Condensation of the easily prepared[4] *p*-[*N*,*N*-bis(2-chloroethyl)amino]benzaldehyde (II) (Benzaldehyde Mustard) with hippuric acid afforded the azlactone III.[5] Treatment of III with methanol containing a catalytic amount of sodium methoxide afforded I. The use of methanol-sulfuric acid to convert III to I was not satisfactory. I can best be converted to phenylpyruvate mustard by the methanolysis-hydrolysis method of Baker.[3]

EXPERIMENTAL[6]

4-[p-[Bis(2-chloroethyl)amino]benzylidene]-2-phenyl-2-oxazolin-5-one (III). A mixture of 59 g. (0.24 mole) of Benzaldehyde Mustard, 48 g. (0.27 mole) of hippuric acid, 20 g. (0.25 mole) of fused sodium acetate, and 70 ml. of acetic anhydride was heated with constant shaking until the mixture had liquefied. It was then heated at 100° for 2 hr., 100 ml. of ethanol added, and the mixture cooled overnight. Filtration, followed by washing with 30 ml. of cold ethanol and 30 ml. of hot water, gave 48.1 g. (51.5%) of orange solid, m.p. 131–134°. This material was of sufficient purity to be used in the next step. One recrystallization from ethyl acetate gave material, m.p. 138–139° (reported,[3] m.p. 139–141°).

Anal. Calcd. for $C_{20}H_{18}Cl_2N_2O_2$: C, 61.71; H, 4.66. Found: C, 61.77; H, 4.76.

Methyl α-benzamido-p-[bis(2-chloroethyl)amino]cinnamate (I). A suspension of 5. g. (0.013 mole) of crude III in 35 ml. of methanol was refluxed with 0.06 g. of sodium methylate until all of the solid had dissolved (about 20 min.). The hot solution was filtered and cooled overnight to give 3.5 g. (64%) of light yellow solid, m.p. 136–137° (reported,[3] m.p. 138–139°), mixed m.p. with III, 115–122°.

Anal. Calcd. for $C_{21}H_{22}Cl_2N_2O_3$: C, 59.86; H, 5.26. Found: C, 59.97; H, 5.35.

Acknowledgment. The author thanks The Dow Chemical Co. for a generous sample of hippuric acid and J. Pattee for the preparation of Benzaldehyde Mustard.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MIAMI
CORAL GABLES, FLA.

(3) A. P. Martinez, W. A. Skinner, W. W. Lee, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, 80, 6050 (1960).

(4) R. C. Elderfield, I. S. Covey, J. R. Geiduschek, W. L. Meyer, A. B. Ross, and J. H. Ross, *J. Org. Chem.*, 23, 1749 (1958).

(5) This azlactone synthesis was modelled after J. S. Buck and W. S. Ide, *Org. Syntheses*, Coll. Vol. II, 55 (1943).

(6) Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points are uncorrected.

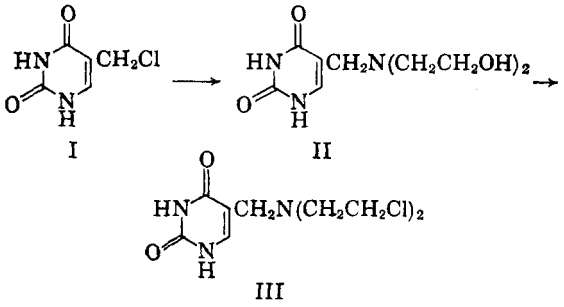
Potential Anticancer Agents.[1] LVI. Synthesis of 5-[Bis(2-chloroethyl)aminomethyl]uracil

LEONARD O. ROSS, WILLIAM W. LEE, M. G. M. SCHELSTRAETE, LEON GOODMAN, AND B. R. BAKER

Received November 17, 1960

5-[Bis(2-chloroethyl)amino]uracil, "uracil mustard," has a broad spectrum of anticancer activity.[2,3] Other nitrogen mustards derived from 5-aminouracil have also been synthesized for evaluation as anticancer agents.[4] As all of these mustards are of the aromatic type and as aliphatic type mustards have considerably greater chemical reactivity, the synthesis of 5-[bis(2-chloroethyl)aminomethyl]-uracil (III) was undertaken in order that it could be evaluated as an anticancer agent.

Although the conversion of 5-(chloromethyl)-uracil (I)[5] to II with diethanolamine would appear to be a straightforward reaction,[6] considerable difficulty was encountered in finding a suitable process for this conversion, as I is extremely



I II III

reactive even with alcohols[5] and diethanolamine is a sluggishly reacting amine. However, when I was treated with diethanolamine in *N*,*N*-dimethylformamide at room temperature in the presence of potassium carbonate, crystalline II was isolated in 97% yield.[7]

The usual difficulties in finding proper conditions for the conversion of II to the mustard III were encountered. In contrast to the aryl type mustards of the uracil series,[2,4] the use of solvents to avoid extensive decomposition from thionyl chloride led to incomplete reaction and variable results. Surprisingly, it was finally found that III was stable to boiling thionyl chloride. Thus, III was readily isolated as its crystalline hydrochloride in 76% yield when II was refluxed for several hours in thionyl chloride.

Of considerable interest is the fact that the hydrochloride of III could be converted to the stable, crystalline free base with aqueous sodium bicarbonate; bis(2-chloroethyl)methylamine (HN_2) free

(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-4-3-ph-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, see W. W. Lee, A. Benitez, C. D. Anderson, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, 83, 1906 (1961).

(2) D. A. Lyttle and H. G. Petering, *J. Am. Chem. Soc.*, 80, 6459 (1958); *J. Natl. Cancer Inst.*, 23, 153 (1959).

(3) M. Lane and M. G. Kelly, *Cancer Res.*, 20, 511 (1960).

(4) A. Benitez, L. O. Ross, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, 82, 4585 (1960).

(5) W. A. Skinner, M. G. M. Schelstraete, and B. R. Baker, *J. Org. Chem.*, 25, 149 (1960).

(6) J. H. Burckhalter, R. J. Seiwald, and H. C. Scarborough, *J. Am. Chem. Soc.*, 82, 991 (1960).

(7) The sluggishness of diethanolamine was also noted in the Mannich reaction when it failed to undergo reaction with formaldehyde and uracil to give II under a variety of conditions.

base has a half-life of only a few minutes in solution. Although III could be recrystallized from ethanol, when a dilute ethanolic solution of III was allowed to stand, gradual decomposition to several products took place, as shown by paper chromatography.

EXPERIMENTAL[8,9]

5-[Bis(2-hydroxyethyl)aminomethyl]uracil (II). A mixture of 0.96 ml. (10.0 mmoles) of diethanolamine, 1.04 g. (7.5 mmoles) of anhydrous potassium carbonate, 10 ml. of *N,N*-dimethylformamide, and 1.12 g. (7.0 mmoles) of I[5] was vigorously stirred at room temperature for 24 hr. protected from moisture. The filtered solution was evaporated to dryness *in vacuo* (bath 70°) leaving a light yellow oil which soon solidified. Trituration with cold absolute ethanol (3 × 1 ml.) at 0–5° gave 1.66 g. (97%) of crystalline product which began to decompose at about 195° but did not melt up to 300°. This material had $\lambda_{max(\mu)}^{Nujol}$ 5.80, 5.95 (C=O of uracil), 9.24, 9.58, 9.71 (C—OH), and moved as a single spot with R_f 0.26 in solvent A, R_f 0.77 in solvent B, and R_f 0.39 in solvent C.

Anal. Calcd. for $C_9H_{15}N_3O_4 \cdot 3/4H_2O$: C, 44.5; H, 6.85; N, 17.3. Found: C, 44.5; H, 6.68; N, 17.5.

5-[Bis(2-chloroethyl)aminomethyl]uracil (III). A mixture of 0.20 g. (0.82 mmole) of II in 10 ml. of thionyl chloride was stirred at room temperature for about 16 hr. protected from moisture, then refluxed for 4 hr. The solution was evaporated to dryness *in vacuo* (bath 40°) and the crystalline hydrochloride of III was triturated with petroleum ether (b.p. 30–60°); yield, 0.20 g. (76%), m.p. 224–226° dec.; $\lambda_{max(m\mu)}^{pH\ 1}$ 262 (ε 8500)[10]; $\lambda_{max(\mu)}^{Nujol}$ 3.20, 3.29 (NH), 5.80, 5.95 (C = O of uracil) and absence of C—OH absorption at 9.24–9.71. The compound moved as a single spot in solvent C and in solvent A (R_f 0.51 and R_f 0.58, respectively).

Anal. Calcd. for $C_9H_{13}Cl_2N_3O_2 \cdot HCl$: C, 35.7; H, 4.69; Cl, 35.1; N, 13.9. Found: C, 35.2; H, 5.14; Cl, 34.9; N, 14.1.

The hydrochloride of III, prepared from 0.50 g. (2.1 mmoles) of II in a similar fashion, was added to 30 ml. of saturated aqueous sodium bicarbonate cooled in an ice bath. After being stirred for 20 min., the mixture was filtered and the product washed with a little ice water; yield, 0.30 g. (54% based on II) of III, m.p. 160–161° dec. Recrystallization from 10 ml. of absolute ethanol with the aid of Norit gave 0.25 g. (45%) of white crystals, m.p. 159–160° dec.; $\lambda_{max(\mu)}^{Nujol}$ 3.20 (NH), 5.85, 6.00 (C=O of uracil) and absence of C—OH at 9.24–9.71. The compound, when dissolved in 0.1*N* hydrochloric acid, moved as a single spot (R_f 0.57) in solvent C. When the compound was dissolved in absolute ethanol, it decomposed on standing, so that several spots were observed on the chromatograms.

Anal. Calcd. for $C_9H_{13}Cl_2N_3O_2$: C, 40.6; H, 4.93; Cl, 26.6; N, 15.8. Found: C, 40.9; H, 4.65; Cl, 26.6; N, 16.0.

DEPARTMENT OF BIOLOGICAL SCIENCES
STANFORD RESEARCH INSTITUTE
MENLO PARK, CALIF.

(8) Melting points were determined on a Fisher-Johns block and are uncorrected.

(9) Paper chromatograms were run by the descending technique on Whatman No. 1 paper in butanol–acetic acid–water (4:1:5) (solvent A), saturated aqueous ammonium sulfate–isopropyl alcohol–water (2:28:70) (solvent B), and isopropyl alcohol-2*N* hydrochloric acid (65:35) (solvent C). Spots were detected by visual examination under ultraviolet light.

(10) Thymine has λ_{max} 264.5 mμ (ε 7,890) for the ionic specie occurring between *p*H 0–7 according to D. Shugar and J. J. Fox, *Biochim. et Biophys. Acta*, **9**, 199 (1952).

Partial Synthesis of 19-Norandrosterone[1]

DAVID K. FUKUSHIMA AND SHIRLEY DOBRINER

Received February 27, 1961

Intramuscular administration of androsterone (3α-hydroxyandrostane-17-one) has been found to cause a significant decrease of serum cholesterol in man.[2] The synthesis of 19-norandrosterone (3α-hydroxy-19-norandrostane-17-one, IV) was undertaken to determine its hypocholesteremic effect since 19-nor analogs of other steroids have often shown enhanced biological activity. The preparation followed that of androsterone.[3] The known 19-norandrostane-3,17-dione (I) was reduced with sodium borohydride to yield 3β-hydroxy-19-norandrostane-17-one (IIa). The 3β-*p*-toluenesulfonate (IIc) of this product was epimerized to 19-norandrosterone (IV) with *N,N*-dimethylformamide according to Chang in less than 50% yield whereas, an 80% yield was realized with the parent C-10 methylated analog.[3] The discrepancy between the reaction of the two materials probably resulted from the ready access of the bulky base to the 2α-H in the case of the 19-norsteroid. The removal of the hydrogen initiated the elimination reaction affording a 35% yield of 19-nor-Δ²-androstene-17-one (V) accompanied by a trace of the Δ³-isomer. 19-Norandrosterone thus obtained was identical with a metabolite assigned this structure which was isolated from urine following administration of 19-nortestosterone to man.[4] The compound showed no hypocholesteremic effect at a dose level effective with androsterone.[5]

EXPERIMENTAL[6]

3β-Hydroxy-19-norandrostane-17-one (IIa). A solution of 3.5 g. of sodium borohydride in 1700 ml. of isopropyl alcohol and 550 ml. of water was slowly added at 20° to a solution of

(1) This investigation was supported in part by a grant from the American Cancer Society and a research grant (CY-3207) from the National Cancer Institute of the National Institutes of Health, United States Public Health Service.

(2) L. Hellman, H. L. Bradlow, B. Zumoff, D. K. Fukushima, and T. F. Gallagher, *J. Clin. Endocrinol. and Metabolism*, **19**, 936 (1959).

(3) F. C. Chang and R. T. Blickenstaff, *J. Am. Chem. Soc.*, **80**, 2906 (1958).

(4) L. L. Engel, J. Alexander, and M. Wheeler, *J. Biol. Chem.*, **231**, 159 (1958).

(5) Private communication, Dr. L. Hellman and Dr. B. Zumoff.

(6) Melting points were determined on a micro hot stage and are corrected. Optical rotations were determined in chloroform and solution unless otherwise stated. Infrared spectra were determined on a Model 21 Perkin-Elmer spectrophotometer; 4000–2750 cm.$^{-1}$ calcium fluoride prism, carbon disulfide; 1800–1600 cm.$^{-1}$ and 1500–1280 cm.$^{-1}$ calcium fluoride prism, carbon tetrachloride; 1300–650 cm.$^{-1}$ sodium chloride prism, carbon disulfide; sh = shoulder.