DL-Willardiine Mustard[1]

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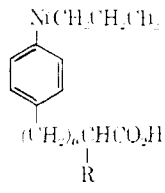
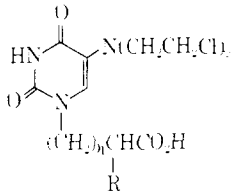
A nitrogen mustard (III) has been synthesized from DL-willardiine. This was nitrated, then the α-amino and carboxyl groups were protected by phthaloylation and esterification. Catalytical hydrogenation in a solvent containing hydrogen chloride smoothly converted the nitro compound to an amine. Hydroxyethylation, chlorination, and stepwise removal of the N-phthaloyl and ethyl ester groups afforded the DL-willardiine mustard III. Neither III nor its ethyl ester exhibited any significant activity against Walker carcinosarcoma 256 (subcutaneous) in rats. Some of the intermediates were screened against other tumor systems and by cell culture with KB cells. No significant activity was observed.

Chlorambucil (Ia)[2] and phenylalanine mustard (Ib)[3] are two clinically useful antitumor agents whose uracil analogs (II and III) may be of interest as antitumor agents. The uracilalkanoic acids IIa and IIb



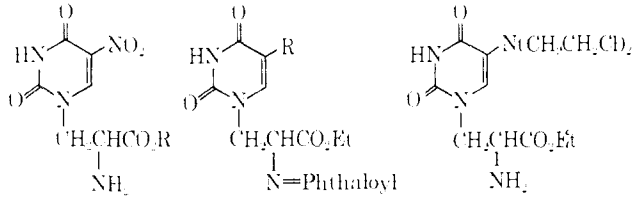
Ia, R = H; n = 2
b, R = NH_2; n = 1



IIa, n = 1; R = H
b, n = 2; R = H
III, n = 1; R = NH_2

have been synthesized.[4] We now report the synthesis and antitumor screening of DL-willardiine mustard (III) and some intermediates.

The route for introducing the mustard group into DL-willardiine[5,6] generally followed that established with the model compounds IIa and IIb.[4] DL-Willardiine[5,6] was nitrated under precise reaction conditions to afford IVa. By standard methods, IVa was converted to the ethyl ester IVb, and then to the N-phthaloyl ester V. Catalytic hydrogenation[7] of V proceeded smoothly in the presence of hydrogen chloride, but very erratically in its absence, to afford the hydrochloride of the amine VI. Hydroxyethylation and chlorination with phosphoryl chloride yielded the blocked mustard VIII. Careful purification of VIII was essential to success in the subsequent steps.



IVa, R = H
b, R = Et

V, R = NO_2
VI, R = NH_2
VII, R = $N(CH_2CH_2OH)_2$
VIII, R = $N(CH_2CH_2Cl)_2$

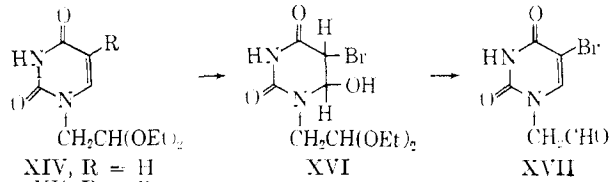
IX

Complete deblocking of VIII to DL-willardiine mustard was attempted. Chromatographic data suggested that after 3 hr of heating in 12 N hydrochloric acid, the deblocking was complete. However, much decomposition had occurred, as indicated by low chlorine analysis and the fact that little, if any, III could be isolated. Stepwise deblocking of VIII was more satisfactory. Reaction with hydrazine at 40° for several days afforded the amino ester IX, which was purified and characterized as the hydrochloride. Heating the pure ester IX briefly in 12 N hydrochloric acid gave the desired DL-willardiine mustard III, as the hydrochloride. A less soluble zwitterionic form of III was isolated by precipitation at pH 2–3.

The mustard III retained different proportions of hydrogen chloride and water depending on the conditions of isolation and drying. The hydrochloride of compound III was stable for weeks at room temperature when kept as a solid, but decomposed rapidly in 1 N hydrochloric acid.

X, R = $CH_2CH(OEt)_2$ XII, R = $CH_2CH(OEt)_2$
XI, R = CH_2CHO XIII, R = CH_2CHO

We examined the possible preparation of 5-nitrowillardiine (IVa) by the sequence 5-nitrouracil → X → XI → IVa. The reaction of 5-nitrouracil with bromoacetal proceeded readily to X in about 50% yield. Hydrolysis of this acetal to the aldehyde XI in aqueous dioxane with a sulfonic acid ion-exchange resin as a catalyst was satisfactory. However, all attempts to convert XI to the amino acid IVa by the Strecker reaction failed. The syrupy diacetal XII was isolated as a by-product in the formation of X.



XIV, R = H
XV, R = Br

XVI

XVII

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center (CCNSC), National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. PH-43-64-500. The opinions expressed in this paper are those of the authors and not necessarily those of the CCNSC.

(2) J. L. Everett, J. J. Roberts, and W. C. J. Ross, *J. Chem. Soc.*, 2386 (1953).

(3) (a) F. Bergel, V. C. E. Bornop, and J. A. Stock, *ibid.*, 1233 (1955); (b) L. F. Larionov, A. S. Kokhlov, E. N. Shkodinskaia, A. S. Vasina, V. I. Trusheikina, and A. M. Novikova, *Lancet*, **269**, 169 (1955).

(4) A. P. Martinez, W. W. Lee, and L. Goodman, *J. Med. Chem.*, **8**, 187 (1965).

(5) (a) J. H. Dewar and G. Shaw, *J. Chem. Soc.*, 583 (1962); (b) A. Kjaer, A. Knudsen, and P. O. Larsen, *Acta Chem. Scand.*, **15**, 1193 (1961).

(6) A. P. Martinez and W. W. Lee, *J. Org. Chem.*, **30**, 317 (1965).

(7) For generally useful methods of nitropyrimidine reduction, see D. J. Brown, "The Pyrimidines," Interscience Publishers, Inc., New York, N. Y., 1962, p 113.

The bromoacetal XV was sought as an intermediate in an alternate, but subsequently abandoned, route to III. The bromination of the uracil acetal XIV[6] to give XV was studied under nonacidic conditions that would not hydrolyze the acetal. Treatment with bromine in pyridine afforded XV, but bromine in aqueous sodium hydroxide gave the 5-bromo-6-hydroxydihydrouracil XVI, isolated as a crystalline compound. While the formation of such 5-bromo-6-hydroxydihydrouracils is well known,[8] the isolation of a relatively stable crystalline one from a uracil lacking a 5-substituent is unusual.[9] Hydrolysis of either acetal XV or XVI afforded the same bromoacetaldehyde XVII.

DL-Willardiine mustard III and a number of intermediates were screened by the Cancer Chemotherapy National Service Center (CCNSC) for antitumor activity according to established CCNSC protocol.[12] The mustard III and its ethyl ester IX were screened against Walker carcinosarcoma 256 (subcutaneous) in albino rats. The results show that neither III nor IX exhibited significant activity.

Several intermediates, X, XI, and XIV, were screened against Sarcoma 180 and leukemia L1210; no significant activity was found. All the intermediates tested in cell culture against KB cells were inactive.

Experimental Section[13]

3-[5-Nitro-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-DL-alanine (5-Nitro-DL-willardiine) (IVa).—To an ice-cooled, stirred mixture of 25.0 g (0.115 mole) of DL-willardiine[5,6] in 50 ml of concentrated H_2SO_4 was added dropwise 11.0 ml of red-fuming HNO_3. The mixture was stirred for 2 hr at ice temperature, 3.5 hr at room temperature; complete solution was attained during this period. The solution was poured over 800 g of crushed ice, and adjusted to pH 5-6 with concentrated NH_4OH. The crystalline precipitate was kept cold overnight, then collected, washed with 400 ml of H_2O, and dried at 50° *in vacuo* to afford 24.1 g (86%) of IVa·H_2O, mp 200-205°. This was homogeneous by paper chromatography (in solvents A and B) and suitable for use in the next step; recrystallization afforded fine needles from H_2O, mp 232-235°. It was homogeneous in solvents A and B with R_f 0.18 and 0.81, respectively.

Anal. Calcd for $C_7H_8N_4O_6$: C, 34.4; H, 3.30; N, 22.95. Found: C, 34.6; H, 3.42; N, 22.96.

In this nitration, larger ratios of red-fuming HNO_3 to H_2SO_4 gave lower yields and other grades of HNO_3 were unsatisfactory. The use of HOAc-H_2SO_4 mixtures was also not satisfactory.

Ethyl 3-[5-Nitro-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-DL-alaninate (Ethyl 5-Nitro-DL-willardiinate) (IVb).—Refluxing 2.60 g (10. 6 mmoles) of the acid IVa in EtOH saturated with gaseous HCl for 4 hr yielded 2.82 g (80%) of IVb, mp 162-164°, homogeneous in solvents A and C with R_f 0.35 and 0.20, respectively.

Anal. Calcd for $C_9H_{12}N_4O_6 \cdot HCl \cdot C_2H_5OH$: C, 37.3; H, 5.40; N, 15.8. Found: C, 37.2; H, 5.22; N, 15.7.

Ethyl 3-[5-Nitro-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-N-phthaloyl-DL-alaninate (V).—A mixture of 16.2 g (0.046 mole) of IVb·HCl·EtOH in 150 ml of pyridine was allowed to react with 7.4 g (0.05 mole) of phthalic anhydride for 1.5 hr at room temperature and 1.5 hr at reflux and worked up by the usual procedure[14] to afford 15.9 g (87%) of V as a tan solid, mp 229-231°, with spectral and chromatographic characteristics similar to the recrystallized samples. This was suitable for use in the next step. Recrystallization of V from EtOAc gave the analytical sample, mp 247-248.° It was homogeneous in solvent ME-2 with R_f 0.86 (starting material, R_f 0.08).

Anal. Calcd for $C_{17}H_{14}N_4O_8$: C, 50.8; H, 3.51; N, 13.93. Found: C, 50.5; H, 3.43; N, 13.66.

Ethyl 3-[5-Amino-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-N-phthaloyl-DL-alaninate (VI).—A mixture of 3.2 g (7.95 mmoles) of V, 400 mg of 5% Pd-C, 80 ml of absolute EtOH, and 3 ml of absolute EtOH saturated with HCl (at 0°) was hydrogenated at room temperature and pressure. After the theoretical amount of H_2 was consumed in 2.7 hr, the mixture was diluted with 50 ml of EtOH, warmed to effect solution of the product, and filtered through Celite to remove the catalyst. The catalyst was thoroughly washed with EtOH. The EtOH filtrate and washes were evaporated to dryness to afford the theoretical yield of the hydrochloride of VI as a white, crystalline solid, mp 192-200° with sintering from 175–190°. This was suitable for use in the next step. The hydrochloride could be converted to the free base VI, identical in properties with the analytical sample below.

In an earlier experiment, hydrogenation of V in 2-methoxyethanol without the use of HCl had given, after recrystallization from EtOH, an 80% yield of VI, mp 207.5-208.5°, homogeneous in solvent C with R_f 0.58 (starting material streaks to R_f 0.10) and solvent ME-20 with R_f 0.81.

Anal. Calcd for $C_{17}H_{16}N_4O_6$: C, 54.8; H, 4.33; N, 15.1. Found: C, 54.5; H, 4.39; N, 14.9.

Ethyl 3-[5-Bis(2-hydroxyethyl)amino-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-N-phthaloyl-DL-alaninate (VII).—A solution of 0.80 g (1.95 mmoles) of VI·HCl, 40 ml of HOAc, 10 ml of ethylene oxide, 5 ml of H_2O, and 2.0 g of anhydrous NaOAc was stirred overnight at room temperature, then evaporated to dryness *in vacuo*. The residue was partitioned between 75 ml each of EtOAc and H_2O. The EtOAc was dried and evaporated *in vacuo* to afford 0.70 g (77%) of material which, after crystallization from EtOAc afforded 0.50 g (55%) of cream-colored crystals of VII, mp 144-144.5°. It moved as a single spot in solvents C and ME-20 with R_f 0.74 and 0.11, respectively.

Anal. Calcd for $C_{21}H_{24}N_4O_8$: C, 54.8; H, 5.25; N, 12.2. Found: C, 54.4; H, 5.45; N, 12.6.

Ethyl 3-[5-Bis(2-chloroethyl)amino-3,4-dihydro-2,4-dioxo-1-(2H)-pyrimidinyl]-N-phthaloyl-DL-alaninate (VIII).—A solution of 0.30 g (0.65 mmole) of the crystalline VII in 2.8 ml of $POCl_3$ was heated for 2.5 hr at 75-80°, then poured onto 30 ml of crushed ice and H_2O, stirred for no more than 5 min, and extracted with CH_2Cl_2. The organic layer was dried and evaporated *in vacuo* to leave 0.43 g of a lime-colored solid foam. Crystallization from 5 ml of absolute EtOH afforded 0.27 g (84%) of light yellow needles of VIII, mp 167-168°. It moved as a single spot with R_f 0.81 in solvent E and with R_f 0.98 in ME-20.

Material from an earlier run was twice recrystallized from EtOH to afford pure VIII, mp 165.5-166.5°.

Anal. Calcd for $C_{21}H_{22}Cl_2N_4O_6$: C, 50.6; H, 4.45; Cl, 14.3; N, 11.3. Found: C, 50.5; H, 4.77; Cl, 13.9; N, 11.4.

Ethyl 3-[5-Bis(2-chloroethyl)amino-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-DL-alaninate (IX).—A mixture of 7.17 g (14.4 mmoles) of VIII, 1.0 ml of H_2O, and 85 ml of 2-methoxyethanol was treated with 1.11 g (34.8 mmoles) of NH_2NH_2 in 5 ml of MeOH, then stirred at 40° for 5 days, and evaporated *in vacuo*. The residue was triturated thoroughly with CH_2Cl_2

(8) (a) See ref 7, pp 172–174, 256–258; (b) S. Y. Wang, *J. Org. Chem.*, **24**, 11 (1959); (c) A. M. Moore and S. M. Anderson, *Can. J. Chem.*, **37**, 590 (1959).

(9) (a) When the 5 position is substituted, the crystalline intermediate has been isolated.[10] When the brominations of uracil are carried out in alcohol, the 5-bromo-6-alkoxyuracils have been isolated.[11] (b) H. A. Lozeron, M. P. Gordon, T. Gabriel, W. Tautz, and R. Duschinsky, *Biochemistry*, **3**, 1844 (1964), have successfully isolated *dl*-5-5-fluoro-6-hydroxydihydrouracil.

(10) (a) K. Dimitrov and B. Kurtev, *Compt. Rend. Acad. Bulgare Sci.*, **11**, 497 (1958); *Chem. Abstr.*, **54**, 1530 (1960); (b) R. Duschinsky, T. Gabriel, W. Tautz, A. Nussbaum, M. Hoffer, E. Grunberg, J. H. Burchenal, and J. J. Fox, *J. Med. Chem.*, **10**, 47 (1967).

(11) B. Kurtev and M. Kirilov, *Bulgar. Akad. Nauk, Otd. Geol.-Geograf. Khim. Nauki, Izv. Khim. Inst.*, **1**, 277 (1951); *Chem. Abstr.*, **47**, 1607 (1953).

(12) *Cancer Chemotherapy Rept.*, **25**, 1 (1962).

(13) Melting points were taken on a Fischer-Johns apparatus and are not corrected. Paper chromatography was done by the descending technique on Whatman No. 1 paper unless otherwise noted (except solvent A). The solvent systems were A, C_6H_6–MeOH–H_2O (2:6:1) run on Schleicher and Schuell No. 2496 acetylated paper; B, 5% aqueous Na_2HPO_4, pH 8.9; C, *n*-BuOH–H_2O (saturated); D, *n*-BuOH–HOAc–H_2O (5:2:3); E, *i*-PrOH–2 *N* HCl (65:35); F, *n*-BuOH–2 *N* HCl (saturated). Thin layer chromatograms (tlc) were run on silica gel HF (F. Merck A. G., Darmstadt) in MeOH–EtOAc (ME) where the per cent of MeOH is denoted by a numeral after ME. For example, ME-2 denotes the above solvent combination containing 2% MeOH. The spots were detected on all chromatograms under ultraviolet light.

(14) H. F. Gram, C. W. Mosher, and B. R. Baker, *J. Am. Chem. Soc.*, **81**, 3103 (1959).

and filtered. The filtrate was saturated with anhydrous HCl then evaporated to dryness *in vacuo*. The residue, after trituration with CH_2Cl_2, was recrystallized from 50 ml of absolute EtOH to give 2.32 g (40%) of IX as a yellow solid, mp 167–178°, homogeneous in solvent E (R_f 0.80), and suitable for use in the next step. The CH_2Cl_2 mother liquors were evaporated to afford 0.80 g of starting material VIII (46% conversion to IX). Recrystallization from EtOH of a similar sample from an earlier run afforded pure IX·HCl, mp 180–183°; it had R_f 0.80 in solvent E.

Anal. Calcd for $C_{13}H_{20}Cl_2N_4O_4 \cdot HCl$: C, 38.7; H, 5.26; Cl, 26.4; N, 13.90. Found: C, 38.8; H, 5.12; Cl, 26.1; N, 14.2.

3-[5-Bis(2-chloroethyl)amino-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl]-DL-alanine (DL-Willardiine Mustard) (III).—A solution of 1.0 g (2.48 mmoles) of the recrystallized IX·HCl in 50 ml of 12 *N* HCl was heated for 30 min on a steam bath, then evaporated to dryness *in vacuo* (20° 1.0 mm). The white, crystalline residue was triturated with 100 ml of Me_2CO, collected, and dried for 2.0 hr at 20° (1.0 mm) to afford 0.98 g (91%) of III·2HCl·1.67H_2O, mp 155–190° (sintered and resolidified, then decomposed without melting at 240°). It moved as a single spot on paper chromatograms when a sample was dissolved in 12 *N* HCl and spotted on Whatman No. 3 paper immediately; R_f 0.67 and 0.36 in solvents E and F, respectively.

Anal. Calcd for $C_{11}H_{16}Cl_2N_4O_4 \cdot 2HCl \cdot 1.67H_2O$: C, 30.2; H, 4.92; Cl, 32.5; N, 12.8. Found: C, 29.8; H, 5.00; Cl, 32.7; N, 12.7.

Samples of III were dried at 35 and 56°. The amount of HCl and H_2O decreased with increasing temperature and time. The samples gave satisfactory analyses.

Some of the dihydrochloride, III·2HCl·1.67H_2O, was dissolved in cold H_2O and the acidity was adjusted to pH 2–3. The white crystalline solid that precipitated was collected, dried at 20° (1.0 mm), and recrystallized from DMF to afford a white solid, mp >300°. It was homogeneous on Whatman No. 3 paper in solvents E and F with R_f 0.67 and 0.37, respectively. On the basis of the above properties and the analysis, the material is presumed to be the zwitterionic form of III.

Anal. Calcd for $C_{11}H_{16}Cl_2N_4O_4$: C, 38.9; H, 4.75; N, 16.5. Found: C, 38.8; H, 4.89; N, 16.2.

1-(2,2-Diethoxyethyl)-5-nitrouracil (X).—By the reported procedure for the preparation of XIV,[6] the reaction of 28.3 g of 5-nitrouracil and 140 g of 2-bromo-1,1-diethoxyethane gave 21.7 g (44%) of the acetal X, mp 91.5–92.5°, and a second crop, 3.4 g (total 51%), mp 88–90°. This was homogeneous in solvents C and B with R_f values of 0.85 and 0.83, respectively (starting material, R_f 0.16 and 0.56, respectively). Recrystallization from Et_2O–petroleum ether (bp 65–110°) afforded the analytical sample of X, mp 90.5–91.5°.

Anal. Calcd for $C_{10}H_{15}N_3O_5$: C, 44.0; H, 5.53; N, 15.4. Found: C, 43.8; H, 5.62; N, 15.4.

5-Nitrouracil-1-acetaldehyde (XI).—A mixture of 11.0 g (0.040 mole) of the acetyl X, 40 cc of Dowex 50-X 8(H), 60 ml of 1,2-diethoxyethane, and 60 ml of H_2O was stirred and heated on a steam bath for 5 hr. The resin was separated by filtration and washed with 1,2-diethoxyethane. The filtrate and washings were concentrated *in vacuo* to about 40 ml, then chilled in ice to afford 7.9 g (91%) of the aldehyde XI as tan crystals, mp 236–237°; it was homogeneous in solvent B with R_f 0.59. Recrystallization from H_2O afforded a lower melting (perhaps because of hydration) sample of XI, mp 228–230°.

Anal. Calcd for $C_6H_5N_3O_5 \cdot H_2O$: C, 33.2; H, 3.25; N, 19.4. Found: C, 33.2; H, 3.40; N, 19.5.

XI gave in quantitative yield, a semicarbazone, mp 251–250.5°;[15] other derivatives were also prepared.[15]

5-Nitrouracil-1,3-diacetaldehyde (XIII).—The mother liquors from several runs from the crystallization of X were evaporated *in vacuo*, and the 50 g of residue was columned through 450 g of neutral alumina, eluting exhaustively with CH_2Cl_2 to yield 30 g of the bisacetal XII, a homogeneous oil with R_f 0.90 in solvent ME-10. Further elution of the column with MeOH afforded an additional 15 g of X.

The oily XII (6.04 g) was hydrolyzed by the procedure used to obtain XI to afford 4.4 g of the diacetaldehyde XIII, a homogeneous solid foam with R_f 0.79 in solvent ME-10. Compound XIII gave a crystalline bis-N[4]-methylthiosemicarbazone.[15]

1-(2,2-Diethoxyethyl)-5-bromouracil (XV).—To a stirred solution of 0.83 g (3.6 mmoles) of 1-(2,2-diethoxyethyl)uracil (XIV)[6] in 5 ml of pyridine was added 0.18 ml (0.58 g, 3.6 mmoles) of Br_2. The solution, protected from moisture, was maintained at 55°, by heat from an infrared lamp, for 2 hr, then evaporated *in vacuo*. The residue was heated with 25 ml of H_2O on a steam bath for 15 min, chilled in ice, collected, and dried to give 0.59 g (53%) of XV, mp 118–120°. Recrystallization from EtOH–H_2O afforded 0.55 g (49%) of XV, mp 121–122°; it was homogeneous in solvent A with R_f 0.39, $\lambda_{max}^{pH\ 1}$ 282 mμ (ε 8140), $\lambda_{max}^{pH\ 7}$ 282 mμ (ε 7900), $\lambda_{max}^{pH\ 11}$ 278 mμ (ε 6170).

Anal. Calcd for $C_{10}H_{15}BrN_2O_4$: C, 39.1; H, 4.92; Br, 26.1; N, 9.13. Found: C, 39.3; H, 5.04; Br, 26.2; N, 9.02.

1-(2,2-Diethoxyethyl)-5-bromo-5,6-dihydro-6-hydroxyuracil (XVI).—A cold, stirred solution of 0.46 g (2 mmoles) of the uracil XIV in 2 ml of 1 *N* NaOH was added dropwise to a 5-ml solution of 0.32 g (2 mmoles) of Br_2 in 5 ml of 1 *N* NaOH. The cold solution was kept in an ice bath under a white, infrared light for 60 min, then neutralized with 5 ml of 1 *N* HCl, and kept cold for 30 min more; the white crystals were collected, washed with ice H_2O, and dried at 56° (1 mm) for 2 hr to afford 0.48 g (79%) of XVI, mp 92.5–93.5°; it has essentially no uv absorption.

Anal. Calcd for $C_{10}H_{17}BrN_2O_5$: C, 36.9; H, 5.27; Br, 24.6; N, 8.62. Found: C, 37.0; H, 5.63; Br, 24.6; N, 8.67.

When the reaction was performed at 85°, using an infrared lamp as heat source, a 40% yield of XVI was obtained. No product was obtained when the experiment was repeated at both temperatures without the infrared lamp.

5-Bromouracil-1-acetaldehyde (XVII). A. From XVI.—A mixture of 0.15 g (0.49 mmole) of XVI, 0.15 g of NH_4Cl, and 5.0 ml of H_2O was heated at reflux temperature for 60 min. The colorless solution was cooled in ice to precipitate a crop of white, shiny plates. This was collected, washed with 10 ml of cold H_2O, and dried at 56° *in vacuo* to afford 0.10 g (87%) of the aldehyde, mp 230–233°, homogeneous with R_f 0.53 in solvent A, $\lambda_{max}^{pH\ 1}$ 282 mμ (ε 8040), $\lambda_{max}^{pH\ 7}$ 282 mμ (ε 7836), $\lambda_{max}^{pH\ 11}$ 281 mμ (ε 6030).

Anal. Calcd for $C_6H_5BrN_2O_3 \cdot H_2O$: C, 28.7; H, 2.81; Br, 31.8; N, 11.2. Found: C, 28.7; H, 2.70; Br, 31.8; N, 11.3.

B. From XV.—A mixture of 100 mg (0.33 mmole) of XV, 0.10 g of NH_4Cl, one drop of 12 *N* HCl, and 2 ml of H_2O was treated as above to afford 50 mg (65%) of XVII, identical with that obtained above (physical properties, ir, and additional chromatography systems).

Acknowledgment.—The authors are indebted to Mr. O. P. Crews and staff for preparation of intermediates and to Dr. Peter Lim and staff for the spectra and paper chromatography.

(15) A. P. Martinez and W. W. Lee, *J. Med. Chem.*, **10**, 1132 (1967).