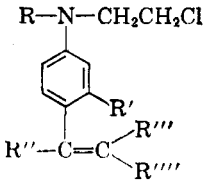
TABLE I

ANALOGUES OF *p*-[BIS(2-CHLOROETHYL)AMINO]BENZYLIDENEMALONONITRILE



R	R′	R″	R‴	R⁗	M.P.[a]	Yield, %	Calcd. Carbon	Calcd. Hydrogen	Found[b] Carbon	Found[b] Hydrogen
CH_2CH_2Cl	CH_3	H	CN	$CONH_2$	204–204.5[c]	59	55.22	5.25	55.00	5.29
C_2H_5	H	H	CN	$CONH_2$	178–178.5[c]	49	60.54	5.81	60.85	5.82
CH_2CH_2Cl	H	H	CN	$CONHC_6H_5$	215–216[c]	97	61.86	4.93	61.77	4.71
CH_2CH_2Cl	CH_3	H	CN	$CONHC_6H_5$	182–182.5[c]	51	62.69	5.26	62.46	5.45
C_2H_5	H	H	CN	$CONHC_6H_5$	180–181[c]	66	67.88	5.70	68.02	5.92
CH_2CH_2Cl	CH_3	H	CN	CN	165–166[d]	65	58.45	4.91	58.63	4.98
CH_2CH_2Cl	H	CN	CN	CN	128–131[d]	90	56.44	3.79	56.38	3.78
CH_2CH_2Cl	CH_3	H	$CO_2C_2H_5$	$CO_2C_2H_5$	92–93[d]	93	56.72	6.26	56.45	6.16
CH_2CH_2Cl	H	H	CN	COC_6H_5	88–89[d]	77	64.35	4.86	64.46	4.92
CH_2CH_2Cl	H	H	H	CO_2H	193–194[c,e]	72	54.18	5.25	54.37	5.40

[a] All melting points are uncorrected. [b] Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Drs. Weiler and Strauss, Oxford, England. [c] Recrystallized from anhydrous chloroform. [d] Recrystallized from absolute ethanol. [e] From malonic acid.

EXPERIMENTAL

Reagents. Benzaldehyde nitrogen mustard,[7] 4-[bis(2-chloroethyl)amino]-*o*-tolualdehyde,[1] and *p*-[*N*-ethyl-*N*-(2-chloroethyl)amino]benzaldehyde[1] were prepared by literature methods. The authors thank Kay-Fries Chemicals, Inc., for several of the chemicals used in this work.

Typical condensation. A mixture of 0.01 mole of aldehyde and 0.01 mole of the active hydrogen compound in 15 to 25 ml. of dry dioxane at 0° was treated with about 0.2 ml. of piperidine. After standing from 2–12 hr. at room temperature, the crystals were filtered or the solution was slowly concentrated until crystals were obtained. The products were recrystallized from an appropriate solvent as shown in Table I.

Condensation with cyanoacethydrazide. Equimolar quantities of cyanoacethydrazide and benzaldehyde nitrogen mustard were heated in absolute ethanol for 10 min. After cooling, a quantitative yield of solid, m.p. 212–214°, was obtained. Washing with hot ethanol and hot chloroform did not change the melting point.

Anal. Calcd. for $C_{14}H_{16}N_4OCl_2$: C, 51.39; H, 4.93; N, 17.12. Found: C, 51.13; H, 4.95; N, 16.80.

The same product was obtained when 0.01 mole of cyanoacethydrazide and 0.02 mole of benzaldehyde nitrogen mustard in dioxane was treated with piperidine.

p-[Bis(2-chloroethyl)amino]phenylethenetricarbonitrile. To 7.4 g. (0.034 mole) of *N,N*-bis(2-chloroethyl)aniline in 18 ml. of dimethylformamide at 25–30° was added slowly 3.84 g. (0.03 mole) of tetracyanoethylene. After stirring for 10 min. at 50–55°, the mixture was cooled and diluted with water to give 8.61 g. of red solid. The properties of this solid are included in Table I.

Acknowledgment. We acknowledge the assistance of J. Pattee and W. Kirsch in the preparation of some of the aldehydes used in this work.

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Synthesis of Potential Anticancer Agents. IV. Phenylpyruvate Mustard[1,2]

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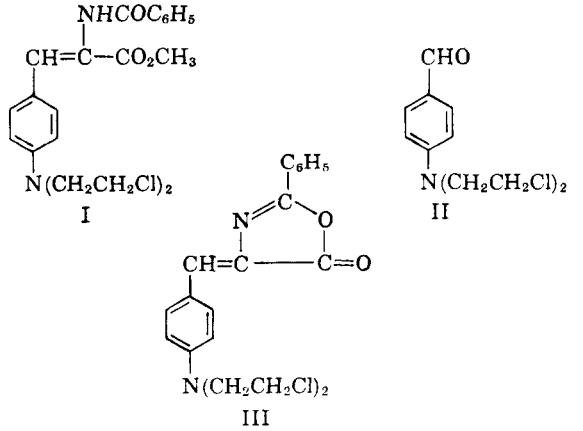
Received January 6, 1961

Baker and co-workers[3] have recently reported a synthesis of *p*-[bis(2-chloroethyl)amino] phenylpyruvic acid (phenylpyruvate mustard) from *p*-nitrobenzaldehyde *via* the key intermediate, methyl α-benzamido-*p*-[bis(2-chloroethyl)amino]cinnamate (I). We have also been working on a synthesis of phenylpyruvate mustard and had prepared I, before the appearance of Baker's report,[3] by a somewhat more convenient route.



(1) Part III, F. D. Popp, *J. Org. Chem.*, 26, 3021 (1961).

(2) This investigation was supported in part by a Research Grant T 177 from the American Cancer Society.

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.

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(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

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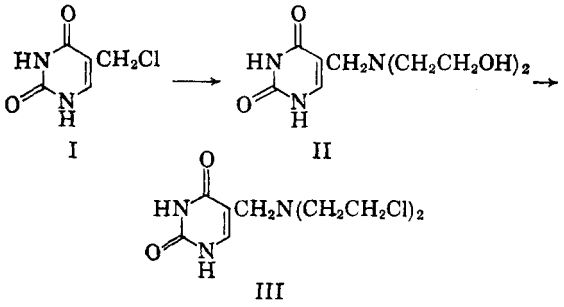
Received November 17, 1960

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.