remaining residue was slowly diluted with 30 ml. of ice water. The resulting solution, which was kept cold, was adjusted to *p*H 6 by stirring it with Amberlite IR-120(H) resin. After filtration of the resin, the solution was taken to *p*H 2.7 with hydrochloric acid and placed in a boiling water bath for 2 hr. The solution, which had darkened, was adjusted to *p*H 7 with ammonium hydroxide, filtered to remove a black precipitate, and further adjusted to *p*H 8.2. To the solution was then added 1.05 mmoles of barium acetate in 2 ml. of water. When the addition of two volumes of ethanol did not yield a precipitate, the solution was evaporated *in vacuo* at room temperature to 10 ml., diluted with four volumes of ethanol, and finally chilled. The solid that formed was collected by centrifugation: yield, 318 mg. This material contained about 35% 9-β-D-ribofuranosyl-9H-purine-6(1H)-thione 5′-phosphate identified by its ultraviolet spectrum and chromatographic behavior.

The crude product was purified by absorption from aqueous solution on a Dowex 1-X2 (formate) ion exchange resin column (1 cm. × 18 cm.). The product was obtained when the column was eluted with 5 *N* formic acid. The formic acid was removed by freeze drying, and a yellow solid was obtained: yield, 34 mg. (9.3%).

Acknowledgment. The authors are indebted to Mr. W. E. Fitzgibbon and the Organic Preparations Section of Southern Research Institute who carried out the large scale synthesis of some of the compounds and to Dr. W. J. Barrett and the Analytical Section of Southern Research Institute who performed the spectral and most of the analytical determinations reported. Some of the analyses reported were performed by the Galbraith Microanalytical Laboratories, Knoxville, Tenn.

BIRMINGHAM 5, ALA.

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

Potential Anticancer Agents.[1] LIII. Alkylating Agents Derived from Some Folic Reductase Inhibitors

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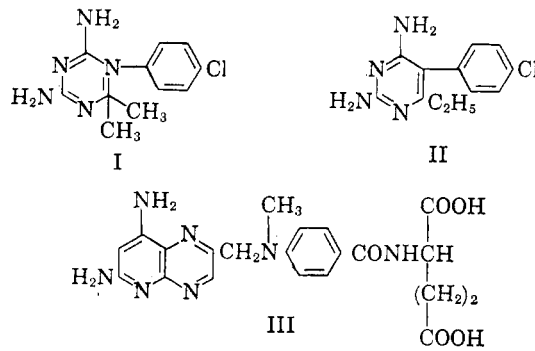
Condensation of 2,2′-(*p*-aminophenylimino)diethanol dihydrochloride (VIII) with cyanoguanidine and acetone afforded the bis(2-hydroxyethyl)amine (X) which, with thionyl chloride, gave the nitrogen mustard (XI) that is related to the folic reductase inhibitor (I). The bis(2-hydroxyethyl)amine hydrochloride (XX) was synthesized by two routes. The preferred path involved the condensation of methyl propionate with {*p*-[bis(2-hydroxyethyl)amino]phenyl}acetonitrile (XIII), or with the blocked derivative (XIV), to give the nitriles (XXII and XVIII), which were converted to the enol ethers (XVII and XVI). Condensation of XVII and XVI with guanidine afforded the pyrimidine bases (XIX and XV) as precursors of XX. Alternatively, the known 2,4-diamino-6-ethyl-5-(*p*-nitrophenyl)pyrimidine (XXIX) was converted to XX by the successive treatments of acetylation, reduction, hydroxyethylation and hydrolysis. Careful treatment of XX with thionyl chloride gave the nitrogen mustard (XXI) that is related to the folic reductase inhibitor, "Daraprim" (II).

A number of the 2,4-diamino-5-aryl-6-alkylpyrimidines[2] and of the 4,6-diamino-1-aryl-1,2-dihydro-2,2-dimethyl-*s*-triazines[3] have shown exceptional activity in the antimalarial field. Typical active compounds of the groups are the 1-*p*-chlorophenyl-*s*-triazine (I) and "Daraprim" (II). There is an obvious structural similarity between I and II so that the marked parallelism of their physiological activities is not surprising. Both I and II are related structurally to the 4-amino derivatives of folic acid [*e.g.*, Amethopterin (III)]; the latter are clinically useful anticancer drugs and function as folic acid antagonists. In certain microbiological systems the groups exemplified by I and II act as inhibitors in the folic acid area; the pyrimidine compounds act as irreversible inhibitors of folic reductase[4] and their action can be reversed by the addition of citrovorum factor[5]; the triazines appear to act as irreversible inhibitors of both folic acid and citrovorum factor.[6] Doctor[7] has observed that



I II

III

(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 *cf.* E. J. Reist, I. G. Junga, M. E. Wain, O. P. Crews, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 2139 (1961).

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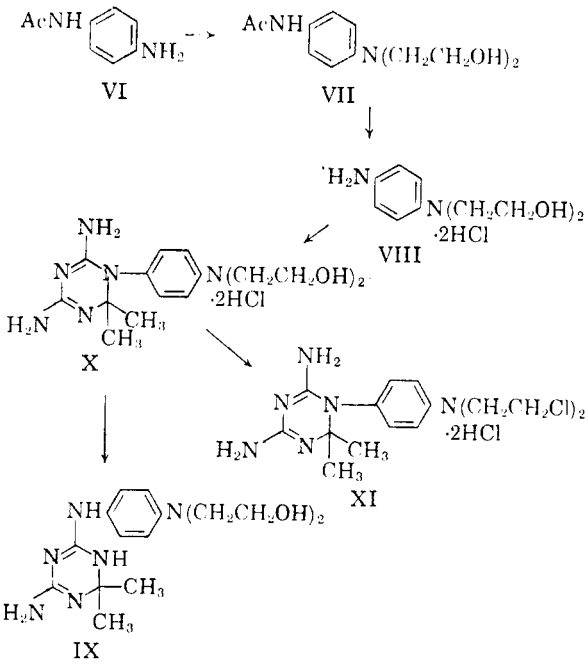
"Daraprim" (II) acts to prevent the conversion of folic acid to citrovorum factor but not the conversion of tetrahydrofolic acid to citrovorum factor thus showing that the blocking action was on folic reductase. Both compounds I and II show effective antitumor action in animals,[8,9] resembling Amethopterin (III) in their general effects but possessing less satisfactory therapeutic indices than III.

The hypothesis of Bergel,[10] namely, that alkylating agents consist of a carrier plus the alkylating group and that differences in effects and side effects on tumors might be related to the differences in the carrier group, suggested that the attachment of alkylating groups to the basic carrier moieties of I and II might provide effective antitumor agents. The preparation of such compounds is the subject of this paper.

In the initial approach to the synthesis of the "triazine mustard" (XI), the 5-*p*-nitrophenyl-*s*-triazine (IV) was prepared according to the directions of Modest[11] by the condensation of cyanoguanidine, *p*-nitroaniline hydrochloride and acetone. Attempts to block the 4- and 6-amino groups by acetylation prior to reduction of the 4′-nitro group of IV caused cleavage of the triazine ring and gave a chromatographically homogeneous compound which appeared to be a monoacetyl derivative of 1-(*p*-nitrophenyl)biguanide (V) and inferred from its ultraviolet spectrum, but which was not otherwise identified.

A more fruitful approach to the synthesis of XI started from 4′-aminoacetanilide (VI). Reaction of VI with ethylene oxide in aqueous acetic acid gave a good yield of 4′-[bis(2-hydroxyethyl)-amino]acetanilide (VII) which was hydrolyzed with hydrochloric acid to give the desired substituted anilinium salt (VIII). Condensation of the amine salt (VIII) with cyanoguanidine and acetone according to Modest's[11] conditions gave the bis(2-hydroxyethyl)amino-*s*-triazine (X) as a chromatographically homogeneous, crystalline solid. As is typical of the 1-aryl-4,6-diamino-*s*-triazines,[11] compound X rearranged to the 4-amino-6-anilino-*s*-triazine (IX) on heating with 0.1*M* sodium hydroxide, as was shown by the characteristic changes in ultraviolet spectra. Reaction of the bis(2-hydroxyethyl)amino-*s*-triazine (X) with thionyl chloride in refluxing methylene chloride gave a good yield of the triazine mustard (XI) isolated as its crystalline dihydrochloride.

In the synthesis of the "Daraprim" mustard (XXI), the technique of preforming the bis(2-hydroxyethyl)aminophenyl moiety, used in the synthesis of the triazine mustard (XI), proved to be the method of choice. The commercially available (*p*-aminophenyl)acetonitrile hydrochloride (XII) was converted to the free base and allowed to react with ethylene oxide in aqueous acetic acid to give a good yield of the crystalline bis-(hydroxyethyl) compound (XIII).



The condensation of XIII with methyl propionate was carried out with sodamide in a mixture of ether and liquid ammonia[12] to give a 47% yield of a product whose infrared spectrum suggested that it was the enolic nitrile (XXII). Treatment of this product (XXII) with ethyl orthopropionate[13] gave a sirup whose infrared spectrum showed no hydroxyl absorption near 3.0 μ; its structure is assumed to be either XVII or a cyclic orthoester involving the two hydroxyl groups of the bis(2-hydroxyethyl)amine moiety. This technique of forming enol ethers of similar β-cyanoketones was developed by Russell and Whittaker,[13] who showed the necessity for conversion of the β-cyanoketones to the enol ethers in order to permit their reaction with guanidine. The reaction of the enol ether (XXII) with guanidine in methanolic sodium methoxide at 150° in a sealed bomb gave a 50% yield of the free base (XIX); the reaction did not proceed at reflux in the methanolic sodium methoxide solution. The free base (XIX) gave the same hydrochloride (XX) as was obtained by the approach utilizing the tetrahydropyranyl blocking group (*cf.* below).

The reaction of XIII with dihydropyran and ethanesulfonic acid[14] gave the bis(tetrahydropyranyl ether) (XIV) as a sirup in quantitative

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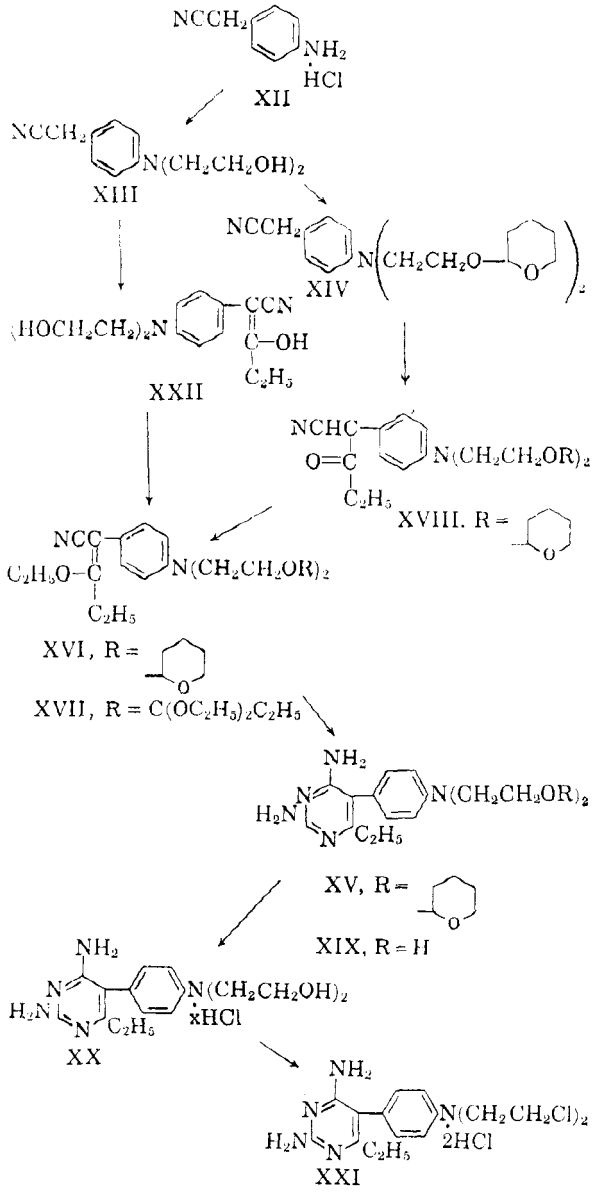
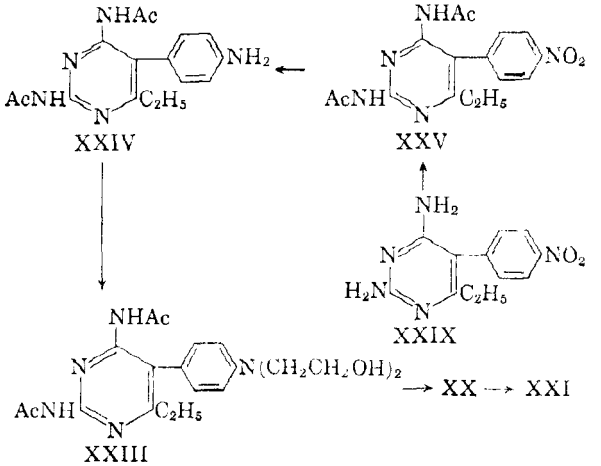
yield. Condensation of XIV with methyl propionate using sodamide in liquid ammonia[12] gave the blocked β-cyanoketone (XVIII) as a crude sirup in about 70% yield. The infrared spectrum of XVIII made it clear that the sirup was a mixture of the keto and enol forms of XVIII. Reaction of XVIII with ethyl orthopropionate[13] gave the enol ether (XVI) as a dark sirup and reaction of XVI with guanidine in methanolic sodium methoxide at 150° yielded 30% of the crystalline, blocked pyrimidine (XV). The over-all yield of XV



from XIII was 19%, an average yield of 65% per step for the 4 steps. Acid hydrolysis removed the tetrahydropyranyl blocking groups and gave the dihydrochloride (XX) of the bis(hydroxyethyl) compound (XIX).

The first attempts to prepare the "Daraprim" mustard (XXI) involved 2,4-diamino-6-ethyl-5-(*p*-nitrophenyl)pyrimidine (XXIX) as a key intermediate. Compound XXIX had previously been prepared by Russell and Hitchings[2] by nitration of 2,4-diamino-6-ethyl-5-phenylpyrimidine (XXVIII) and this method was used in the present work. Unsuccessful attempts were made to prepare the *p*-nitro analog of 3-oxo-2-phenyl-2-pentanenitrile (XXVI) which might have been useful for the synthesis of XXIX by a direct condensation reaction. The condensation of *p*-nitrophenylacetonitrile with methyl propionate using sodamide in liquid ammonia, however, failed—only highly colored tars were formed under the strongly basic conditions. The first attempts to prepare the β-cyano ketone (XXVI), a precursor of the desired XXIX, used methanolic sodium methoxide as the medium for the condensation of phenylacetonitrile and methyl propionate[2] and gave very low yields of product. A reasonable yield (66%) of XXVI resulted when sodium in liquid ammonia was used for the condensation, as described by Eby and Hauser,[12] and when both reactants were carefully purified. Reaction of XXVI with ethyl orthopropionate[13] at reflux smoothly gave 2-ethoxy-2-phenyl-2-pentenenitrile (XXVII) and reaction of XXVII with guanidine in refluxing methanolic sodium methoxide[2] gave a 55% yield of the pyrimidine (XXVIII). Nitration of XXVIII was carried out with a nitric acid–sulfuric acid mixture to give a good yield of the crude nitro compound (XXIX)[2] which contained some of the starting material (XXVIII) and which could be purified only with large losses. The crude product (XXIX) was directly acetylated with refluxing acetic anhydride



to give a 23% yield, based on XXVIII, of the recrystallized diacetate (XXV).

When the hydrogenation of the nitro diacetate (XXV) was conducted at room temperature, the product was not pure and it seemed likely that the newly formed aromatic amino group had been transacetylated by one of the acetamido groups of the pyrimidine ring. When the hydrogenation of XXV was carried out with a palladium catalyst at 0–15°, a good yield of the 5-(*p*-aminophenyl)-

pyrimidine (XXIV) was formed. Conventional reaction of XXIV with ethylene oxide in aqueous acetic acid gave the bis(2-hydroxyethyl)amino compound (XXIII) as a glass and hydrolysis with 6*N* hydrochloric acid gave the desired diaminopyrimidine (XX) as a hydrochloride, identical in ultraviolet spectra and paper chromatographic behavior with XX isolated from the alternative appproach described above; the isolated sample of XX from the approach through XXV, however, contained less hydrogen chloride than the analytical sample of XX prepared *via* XIII. The approaches to XX *via* the bis(2-hydroxyethyl)aminonitrile (XIII) were preferred to the longer sequence based on XXVI.

Conversion of the hydroxy compound (XX) to the desired mustard (XXI) was achieved by a carefully controlled reaction with thionyl chloride. When XX was heated with thionyl chloride at 65–70° for thirty-five minutes, a 70% yield of the dihydrochloride (XXI) could be isolated. Shorter heating periods gave incomplete reaction and a longer heating period led to extensive tar formation.

EXPERIMENTAL[15]

Acetylation of 4,6-diamino-1,2-dihydro-2,2-dimethyl-1-p-nitrophenyl-s-triazine (IV). A mixture of 3.0 ml. of acetic anhydride and 0.300 g. (1.0 mmole) of *p*-nitrophenyl-*s*-triazine hydrochloride (IV)[11] was heated under reflux for 20 min. Complete solution was attained within 5 min. and solid precipitated after 10–15 min. The mixture was cooled, the solid separated by centrifugation, then washed with ether; yield, 0.220 g. of product, m.p. 278–282°. Addition of ether to the mother liquors gave 0.04 g. more of product. After thorough drying *in vacuo* at 100°, the solid had m.p. 273–275°; $\lambda_{max(\mu)}^{Nujol}$ 3.12 (NH), 5.81 (amide C=O), 6.05 (C=N), 6.45 and 7.46 (NO_2), 11.64 (*p*-disubstituted benzene); $\lambda_{max(m\mu)}^{C_2H_5OH}$ 223 (ε 15,100), 317 (ε 14,500). On paper chromatography in solvents A and D, the product showed single spots with R_{Ad} 1.47 and 1.66, respectively, compared with values of 1.15 and 1.36 for the *p*-nitrophenyl-*s*-triazine (IV).

Anal. Calcd. for $C_{10}H_{12}N_6O_3$ (a monoacetate of the *p*-nitrophenylbiguanide): C, 45.4; H, 4.58. Found: C, 45.7; H, 5.30.

In the ultraviolet, *p*-nitrophenylbiguanide hydrochloride[11] had $\lambda_{max(m\mu)}^{H_2O}$ 230 (ε 14,400), 325 (ε 11,600), while the *p*-nitrophenyl-*s*-triazine hydrochloride (IV) had $\lambda_{max(m\mu)}^{H_2O}$ 240 (ε 14,000).

4'-[Bis(2-hydroxyethyl)amino]acetanilide (VII). To a cold (0°) solution of 9.0 g. (0.06 mole) of *p*-aminoacetanilide (VI) in 54 ml. of 50% aqueous acetic acid was added 22.0 ml. (19.6 g., 0.45 mole) of ethylene oxide and the solution was allowed to stand 18 hr. at 0–5° and 7 hr. at room temperature. Evaporation *in vacuo* at 50° left a purple sirup which was dissolved in 90 ml. of chloroform. Upon being chilled, the solution deposited 14.6 g. (100%) of crystalline solid which was recrystallized from 60 ml. of water to give 10.2 g. (71%) of product, m.p. 142.5–144.5°. An analytical sample, recrystallized again from water, had m.p. 141–142.5°; $\lambda_{max(\mu)}^{Nujol}$ 3.0, 3.1 (OH, NH), 6.05 (amide C=O), 6.45 (amide II), 9.45 (C—OH), 12.15 (*p*-disubstituted benzene).

Anal. Calcd. for $C_{12}H_{18}N_2O_3$: C, 60.5; H, 7.61; N, 11.8. Found: C, 60.6; H, 7.56; N, 11.8.

2,2'-(p-Aminophenylimino)diethanol dihydrochloride (VIII). A solution of 3.0 g. (12.6 mmoles) of the acetanilide (VII) in 15 ml. of 6*M* hydrochloric acid was heated, under nitrogen, on the steam bath for 75 min. The solution was evaporated *in vacuo* and the residue was dissolved in 30 ml. of hot, absolute ethanol. The ethanol solution was diluted with benzene to the cloud point (5 ml. required) and was then stirred rapidly while the solution cooled to give 2.3 g. (69%) of white, crystalline, hygroscopic solid, whose melting point behavior was erratic because of the extreme hygroscopicity; $\lambda_{max(\mu)}^{Nujol}$ 2.95 (OH), 3.85, 6.1 and 6.35 (NH_3^+), 12.10 (*p*-disubstituted benzene).

Anal. Calcd. for $C_{10}H_{16}N_2O_2 \cdot 2HCl$: C, 44.8; H, 6.75; Cl, 26.4. Found: C, 44.6; H, 6.67; Cl, 26.3.

2,2'-[p-(4,6-Diamino-1,2-dihydro-2,2-dimethyl-s-triazin-1-yl)phenylimino]diethanol hydrochloride (X). To 3.0 ml. of absolute ethanol was added 0.54 g. (2 mmoles) of the bis(2-hydroxyethyl)amine hydrochloride (VIII), 0.18 g. (2.1 mmoles) of cyanoguanidine, and 2 ml. of acetone. The mixture was heated under reflux for 3 hr., a yellow solid being deposited after 15 min. The mixture was allowed to stir overnight and the solid was separated to yield 0.38 g. (57%) of product, m.p. 219–221°; $\lambda_{max(\mu)}^{KBr}$ 3.0 (OH), 6.0 and 6.15 (NH_2), 6.40 and 6.60 (triazine ring), 9.50 and 9.65 (C—OH), 12.20 (*p*-disubstituted benzene); $\lambda_{max(m\mu)}^{H_2O}$ 240 (ε 11,100), 267 (ε 23,300); $\lambda_{max(m\mu)}^{0.1\ N\ NaOH}$ 247 (ε 12,200).[20] On paper chromatography in solvent A, the product showed a single spot with R_{Ad} 0.84.

Anal. Calcd. for $C_{15}H_{24}N_6O_2 \cdot HCl$: C, 50.4; H, 7.07; N, 23.5. Found: C, 49.9; H, 7.18; N, 23.5, 23.6.

4,6-Diamino-1-{p-[bis(2-chloroethyl)amino]phenyl}-1,2-dihydro-2,2-dimethyl-s-triazine dihydrochloride (XI). A mixture of 0.30 g. (0.84 mmole) of the *s*-triazine (X), 1.0 ml. (13.8 mmoles) of thionyl chloride, and 9 ml. of methylene chloride was heated under reflux, with stirring, for 1 hr. The suspension was cooled to room temperature, filtered, and the solid was washed with 5 ml. of methylene chloride; yield, 0.25 g. (76%), m.p. 216.5–217.5°. An analytical sample, obtained by recrystallization from absolute ethanol, had m.p. 220–221°; $\lambda_{max(\mu)}^{Nujol}$ 3.1 (NH), 3.8 (NH_3^+), 5.80 and 5.95 ($C=N^+$), 12.0 and 12.45 (*p*-disubstituted benzene); there was no C—OH absorption in the 9–10 μ region; $\lambda_{max(m\mu)}^{H_2O}$ 240 (shoulder, ε 6750), 265 (ε 24,800). On paper chromatography in solvents A and D, the product moved as a single spot with R_{Ad} 1.55 and 1.40, respectively.

Anal. Calcd. for $C_{15}H_{22}N_6Cl_2 \cdot 2HCl$: C, 41.8; 5.63; Cl, 33.0; Cl^-, 16.5. Found: C, 42.2; H, 5.68; Cl, 32.9; Cl^-, 16.3.

{p-[Bis(2-hydroxyethyl)amino]phenyl}acetonitrile (XIII). To 200 ml. of 10% aqueous sodium carbonate solution was added 21.8 g. (0.129 mole) of *p*-aminophenylacetonitrile hydrochloride (XII) and the mixture was extracted with two 40-ml. portions of chloroform. The chloroform solution was dried over potassium carbonate, filtered, and the filtrate evaporated *in vacuo* to give 14.85 g. (0.111 mole) of the free

(15) Boiling points and melting points are uncorrected; the latter were obtained with the Fisher-Johns Apparatus. Paper chromatography was done by the descending technique on Whatman No. 1 paper and the spots were detected by visual examination under ultraviolet light. Adenine was used as a standard and the spots were located relative to R_{Ad} 1.00. These solvent systems were used: A,[16] 1-butanol-acetic acid-water (4/1/5); B, 85% ethanol; C,[17] water-saturated 1-butanol; D,[18] benzene-methanol-water (2/6/1); E,[19] isopropyl alcohol–2*M* hydrochloric acid (65/35).

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(20) Solution heated 1 hr. at 100° to cause rearrangement to the 6-anilino-*s*-triazine (IX).[11]

base of XII which was dissolved in 70 ml. of 50% aqueous acetic acid. Ethylene oxide (27 ml., 0.55 mole) was added to the cold (0-5°) acetic acid solution and the solution was allowed to warm to room temperature and stand for 19 hr. before being evaporated to dryness *in vacuo* (10 mm., 35-40°). The residue was dissolved in 150 ml. of methylene chloride and the solution was washed with 100 ml. of 10% aqueous potassium carbonate solution. The aqueous wash was extracted with two 75-ml. portions of methylene chloride and these extracts were combined with the original methylene chloride solution. The combined extracts were dried over potassium carbonate, filtered, and the filtrate evaporated *in vacuo*. The residue (25.3 g.) was recrystallized from 75 ml. of ethyl acetate to yield 18.6 g. (76%) of product, m.p. 84.5–86.5°. An analytical sample prepared from another run had m.p. 85–86°; $\lambda_{max(\mu)}^{Nujol}$ 3.10, 3.20 (OH), 4.45 (C≡N), 9.35 and 9.45 (C—OH), 12.20 and 12.30 (*p*-disubstituted benzene).

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.4; H, 7.32; N, 12.7. Found: C, 65.2; H, 7.44; N, 12.2.

2-{p-[Bis(2-hydroxyethyl)amino]phenyl}-3-hydroxy-2-pentenenitrile (XXII). Sodium (0.70 g., 30 mmoles) and a crystal of hydrated ferric nitrate was dissolved in 30 ml. of liquid ammonia in a flask equipped with a stirrer and a Dry Ice condenser and protected from moisture, then 2.0 g. (9.1 mmoles) of XIII was added. After stirring 5 min., 1.6 g. (1.8 mmoles) of methyl propionate was added followed by 20 ml. of ether. The mixture was stirred vigorously for 45 min. and the ammonia was evaporated on the steam bath. The resulting mixture was poured over 30 g. of ice and enough water was added to dissolve completely the solid (final volume of water *ca.* 75 ml.). The separated aqueous layer was washed with 20 ml. of methylene chloride, then adjusted to *p*H 7 with glacial acetic acid and extracted with eight 20-ml. portions of methylene chloride. The combined methylene chloride extracts were dried over magnesium sulfate, filtered, and the filtrate evaporated *in vacuo* to leave 1.66 g. (66%) of solid, which was recrystallized from 5 ml. of ethyl acetate to give 1.17 g. (47%) of solid, m.p. 91–93°. A second such recrystallization gave the analytical sample, m.p. 97–98°; $\lambda_{max(\mu)}^{Nujol}$ 2.99, 3.15 (OH), 3.70 (acidic OH), 4.55 (conjugated C≡N), 6.12 (C=C), 9.50 (C—OH) 12.23 (*p*-disubstituted benzene); there was no carbonyl absorption in the 5.7–6.0 μ region. On paper chromatography in solvent C, the product moved as a single spot with R_{Ad} 2.51.

Anal. Calcd. for $C_{15}H_{20}N_2O_3$: C, 65.2; H, 7.30; N, 10.1. Found: C, 65.3; H, 7.38; N, 10.4.

When the reaction of XIII with methyl propionate using sodamide was conducted in liquid ammonia alone, a low yield of a solid, m.p. 182–185°, was isolated. Its infrared spectrum that it might be the keto form of XXII; $\lambda_{max(\mu)}^{Nujol}$ 2.90, 3.00 (OH), 4.45 (C≡N), 5.80 (C=O), 9.30 and 9.45 (C—OH), 12.05 (*p*-disubstituted benzene).

Anal. Calcd. for $C_{15}H_{20}N_2O_3$: C, 65.2; H, 7.30; N, 10.1. Found: C, 64.3; H, 6.67; N, 10.7. There was insufficient material for further purification.

(p-{Bis[2-(tetrahydropyran-2-yloxy)ethyl]amino}phenyl)-acetonitrile (XIV). To a suspension of 11.0 g. (50 mmoles) of the bis(2-hydroxyethyl)amine (XIII) in 100 ml. of methylene chloride was added 11.2 g. (0.133 mole) of dihydropyran and the mixture was cooled to 5°. To this stirred suspension was added 5.5 g. (50 mmoles) of ethanesulfonic acid over a 5-min. period, the temperature being maintained below 30°. The mixture was allowed to stand at room temperature for 2 hr. and was added dropwise, but rapidly, to 110 ml. of 10% aqueous potassium carbonate solution with good stirring. The methylene chloride layer was separated, washed with 100 ml. of water, dried over potassium carbonate, filtered, and the filtrate evaporated *in vacuo* leaving 19.6 g. (101%) of dark sirup; $\lambda_{max(\mu)}^{film}$ 4.45 (C≡N), 8.80, 8.90, 9.30, 9.65 (ether C—O—C), 12.30 (*p*-disubstituted benzene).

2-(p-{Bis[2-(tetrahydropyran-2-yloxy)ethyl]amino}phenyl-3-oxo-2-pentenenitrile (XVIII). To a solution of 0.90 g. (38 mmoles) of sodium and a crystal of hydrated ferric nitrate in 100 ml. of liquid ammonia was added a solution of 7.50 g. (19 mmoles) of the blocked nitrile (XIV) in 8 ml. of ether. The mixture was stirred 5 min. and 3.3 g. (38 mmoles) of methyl propionate was added rapidly, dropwise. The solution was stirred 1.5 hr. and the ammonia was evaporated on the steam bath as 100 ml. of ether was added simultaneously. The resulting mixture was poured over 100 g. of ice and water and when the ice had melted, the layers were separated. The aqueous layer was extracted with 50 ml. of ether and the ethereal wash was back-extracted with 25 ml. of water which was combined with the original aqueous layer. The combined aqueous solutions were adjusted to *p*H 8 with glacial acetic acid and were extracted with three 50-ml. portions of ether; these combined ether extracts were dried over magnesium sulfate, filtered, and the filtrate evaporated *in vacuo* to give 6.0 g. (70%) of dark sirup; $\lambda_{max(\mu)}^{film}$ 2.90 and 3.10 (OH), 3.70 (acidic OH), 4.45 (C≡N), 4.55 (conjugated C≡N), 5.80 (C=O), 6.20 (C=C and phenyl), 8.80, 8.90, 9.35, 9.65 (ether C—O—C), 12.30 (*p*-disubstituted benzene).

2-(p-{Bis[2-(tetrahydropyran-2-yloxy)ethyl]amino}phenyl)-3-ethoxy-2-pentenenitrile (XVI). A mixture of 6.0 g. (13.3 mmoles) of the crude β-cyano ketone (XVIII) and 18 ml. of triethyl orthopropionate was distilled, using a short Vigreux column, and ethanol and ethyl propionate (b.p. 99–100°) were collected. When the vapor temperature rose to 105°, the residue was evaporated *in vacuo* (2 mm., 60°) to give 5.7 g. (89%) of a dark sirup; $\lambda_{max(\mu)}^{film}$ 4.55 (conjugated C≡N), 6.20 (C=C and phenyl), 8.78, 8.88, 9.30, 9.65 (ether C—O—C), 12.25 (*p*-disubstituted benzene).

2-{p-[Bis(2-hydroxyethyl)amino]phenyl}-3-ethoxy-2-pentenenitrile, bis(diethylorthopropionate) (XVII). A mixture of 5.0 g. (18.1 mmoles) of the enol (XXII) and 15 ml. of triethyl orthopropionate was treated as in the preparation of XVI. Evaporation of the residue left 8.4 g. of sirup; $\lambda_{max(\mu)}^{film}$ 4.55 (conjugated C≡N), 6.20 (C=C and phenyl), 8.90, 9.15, 9.45, 9.85 (ether C—O—C), 12.20 (*p*-disubstituted phenyl); there was no —OH absorption near 3.0 μ.

2,4-Diamino-5-(p-{bis[2-(tetrahydropyran-2-yloxy)ethyl]-amino}phenyl)-6-ethylpyrimidine (XV). To a stirred solution of 0.25 g. (4.8 mmoles) of sodium methoxide in 5 ml. of methanol was added 0.23 g. (2.4 mmoles) of guanidine hydrochloride and to this solution was added a solution of 1.0 g. (2.1 mmoles) of enol ether (XVI) in 3 ml. of methanol. The resulting mixture was heated at 150° in a stainless steel bomb for 6 hr. After being cooled, the mixture was evaporated to dryness *in vacuo* and the residue was partitioned between 10 ml. of water and 10 ml. of ether. The ether layer was dried over potassium carbonate, filtered, and the filtrate evaporated *in vacuo* to give 0.66 g. of solid. The solid was recrystallized from 10 ml. of a 3:1 ether–ethyl acetate mixture to yield 0.30 g. (30%) of solid, m.p. 66–72°; $\lambda_{max(\mu)}^{Nujol}$ 2.90, 3.05; 3.18 (NH), 5.78 (C=O, weak), 6.15, 6.35 (NH_2, phenyl and pyrimidine ring), 8.80, 8.93, 9.31, 9.66 (ether C—O—C), 12.30 (*p*-disubstituted phenyl). Repeated recrystallizations failed to improve the melting point or to remove the small amount of impurity which gave the 5.78 μ absorption and which was not due to ethyl acetate contamination.

2,2'-[p-(2,4-Diamino-6-ethyl-5-pyrimidinyl)phenylimino]-diethanol (XIX). A solution of 2.0 g. (37.0 mmoles) of sodium methoxide in 20 ml. of methanol was prepared and to it was added 1.7 g. (18 mmoles) of guanidine hydrochloride and a solution of 8.4 g. (15 mmoles) of the enol ether (XVII) in 15 ml. of methanol. The mixture was heated at 150° in a stainless steel bomb for 5.5 hr. and the resulting mixture, after cooling, was evaporated *in vacuo*. The residue was partitioned between 50 ml. of ether and 50 ml. of water and the insoluble material was collected by filtration. The insoluble product was washed with water and ether to give 2.9 g. (50% yield from XXII) of the pyrimidine free base (XVb); $\lambda_{max(\mu)}^{Nujol}$ 2.8, 2.9, 3.0, and 3.15 (OH, NH), 6.05, 6.15, 6.35-6.40 (NH_2, phenyl, and pyrimidine ring), 9.38, 9.55 (C—OH), 12.20 (*p*-disubstituted benzene).

For analysis, 0.100 g. of the crude solid was recrystallized from 75 ml. of hot water, affording 0.060 g. of crystalline product, m.p. 237–239° dec., which had the same infrared spectrum as the crude material. On paper chromatography in solvent E, compound XIX moved as a single spot with R_{Ad} 1.03.

Anal. Calcd. for $C_{16}H_{23}N_5O_2$: C, 60.2; H, 7.30; N, 22.0. Found: C, 60.7; H, 7.48; N, 21.9.

2,2'-[p-(2,4-Diamino-6-ethyl-5-pyrimidinyl)phenylimino]-diethanol dihydrochloride (XX). *A. From XV.* A solution of 4.60 g. (9.5 mmoles) of the blocked pyrimidine (XV) and 20 ml. of 1*M* hydrochloric acid was heated for 1 hr. on the steam bath, then the cooled solution was extracted with 10 ml. of benzene. The aqueous phase was filtered and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized from an absolute ethanol-ether mixture to give 2.1 g. (57%) of solid, m.p. 242–245°. From a previous run an analytical sample, m.p. 240–244°, had been obtained; $\lambda^{Nujol}_{max(\mu)}$ 2.90, 3.02, 3.18 (OH, NH), 3.63, 3.73 (NH^+), 6.03 (NH_2), 9.55 (C—OH), 12.35 (*p*-disubstituted benzene); $\lambda^{pH\ 1}_{max(\mu}$ 212 (ε 34,600); broad maximum 268–274 (ϵ_{272} 8190). On paper chromatography in solvent E, the product moved as a single spot with R_{Ad} 1.03.

Anal. Calcd. for $C_{16}H_{23}N_5O_2 \cdot 2HCl$: C, 49.3; H, 6.44; Cl, 18.2. Found: C, 49.1; H, 6.62; Cl, 17.6.

B. From XIX. The base XIX (0.73 g.) was dissolved in 10 ml. of 1*M* hydrochloric acid, the solution was warmed 15 min. on the steam bath, and evaporated to dryness *in vacuo*. The residue was recrystallized from 6 ml. of absolute ethanol to give 0.30 g. (33%) of solid whose infrared spectrum was identical with that of XX described above. No effort was made to improve the yield by isolating the product in the mother liquors.

C. From XXIII. To 4 ml. of 6*M* hydrochloric acid was added 0.40 g. (1.0 mmole) of the diacetamidopyrimidine (XXIII, *cf.* below) and the solution was heated on the steam bath for 1 hr. The solution was evaporated to dryness *in vacuo* and the residue was recrystallized from absolute ethanol to yield 0.25 g. (64%) of product, m.p. 233–237°. A second recrystallization from absolute ethanol gave 0.09 g., m.p. 239–242° (prior sintering), whose infrared spectrum showed good general agreement with that of the analytical sample of XX but possessed some distinct differences, probably due to a difference in hydrochloride content. In the ultraviolet, the product had $\lambda^{pH\ 1}_{max(m\mu)}$ 211 (ε 34,200),[21] broad maximum 268–274 (ϵ_{272} 8000).[21] On paper chromatography in solvent E, the compound moved identically with authentic XX, R_{Ad} 1.03.

Anal. Calcd. for $C_{16}H_{23}N_5O_2 \cdot 1.6HCl$: C, 51.2; H, 6.60; Cl, 15.1. Found: C, 51.0; H, 6.71; Cl, 14.6.

3-Oxo-2-phenyl-2-pentanenitrile (XXVI). Condensation of 4.40 g. (0.050 mole) of methyl propionate (redistilled, b.p. 79.5–80°) with 11.7 g. (0.100 mole) of phenylacetonitrile [washed with sodium bicarbonate solution, dried, and distilled, b.p. 95–96° (7 mm.)] in 125 ml. of liquid ammonia with the use of 2.3 g. (0.10 g.-atom) of sodium was carried out according to the procedure described for the preparation of XVIII. Evaporation of the final, dried ether extracts *in vacuo* left 5.7 g. (66%) of white crystals, m.p. 57–58°. One recrystallization from benzene-petroleum ether (b.p. 62–70°) (1:2) gave the analytical material, m.p. 58–59° (a large-scale preparation gave the crystal form, m.p. 71–72°, in agreement with the m.p. 70–72° reported by Eby and Hauser[12]); $\lambda^{Nujol}_{max(\mu)}$ 4.45 (C≡N), 5.75 (C=O), 13.3 and 14.3 (monosubstituted benzene).

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.3; H, 6.40; N, 8.09: Found: C, 76.5; H, 6.58; N, 8.10.

2-Ethoxy-2-phenyl-2-pentenenitrile (XXVII). A mixture of 35 ml. of triethyl orthopropionate and 10.0 g. (0.058 mole) of β-cyano ketone (XXVI) was processed according to the procedure of Russell and Whittaker[13] to give 11.8 g. (102%) of the enol ether (XXVII) as a sirup; $\lambda^{film}_{max(\mu)}$ 4.55 (conjugated C=N), 6.25 (C≡C), 9.30 (ether C—O—C), 13.1 and 14.35 (monosubstituted phenyl).

2,4-Diamino-6-ethyl-5-phenylpyrimidine (XXVIII). With 2.34 g. (11.6 mmoles) of crude enol ether (XXVII), 0.66 g. (12.2 mmoles) of sodium methoxide, 1.10 g. (11.7 mmoles) of guanidine hydrochloride, and 6 ml. of methanol by the procedure of Russell and Hitchings,[2] 1.40 g. (57%) of chromatographically homogeneous product, m.p. 250–251°, was isolated. After two recrystallizations from absolute ethanol, the product had m.p. 243–245.5° (Russell and Hitchings[2] reported m.p. 237–240°); $\lambda^{Nujol}_{max(\mu)}$ 2.95, 3.05, 3.20, and 6.10 (NH), 6.35 (pyrimidine ring), 13.10 and 14.20 (monosubstituted benzene); $\lambda^{95\%\ C_2H_5OH}_{max(m\mu)}$ 278 (ε 8450). On paper chromatography in solvents A and B, the product moved as a single spot with R_{Ad} 1.43 and 1.34, respectively.

Anal. Calcd. for $C_{12}H_{14}N_4$: C, 67.3; H, 6.59; N, 26.2. Found: C, 67.5; H, 6.83; N, 26.1.

2,4-Diamino-6-ethyl-5-(p-nitrophenyl)pyrimidine (XXIX). To 16 ml. of cold (0–5°) concd. sulfuric acid was added 2.70 g. (12.6 mmoles) of the pyrimidine (XXVIII) and the mixture was stirred until complete solution was attained. To the solution was added 1.35 ml. (21.6 mmoles) of concd. nitric acid over a 25-min. period while maintaining the temperature below 15°. The solution was allowed to stand in the ice bath 30 min. and at room temperature 30 min., and was poured over 175 g. of ice. The resulting solution was adjusted to *p*H 10 with 30% aqueous sodium hydroxide solution, maintaining the temperature below 15°. The yellow precipitate was collected and washed with water to yield 3.30 g. (100%) of a crude product. A small sample was recrystallized from dimethylformamide, with much loss, to yield a product, m.p. >300°, that was homogeneous on paper chromatography in solvents A and *B*, R_{Ad} 1.26 and 1.10, respectively, and clearly free from starting material (XXVIII); $\lambda^{Nujol}_{max(\mu)}$ 2.85, 2.95, 3.12, 6.00, and 6.12 (NH), 6.33 and 6.40 (pyrimidine ring), 7.40 (NO_2), 11.65 (*p*-disubstituted benzene); $\lambda^{2\text{-methoxyethanol}}_{max(m\mu)}$ 235 (ε 13,600), 285 (ε 12,800), 345 (ε 3900).

Russell and Hitchings[2] reported compound XXIX as a microcrystalline powder which melted above 350° with decomposition.

2,4-Diacetamido-6-ethyl-5-(p-nitrophenyl)pyrimidine (XXV). A mixture of 3.30 g. (12.6 mmoles) of crude *p*-nitrophenylpyrimidine (XXIX) and 21 ml. of acetic anhydride was heated under reflux for 20 min. The hot solution was filtered rapidly and the filtrate was diluted with 80 ml. of ether and chilled to give 1.20 g. of solid which was removed by filtration. From the filtrate another 0.30 g. of product was obtained after further chilling. The total product was recrystallized from 35 ml. of 95% ethanol to give 1.0 g. (23%) of solid with the double melting point 217° and 227–230°. An analytical sample was obtained by another recrystallization from 95% ethanol, m.p. 229.5–231.5°; $\lambda^{Nujol}_{max(\mu)}$ 3.10 (NH), 5.90 and 5.95 (amide C=O), 6.28 and 6.35 (pyrimidine ring), 7.44 (NO_2), 11.70 (*p*-disubstituted benzene); $\lambda^{C_2H_5OH}_{max(m\mu)}$ 233 (ε 26,800), 282 (ε 17,600). The sample was chromatographically homogeneous in solvent C, R_{Ad} 3.50.

Anal. Calcd. for $C_{16}H_{17}N_5O_4$: C, 56.0; H, 4.99; N, 20.4. Found: C, 56.3; H, 5.31; N, 20.3, 20.4.

5-(p-Aminophenyl)-2,4-diacetamido-6-ethyl pyrimidine (XXIV). A stirred suspension of 1.0 g. (2.9 mmoles) of *p*-nitrophenylpyrimidine (XXV), 0.05 g. of 5% palladium-on-carbon, and 10 ml. of methanol was hydrogenated with 1 atmosphere of hydrogen at 0–15°. One mole of hydrogen was absorbed after 5 hr., the suspension was filtered, and the filtrate evaporated *in vacuo* to leave 0.78 g. (86%) of a white glass. This residue was recrystallized from 2 ml. of ethyl acetate to yield 0.55 g. (62%) of product, m.p. 171–172°. A second recrystallization from ethyl acetate gave white crystals, m.p. 171–172.5°; $\lambda^{Nujol}_{max(\mu)}$ 2.95, 3.05 (NH), 5.90 (amide C=O), 6.25 and 6.35 (pyrimidine ring), 12.20 (*p*-disubstituted benzene); $\lambda^{2\text{-methoxyethanol}}_{max(m\mu)}$ 227 (ε 26,200), 251 (ε 22,900), 280 (ε 15,800). The compound was homo-

(21) ε values calculated using the analytical values found for the product.

geneous on paper chromatography in solvents A and D with R_{Ad} 1.51 and 1.60, respectively.

Anal. Calcd. for $C_{16}H_{19}N_5O_2$: C, 61.3; H, 6.11; N, 22.4. Found: C, 61.9; H, 6.48; N, 22.2.

2,2'-[p-(2,4-Diacetamido-6-ethyl-5-pyrimidinyl)phenylimino]diethanol (XXIII). To a cold (0°) solution of 0.45 g. (1.44 mmoles) of the *p*-aminophenylpyrimidine (XXIV) in 2.5 ml. of 50% aqueous acetic acid was added 0.50 g. (11.0 mmoles) of ethylene oxide and the solution was kept at 0° for 15 hr., then was evaporated to dryness *in vacuo* at 40°. The residue was dissolved in 10 ml. of chloroform, the chloroform was washed with 5 ml. of saturated aqueous sodium bicarbonate solution and the bicarbonate wash back-extracted with 5 ml. of chloroform. The chloroform extracts were combined, dried over magnesium sulfate, filtered, and the filtrate evaporated *in vacuo* to leave 0.42 g. (73%) of a white glas ; $\lambda_{max(\mu)}^{film}$ 3.0–3.1 (OH, NH), 5.90 (amide C=O), 6.30 (pyrimidine ring, amide NH), 9.55 (C—OH), 12.25 (*p*-disubstituted benzene). The crude product was hydrolyzed to diaminopyrimidine (XX) as described above.

2,4-Diamino-5-{p-[bis(2-chloroethyl)amino]phenyl}-6-ethylpyrimidine dihydrochloride (XXI). A stirred suspension of 0.500 g. (1.27 mmoles) of the bis(2-hydroxyethyl)amine dihydrochloride (XX) in 10 ml. of thionyl chloride was heated at 65–70° for 35 min., then was evaporated *in vacuo* (bath temperature 20–25°), leaving a dark solid residue. The residue was triturated with 4 ml. of cold absolute ethanol, yielding 0.450 g. of undissolved solid whose infrared spectrum and paper chromatogram showed it to contain a small amount of starting hydroxy compound (XX). The solid was largely dissolved in 20 ml. of absolute ethanol at room temperature by vigorous stirring and the solution was freed of 0.018 g. of XX by filtration. Ethanolic hydrogen chloride (10 ml. of a solution saturated at 10°) was added to the filtrate, which was then evaporated *in vacuo* (bath at 25°), affording 0.35 g. (70%) of tan solid which decomposed in the range 260–280° but did not melt. Its infrared spectrum was identical with that of the analytical sample. The analytical sample, obtained by washing the product with cold ethanolic hydrogen chloride and drying over phosphorus pentoxide at room temperature, had $\lambda_{max(\mu)}^{Nujol}$ 3.02, 3.10 and 3.18 (NH), 4.21–4.60 (NH^+), 6.10 and 6.13 (pyrimidine ring), 11.31 (*p*-disubstituted benzene); there was no C—OH absorption in the 9.5–9.8 μ region. On paper chromatography in solvent E, the product moved as a single spot with R_{Ad} 2.90, easily distinguished from XX (R_{Ad} 1.03).

Anal. Calcd. for $C_{16}H_{21}Cl_2N_5 \cdot 2HCl$: C, 45.0; H, 5.43; Cl, 33.2; N, 16.3. Found: C, 45.0; H, 5.07; Cl, 33.2; N, 16.3.

Compound XXI lost hydrogen chloride on heating and a sample dried at 100° showed the following analysis:

Found: C, 45.9; H, 5.89; Cl, 31.4; N, 16.3.

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[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

Lactones Derived from 17β-Hydroxyandrostan-16β-ylacetic Acids[1]

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The condensation of 3β-hydroxy-17-oxo-5-androstene with glyoxylic acid gave rise to 3β-hydroxy-17-oxo-5-androsten-16-ylidenacetic acid. The latter served as the intermediate to prepare 3β,17β-dihydroxy-5-androsten-16β-ylacetic acid lactone and its saturated analog. These lactones were converted in turn to 17β-hydroxy-3-oxo-4-androsten-16β-ylacetic acid lactone, 17β-hydroxy-3-oxo-5α-androstan-16β-ylacetic acid lactone, and 17β-hydroxy-3-oxo-1,4-androstadien-16β-ylacetic acid lactone.

As part of a study of new ring D substituted steroids, it became desirable to make some of the lactones having a two-carbon side chain at position 16. This series was approached by condensation of the available 3β-hydroxy-17-oxo-5-androstene (I) with glyoxylic acid to obtain the desired 3β-hydroxy-17-oxo-5-androsten-16-ylidenacetic acid (IIa) in good yield. The recently described method of Newman, Sagar, and Cochrane[2] for this type of glyoxylic acid condensation was used. The new compound IIa was further characterized by preparing the corresponding acetate IIb, the methyl ester IIc, and the acetate methyl ester IId.

The reduction of IIa with sodium borohydride afforded 3β,17β-dihydroxy-5-androsten-16-ylidenacetic acid (IIIa), and the latter (IIIa) was converted into the diacetate IIIb. In accordance with established principles, the newly formed hydroxy group on C-17 of IIIa was assigned the β-position. The side chain at C-16 of II lay in the general plane of the molecule and for that reason was not expected to interfere with the attack of the reducing agent from the less hindered α-side.[3]

Partial hydrogenation of IIIb led to the isolation of 3β,17β-diacetoxy-5-androsten-16β-ylacetic acid (IV), while complete hydrogenation gave 3β,17β-diacetoxy-5α-androstan-16β-ylacetic acid (V). The reduction of IV gave V as expected. After the treatment of IV or V with potassium hydroxide and subsequently hydrochloric acid, the 3β,17β-dihydroxy-5-androsten-16β-ylacetic acid lactone (VIII) and the 3β,17β-dihydroxy-5α-androstan-16β-ylacetic acid lactone (VI), respectively, were obtained.

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