Bisquaternary ammonium salts. The two following procedures are representative of the methods used in preparing the bisquaternary ammonium salts. The first method was used for compounds 1–5 (Table I) and the second method was used for compounds 6–10.

Bis-2-dimethylaminoethyl 3-(p-nitrophenyl)glutarate bismethiodide. In a 250-ml. flask fitted with a Dean-Starke water trap[13] were placed 150 ml. of dry toluene, 8 g. (0.034 mole) of 3-(*p*-nitrophenyl)glutaric anhydride, and 10 ml. (0.10 mole) of 2-dimethylaminoethanol. This mixture was refluxed for 2 days, by which time no more water was being collected in the trap. The solution was washed with three-30 ml. portions of water and the toluene was evaporated. The resulting oil was taken up in 50 ml. of methanol, and 8 ml. of methyl iodide was carefully added. Reaction occurred readily as evidenced by spontaneous refluxing of the solution. The mixture was refluxed for 1 hr., allowed to stand overnight, and cooled to complete precipitation of the product. Recrystallization from 100 ml. of methanol gave 14.1 g. (61% based on anhydride), m.p. 193.5–194.5°.

Gentle saponification of the water washings followed by acidification resulted in the recovery of 3.3 g. of 3-(*p*-nitrophenyl)glutaric acid. This represents 38% of the starting anhydride.

Bis-2-diethylaminoethyl 3-(m-nitrophenyl)glutarate bisethiodide. Using the same procedure as above, 8 g. (0.034 mole) of 3-(*m*-nitrophenyl)glutaric anhydride and 10 ml. (0.073 mole) of 2-diethylaminoethanol were esterified in toluene. Following the washing and evaporation of toluene, the oil was taken up in 50 ml. of absolute ethanol and treated as above with 6 ml. of ethyl iodide. The product was recrystallized from absolute ethanol to give 18.4 g. (71%), m.p. 154–156°. Saponification of the washings gave 1.3 g. of 3-(*m*-nitrophenyl)glutaric acid, equivalent to 15% of the anhydride used as starting material.

(13) E. W. Dean and D. D. Starke, *Ind. Eng. Chem.*, **12**, 486 (1920)

LEXINGTON, KY.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MIAMI]

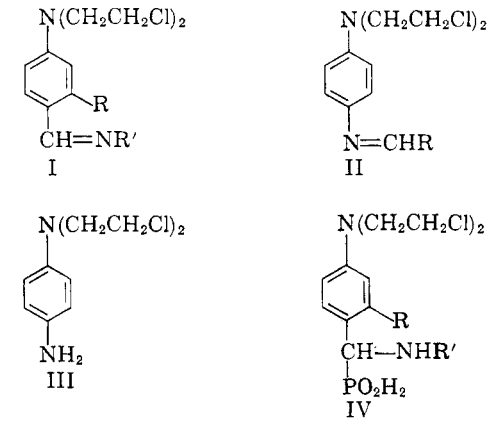
Synthesis of Potential Anticancer Agents. V. Schiff Bases and Related Compounds[1-2]

FRANK D. POPP AND WARREN KIRSCH

Received March 10, 1961

Schiff bases have been prepared by the condensation of amines with benzaldehyde nitrogen mustard and with 4-[bis(2-chloroethyl)amino]-*o*-tolualdehyde; and by the condensation of aldehydes with *N,N*-bis(2-chloroethyl)-*p*-phenylenediamine. Several of these Schiff bases have been converted to aminophosphinic acids.

Some time ago we reported the condensation of benzaldehyde mustard {[*p*-[*N,N*-bis(2-chloroethyl)-amino]benzaldehyde}4-[bis(2-chloroethyl)amino]-*o*-tolualdehyde, *p*-diethylaminobenzaldehyde, and *p*-[*N*-ethyl-*N*-(2-chloroethyl)amino]benzaldehyde with a variety of amines.[4] Although the Schiff bases prepared from the last two aldehydes exhibited little or no activity against the Dunning lukemia in rats, the Schiff bases (I) from the first two aldehydes exhibited, in many cases, wide ranges of activity as well as a few cures.[5] On the basis of the compounds reported earlier[4] little could be derived in the way of structure to activity relations except that, with the same amine, the Schiff bases (I. R = CH_3) from 4-[bis(2-chloroethyl)amino]-*o*-tolualdehyde were



generally more active than the ones from benzaldehyde mustard.

In order to determine if any structure to activity relationships exist and in hopes of finding a more active anticancer agent we have now extended this series to include those Schiff bases listed in Table I. As before[4] the crystalline Schiff bases (I) were obtained by heating the reactants in absolute ethanol.

Although the screening data are not complete, it appears[5] that the Schiff bases from cycloalkylamines are the most active of the anils from aliphatic amines. Further, *N*-[4-bis(2-chloroethyl)amino-2-methylbenzylidene] cyclopentylamine (I. R = CH_3, R' = cyclopentyl) was the most active Schiff

(1) Part IV, F. D. Popp, *J. Org. Chem.*, **26**, 3020 (1961).

(2) This investigation was supported by a Research Grant (T 177) from the American Cancer Society, a Research Grant (CY 4814) from the National Cancer Institute, U. S. Public Health Service, and a grant from an American Cancer Society Institutional Grant to the University of Miami.

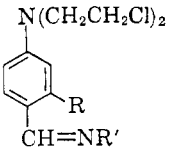
(3) Presented in part before the Division of Medicinal Chemistry of the American Chemical Society, St. Louis, Mo., March 1961; and in part at the Caribbean Chemical Symposium at the University College of the West Indies, Jamaica, April 1961.

(4) F. D. Popp, *J. Org. Chem.*, **26**, 1566 (1961).

(5) Drs. Ralph Jones, Jr., and Leo Rane, private communication. Detailed screening results of the compounds mentioned will be reported elsewhere at a later date.

TABLE I

CONDENSATIONS OF AMINES WITH ALDEHYDE MUSTARDS



Amine Used ($R'NH_2$)	R	Formula	Yield, %	M.P.	Calcd. C, %	Calcd. H, %	Found[a] C, %	Found[a] H, %
Cyclopropylamine	CH_3	$C_{15}H_{20}N_2Cl_2$	75	64–65	60.20	6.74	60.22	6.63
Cyclohexylamine	CH_3	$C_{18}H_{26}N_2Cl_2$	75	85–87	63.34	7.68	63.45	7.61
Cycloheptylamine	CH_3	$C_{19}H_{28}N_2Cl_2$	90	66–68	64.22	7.94	64.42	8.02
Cyclooctylamine	CH_3	$C_{20}H_{30}N_2Cl_2$	85	75–77	65.03	8.19	64.83	7.94
2,2,4,4-Tetramethylcyclobutane-1,3-diamine	H	$C_{30}H_{40}N_4Cl_4$	66	180–182	60.20	6.74	60.23	6.97
2,2,4,4-Tetramethylcyclobutane-1,3-diamine	CH_3	$C_{32}H_{44}N_4Cl_4$	58	175–176	61.34	7.08	61.38	7.00
1,4-Bisaminomethylcyclohexane	CH_3	$C_{32}H_{44}N_4Cl_4$	89	156–157	61.34	7.08	61.69	7.23
Myristylamine	H	$C_{25}H_{42}N_2Cl_2$	89	43–44	68.00	9.59	68.10	9.41
Palmitylamine	H	$C_{27}H_{46}N_2Cl_2$	85	49–50	69.06	9.86	69.33	9.58
Stearylamine	H	$C_{29}H_{50}N_2Cl_2$	96	56–57	69.99	10.13	70.03	10.04
p-Fluoroaniline	CH_3	$C_{18}H_{19}N_2Cl_2F$	90	110–111	61.19	5.42	61.13	5.63
p-Chloroaniline	CH_3	$C_{18}H_{19}N_2Cl_3$	73	80–82	58.47	5.18	58.39	5.44
p-Iodoaniline	CH_3	$C_{18}H_{19}N_2Cl_2I$	80	119–120	46.87	4.15	47.06	4.45
p-Aminophenol	H	$C_{17}H_{18}N_2OCl_2$	88	164–166	60.54	5.38	60.37	5.53
p-Aminophenol	CH_3	$C_{18}H_{20}N_2OCl_2$	95	188–189	61.54	5.74	61.42	5.71
p-Dimethylaminoaniline	H	$C_{19}H_{23}N_3Cl_2$	77	140–142	62.64	6.36	62.77	6.59
3-Aminoquinoline	CH_3	$C_{21}H_{21}N_3Cl_2$	85	139–140	65.29	5.48	65.43	5.57
5-Aminoquinoline	CH_3	$C_{21}H_{21}N_3Cl_2$	72	148–150	65.29	5.48	65.56	5.34
2-Amino-9-fluorenone	CH_3	$C_{25}H_{22}N_2Cl_2O$	96	156–157	68.65	5.07	68.64	5.09
2-Florenamine	CH_3	$C_{25}H_{24}N_2Cl_2$	95	122–123	70.92	5.71	70.74	5.95
4-Amino-2′,3-dimethylazobenzene	H	$C_{25}H_{26}N_4Cl_2$	33	120–122	66.22	5.78	66.14	5.84
2-Aminochrysene	H	$C_{29}H_{24}N_2Cl_2$	67	129–130	73.88	5.13	73.77	5.09
12-Ethyl-6-aminochrysene	H	$C_{31}H_{28}N_2Cl_2$	80	122–125	74.54	5.65	74.36	5.82
3,3′-Dimethoxy-4,4,-diaminobiphenyl	H	$C_{36}H_{38}N_4O_2Cl_4$	38	166–169	61.72	5.47	61.43	5.67
3,3′-Dimethoxy-4,4,-diaminobiphenyl	CH_3	$C_{38}H_{42}N_4O_2Cl_4$	68	190–192	62.64	5.81	62.34	5.51

[a] Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Drs. Weiler and Strauss, Oxford, England.

base from the cycloalkylamines. The analogy of the centering of activity in the cyclopentyl system in this work and in 1-aminocyclopentane-1-carboxylic acid as reported by others[6] is of interest.

In order to study variations in activity with changes in structure several Schiff bases (II) were prepared by condensing *N*,*N*-bis(2-chloroethyl)-*p*-phenylenediamine (III)[7] with aldehydes. In this manner the nitrogen mustard group was on the ring attached to the nitrogen rather than the carbon of the imine. Surprisingly, preliminary screening results[5] indicate that these Schiff bases (II) are considerably more toxic than those from the nitrogen mustard aldehydes. With these results on the first few compounds this series was discontinued. The compounds prepared are shown in Table II.

Another variation of the Schiff bases structure was attempted by the reaction of the anil with hypophosphorus acid to give an aminophosphinic acid (IV).[8,9] It was hoped that the phosphinic acid would change the solubility sufficiently to improve the activity of the compound. Unfortunately this was not the case and screening results[5] indicate that the aminophosphinic acids (IV) were considerably less active than the parent Schiff bases (I). Since a Schiff base could not be obtained from 1-aminocyclopentane-1-carboxylic acid,[6] an attempt was made to treat this amino acid and 4-[bis(2-chloroethyl)amino]-*o*-tolualdehyde directly with hypophosphorous acid. The hypophosphorous acid salt of 1-aminocyclopentane-1-carboxylic acid was obtained rather than the aminophosphinic acid as contrasted with the reaction of *N*-[4-bis(2-chloroethyl)amino - 2 - methylbenzylidene]cyclopentylamine and hypophosphorous acid and the reaction of cyclopentylamine, 4-[bis(2-chloroethyl)amino]-*o*-tolualdehyde, and hypophosphorous acid where the identical aminophosphinic acid was obtained in each case. The aminophosphinic acids are recorded in Table III.

(6) T. A. Connors and W. C. J. Ross, *J. Chem. Soc.*, 2119 (1960).

(7) J. L. Everett and W. C. J. Ross, *J. Chem. Soc.*, 1972 (1949).

(8) H. Schmidt, *Chem. Ber.*, **81**, 477 (1948).

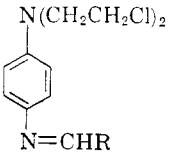
(9) W. M. Linfield, A. T. Guttmann, B. C. Brown, and E. Jungermann, Abstracts, 138th Meeting, American Chemical Society, New York, N. Y., September 1960, page 18-O.

EXPERIMENTAL

Schiff base formation from mustard aldehydes. A mixture of 0.01 mole of mustard aldehyde and 0.01 mole of amine in a minimum of absolute ethanol was refluxed for 30 min. on a steam bath. In most cases the product crystallized on cool-

TABLE II

SCHIFF BASES FROM *N,N*-BIS(2-CHLOROETHYL)-*p*-PHENYLENEDIAMINE

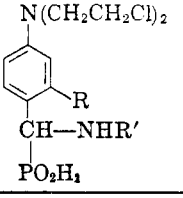


Aldehyde Used (RCHO)	Formula	Yield, %	M.P.	Calcd. C, %	Calcd. H, %	Found[a] C, %	Found[a] H, %
p-Bromobenzaldehyde	$C_{17}H_{17}N_2Cl_2Br$	64	134–135	51.02	4.28	51.08	4.36
p-Chlorobenzaldehyde	$C_{17}H_{17}N_2Cl_3$	53	136–137	57.40	4.82	57.21	4.82
p-Hydroxybenzaldehyde[b]	$C_{17}H_{18}N_2OCl_2$	50	172–174	60.54	5.38	60.72	5.41
p-[*N,N*-Bis(2-chloroethyl)amino]benzaldehyde	—	85	134–136[c]	—	—	—	—
4-[Bis(2-chloroethyl)amino]-*o*-tolualdehyde	$C_{22}H_{27}N_3Cl_4$	67	138–139	55.59	5.72	55.37	5.68

[a] Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Drs. Weiler and Strauss, Oxford, England. [b] First prepared in this laboratory by R. Alaimo. [c] Reported m.p. 134–135°, W. C. J. Ross, G. P. Warwick, and J. J. Roberts, *J. Chem. Soc.*, 3110 (1955).

TABLE III

AMINOPHOSPHINIC ACIDS



Amine ($R'NH_2$)	R	Formula	Yield, %	M.P.[b]	Calcd. C, %	Calcd. H, %	Found[a] C, %	Found[a] H, %
Cyclopentylamine	CH_3	$C_{17}H_{27}N_2Cl_2PO_2$[c]	70	210–211	51.91	6.92	52.00	6.83[d]
2-Aminoanthracene	H	$C_{25}H_{25}N_2Cl_2PO_2$[e]	31	155–175	61.61	5.17	61.84	5.22
Stearylamine	H	$C_{29}H_{53}N_2Cl_2PO_2$[e]	95	80–115	71.69	9.48	61.49	9.56
		$C_{29}H_{53}N_2Cl_2PO_2,H_3PO_2$[f]	68	65–75	55.32	8.97	55.18	8.70[g]
2,2,4,4-Tetramethylcyclobutan-1,4-diamine	H	$C_{30}H_{46}N_4Cl_4P_2O_4$[e]	25	210	49.32	6.35	48.99	6.32

[a] Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Drs. Weiler and Strauss, Oxford, England. [b] All melting points are approximate and are accompanied by decomposition. [c] The same product was obtained using ethanol or benzene as reaction solvent or using the aldehyde, amine, and hypophosphorous acid. [d] Calcd.: N, 7.13; Found: N, 7.08. [e] Reaction carried out in absolute ethanol. [f] Reaction carried out in benzene. [g] Calcd.: N, 4.45; Found: N, 4.54.

ing, although in a few cases it was necessary to partially concentrate the ethanol. The products of this reaction are shown in Table I. In all cases the products were recrystallized from or washed with absolute ethanol to obtain analytical samples.

Schiff base formation from the monomustard of p-phenylenediamine. Stannous chloride (13.1 g.) was added with shaking and cooling to 8.75 g. of *N,N*-bis(2-chloroethyl)-*p*-nitrosoaniline[7] in 190 ml. of concd. hydrochloric acid. The mixture was filtered and the residue dissolved in water and made basic with sodium hydroxide. The basic solution was extracted several times with benzene and the extract was dried over sodium sulfate. The dried extract was then refluxed for 30 min. with 0.01 mole of aldehyde and the benzene concentrated to give the crude Schiff base. The products of this reaction are shown in Table II.

Aminophosphinic acids. A mixture of 0.005 mole of Schiff bases and about 1 g. of concd. hypophosphorous acid was dissolved in absolute ethanol or benzene and refluxed for 2.5 hr. In some cases the product crystallized on cooling; in other cases partial concentration of the solvent or addition of ether was necessary. The products are shown in Table III.

Hypophosphorous acid salt of 1-aminocyclopentane-1-carboxylic acid. A mixture of 0.01 mole of 1-aminocyclopentane-1-carboxylic acid, 0.01 mole of 4-[bis(2-chloroethyl)amino]-*o*-tolualdehyde, and 2 g. of hypophosphorous acid (concentrated) in absolute ethanol or benzene was refluxed for 2 hr. Cooling gave 1.19 g. of white solid, m.p. about 350°.

Anal. Calcd. for $C_6H_{11}NO_2 \cdot H_3PO_2$: C, 36.93; H, 7.23. Found: C, 37.13; H, 7.35.

Acknowledgment. We acknowledge the assistance of J. Pattee in the preparation of some of the starting materials. We would also like to thank the many companies who donated samples for this work and would like to thank Dr. Leo Rane for many helpful discussions.

CORAL GABLES, FLA.