10% aqueous KOH and 1 cc. dimethyl sulfate. Work-up gave an oil which could not be crystallized. Sublimation at 70° under $2.5 \times 10^{-3}$ mm. Hg (cold finger apparatus) gave 0.015 g. of colorless oil which could not be crystallized.

*Anal.* Calcd. for $C_{20}H_{28}O$: C, 84.45; H, 9.92. Found: C, 84.40; H, 9.96.

Acetylation of Va (pyridine, acetic anhydride, room temp.) gave a non-crystallizable oil which was not analyzed. This oil on saponification gave free V, m.p. 126–128°.

*Acknowledgment.* The author wishes to express to Dr. James Leathem of Rutgers University his appreciation for providing the preliminary bioassays and to the Central Research Department, Anheuser-Busch, Inc., for permission to publish that portion of the work performed in their laboratories.

KANSAS CITY, KANSAS

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

# Synthesis of Potential Anticancer Agents. I. Nitrogen Mustards Derived from *p*-[*N*,*N*-Bis(2-chloroethyl)amino]benzaldehyde[1]

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*Received June 23, 1958*

An improved synthesis of *p*-[*N*,*N*-bis(2-chloroethyl)amino]benzaldehyde (benzaldehyde mustard) is described. Nitrogen mustard derivatives of cinchophen and barbituric acid have been prepared. Condensation products of benzaldehyde mustard and active methyl derivatives of selected heterocyclic compounds have been prepared. Representative benzylidene acyl hydrazides have been prepared from benzaldehyde mustard.

Compounds containing the β,β′-bischloroethylamino grouping, otherwise known as nitrogen mustards, have frequently displayed selective action against neoplastic cells as compared to normal cells.[2] The concept of a pharmacologically active substance being composed of an active moeity and a carrier moeity was first put forward by Ing.[3] The genesis of the present study was based on this concept.

Considerable information is at hand concerning the absorption and fate of the drug, cinchophen (2-phenylquinoline-4-carboxylic acid)[4] so that it seemed reasonable to expect that cinchophen might act as a carrier molecule to direct a mustard grouping to some effective locus of action. A logical

(1) This work was supported by Research Grant CY-2961 from the National Cancer Institute of the Public Health Service.

(2) The entire field has been reviewed in the monograph *Comparative Clinical and Biological Effects of Alkylating Agents*, Annals of the New York Academy of Sciences, Vol. 68, Art. 3 (April 24, 1958).

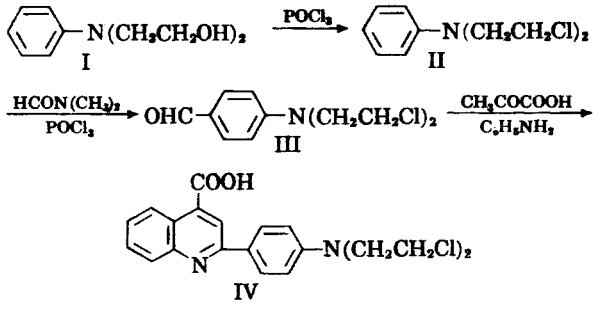
(3) H. R. Ing, *Trans. Faraday Soc.*, **39**, 372 (1943); see also ref. 2, p. 1238.

(4) L. S. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics*, 2nd ed., The Macmillan Co., New York, 1955, p. 301.

position for incorporation of such a group appeared to be the *para* position of the 2-phenyl group.

For the preparation of 2-[4′-[*N*,*N*-bis(2-chloroethyl)amino]phenyl]quinoline-4-carboxylic acid (IV) initial investigations were directed toward finding suitable methods for alkylating 2-(4′-aminophenyl)quinoline-4-carboxylic acid. Either ethylene oxide or ethylene chlorohydrin would be expected to produce the *N*,*N*-bis(2-hydroxyethyl)-amino compound,[5] the hydroxyl groups of which could then be replaced by chlorine by standard methods for the preparation of nitrogen mustards. However, quantitative dialkylation was difficult, and the extreme and closely similar insolubilities of the starting material, monoalkylated product, and the desired dialkylated product in most solvents made fractional crystallization at best tedious and wasteful. Attention was therefore directed to an alternate synthesis.

The Doebner quinoline synthesis proceeds normally with *p*-aminobenzaldehydes,[6] the conditions of this synthesis appear to be sufficiently mild to apply in the presence of the solvolytically active nitrogen mustard grouping, and the intermediate *p*-[*N*,*N*-bis(2-chloroethyl)aminobenzaldehyde has been described.[7] This approach was accordingly adopted.




Chlorination of *N*-phenyldiethanolamine (I) has been reported by Ross[5] and the subsequent introduction of the *p*-formyl group to yield III has been described by Anker and Cook.[7] Chlorination of I with phosphorus oxychloride proceeded well, but the ease of isolation of the product (II) was greatly facilitated by modification of Ross' procedure as given in the experimental part. The formylation step leading to III was done following the procedure of Campaigne and Archer,[8] which substitutes dimethylformamide for *N*-methylformanilide as used by Anker and Cook.[7] Excellent yields of III were thus obtained.

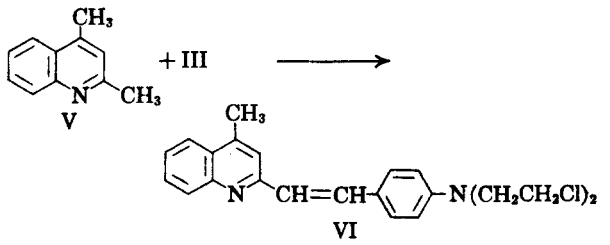
Under the standard Doebner conditions, III reacted smoothly with aniline and pyruvic acid. Slightly less than one equivalent of aniline was used to minimize the possibility of piperazine formation by reaction of the mustard group with any excess aniline. No difficulty from this source was encountered.

Cinchophen mustard (IV) showed no tendency to undergo solvolysis with ethanol. It is slightly soluble in 10% hydrochloric acid and soluble in concentrated hydrochloric acid forming a red solution typical of the 4′-aminocinchophen derivatives. It was soluble in 10% sodium carbonate solution forming a yellow solution likewise characteristic of these compounds. In sodium hydroxide some tar formation occurred. These solubility data indicate that the Doebner reaction proceeded as formulated to give IV and not the annoying by-product sometimes obtained, which in this case would be 1-phenyl-5-{*p*-[*N*,*N*-bis(2-chloroethyl)amino]phenyl}-2,3-pyrrolidinedione-3-anil. Further, IV gives a precipitate slowly with cold alcoholic silver nitrate and instantly when hot. This is highly suggestive that the mustard function is intact and not in the form of the cyclized ethylenimmonium salt which would be expected to react instantly with silver ion even in the cold.

With benzaldehyde mustard (III) readily available, attention was next directed to its incorporation into other molecules which may be expected to show tumor inhibitory properties. For this purpose advantage was taken of the reactivity of the aldehyde group in III in various condensation reactions involving active methylene groups and hydrazides. Condensation of III with 3-methyl-1-phenyl-5-pyrazolone,[7] with 6-ethoxythioindoxyl[7] and with oxindole[9] has been reported. Anker and Cook[7] prepared a number of cyanine dyes by condensation of III with various quaternized heterocyclic systems containing activated methyl groups. In view of the sensitivity of the mustard grouping in III the choice of a condensing agent is rather severely limited.

2-[*p*-(Dimethylamino)styryl]quinoline has been mentioned as a tumor growth inhibitor[10] and considerable literature exists on 4-(*p*-(dimethylamino)-styryl]quinoline.[11] It therefore seemed advisable to investigate condensation of III with representative methylquinolines. Since 2,4-dimethylquinoline (V) presented the possibility of the introduction of two mustard groups, this was selected for investigation. A series of experiments involving condensation of III with V in the presence of catalysts such as acetic anhydride, zinc chloride, and hydrochloric acid was carried out. With the latter two only intractable tars were obtained. However, when acetic anhydride was the catalyst, a monostyryl derivative was obtained as the hydro-

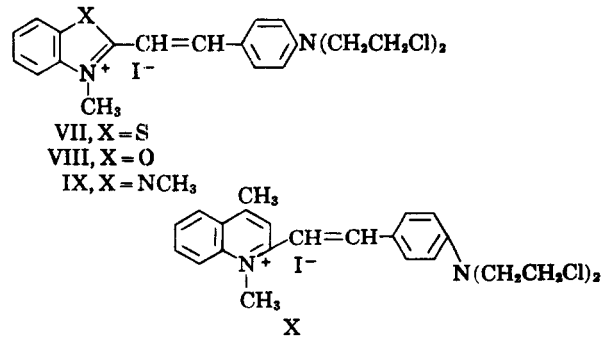
(5) W. C. J. Ross, *J. Chem. Soc.*, 183 (1949).
(6) R. Cuisa, *Gazz. chim. ital.*, **46**, I, 135 (1916); R. F. Brown *et al.*, *J. Am. Chem. Soc.*, **68**, 2705 (1946).
(7) R. M. Anker and J. H. Cook, *J. Chem. Soc.*, 489 (1944).
(8) E. Campaigne and W. L. Archer, *Org. Syntheses*, **33**, 27 (1953).
(9) Brit. Patent 595,571, Dec. 9, 1947.
(10) W. J. P. Neish, *Rec. trav. chim.*, **67**, 374 (1948).
(11) See C. T. Bahner and R. Neely, *J. Org. Chem.*, **22**, 1109 (1957), and references contained therein.



chloride. We believe that this substance is the hydrochloride of 2-[4′-[*N*,*N*-bis(2-chloroethyl)]-amino)styryl-4-methylquinoline (VI) for the following reasons. In general, the reactivity of a 4-methyl group in quinoline is less than that of a 2-methyl group. In order to secure condensation of lepidine with benzaldehyde, use of zinc chloride and relatively high temperatures is necessary.[12,13] Further, Kaslow and Stayner report that whereas 2-styrylquinoline can be prepared with acetic anhydride, zinc chloride is necessary for the preparation of 4-styrylquinoline.

Attempted condensation of III with 2-methylbenzimidazole in the presence of acetic anhydride or piperidine and hydrochloric acid resulted either in tar formation or in recovery of starting materials. The stability of III under these conditions is noteworthy. It appears that the aldehyde group of III is much less reactive in these condensations than the aldehyde group of benzaldehyde.

In view of the successful preparation of a series of cyanine dyes from III,[7] attention was turned to condensation of III with quaternized heterocycles. 2,3-Dimethylbenzothiazolium iodide, 2,3-dimethylbenzoxazolium iodide, and 1,2,3-trimethylbenzimidazolium iodide condensed easily with III in refluxing ethanol with piperidine as catalyst to give VII, VIII, and IX, respectively. The products crystallized directly in pure form, but some decomposition occurred on recrystallization. It is interesting that the benzothiazolium salt was considerably more reactive than the benzimidazolium salt which required a much longer time for reaction to go to completion.[14]

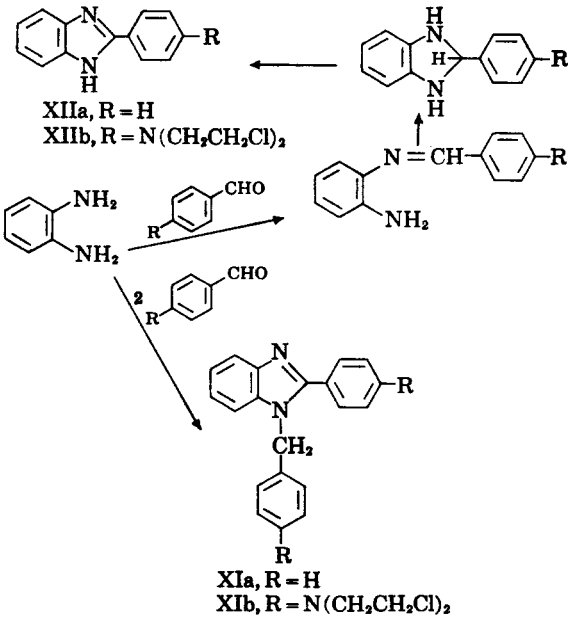


In contrast to these facile condensations, when condensation of 1,2,4-trimethylquinolinium iodide with III was attempted with piperidine as a catalyst no product could be isolated. However, when the reactants were boiled in acetic anhydride X was readily obtained. The structure of X is based on arguments similar to those used for VI.

Condensation of III with barbituric acid was almost instantaneous without a catalyst and gave a substantially quantitative yield of 5-(4′-[*N*,*N*-bis(2-chloroethyl)amino]benzylidene)barbituric acid.

Cinchophen hydrazide condenses with benzaldehyde in refluxing ethanol to give the benzylidene derivative in high yield.[15] Under the same conditions the *p*-(*N*,*N*-bis(2-chloroethyl)amino]-benzylidene hydrazide was formed from III. The analogous hydrazide mustards from *p*-aminobenzoic acid hydrazide and isonicotinic acid hydrazide were formed even more easily.

Finally, direct condensation of III with *o*-phenylenediamine was investigated. Depending on conditions, *o*-phenylenediamine can cyclize with benzaldehyde in two ways to give either XI*a* or XII*a*. Compounds of the type of XI are formed when salts of aromatic *o*-diamines are treated with aldehydes.[16] Compounds of the type of XII are formed when *o*-phenylenediamine and the aldehyde are refluxed in benzene solution in the presence of palladium on charcoal catalyst or alone in nitrobenzene.[17]



When III was refluxed with *o*-phenylenediamine in nitrobenzene for ten minutes, a greenish gray solid, m.p. 283°, was formed. No solvent could be

(12) O. Fischer, G. Scheibe, P. Merkel, and R. Muller, *J. prakt. Chem.*, [2] **100**, 86 (1920).

(13) C. E. Kaslow and R. D. Stayner, *J. Am. Chem. Soc.*, **67**, 1716 (1945).

(14) *Cf.* J. B. L. Smith, *J. Chem. Soc.*, **123**, 2288 (1923).

(15) H. John, *Ber.*, **59**, 1447 (1926).

(16) A. Ladenburg, *Ber.*, 11, 590, 600, 1648 (1878); A. Ladenburg and T. Engelbrecht, *Ber.*, **11**, 1653 (1878).

(17) D. Jerchel, M. Kracht, and K. Krucker, *Ann.*, **590**, 232 (1954).

found for recrystallization. However, when III and *o*-phenylenediamine were refluxed in benzene in the presence of palladium on charcoal with a stream of air crystalline material which could be recrystallized from methanol was obtained. The infrared spectra of the two substances showed marked differences. Analytical data for the crystalline substance agreed with those demanded by structure XIIb.

Results of tests of these compounds against experimental tumors will be reported elsewhere.

## EXPERIMENTAL[18,19]

*N,N-bis(2-chloroethyl)aniline* (II). The procedure was a modification of that of Ross.[5] To 170 g. (102 ml., 1.1 mole) of phosphorus oxychloride chilled in an ice bath 100 g. (0.55 mole) of *N*-phenyldiethanolamine (Tennessee Eastman Co. technical grade) was slowly added. After the addition was complete, the mixture was warmed on the steam bath for 1 hr. and then taken up in 500 ml. of benzene. The benzene solution was poured onto 500 g. of ice and the layers were separated. The aqueous layer was washed with three 50-ml. portions of benzene and the combined benzene solutions were dried over anhydrous magnesium sulfate. Removal of the benzene left an oil which was taken up in the minimum amount of hot absolute methanol. On chilling with stirring 98 g. (82%) of product, m.p. 41–45°, separated (reported m.p. 49°). By use of this inverse quenching of the reaction mixture no difficulty in inducing the crude material to crystallize was encountered, even when the alumina chromatography step included in the procedure of Ross was omitted.

*p-[N,N-bis(2-chloroethyl)amino]benzaldehyde* (III). A method similar to that described by Campaigne and Archer[6] for the formylation of dimethylaniline was used. To an ice cold solution of 70 g. (42 ml., 0.46 mole) of phosphorus oxychloride in 340 ml. of dimethylformamide was added slowly with stirring and cooling in ice a solution of 98 g. (0.45 mole) of *N,N*-bis(2-chloroethyl)aniline in 340 ml. of dimethylformamide. After the addition was complete, the solution was held at 5° for 15 min. and then warmed to 40° for 2 hr. The mixture was poured into one kilogram of ice and water and the purple solid which precipitated rapidly was filtered off at once. This was starting material. The filtrate rapidly deposited a copious precipitate of the desired aldehyde as long tan needles, m.p. 85–88°. After one recrystallization from ethanol 81 g. (73%) of white product, m.p. 85–88°, was obtained. Reported m.p. 88.5°.[7]

In larger scale runs complete removal of the purple contaminant was not accomplished in the initial workup. In order to remove this a solution of the crude product in benzene–petroleum ether was passed over a column of alumina which retained the pigment. Also the amount of dimethylformamide used could be halved.

*2-{4-[N,N-(bis-2-chloroethyl)amino]phenyl}quinoline-4-carboxylic acid* (IV). To a refluxing solution of 65 g. (0.264 mole) of III and 24 g. (0.272 mole) of pyruvic acid in 750 ml. of ethanol was added dropwise a solution of 24 g. (0.258 mole) of aniline in 250 ml. of ethanol. After the addition was complete, the solution was refluxed for 2 hr. and cooled to room temperature with stirring. The orange solid, 50 g. (50% based on aniline), was collected. After several recrystallizations from dimethylformamide-methanol (70% recovery) the material as a rule melted at 200–202° with decomposition although this was somewhat variable.

*Anal.* Calcd. for $C_{20}H_{18}Cl_2N_2O_2$: C, 61.7; H, 4.7; Cl, 18.2; N, 7.2. Found: C, 61.8, 61.6; H, 5.1, 5.0; Cl, 18.3, 18.3; N, 7.4, 7.1.

The compound is slightly soluble in 10% hydrochloric acid, soluble in concentrated hydrochloric acid, and soluble in 10% sodium carbonate. It is insoluble in water and slightly-soluble in ethanol, dioxane, acetonitrile, and propylene glycol. It gives a slow precipitate with alcoholic silver nitrate in the cold and a rapid precipitate when hot.

*2-{4-[N,N-bis(2-chloroethyl)amino]styryl}-3-methylbenzothiazolium iodide* (VII). A mixture of 4.0 g. (0.014 mole) of 2,3-dimethylbenzothiazolium iodide,[20] 4.0 g. (0.016 mole) of III, 125 ml. of absolute ethanol and 6 drops of piperidine was heated under reflux with stirring. The solution became dark red and after 2 hr. a dark solid separated. After cooling with stirring, the reddish brown crystals were collected and washed with ethanol. The yield of material, m.p. 205.5° (dec.), which was analytically pure, was 5.0 g. (71%). The substance could be recrystallized from methanol or from acetic acid. However, the melting point of the material from either of these solvents was lowered.

*Anal.* Calcd. for $C_{20}H_{21}Cl_2INS$: C, 46.3; H, 4.1, N, 5.4. Found: C, 46.2; H, 4.1; N, 5.4.

*2-{4'-[N,N-bis(2-chloroethyl)amino]styryl}-3-methylbenzoxazolium iodide* (VIII) was prepared by the above procedure from 2,3-dimethylbenzoxazolium iodide[21] except that 50 ml. of absolute ethanol were used. The yield of lustrous magenta crystals, m.p. 202.5–203.5° (dec.), was 59%. Recrystallization from 1:1 ethanol–methanol lowered the melting point.

*Anal.* Calcd. for $C_{20}H_{21}Cl_2IN_2O$: C, 47.7; H, 4.2; N, 5.6. Found: C, 47.6; H, 4.1; N, 5.5.

*2-{4'-[N,N-bis(2-chloroethyl)amino]styryl}-1,3-dimethylbenzimidazolium iodide* (IX). The above procedure was applied to 1,2,3-trimethylbenzimidazolium iodide[22] using 75 ml. of absolute ethanol and 1 ml. of piperidine. The reflux period was 6 hr. The yield of fine yellow crystals, m.p. 219° (dec.), was 54%.

*Anal.* Calcd. for $C_{21}H_{24}Cl_2IN_3$: C, 48.8; H, 4.7; N, 8.1. Found: C, 48.5; H, 4.5; N, 7.9.

*2-{4'-[N,N-bis(2-chloroethyl)amino]styryl}-1,4-dimethylquinolinium iodide* (X). A mixture of 3.0 g. (0.01 mole) of 1,2,4-trimethylquinolinium iodide, 2.46 g. (0.01 mole) of III, and 30 ml. of acetic anhydride was refluxed for 1 hr. The dark solution was cooled and poured into 200 ml. of ether. The solid was collected, washed with 200 ml. of ether, ground in a mortar, and triturated with 100 ml. of ether. The dark red microcrystalline powder did not react with 2,4-dinitrophenylhydrazine. It was suspended in ether, left overnight with occasional shaking, and collected. After three such treatments the m.p. was 87–93° (dec.). Yield 76%.

*Anal.* Calcd. for $C_{23}H_{25}Cl_2IN_2$: C, 52.4; H, 4.8; N, 5.3. Found: C, 52.4; H, 4.9; N, 5.4.

*2-{4'-[N,N-bis-(2-chloroethyl)amino]styryl}-4-methylquinoline hydrochloride* (VI). A mixture of 2.5 g. (0.02 mole) of III, 3.1 g. (0.02 mole) of 2,4-dimethylquinoline, and 1.0 g. (0.01 mole) of acetic anhydride was refluxed at 135–140° for 4 hr. The dark, oily material which formed was taken up in ethanol and an ethereal solution of hydrogen chloride was added. Crystallization of the hydrochloride was initiated by vigorous scratching and gradual cooling. After several recrystallizations from ethanol-ether red crystals, m.p. 220–222°, were obtained.

*Anal.* Calcd. for $C_{22}H_{23}Cl_3N_2$: C, 62.6; H, 5.5. Found: C, 62.6; H, 5.4.

*2-{4'-[N,N-bis(2-chloroethyl)amino]phenyl}benzimidazole* XII*b*. A solution of 3.24 g. (0.03 mole) of *o*-phenylenediamine and 7.4 g. (0.03 mole) of III in 500 ml. of benzene was refluxed with 2 g. of 5% palladium on charcoal for 18

(18) All melting points are corrected.

(19) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(20) W. H. Mills, *J. Chem. Soc.*, **121**, 455 (1922).

(21) L. M. Clark, *J. Chem. Soc.*, 234 (1926).

(22) O. Fischer, *Ber.*, **25**, 2838 (1892).

hr. during which air was passed through the mixture. After filtering the hot solution, almost colorless needles, m.p. 139–140°, deposited on cooling. The yield was 7.3 g. (73%). Recrystallization from methanol resulted in lowering of the melting point.

*Anal.* Calcd. for $C_{17}H_{17}Cl_2N_3$: C, 61.1; H, 5.1; N, 12.6. Found: C, 61.5; H, 5.1; N, 12.7.

*2-Phenylquinoline-4-carbox-[4′-bis(2-chloroethyl)amino]-benzylidenehydrazide.* A mixture of 5.0 g. (0.019 mole) of 2-phenylquinoline-4-carboxhydrazide.[23,24] 4.7 g. (0.019 mole) of III and 350 ml. of absolute ethanol was heated under reflux. After 1 hr. yellow needles began to separate. After heating for 5 hr. and cooling 9.2 g. (99%) of the hydrazide, m.p. 208.5–210.5° with darkening at 180°, separated. Recrystallization from 30 ml. of dimethylformamide and 200 ml. of ethanol gave clusters of fine yellow needles, m.p. 214.5–215.5° (dec.). The infrared spectrum showed bands at 3160 and 1650 cm.

*Anal.* Calcd. for $C_{27}H_{24}Cl_2N_4O_2$: C, 66.0; H, 4.9; Cl, 14.4; N, 11.4. Found: C, 66.1; H, 4.9; Cl, 14.6; N, 11.5.

*4-Aminobenz[4′-bis(2-chloroethyl)amino]benzylidenehydrazide.* This was prepared as in the above case from 4-aminobenzhydrazide.[25] The hydrazide separated after 10 min. and refluxing was continued for 20 min. The yield of crude material, m.p. 183.5–184.5°, was quantitative. Recrystallization from 1:5 dimethylformamide–absolute ethanol gave pale yellow needles, m.p. 185.5°. The infrared spectrum showed bands at 3350, 3200, and 1620 cm.$^{-1}$

*Anal.* Calcd. for $C_{18}H_{20}Cl_2N_4O$: C, 57.0; H, 5.3; Cl, 18.7; N, 14.8. Found: C, 57.1; H, 5.2; Cl, 18.6; N, 14.7.

*4-Aminopyridinecarbox[4′-bis(2-chloroethyl)amino]benzylidenehydrazide.* The procedure was the same as in the above cases starting from isonicotinic acid hydrazide.[26] After refluxing for 20 min., the deep yellow solution was filtered hot. On cooling the hydrazide, m.p. 202.5–204.5° (dec.) with darkening at 195°, crystallized. Recrystallization from 1:6 dimethylformamide–absolute ethanol raised the m.p. to 203–205.5° (dec.). The infrared spectrum showed bands at 3160 and 1650 cm.$^{-1}$

*Anal.* Calcd. for $C_{17}H_{18}Cl_2N_4O$: C, 55.9; H, 5.0; Cl, 19.4; N, 15.3. Found: C, 56.2; H, 4.9; Cl, 19.3; N, 15.6.

*5-{4′-[N,N-bis(2-chloroethyl)amino]benzylidene}barbituric acid.* A warm solution of 1.23 g. (0.005 mole) of III in 25 ml. of ethanol was added to a warm solution of 0.64 g. (0.005 mole) of barbituric acid in 6 ml. of water. After heating on the steam bath for 2 min., 1.1 g. of orange crystals, m.p. 268° (dec.) separated. From the mother liquor another 570 mg. was obtained, making the total yield 94%. No further purification was necessary. The compound is sparingly soluble in most solvents and quite soluble in dimethylformamide.

*Anal.* Calcd. for $C_{15}H_{15}Cl_2N_3O_3$: C, 50.6; H, 4.2; N, 11.7. Found: C, 50.7; H, 4.2; N, 11.9.

*Acknowledgment.* We acknowledge the assistance of James Hudson and Karl Lindfors in the preparation of certain intermediates.

ANN ARBOR, MICH.

(23) H. John, *Ber.*, **59B**, 1447 (1926).

(24) R. I. Meltzer, *et al.*, *J. Am. Pharm. Assoc.*, **42**, 594 (1953).

(25) T. Curtius, *J. prakt. Chem.*, [2] **95**, 335 (1917).

(26) Supplied by the Cancer Chemotherapy National Service Center.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

# Potential Anticancer Agents.[1] X. Synthesis of Nucleosides Derived from 6-Deoxy-D-glucofuranose

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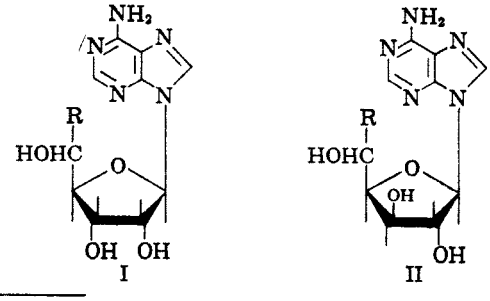
6-Amino- and 2,6-diamino-9-(6′-deoxy-β-D-glucofuranosyl)purine (XV and XVI) have been synthesized from D-glucose *via* the key intermediates 6-deoxy-1,2-*O*-isopropylidene-D-glucofuranose (VII) and 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-6-deoxy-D-glucofuranose (IX).

Synthesis of 5′-*C*-alkylpentofuranosyl nucleosides as possible inhibitors of cellular synthesis or utilization of nucleosides (I, R = H) and nucleotides has been the subject of several previous papers of this series. 9-α-L-Rhamnofuranosyladenine[2] was synthesized from rhamnose. Similarly, the two possible 5-*C*-methyl-D-ribose nucleosides (I, R = $CH_3$), namely, 9-(6′-deoxy-β-D-allofuranosyl) adenine[3] and 9-(6′-deoxy-α-L-talofuranosyl)adenine,[4] have been described. Since 9-β-D-xylofuranosyladenine (II, R = H)[2] has shown weak anticancer activity against Carcinoma 755,[5] the synthesis and




(1) This program is under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, and is in collaboration with the Sloan-Kettering Institute of Cancer Research. For the preceding paper of this series *cf.* R. Koehler, L. Goodman, J. DeGraw, and B. R. Baker, *J. Am. Chem. Soc.*, in press.

(2) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 966 (1957).

(3) E. J. Reist, R. R. Spencer, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 3692 (1958).

(4) E. J. Reist, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, in press..

(5) Dr. F. M. Schabel, Jr., Southern Research Institute, Birmingham, Ala., unpublished results.