chloroethylamino)adenine dihydrochloride in 20 ml. of water was treated with 1.0 g. of potassium thiosulfate and heated to reflux for 7 hr. After the addition of 8 ml. of concd. hydrochloric acid the solution was heated for 1 more hour and left to stand at room temperature overnight. The solvent was removed under vacuum and the residue extracted with carbon disulfide. The product was dissolved in water, neutralized with ammonium hydroxide, and treated with 8 ml. of 3% hydrogen peroxide. A yield of 0.15 g. (11%) of disulfide was obtained.

The product showed an infrared spectrum identical with that of the compound obtained by the debenzylation of 8-(β-benzylthioethylamino)adenine. A mixed melting point of the two samples was not depressed.

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE DIVISION OF LIFE SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents. LXIII.[1] Analogs of Chlorambucil. IX.[2] A Benzylic Analog of Phenoxyacetic Acid Mustard

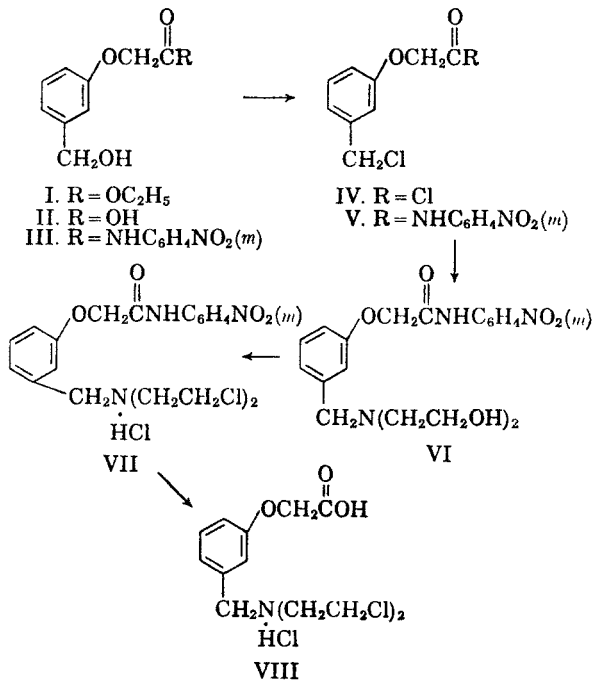
ABELARDO P. MARTINEZ, WILLIAM W. LEE, AND B. R. BAKER

Received May 12, 1961

m-[Bis(2-chloroethyl)aminomethyl]phenoxyacetic acid hydrochloride (VIII), a benzylic type analog of phenoxyacetic acid mustard, has been synthesized for anticancer evaluation. In the synthesis *via* *m*-(hydroxymethyl)phenoxyacetic acid, *m*-nitroaniline has been found to be a useful blocking group for the carboxyl function, since the esters were not sufficiently unreactive.

Chlorambucil,[3,4] 4-{*p*-[bis(2-chloroethyl)amino]-phenyl}butyric acid, and phenylalanine mustard[5,6] both have interesting anticancer properties which differ from each other. Although Chlorambucil is highly effective against the Walker rat sarcoma 256, it shows little activity against sarcoma 180, adenocarcinoma 755 or leukemia L-1210 in the mouse. Against the last three tumors, the phenylalanine mustard is effective.

Since aliphatic mustards are chemically more reactive than the corresponding aryl mustards, a change in tumor spectrum or efficiency or both might be anticipated in benzylic type analogs of Chlorambucil and phenylalanine. Benzylic type analogs of Chlorambucil[7] have been prepared, but



unfortunately are, like Chlorambucil, inactive against sarcoma 180, adenocarcinoma 755 or leukemia L-1210 in the mouse. On the other hand, the phenoxyacetic acid mustards[8,9] show an animal tumor spectrum more like phenylalanine mustard than like Chlorambucil. Comparison of the benzylic analogs with the parent arylphenoxyacetic acid mustards against the three mouse tumors is there-

(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 are not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series see K. A. Hyde, E. M. Acton, W. A. Skinner, L. Goodman, J. Greenberg, and B. R. Baker, *J. Med. Pharm. Chem.*, in press.

(2) For paper VIII on Chlorambucil see K. A. Hyde, E. M. Acton, W. A. Skinner, L. Goodman, and B. R. Baker, *J. Org. Chem.*, **26**, 3551 (1961).

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

(4) R. W. Rundles, J. Grizzle, W. N. Bell, C. C. Corley, W. B. Frommeyer, B. G. Greenberg, C. M. Huguley, Jr., G. W. James III, R. Jones, Jr., W. E. Larsen, V. Loeb, L. A. Leone, J. G. Palmer, W. H. Riser, Jr., and S. J. Wilson, *Am. J. Med.*, **27**, 424 (1959).

(5) F. Bergel, V. C. E. Burnop, and J. A. Stock, *J. Chem. Soc.*, 1223 (1955); F. Bergel and J. A. Stock, *J. Chem. Soc.*, 2409 (1954).

(6) L. F. Larionov, A. S. Khokhlov, E. N. Shkodinskaia, O. S. Vasina, V. I. Trusheikina, and A. M. Novikova, *Lancet*, **269**, 169 (1955).

(7) W. A. Skinner, A. P. Martinez, H. F. Gram, L. Goodman, and B. R. Baker, Paper XLIII of this series, *J. Org. Chem.*, **26**, 148 (1961).

(8) W. Davis, J. J. Roberts, and W. C. J. Ross, *J. Chem. Soc.*, 890 (1955).

(9) W. A. Skinner, A. P. Martinez, and B. R. Baker, Paper XLVI of this series, *J. Org. Chem.*, **26**, 152 (1961).

fore of interest. For these comparisons, the benzylic mustard, *m*-[bis(2-chloroethyl)aminomethyl]phenoxyacetic acid hydrochloride (VIII), has been synthesized. It is also a potential irreversible inhibitor of lactic dehydrogenase.[10]

Synthesis of the desired mustard VIII appears to be feasible by several routes. Those routes employing an ester blocking group for the carboxyl function were unsuccessful since the esters were too reactive.

The reaction sequence finally chosen utilized *m*-nitroaniline as a blocking group for the carboxyl function which was anticipated to offer the advantages of crystallinity, easy detection in paper chromatography, and little likelihood of transamidation. This sequence is quite attractive if in the final step, the acid hydrolysis in the anilide VII to the mustard acid VIII could be accomplished without destruction of VIII. While esters have been frequently employed as blocking groups in mustard synthesis, the more difficultly hydrolyzed amides have not been utilized much. The benzamido blocking group has been successfully removed from the very sensitive phenyl pyruvate mustard.[11] It seems reasonable that removal of the nitroanilide blocking group should be feasible. This was found to be the case.

The condensation of *m*-hydroxybenzyl alcohol with α-chloro-*m*-nitroacetanilide[12] gave a 62% yield of the anilide III, m.p. 174–175°. Treatment of III with thionyl chloride at room temperature for thirty minutes gave an almost quantitative yield (94%) of the chloromethyl derivative V, m.p. 141–143°. Reaction of V with excess diethanolamine in refluxing chloroform for four hours afforded the crystalline amine VI in 70–90% yields; transamidation was not a problem. Heating VI in refluxing thionyl chloride for thirty minutes gave the hydrochloride of the mustard anilide VII as a broadly melting amorphous foam in high yield. Attempts to crystallize this hygroscopic foam were not successful. The amorphous hydrochloride VII was suitable for conversion to the desired mustard acid VIII. The analytical sample of the hydrochloride VII was obtained by one precipitation from a chilled methylene chloride solution by dilution with petroleum ether.

Hydrolysis of the anilide VII to the acid VIII did not proceed in concentrated hydrochloric acid because of the low solubility of VII. The hydrolysis was performed satisfactorily in 4*N* hydrochloric acid (three volumes) diluted with 1,2-dimethoxyethane (one volume). The formation of *m*-nitroaniline could be followed spectrophotometrically; it was established that a reaction time between two to three hours at 80° was necessary for complete hydrolysis. The *m*-nitroaniline was separated from the mustard acid VIII by continuous chloroform extraction of an O.1*N* hydrochloric acid solution of the reaction products. At this *p*H, the hydrochloride of *m*-nitroaniline is sufficiently dissociated so that the free base can be removed by continuous chloroform extraction, but the more stable hydrochloride VIII is retained in the aqueous phase. In this manner, *m*-[bis(2-chloroethyl)aminomethyl]-phenoxyacetic acid hydrochloride (VIII) was obtained as an oil in 65% yield. This oil was homogeneous on paper and was analytically pure after precipitation from acetone by dilution with ether. Attempts to prepare crystalline derivatives with picric acid and 2-nitroindane-1,3-dione[13] were unsuccessful.

In order to avoid the use of the vesicant, α-chloro-*m*-nitroacetanilide, the preparation of V starting from *m*-(hydroxymethyl)phenoxyacetic acid (II) instead of *m*-hydroxybenzyl alcohol was examined.

The crystalline acid II could be prepared in essentially quantitative yield by alkaline hydrolysis of the crude liquid ester I. Acid hydrolysis was not satisfactory since it gave high-melting, ether-insoluble by-products along with low yields of the ether soluble II.

Treatment of II with hot thionyl chloride afforded the chloromethyl acid chloride IV. This was not isolated, but was immediately dissolved in methylene chloride and treated with a methylene chloride solution of a 2:1 mole ratio of *m*-nitroaniline at room temperature to give the chloromethylanilide V, m.p. 143.5–145°, in good yield. Actually, II could be converted to VI in 89% overall yield without isolation of the intermediates IV and V; this was considered to be the method of choice for the synthesis of VI from II. Note that the inverse addition of a 2:1 ratio of *m*-nitroaniline to IV avoided the replacement of the reactive benzylic halogen by *m*-nitroaniline.

EXPERIMENTAL[14]

Ethyl m-(hydroxymethyl)phenoxyacetate (I). To a solution of 1.00 g. (44 mmoles) of sodium in 100 ml. of absolute

(10) B. R. Baker, *Cancer Chemotherapy Reports*, **4**, 1 (1959), published by the National Cancer Institute; B. R. Baker, W. W. Lee, W. A. Skinner, A. P. Martinez, and E. Tong, *J. Med. Pharm. Chem.*, **2**, 633 (1960).

(11) A. P. Martinez, W. A. Skinner, W. W. Lee, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **82**, 6050 (1960).

(12) E. Abderhalden, E. V. Ehrenwall, E. Schwab, and O. Zumstein, *Fermentforschung*, **13**, 408 (1932); *Chem. Abstr.*, **27**, 107 (1933).

(13) B. E. Christensen, C. H. Wang, I. W. Davies, and D. Harris, *Anal. Chem.*, **21**, 1573 (1949).

(14) Melting points are uncorrected and 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 except where stated otherwise. The solvent systems used were: (A) 5% Disodium hydrogen phosphate.[15] (B) Chloroform-ethanol-water (10/10/6), lower phase.[16] (C) *n*-Butyl alcohol-water (saturated).[17] (D) Benzene-methanol-water (2/6/1) on Schleicher and Schuell No. 2496 or Ederol acetylated paper.[18] (E) Benzene-methanol-water (2/6/1) (F) *i*-Propyl alcohol–2*N* hydrochloric acid (65/35).

ethanol was added 5.0 g. (40 mmoles) of *m*-hydroxybenzyl alcohol. The mixture was heated to reflux, a 25-ml. solution of 4.9 g. (40 mmoles) of ethyl chloroacetate in absolute ethanol was added rapidly, and heating under reflux was continued overnight for 18 hr. An additional portion of 0.20 g. (8.7 mmoles) of sodium in 10 ml. of ethanol followed by 1.0 g. (8.2 mmoles) of ethyl chloroacetate in 10 ml. of ethanol were added, then heating under reflux was continued for 5 hr. more; at this time the reaction mixture gave only a faint test with ferric chloride solution. The reaction mixture was evaporated to dryness *in vacuo*, the residue was taken up in 50 ml. of ethyl acetate and was extracted successively with 50-ml. portions of 4*N* sodium hydroxide solution and water. The ethyl acetate solution was dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo* to yield 5.82 g. (69%) of I as a light amber oil which gave a negative ferric chloride test and could be hydrolyzed to the acid II in quantitative yields. I had $\lambda_{max(\mu)}^{Nujol}$ 2.9 (OH), 5.70 (ester C=O), 8.25, 8.60, (ester C—O—C), 12.75 (*m*-substituted phenyl) and moved as a single spot in solvent systems C, with R_f 0.79 (R_f 0.78 for starting material) and A, with R_f 0.70 (R_f 0.78 for starting material). Diazotized sulfanilic acid was used to detect both starting material and I; the latter could not be detected consistently.

m-(Hydroxymethyl)phenoxyacetic acid (II). A mixture of 3.19 g. (15.2 mmoles) of ethyl *m*-(hydroxymethyl)phenoxyacetate, 8.5 ml. of ethanol and 16.5 ml. of 1*N* aqueous sodium hydroxide solution was heated in a steam bath for 1 hr. The ethanol was evaporated *in vacuo* (bath 40°), the residue was taken up in 25 ml. of water and washed with 30 ml. of ether. The aqueous solution was acidified to *p*H 1 with hydrochloric acid and extracted with 125 ml. of ethyl acetate in three portions. The combined extracts were dried with magnesium sulfate and evaporated *in vacuo* to afford 2.78 g. (100%) of II m.p. 110–111°; R_f 0.15 in solvent C, detected with bromocresol green indicator.

Recrystallization of a similar preparation from ether-petroleum ether (b.p. 30–60°) gave white crystals, m.p. 108–109°; $\lambda_{max(\mu)}^{Nujol}$ 2.92 (OH), 3.6–4.5 (acidic hydrogen), 5.72 (carboxyl C=O), 8.20, 8.50 (aryl C—O—C and CO_2H), 9.22, 9.38 (C—OH and aryl C—O—C); R_f 0.15 in solvent C, detected with bromocresol green indicator.

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.4; H, 5.54. Found: C, 59.4; H, 5.64.

Attempts to make this compound from *m*-hydroxybenzyl alcohol and chloroacetic acid in aqueous base were not successful.

2[m-(Hydroxymethyl)phenoxy]-3'-nitroacetanilide (III) To 112 ml. of absolute ethanol were successively added, as each addition dissolved, 1.02 g. (45 mmoles) of sodium, 5.5 g. (44 mmoles) of *m*-hydroxybenzyl alcohol and 9.50 g. (44 mmoles) of α-chloro-*m*-nitroacetanilide. The reaction mixture was heated at reflux for 4 hr. protected from moisture. It was cooled to 0° and the solid was collected on a filter, washed with cold ethanol, triturated thoroughly with 200 ml. of water to afford 8.3 g. (62%) of III, m.p. 174–175°. Recrystallization from absolute ethanol gave 8.2 g. of analytically pure VII, m.p. 174–175°; $\lambda_{max(\mu)}^{Nujol}$ 2.88 (OH), 2.97 (NH), 5.98 (amide C=O), 6.45 (amide II, NO_2), 7.42 (NO_2), 9.69 (C—OH). It moved as a single spot in solvent E (R_f 0.85) and C (R_f 0.81).

Anal. Calcd. for $C_{15}H_{14}N_2O_5$: C, 59.6; H, 4.67; N, 9.28. Found: C, 59.5; H, 4.80; N, 9.34.

2-[m-(Chloromethyl)phenoxy]-3'-nitroacetanilide (V). A mixture of 0.60 g. (2.0 mmoles) of III and 5 ml. of thionyl chloride was stirred for 30 min. at room temperature. The mixture was evaporated *in vacuo* to dryness (bath 50°), 20 ml. of ethylene dichloride was added, and the evaporation was repeated to give 0.63 g. (99%) of V as a tan solid. Recrystallization from methylene chloride–petroleum ether (b.p. 30–60°) afforded a 94% yield of analytically pure V, m.p. 141–143°; $\lambda_{max(\mu)}^{Nujol}$ 3.0 (NH), 5.90, (amide C=O), 6.50 (amide II, NO_2), 7.35 (NO_2). It moved as a single spot in solvent D with R_f 0.20, in E with R_f 0.85, and in solvent C with R_f 0.80, but could not be resolved from III.

Anal. Calcd. for $C_{15}H_{13}ClN_2O_4$: C, 56.3; H, 4.09; N, 8.75; Cl, 11.0. Found: C, 56.2; H, 4.22; N, 8.65; Cl, 11.0.

2-{m-[Bis(2-hydroxyethyl)aminomethyl]phenoxy}-3'-nitroacetanilide (VI). *A. From 2-[m-(chloromethyl)phenoxy]-3'-nitroacetanilide* (V). A solution of 2.5 g. (7.8 mmoles) of V and 8.0 g. (76 mmoles) of diethanolamine in 100 ml. of chloroform was heated at reflux for 6 hr. The resultant two-phase mixture was washed with water (2 × 100 ml.). The chloroform layer was dried over anhydrous magnesium sulfate, filtered, and the filtrate was evaporated to dryness *in vacuo* to afford 3.0 g. (100% y) of a yellow solid, m.p. 109–112°. Recrystallization from methylene chloride-petroleum ether (b.p. 30–60°) gave 2.8 g. (92% y) of VI m.p. 110–112°.

The product from a similar run was recrystallized from methylene chloride to give the analytical sample of VI, m.p. 110–112°; $\lambda_{max(\mu)}^{Nujol}$ 3.01 (OH,NH), 5.92, (amide C=O), 6.50 (amide II, NO_2), and 9.60 (C—OH). It moved as a single spot in solvent D with R_f 0.61.

Anal. Calcd. for $C_{19}H_{23}N_3O_6$: C, 58.6; H, 5.95; N, 10.8. Found: C, 58.1; H, 5.96; N, 10.6.

In preparation B, a higher melting crystal form was obtained; this lower melting form was not subsequently encountered.

B. From m-(hydroxymethyl)phenoxyacetic acid (II). A solution of 0.50 g. (2.28 mmoles) of *m*-(hydroxymethyl)phenoxyacetic acid (II) in 5 ml. of thionyl chloride was heated at reflux for 3 hr., evaporated *in vacuo*, the residue dissolved in 20 ml. of ethylene dichloride, and the solution again evaporated *in vacuo* to leave 0.72 g. (96%) of crude *m*-(chloromethyl)phenoxyacetyl chloride (IV). This was dissolved in 20 ml. of methylene chloride and stirred while a solution of 0.75 g. (4.56 mmoles) of *m*-nitroaniline in 20 ml. of methylene chloride was added during about 15 min. The resultant light yellow mixture was stirred for 10 min. more, treated with anhydrous hydrogen chloride until the yellow color of free *m*-nitroaniline was gone, filtered through a Celite pad, and the precipitate washed with methylene chloride. The combined filtrate and washings were evaporated to dryness to afford a white residue of 2-[*m*-(chloromethyl)phenoxy]-3'-nitroacetanilide, V, m.p. 141–144°.

The residue of V was dissolved in 20 ml. of chloroform containing 2.0 g. (19 mmoles) of diethanolamine. The solution was refluxed for 6 hr., cooled, washed with 25 ml. of water and then extracted with 25 ml. of 5% hydrochloric acid. The aqueous acid layer was neutralized with saturated aqueous sodium bicarbonate then extracted with 25 ml. of methylene chloride. The extract, dried with magnesium sulfate, was evaporated to dryness *in vacuo* to afford 0.79 g. (89% from II) of VI, m.p. 121.5–123°, which was identical to VI, m.p. 108–109°, prepared by method A, by infrared spectra and paper chromatography.

Two recrystallizations from ethanol–petroleum ether (b.p. 30–60°) gave an 80% yield of the analytically pure VI, m.p. 119–121°.

Anal. Calcd. for $C_{19}H_{23}N_3O_6$: C, 58.6; H, 5.95; N, 10.8. Found: C, 58.8; H, 5.84; N, 10.6.

2{m-[Bis-(2-chloroethyl)aminoethyl]phenoxy}-3'-nitroacetanilide hydrochloride (VII). A mixture of 2.30 g. (5.9 mmoles) of VI and 10 ml. of thionyl chloride was refluxed for 1 hr. The excess thionyl chloride was removed *in vacuo*, 20 ml. of ethylene dichloride was added, and the evaporation *in vacuo* was repeated. The semisolid foam, which could not be crystallized, was dissolved in 25 ml. of hot methylene

(15) C. E. Carter, *J. Am. Chem. Soc.*, **72**, 1466 (1950).

(16) T. H. Kritchevsky and A. Tiselius, *Sci.*, **114**, 299 (1952).

(17) J. G. Buchanan, C. A. Dekker, and A. G. Long, *J. Chem. Soc.*, 3162 (1950).

(18) T. Wieland and W. Kracht, *Angew. Chem.*, **69**, 172 (1957).

chloride, then hot petroleum ether (b.p. 30–60°) was added to the point of turbidity. The solution was chilled in an acetone–Dry Ice bath and the supernatant solvent decanted to leave an oily precipitate. This was dried *in vacuo* at 35–40° (0.5 mm.) to afford 2.30 g. (84%) of VII as a white hygroscopic foam; $\lambda_{max(\mu)}^{Nujol}$ 2.99 (NH), 3.6–4.5 (R_4N^+), 5.90 (amide C—O), 6.50 (amide II, NO_2), 7.35 (NO_2), free of absorption at 9.60 (C—OH). It moved as a single spot in solvent C with R_f 0.94 but could not be separated here or in other solvent systems from starting material.

Anal. Calcd. for $C_{19}H_{21}Cl_2N_3O_4 \cdot HCl$: C, 49.3; H, 4.78; N, 9.08; Cl, 23.0. Found: C, 49.4; H, 4.83; N, 9.22; Cl, 22.8.

m-[Bis-(2-chloroethyl)aminomethyl]phenoxyacetic acid hydrochloride (VIII). To a hot solution of 0.50 g. (1.08 mmoles) of VII in 5 ml. of 1,2-dimethoxyethane was added 15 ml. of hot 4*N*-hydrochloric acid solution. After being heated at 80° (bath temperature) for 2.25 hr., the mixture was evaporated to dryness *in vacuo* (up to 50°/0.5 mm.). The residue was dissolved in 15 ml. of 0.1*N* hydrochloric acid solution, then continuously extracted with chloroform until the lower chloroform layer was free of the yellow color of *m*-nitroaniline. The aqueous phase was separated and evaporated to dryness *in vacuo* (40° '0.5 mm.) to afford 0.25 g. (65%) of VIII as a yellow amber oil which could not be crystallized.

The analytical sample of VIII was obtained by dissolving 120 mg. of the oil in acetone, filtering to remove a trace of insoluble material, diluting the filtrate with ether and allowing an oil to precipitate overnight. The supernatant solvent was removed by decantation and the oil was dried *in vacuo* to afford 100 mg. of VIII as a light amber oil; λ_{max}^{film} 3.0–4.2 (CO_2H and NR_4H^+), 5.70 (carboxyl C=O), 7.80 (aryl C—O—C), 12.6 (*m*-substituted benzene), 13.4 (C—Cl). It moved as a single spot in solvents D with R_1 0.82 (starting material streaks to R_f 0.7) and F with R_f 0.79 (R_f 1.0 for starting material) and could be detected by ultraviolet light, diazotized sulfanilic acid or iodoplatinate spray.[19] Freshly prepared solutions of VIII in acetone gave single spots. On standing, these solutions gave streaks on paper chromatograms.

Anal. Calcd. for $C_{13}H_{17}Cl_2NO_3 \cdot HCl$: C, 45.6; H, 5.29; Cl, 31.0; N, 4.09. Found: C, 45.7; H, 5.21; Cl, 30.4; N, 4.42.

Acknowledgment. The authors wish to thank Dr. Peter Lim for interpretation of the infrared absorption spectra and his staff for the paper chromatography and spectrophotometry. The authors are also indebted to Mr. O. P. Crews and his staff for large-scale preparation of certain intermediates.

MENLO PARK, CALIF.

(19) L. R. Goldbaum and L. Kazyak, *Anal. Chem.*, 28, 1289 (1956).

[CONTRIBUTION FROM THE RESEARCH INSTITUTE OF TEMPLE UNIVERSITY]

Fluorine-Containing Potential Anticancer Agents. I. Synthesis of Some Trifluoromethylpyrimidines[1]

SHOJI INOUE, ANDREW J. SAGGIOMO, AND EDWARD A. NODIFF[2]

Received May 24, 1961

Various 2- and 6-trifluoromethylpyrimidines have been synthesized for evaluation as cancer chemotherapeutic agents.

Recent investigations have shown that the introduction of fluorine into some pyrimidines produces compounds which inhibit tumor growth[3,4]

Despite this discovery, very few new fluoropyrimidines[5–10] have been prepared for screening against neoplasms. A program has therefore been initiated in this laboratory to synthesize various new fluorine-containing pyrimidines and condensed pyrimidine systems for evaluation as cancer chemotherapeutic agents.

As the first stage in this program, a series of 2-trifluoromethylpyrimidines was prepared as shown in schemes A and B.

Trifluoroacetamidine (I) was prepared in 95% yield from trifluoroacetonitrile and ammonia by the method of Reilly and Brown.[11] The condensation of I with ethyl formylacetate, ethyl acetoacetate, ethyl trifluoroacetoacetate, diethyl malonate and ethyl cyanoacetate afforded 4-hydroxy-2-trifluoromethylpyrimidine (II), 4-hydroxy-6-methyl-2-trifluoromethylpyrimidine (III), 2,6-bistrifluoromethyl - 4 - hydroxypyrimidine (IV), 4,6 - dihydroxy-2-trifluoromethylpyrimidine (V) 6-amino-4-hydroxy-2-trifluoromethylpyrimidine (VI), respectively. The chlorination of II, III, IV, V, and VI with phosphorus oxychloride in dimethylaniline gave the corresponding chloro compounds VII, VIII, IX, X and XI, respectively. The derivatives VII,

(1) The support of this investigation by the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service, under Research Grant CY-4270 (C1) is gratefully acknowledged.

(2) To whom inquiries may be addressed.

(3) R. Duschinsky, E. Pleven, and C. Heidelberger, *J. Am. Chem. Soc.*, 79, 4559 (1957).

(4) C. Heidelberger, L. Griesbach, B. J. Montag, D. Mooren, and O. Cruz, *Cancer Research*, 18, 305 (1958).

(5) A. Giner-Sorolla and A. Bendich, *J. Am. Chem. Soc.*, 80, 5744 (1958).

(6) E. D. Bergmann, S. Cohen, and I. Shahak, *J. Chem. Soc.*, 3278 (1959).

(7) J. A. Barone, E. Peters, and H. Tieckelmann, *J. Org. Chem.*, 24, 198 (1959).

(8) J. A. Barone, H. Tieckelmann, R. Guthrie, and J. Holland, *J. Org. Chem.*, 25, 211 (1960).

(9) J. A. Barone and H. Tieckelmann, *J. Org. Chem.*, 26, 598 (1960).

(10) C. Kaiser and A. Burger, *J. Org. Chem.*, 24, 113 (1959).

(11) W. L. Reilly and H. C. Brown, *J. Am. Chem. Soc.*, 78, 6032 (1956).