The gummy residue became crystalline after trituration with 200 ml. of acetone, and the white solid was recrystallized from 95% ethanol. Four and eight-tenths grams (50%) of a product softening at 134–136° was obtained. Digestion of 1 g. of this material in 40 ml. of absolute methanol produced 0.9 g. of white powder, melting at 173° with decomposition.

Other Amino Acid Derivatives of Kojic Acid.—The conditions used for the preparation of DL-leucine and DL-isoleucine Mannich derivatives of kojic acid were similar to those used for the valine derivative. The methionine derivative was prepared in a similar manner, although more heating was required.

Attempted Preparation of Derivatives from Other Amino Acids.—L-Aspartic acid, L-asparagine, L-glutamic acid, L-glutamine, DL-phenylalanine, and DL-tyrosine failed to give satisfactory results with kojic acid and formaldehyde. Phenylalanine and tyrosine were too insoluble to permit reaction. Glutamic acid, glutamine, and asparagine appeared to be too unreactive. These amino acids were recovered more or less unchanged when conditions similar to the preparation of the valine derivative were used. If prolonged heating was used, mixtures, contaminated with decomposition products, were obtained.

Acknowledgment.—The authors wish to thank the Geschickter Fund for Medical Research, Washington, D. C., for help and cooperation in carrying out this research program.

Antineoplastic Agents. VI. Mannich Base Nitrogen Mustards (Part B)[1-3]

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A Mannich-type reaction involving bis(2-chloroethyl)amine, formaldehyde, and several amides has been investigated. Bis(2-chloroethyl)amine was shown to condense in ethanol–formalin solution with phthalimide, saccharin, isatin, and isatin thiosemicarbazone to yield (51–89%) the corresponding nitrogen mustard Mannich bases II, IV, and VI. The reaction was found to follow other courses under acidic conditions. Formation of *N*-methylbis(2-chloroethyl)amine and conversion of saccharin to alkoxymethylene (VII) and bismethylene (VIII) derivatives occurred in acidic media.

Nitrogen mustards, *viz.*, *N*-substituted bis(2-chloroethyl)amines, are commonly prepared[4] by chlorinating an appropriate bis(2-hydroxyethyl)-amine using thionyl chloride or a phosphorus halide.[4a-e] Other procedures include: condensations employing bis(2-chloroethyl)amine in a Mannich-type reaction [1,4f] or with an alkyl halide,[4g] aluminum chloride–lithium aluminum hydride reduction of *N*,*N*-bis(2-chloroethyl)amides,[2] and syntheses employing a previously prepared nitrogen mustard.[4h-l]

Recently we described the preparation of nitrogen mustards derived from cyclohexanone and a variety of acetophenones employing a Mannich reaction between the respective ketone, formaldehyde, and bis(2-chloroethyl)amine.[1] The potential value of this mild reaction as a route to nitrogen mustard derivatives of certain natural products emphasized the desirability of extending our initial investigation to Mannich-type reactions involving *N*-substitution (*e.g.*, I→II).

A number of amides and nitrogen heterocyclic compounds containing a labile N—H bond have been condensed with formaldehyde and a primary or secondary amine.[5] Generally, a neutral solvent composed of ethanol and formalin provides a satisfactory medium for this reaction. On occasion condensation is essentially complete within a few minutes at ice bath temperature[6]; however, reaction periods of one or more hours at room temperature or above are more frequently encountered.[5]

In contrast to our previous experience[1] with bis-(2-chloroethyl)amine in Mannich reactions leading to C-alkylation, this amine readily condensed with phthalimide (Ia), saccharin (III), isatin (Va), and isatin thiosemicarbazone (Vb) in ethanol–formalin (37%) solution. The corresponding Mannich base nitrogen mustards (II, IV and VI) were obtained in

(1) Part A; G. R. Pettit and J. A. Settepani, *J. Med. Pharm. Chem.*, **6**, 296 (1962).

(2) Refer to G. R. Pettit, M. F. Baumann, and K. N. Rangammal, *J. Med. Pharm. Chem.*, **6**, in press (1962) for contribution V.

(3) This investigation was aided by Grant No. T-79B from the American Cancer Society.

(4) For recent examples, consult ref. 2 (footnote 4), and: (a) E. J. Reist, R. R. Spencer, M. E. Wain, I. G. Junga, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 2821 (1961); (b) A. H. Soloway and E. Nyilas, *ibid.*, **26**, 1091 (1961); (c) S. Chu, J. E. Harris, and H. G. Mautner, *ibid.*, **25**, 1759 (1960); (d) J. F. Allen and N. B. Chapman, *J. Chem. Soc.*, 1482 (1960); (e) T. L. Fletcher and W. H. Wetzel, *J. Org. Chem.*, **25**, 1348 (1960); (f) R. C. Elderfield and J. R. Wood, *ibid.*, **26**, 3042 (1961); (g) Ya. L. Gol'dfarb and M. S. Kondakova, *Zhur. Obshchei Khim.*, **30**, 102 (1960). (h) F. D. Popp, *J. Org. Chem.*, **26**, 3020 (1961); (i) A. M. Creighton, L. N. Owen, and G. R. White, *J. Chem. Soc.*, 2375 (1961); (j) R. H. Wiley and G. Irick, *J. Org. Chem.*, **26**, 593 (1961); (k) F. Bergel and J. A. Stock, *J. Chem. Soc.*, 3658 (1960); (l) A. Ya. Berlin and V. P. Bronovitskaya, *Zhur. Obshchei Khim.*, **30**, 324 (1960).

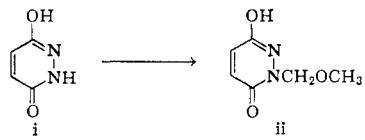
(5) A review of recent studies pertinent to this subject and leading references to prior investigations may be obtained by consulting: V. I. Stravrovskaya and M. O. Kolosova, *Zhur. Obshchei Khim.*, **30**, 689 (1960); J. H. Burckhalter and D. R. Dill, *J. Org. Chem.*, **24**, 562 (1959); W. J. Gottstein, W. F. Minor, and L. C. Cheney, *J. Am. Chem. Soc.*, **81**, 1198 (1959); S. Swaminathan, S. Ranganathan, and S. Sulochana, *J. Org. Chem.*, **23**, 707 (1958); H. W. Heine, M. B. Winstead, and R. P. Blair, *J. Am. Chem. Soc.*, **78**, 672 (1956); and a text by B. Reichert, *Die Mannich-Reaktion*, Springer Verlag, Berlin, 1959.

(6) *Cf.*, C. C. Bombardieri and A. Taurins, *Can. J. Chem.*, **33**, 923 (1955).

51–89% yields following a one- to three-hour reaction period at room temperature. Substitution of *N*-hydroxymethylenephthalimide (Ib) for phthalimide and formalin necessitated a longer reaction period and led to a smaller yield (48%) of imide II. Preparation of nitrogen mustard VIb was considered important in view of the pronounced antiviral activity of *N*-ethylisatin thiosemicarbazone (Vc).[7,8]

An attempt to obtain saccharin derivative IV by substituting bis(2-chloroethyl)amine hydrochloride for the parent amine and heating the reaction mixture at reflux for 12 hr. gave instead 1,1,3-trioxo - 2 - ethoxymethylenebenzo[*d*]isothiazoline (VIIa). After replacing the amine hydrochloride with a small quantity of hydrochloric acid the procedure was repeated and found to provide an identical amount (71%) of acetal VIIa. Similarly, a solvent containing methanol or propanol gave respectively alkoxy derivatives VIIb and VIIc. The reaction employing methanol, however, required more vigorous conditions.

Acetal (VII) formulations were first indicated for substances VIIa–c on the basis of elemental compositions and strong absorption in the 1100-cm.$^{-1}$ region of their infrared spectra consistent with an ether linkage. Unequivocal support for these assignments was obtained by condensing[9] chloromethyl methyl ether with sodium saccharin in dimethylformamide solution.[10] The product was



i ii

identical with methoxy acetal VIIb prepared from saccharin, formaldehyde, and methanol.[11]

When synthesis of nitrogen mustard IV was attempted using saccharin, paraformaldehyde, and bis(2-chloroethyl)amine hydrochloride in acetic acid[12] solution, the reaction again proceeded in an interesting manner. Methylenebisisothiazoline VIII separated as the reaction progressed and *N*-methylbis(2-chloroethyl)amine (IX) constituted the major basic product. Amine IX was conveniently isolated as its perchlorate derivative. Replacing the amine hydrochloride with a small volume of hydrochloric acid led to essentially the same yield (19%) of saccharin condensation product (VIII).[13,14] In another experiment, omitting saccharin provided a useful route to nitrogen mustard IX[15] (76% yield of perchlorate derivative). The structures of these products (VIII and IX) are consistent with infrared spectral data and were confirmed by comparison with authentic specimens.

The ready conversion of amides I, III, and V to bis(2-chloroethyl)aminomethylene derivatives using an essentially neutral ethanol–formalin Mannich reaction technique suggests that this procedure will be useful for preparation of related nitrogen mustards.

Experimental[16]

N-[Bis(2-chloroethyl)amino]methylenephthalimide (II). **A. From Phthalimide.**—An ethereal solution of bis(2-chloroethyl)amine was prepared by adding the corresponding hydrochloride[17] (1.1 g., 0.006 mole) to a cold solution of sodium hydroxide (0.3 g.) in water (3 ml.) and extracting with ether. The combined ether extract was washed with ice water, dried over magnesium sulfate, and concentrated *in vacuo* at ice bath temperatures. Phthalimide (0.88 g., 0.006 mole) was then added to a cold (ice bath) solution of the oily residue in 4 ml. of 3:1 ethanol–formalin (37%). After warming to *ca.* 35° for several minutes in order to complete dissolution of phthalimide the solution was maintained at room temperature for 1 hr. Cooling the reaction mixture led to a first crop (1.4 g.) of crystalline product melting at 79–80° and a second (0.09 g.) at 76–79°: total yield 89%. Two recrystallizations of the first crop from ethanol–ether gave a pure sample as colorless plates; m.p. 81–81.5°, ν_{max}^{KBr} 1770 and 1705 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{14}Cl_2N_2O_2$: C, 51.83; H, 4.68; Cl, 23.54; N, 9.30. Found: C, 51.97; H, 5.03; Cl, 24.02; N, 9.01.

B. From *N*-Hydroxymethylenephthalimide (Ib).—To a solution of bis(2-chloroethyl)amine (prepared from 1.1 g. of the hydrochloride as described in procedure A), in cold (ice bath) ethanol (4 ml.) was added 1.1 g. (0.006 mole) of

(7) P. W. Sadler, *J. Chem. Soc.*, 243 (1961). See also P. W. Sadler, *J. Org. Chem.*, **26**, 1315 (1961).

(8) Substances such as indoline VIb which might be expected to interfere with nucleic acid syntheses *in vivo* are of particular interest.

(9) *Cf.*, H. L. Rice and G. R. Pettit, *J. Am. Chem. Soc.*, **76**, 302 (1954).

(10) Additional evidence favoring the proposed reaction course is provided by the recent observations of H. Feuer and R. Harmetz, *J. Org. Chem.*, **24**, 1501 (1959). A reaction mixture prepared from maleic hydrazide, paraformaldehyde, concentrated hydrochloric acid, and methanol or ethanol was found to yield analogous acetals (*e.g.*, i → ii). This reaction was discovered during an attempt to use maleic hydrazide and dimethylamine hydrochloride in a Mannich condensation. Two possible mechanistic pathways leading to acetals of this type have also been discussed by Fauer and Harmetz. *Cf.*, also, W. B. Whalley, E. L. Anderson, F. DuGan, J. W. Wilson, and G. E. Ullyot, *J. Am. Chem. Soc.*, **77**, 745 (1955).

(11) Application of this reaction to other substances containing a nonbasic N—H group was not attempted in the present study.

(12) A number of Mannich reactions have been accomplished using acetic acid as solvent. For example, see references 4f, 5, G. I. Gregory and A. G. Long, *J. Chem. Soc.*, 3059 (1961), and F. F. Blicke and F. J. McCarty, *J. Org. Chem.*, **24**, 1069 (1959).

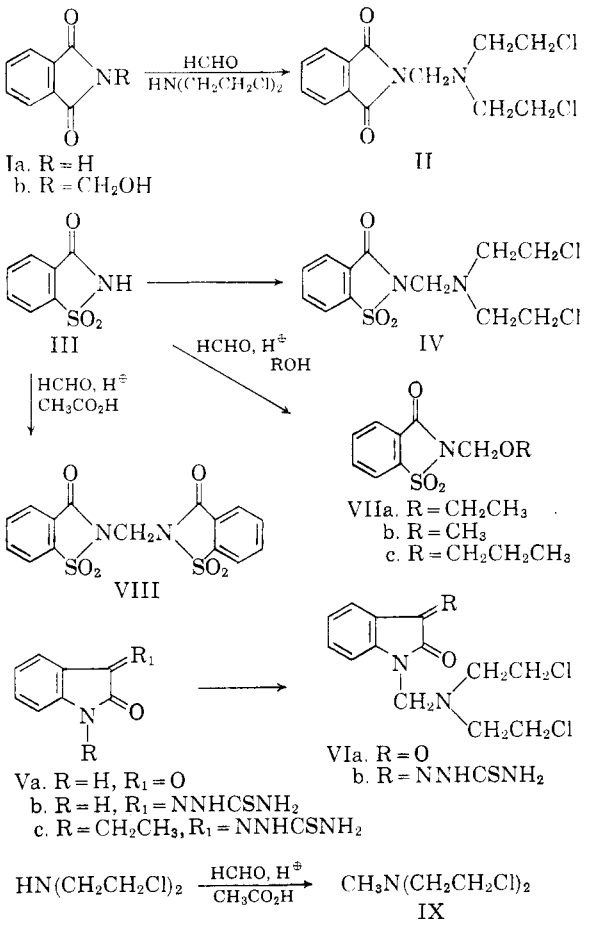
(13) H. Eckenroth and G. Koerppen, *Ber.*, **30**, 1265 (1897) prepared this substance by warming a solution of formaldehyde and saccharin in 70% aqueous sulfuric acid.

(14) The recent preparation of benzothiadiazines from *o*-aminobenzenesulfonamides, using paraformaldehyde and hydrogen chloride in ethyl acetate solution, is pertinent to this subject. Several leading references to reactions between sulfonamides and aldehydes have also been presented by L. H. Werner, A. Halamandaris, S. Ricca, Jr., L. Dorfman, and G. de Stevens, *J. Am. Chem. Soc.*, **82**, 1161 (1960).

(15) This reaction may be considered a modification of the Eschweiler methylation procedure. See: W. Eschweiler, *Ber.*, **38**, 880 (1905); H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933). Preparation of *N*-methylbis(2-chloroethyl)amine is generally accomplished as described by J. T. Abrams, R. L. Barker, W. E. Jones, H. W. Vallender, and F. N. Woodward, *J. Soc. Chem. Ind.* (London), **68**, 280 (1949).

(16) Melting points are uncorrected and were observed using open Kimble glass capillaries in a silicone-oil bath. The infrared spectra were recorded by Dr. R. A. Hill of this laboratory and the microanalyses were provided by Dr. A. Bernhardt, Max Planck Institut, Mülheim, Germany.

(17) F. G. Mann, *J. Chem. Soc.*, 461 (1934).



N-hydroxymethylenephthalimide.[18] Following an overnight reaction period at room temperature the mixture was refrigerated and filtered. The crystalline product (II), m.p. 79–80°, weighed 0.81 g. (48%) and was identical[19] with a specimen of nitrogen mustard II obtained using procedure A.

1,1,3-Trioxo-2-[bis(2-chloroethyl)amino]methylenebenzo-[*d*]isothiazoline (IV).—Saccharin (2.2 g., 0.012 mole) was added in small amounts to a cold (ice bath) solution composed of bis(2-chloroethyl)amine (prepared from 2.2 g. of the hydrochloride derivative, *cf.*, II) and 8 ml. of 3:1 ethanol–formalin (37%). The imide (III) dissolved quickly and almost immediately Mannich base IV began to crystallize. Following a 1-hr. period at room temperature the mixture was cooled, and the heat-sensitive crystalline product was collected, yield and 2.9 g. (89%), m.p. 90–92°. An analytical sample crystallized from acetone–ether as colorless plates; m.p. 94–94.5°, ν_{max}^{KBr} 1732 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{14}Cl_2N_2SO_3$: C, 42.74; H, 4.18; Cl, 21.03, N, 8.31; S, 9.51. Found: C, 42.89; H, 4.10; Cl, 20.98; N, 8.41; S, 9.53.

1-[Bis(2-chloroethyl)amino]methylene-2,3-dioxoindoline (Va).—Isatin (1.8 g.) was converted to nitrogen mustard VIa in 65% yield (2.2 g., m.p. 80–81.5°) as illustrated using phthalimide (*cf.* II). In this case an additional 10-ml. quantity of ethanol was needed to dissolve the amide. Two recrystallizations from ether yielded an analytical sample as pale orange prisms melting at 85.5–86.5°, ν_{max}^{KBr} 1740 and 1610 cm.$^{-1}$. The product was light-sensitive and gradually became deep orange-colored.

Anal. Calcd. for $C_{13}H_{14}Cl_2N_2O_2$: C, 51.83; H, 4.68; Cl, 23.54; N, 9.30. Found: C, 52.40; H, 4.82; Cl, 23.49; N, 9.14.

1-[Bis(2-chloroethyl)amino]methylene-2-oxoindoline 3-Thiosemicarbazone (VIb).—The following procedure was carried out in the dark. A suspension of isatin thiosemicarbazone (1.1 g., 0.005 mole) in 1:1 ethanol–water (100 ml.) was warmed (steam bath) before adding successively a solution of bis(2-chloroethyl)amine (from 3.3 g., 0.018 mole, of the corresponding hydrochloride) in 10 ml. of ethanol and 37% formalin (4 ml.). After a 2-hr. period at room temperature the crystalline product (0.96 g., 51%), dec. 157–157.5°, was collected. This specimen was used for microanalyses. Attempts at further purification by recrystallization led to extensive decomposition, as evidenced by broadening of the melting point range (*e.g.*, to dec. 201–215°).[20] Thin layer chromatography (ethanol mobile phase on Silica Gel G) of the light-sensitive product used for elemental analyses, indicated that it was homogeneous. The infrared spectrum of this substance exhibited strong absorption at 3380 and 1688 cm.$^{-1}$ (KBr).

Anal. Calcd. for $C_{14}H_{17}Cl_2N_5OS$: C, 44.93; H, 5.00; Cl, 18.95; N, 18.71; S, 8.57. Found: C, 45.31; H, 4.98; Cl, 18.59; S, 8.10. Microanalytical values for nitrogen (16.40, 17.29) were inconclusive.

1,1,3-Trioxo-2-ethoxymethylenebenzo[*d*]isothiazoline (VIIa).—Saccharin (5.5 g.) was added to a solution composed of concd. hydrochloric acid (0.2 ml.), 37% formalin (4 ml.), and ethanol (10 ml.). Following a 12-hr. period at reflux the mixture was diluted with water (5 ml.) and cooled. The first crop of crystalline product weighed 4.7 g., m.p. 79–81°. A second crop melted at 76–79° and weighed 0.4 g. (total yield, 71%). Two recrystallizations from ether converted the higher melting material to an analytical sample; colorless leaflets, m.p. 80.5–81°, ν_{max}^{KBr} 1742, 1079, and 1060 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{11}NO_4S$: C, 49.79; H, 4.59; N, 5.81; S, 13.27. Found: C, 49.87; H, 4.50; N, 6.01; S, 13.07.

1,1,3-Trioxo-2-methoxymethylenebenzo[*d*]isothiazoline (VIIb). Procedure A.—A solution of saccharin (3.3 g.), 37% formalin (2 ml.) and 2 drops of concd. hydrochloric acid in methanol (20 ml.) was heated at *ca.* 110° for 12 hr. in an autoclave (Hastelloy B). After cooling, the solution was concentrated *in vacuo* and the residue was recrystallized from methanol–ether; yield, 0.72 g. (21%), m.p. 83–85°. The mother liquors were found to consist largely of saccharin. Following several recrystallizations from methanol–ether a pure specimen of ether VIIb was obtained as colorless plates melting at 87.5–88.5°, ν_{max}^{KBr} 1740, 1098, and 1072 cm.$^{-1}$.

Anal. Calcd. for $C_9H_9NO_4S$: C, 47.58; H, 4.01; N, 6.17; S, 14.09. Found: C, 47.59; H, 4.26; N, 6.07; S, 14.24.

The product (VIIb) was identical[19] with an authentic sample prepared as described in procedure B.

Procedure B.—A dimethylformamide (10 ml.) solution of sodium saccharin (1.3 g.) and chloromethyl methyl ether (0.5 g.) was heated at steam bath temperature for 1 hr. After dilution with water, and cooling, the crystalline product (0.9 g., 58%), m.p. 81–83°, was collected. Recrystallization from methanol–ether raised the melting point to 84.5–86°.

1,1,3-Trioxo-2-propoxymethylenebenzo[*d*]isothiazoline (VIIb).—Conversion of saccharin (2.2 g.) to the propoxymethylene derivative VIIb was accomplished in propanol (10 ml.) solution as illustrated for preparation of the ethoxy analog VIIa. In this case the reaction mixture was concentrated *in vacuo* to a viscous oil. Crystallization of the oil from ethanol–ether yielded 2.1 g. (74%) of product melting at 63–64°. Several recrystallizations from ether gave a

(18) M. B. Winstead and H. W. Heine, *J. Am. Chem. Soc.*, **77**, 1913 (1955).

(19) As evidenced by mixture melting point determination and infrared spectral comparison in potassium bromide.

(20) Instability has been encountered with other Mannich bases of this type. See, for example, ref. 5.

pure sample as colorless plates; m.p. 65–65.5°, ν_{max}^{KBr} 1734, 1087, and 1063 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{13}NO_4S$: C, 51.77; H, 5.09; N, 5.49; S, 12.55. Found: C, 51.71; H, 4.86; N, 5.50; S, 12.54.

2,2′-Methylenebis(1,1,3-trioxo-benzo[*d*]isothiazoline) (VIII).—A solution composed of saccharin (3.3 g.), paraformaldehyde (0.6 g.), concd. hydrochloric acid (0.2 ml.), and acetic acid (20 ml.) was heated at steam bath temperature for 10 hr. After the first 3-hr. period, 0.3 g. of paraformaldehyde was added to the mixture. The crystalline product (VIII, 0.6 g.), m.p. 285–289°, which formed as the reaction progressed, was collected by filtration. Mixture melting point determination and infrared spectral comparison, in potassium bromide, with an authentic specimen (m.p. 286–289°) of methylenebisisothiazoline[13] (VIII) confirmed the identical nature of both substances.

In a prior experiment, essentially the same yield of product (VIII) was obtained when the reaction mixture also contained bis(2-chloroethyl)amine hydrochloride (3.3 g.). Under these conditions the amine was converted to its *N*-methyl derivative (see below).

***N*-Methylbis(2-chloroethyl)amine (IX) perchlorate.**—A solution of bis(2-chloroethyl)amine hydrochloride[17] (1.1 g.) and paraformaldehyde (0.2 g.) in glacial acetic acid (4 ml.) was heated overnight at steam bath temperature. The mixture was then concentrated *in vacuo* to a mobile oil and diluted with cold water (3 ml.) followed by 70% perchloric acid (2 ml.). The crystalline product (IX perchlorate) which separated weighed 1.1 g. (76%) and melted at 95–98°. Two recrystallizations from ethanol afforded a pure specimen as colorless leaflets, m.p. 106–107°. The perchlorate was added to cold 10% aqueous sodium hydroxide and the liberated amine was extracted with ether. Hydrogen chloride was conducted into the dry (magnesium sulfate) ethereal extract and the hydrochloride derivative of IX was collected. An analytical sample crystallized from acetone as colorless plates melting at 110–110.5° (lit.,[21] m.p. 108–110°).

Anal. Calcd. for $C_5H_{12}Cl_3N$: C, 31.19; H, 6.28; Cl, 55.26; N. 7.28. Found: C, 31.37; H, 6.74; Cl, 54.94; N, 7.08.

The hydrochloride was identical[19] with a commercial sample (Bios Laboratories) of *N*-methylbis(2-chloroethyl)-amine hydrochloride (m.p. 110°).

(21) M. Ishidate and S. Tsukagoshi, *Chem. Pharm. Bull.* (Tokyo), **8**, 87 (1960).

Potential Anticancer Agents.[1] LXXI. Some Diaminopyrimidines and Diamino-*s*-triazines Related to Daraprim

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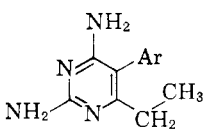
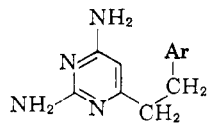
2,4-Diamino-6-phenethylpyrimidines (II) were formed by condensation of 5-aryl-3-ketovalerates with guanidine carbonate to afford 2-amino-4-hydroxy-6-phenethylpyrimidines, which were chlorinated and aminated. 2,4-Diamino-6-phenethyltriazines (III) formed on condensation of biguanide with hydrocinnamates. Ring-halogenated hydrocinnamic acids were common intermediates to II and III. 2,4-Diamino-6-styryltriazines (XVIII) were obtained from 2,4-diamino-6-methyltriazine and halobenzaldehydes in concentrated sulfuric acid.

An earlier paper[3] in this series described the synthesis of nitrogen mustards derived from Daraprim (I) and from a related diaminodihydro-*s*-triazine. Study of further structural modifications of Daraprim was prompted by a continuing interest in these diamino heterocycles, which function in a variety of systems as folic acid antagonists like the structurally related drug, Amethopterin; the latter is clinically useful against cancer. In particular it was of interest to see what biological effect, if any, would result by transferring the 5-aryl group of I to the 6-ethyl group, to form the 6-phenethyl derivatives (II). At the same time, study of similarly substituted triazines (III)[4] would be permitted by their easy synthesis from intermediates required for preparing II.

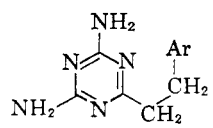
In devising a synthetic scheme for II, it appeared that a series of ring-halogenated hydrocinnamic acids could serve as precursors to both II and III. Condensation of β-ketocarboxylic



I. Ar = *p*-ClC_6H_4



IIa. Ar = C_6H_5
b. Ar = *p*-FC_6H_4
e. Ar = *m,p*-$Cl_2C_6H_3$



IIIa. Ar = C_6H_5
b. Ar = *p*-FC_6H_4
c. Ar = *p*-ClC_6H_4
d. Ar = *o*-ClC_6H_4
e. Ar = *m,p*-$Cl_2C_6H_3$

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, see B. Weinstein, O. P. Crews, M. A. Leaffer, B. R. Baker, and L. Goodman, *J. Org. Chem.*, **27**, 1389 (1962).

(2) (a) To whom reprint requests should be addressed; (b) Present address: School of Pharmacy, University of Buffalo, Buffalo, N. Y.

(3) J. I. DeGraw, L. O. Ross, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 1933 (1961).

(4) For summary of antifolic activity and antitumor properties of related dihydrotriazines, see E. J. Modest in *Heterocyclic Compounds*, Vol. 7, ed. by R. C. Elderfield, John Wiley and Sons, Inc., New York, 1961, p. 717.