the quinic acid are recorded in Table I. One of the products gave the same R_f values on paper chromatograms as quinide. The zone with R_f 0.15 on the *n*-butyl alcohol–acetic acid–water developed chromatograms of the fused quinic acid was cut out, sewn onto another chromatography paper, and developed in the benzyl alcohol–*tert*-butyl alcohol–isopropyl alcohol–water system. Zones appeared at R_f values 0.07, 0.24, and 0.53. The middle one, labeled "FQ-III-B," proved to be identical with a zone obtained on paper chromatograms of cigarette smoke as described previously.

On heating quinic acid with 6*N* hydrochloric acid for 1 hr. at 100°, Cartwright and Roberts[4] found that, in addition to quinic acid itself, three trace spots also make their appearance on paper chromatograms. One of these was indicated to be quinide.

Preparation of quinide. Quinide was prepared from quinic acid by the procedure of Panizzi and co-workers.[6]

Acknowledgment. This research was supported in part by the National Institutes of Health.

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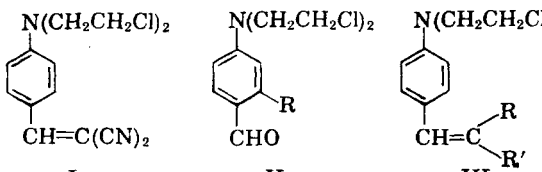
(6) L. Panizzi, M. L. Scarpati, and R. Scarpati, *Gazz. chim. ital.*, 84, 806 (1954); *Chem. Abstr.* 50, 882 (1956).

Synthesis of Potential Anticancer Agents. III. Compounds Related to *p*-[Bis(2-chloroethyl)amino]benzylidenemalononitrile[1,2]

FRANK D. POPP

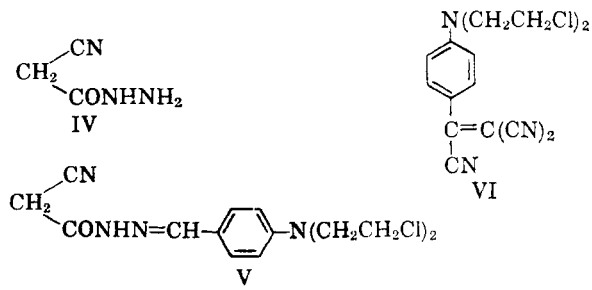
Received December 21, 1960

We have recently reported[3] the preparation of *p*-[bis(2-chloroethyl)amino]benzylidenemalononitrile (I) and several related compounds from the Knoevenagel reaction of *p*-[*N*,*N*-bis(2-chloroethyl)-amino]benzaldehyde (benzaldehyde nitrogen mustard) (II. R = H). I has been reported[4] to exhibit activity against the Dunning leukemia in rats over a wide dosage range and is currently undergoing further extensive pharmacological testing. With this great interest developing in compound I, it was decided to prepare additional related compounds. Of the compounds (III) prepared earlier,[3] those from ethyl malonate and cyanoacetamide also exhibited some activity[4] so it was decided to include analogues of these in this study. In our work with Schiff bases[1] it was found[4] that compounds prepared from 4-[bis(2-chloroethyl)amino]-*o*-tolualdehyde (II. R = CH_3) were somewhat more active than those from benzaldehyde nitrogen mustard and the same amine. This approach was therefore also tried in this series.



I II III

Malononitrile, cyanoacetamide, α-cyanoacetanilide, malonic acid, ethyl malonate, and benzoylacetonitrile were condensed with the appropriate aldehydes in dioxane using piperidine as a catalyst to give the compounds shown in Table I. Reaction of cyanoacethydrazide (IV) with benzaldehyde nitrogen mustard under a variety of conditions gave only compound V. V was very insoluble in most solvents and apparently this insolubility prevented further reaction.



The tricyanoethylene (VI) was prepared by condensation of *N*,*N*-bis(2-chloroethyl)aniline with tetracyanoethylene.[5] An attempt to convert VI to 4-(2-cyano-3-maleimidyl)-*N*,*N*-bis(2-chloroethyl)-aniline by controlled hydrolysis with concentrated hydrochloric acid[6] failed to give an identifiable product. An attempt to prepare the *N*-phenylmaleimide from *N*,*N*-bis(2-chloroethyl)aniline, sodium cyanide and *N*-phenyldichloromaleimide[6] gave only recovered starting materials.

Although the screening will be reported later in more detail,[4] it can be mentioned than the tricyano compound VI was much less active than the dicyano compound I and the compounds from α-cyanoacetanilide were less active than those from cyanoacetamide. The one arm mustards, prepared from *p*-[*N*-ethyl-*N*-(2-chloroethyl)amino]benzaldehyde, were inactive.

(1) Part II., F. D. Popp, *J. Org. Chem.*, 26, 1566(1961).

(2) This investigation was supported in part by Research Grant CY 4814 from the National Cancer Institute, U. S. Public Health Service, and in part by a Research Grant T 177 from the American Cancer Society. Presented in part before the Division of Medicinal Chemistry at the 139th Meeting of the American Chemical Society, St. Louis, Mo., March 21–30, 1961.

(3) F. D. Popp, *J. Chem. Soc.*, 5271(1960).

(4) Drs. Ralph Jones, Jr., and Leo Rane, private communication. Complete screening data on the compounds mentioned will be published elsewhere at a later date.

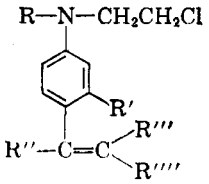
(5) B. C. McKusick, R. E. Heckert, T. L. Cairns, D. D. Coffman, and H. F. Mower, *J. Am. Chem. Soc.*, 80, 2806 (1958). We would like to thank Dr. McKusick for a generous sample of tetracyanoethylene.

(6) E. L. Martin, C. L. Dickinson, and J. R. Roland, *Abstracts*, 138th Meeting of the American Chemical Society, New York, Sept., 1960, page 94P. We would like to thank Dr. Martin for experimental details and samples.

(7) 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).

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.

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

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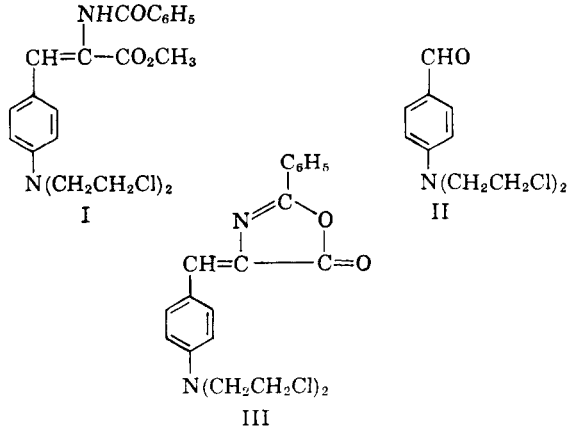
Baker and co-workers[3] have recently reported a synthesis of *p*-[bis(2-chloroethyl)amino] phenylpyruvic acid (phenylpyruvate mustard) from *p*-nitrobenzaldehyde *via* the key intermediate, methyl α-benzamido-*p*-[bis(2-chloroethyl)amino]cinnamate (I). We have also been working on a synthesis of phenylpyruvate 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.