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

Synthesis of Potential Anticancer Agents. II. Some Schiff Bases[1,2]

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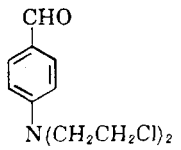
The treatment of *N*-(*m*-tolyl)diethanolamine and *N*-phenyl-*N*-ethylethanolamine with phosphorus oxychloride and then phosphorous oxychloride–dimethylformamide has given 4-[bis(2-chloroethyl)amino]-*o*-tolualdehyde and *p*-[*N*-ethyl-*N*-(2-chloroethyl)amino]benzaldehyde, respectively. These aldehydes and benzaldehyde nitrogen mustard have been condensed with a variety of amines. Some reactions of these Schiff bases are discussed.

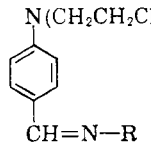
The convenient synthesis[3] of *p*-[*N*,*N*-bis(2-chloroethyl)amino]benzaldehyde (benzaldehyde nitrogen mustard) (I) in high yield from commercially available *N*-phenyldiethanolamine has provided a useful intermediate for the incorporation of the nitrogen mustard grouping into molecules which might be expected to show tumor inhibitory properties.

Benzaldehyde nitrogen mustard (I) has been used in the Doebner quinoline synthesis,[3] has been condensed with hydrazides[3] and active methylene groups,[1,3,4] and treated with amines to form Schiff bases.[5]

Ross and co-workers[5] reported the condensation of I with aniline, *p*-anisidine and 3-nitroaniline. These workers point out that the azomethine linkage in these compounds could be regarded as an isostere of two cytotoxic agents, namely the related azo compounds and stilbenes. They fail, however, to carry the series further. With a supply of I available from earlier work[1] it was decided to prepare several additional compounds in this series. Several of these were reported active against the Dunning leukemia in rats and apparently had a very wide safety margin.[6] With these screening results in mind we prepared a large variety of anil derivatives (II) of benzaldehyde nitrogen mustard (I) in order to study the scope of the reaction and to obtain some potentially useful derivatives. The amines selected for anil formation with I were of as wide a variety as possible. In particular attempts were made to use some physiologically active amines which might help act as improved carrier portions of the molecule. The crystalline Schiff bases obtained are listed in Table I.



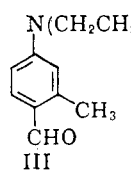
I



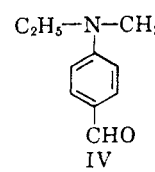
II

Attempts to use heterocyclic amines[7] in which the amino group could exist as an imine gave, for the most part, recovered starting materials. An additional group of amines,[8] largely aliphatic, gave viscous oils which could not be induced to crystallize. Attempted distillation of several of these oils resulted in decomposition. Examination of the infrared spectra of many of these oils indicated that the condensation had taken place.

It was next decided to prepare some related Schiff bases from other aldehydes in order to obtain some correlation of activity with the alkylating function portion of the molecule. These Schiff bases from aldehydes other than I are shown in Table II. A few anils were prepared from *p*-diethylaminobenzaldehyde to compare the diethylamino and bis(2-chloroethyl)amino groupings. With *m*-tolyldiethanolamine and *N*-phenyl-*N*-ethylethanolamine readily available the aldehydes III and IV were prepared by treatment with phosphorus oxychloride followed by formylation with dimethylformamide–phosphorus oxychloride as described[3] for the preparation of I. These aldehydes were then allowed to react with several amines. It is of in-



III



IV

(1) Part I, F. D. Popp, *J. Chem. Soc.*, 5271 (1960).

(2) This investigation was supported in part by Research Grant CY 4814 from the National Cancer Institute, U. S. Public Health Service, in part by a Research Grant (T 177) from the American Cancer Society, and in a small part by funds from an Institutional Grant of the American Cancer Society to the University of Miami. Presented in part before the Southeastern Regional meeting of the A.C.S., Birmingham, Alabama, November 3–5, 1960.

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

(4) H. L. Chou, H. C. Lin, and C. Y. Yuan, *K'o Hsueh T'ung Pao*, **14**, 457 (1959); *Chem. Abstr.*, **54**, 7716 (1960).

(5) W. C. J. Ross, G. P. Warwick, and J. J. Roberts, *J. Chem. Soc.*, 3110 (1955).

(6) Dr. Ralph Jones, Jr., private communication. The screening results will be published elsewhere at a later date.

(7) The following heterocyclic amines did not form Schiff bases: 2-amino-3-methylpyrazine, 2-amino-6-methylpyridine, 3-amino-2,5-dimethylpyrazine, 2-aminopyrimidine, 2-aminopyridine, 9-aminoacridine, and benzoguanamine.

(8) The following amines gave oils with I: aminoacetal, 2-ethylhexylamine, furfurylamine, allylamine, cyclooctylamine, *m*-aminobenzonitrile, butylamine, *N*-(2-aminoethyl)-piperazine, 3-aminopropanol, benzylamine, cyclopentylamine, 3-aminopyridine, 2-aminobiphenyl, 1,3-diaminopropane, and 4,4′-oxydianiline.

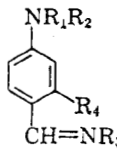
TABLE I

CONDENSATIONS OF AMINES WITH BENZALDEHYDE NITROGEN MUSTARD

Amine	Formula	Yield, %	M.P.	Calcd. C	Calcd. H	Found[a] C	Found[a] H
1-Amino-3-nitroguanidine	$C_{12}H_{15}N_6O_2Cl_2$	74	168–169	41.51	4.65	41.61	4.58
2-Aminoethanol	$C_{13}H_{18}N_2OCl_2$	75	92–93	53.99	6.27	53.91	6.21
p-Bromoaniline	$C_{17}H_{17}N_2Cl_2Br$	97	122–123	51.02	4.28	51.14	4.54
p-Chloroaniline	$C_{17}H_{17}N_2Cl_3$	96	116–117	57.40	4.82	57.42	4.57
p-Nitroaniline	$C_{17}H_{17}N_3O_2Cl_2$	84	152–154	55.75	4.68	55.49	5.07
m-Nitroaniline	$C_{17}H_{17}N_3O_2Cl_2$	30	127–129[b]				
2-Amino-4-nitrophenol	$C_{17}H_{17}N_3O_3Cl_2$	44	137–139	53.41	4.48	53.21	4.41
Aniline	$C_{17}H_{18}N_2Cl_2$	98	59–61[c]				
2-Aminobenzimidazole	$C_{18}H_{18}N_4Cl_2$	88	180–182	59.84	5.02	59.48	5.26
5-Amino-2-benzimidazolethiol	$C_{18}H_{18}N_4SCl_2$	96	>350	54.96	4.61	54.90	4.76
p-Anisidine	$C_{18}H_{20}N_2OCl_2$	88	92–93[d]	61.54	5.74	61.59	5.76
p-Amino-α-chloroacetophenone	$C_{19}H_{19}N_2OCl_3$	77	121–122	57.37	4.82	57.33	5.22
p-Aminoacetophenone	$C_{19}H_{20}N_2OCl_2$	89	131–133	62.81	5.55	62.82	6.03
p-Aminophenylacetic acid	$C_{19}H_{20}N_2O_2Cl_2$	89	148–150	60.16	5.32	60.28	5.31
p-Aminophenylmercaptoacetic acid	$C_{19}H_{20}N_2O_2SCl_2$	89	132–134	55.47	4.90	55.19	5.06
Methyl 3-amino-4-hydroxybenzoate	$C_{19}H_{20}N_2O_3Cl_2$	92	164–166	57.73	5.10	57.52	5.50
β-Phenylethylamine[e]	$C_{19}H_{22}N_2Cl_2$	94	77–78	65.33	6.35	65.22	6.26
Ethyl *p*-aminobenzoate	$C_{20}H_{22}N_2O_2Cl_2$	77	103–105	61.07	5.64	60.72	6.08
1-Nitro-6-aminorophthalene	$C_{21}H_{19}N_3O_2Cl_2$	93	165–166	60.58	4.60	60.14	4.68
α-Naphthylamine	$C_{21}H_{20}N_2Cl_2$	91	104–105	67.93	5.43	68.02	5.49
β-Naphthylamine	$C_{21}H_{20}N_2Cl_2$	98	93–95	67.93	5.43	67.66	5.36
β-(3,4-Dimethoxyphenyl)ethylamine[e]	$C_{21}H_{26}N_2O_2Cl_2$	98	74–75	61.61	6.40	61.59	6.31
2-Amino-3-naphthoic acid	$C_{22}H_{20}N_2O_2Cl_2$	90	202–203	63.62	4.85	63.48	4.90
4-Aminoantipyrine	$C_{22}H_{24}ON_4Cl_2$	96	198–199	61.25	5.61	61.50	5.66
2-Aminoanthracene	$C_{25}H_{22}N_2Cl_2$	85	144–145	71.26	5.26	71.49	5.43

[a] Spang Microanalytical Laboratory, Ann Arbor, Mich. [b] Reported[5] m.p. 126–128.5°. [c] Reported[5] m.p. 62–64°. [d] Reported[5] m.p. 93°. [e] See Ref. 10.

TABLE II

SCHIFF BASES  FROM ALDEHYDES OTHER THAN I

Amine Used (R_3NH_2)	R_1	R_2	R_4	Formula	Yield, %	M.P.	Calcd. C	Calcd. H	Found[a] C	Found[a] H
p-Bromoaniline	C_2H_5	CH_2CH_2Cl	H	$C_{17}H_{18}N_2BrCl$	87	94–95	55.83	4.96	55.78	5.16
p-Bromoaniline	C_2H_5	C_2H_5	H	$C_{17}H_{19}N_2Br$	94	99–100	61.64	5.78	61.56	5.63
3-Aminopyridine	CH_2CH_2Cl	CH_2CH_2Cl	CH_3	$C_{17}H_{19}N_3Cl_2$	49	126–127	60.72	5.69	60.82	5.65
Cyclopentylamine	CH_2CH_2Cl	CH_2CH_2Cl	CH_3	$C_{17}H_{24}N_2Cl_2$	57	77–78	62.38	7.39	62.34	7.38
p-Bromoaniline	CH_2CH_2Cl	CH_2CH_2Cl	CH_3	$C_{18}H_{19}N_2BrCl_2$	85	103–104	52.19	4.62	51.97	5.04
p-Anisidine	C_2H_5	C_2H_5	H	$C_{18}H_{22}N_2O$	81	99–100	76.56	7.85	76.62	7.80
p-Aminophenyl mercaptoacetic acid	CH_2CH_2Cl	CH_2CH_2Cl	CH_3	$C_{20}H_{22}N_2O_2SCl_2$	83	155–157	56.47	5.27	56.29	5.37
Methyl 3-amino-4-hydroxybenzoate	CH_2CH_2Cl	CH_2CH_2Cl	CH_3	$C_{20}H_{22}N_2O_3Cl_2$	87	185–186	58.68	5.42	58.57	5.62
4-Aminoantipyrine	C_2H_5	CH_2CH_2Cl	H	$C_{22}H_{27}N_4OCl$	98	174–175	66.07	6.35	66.16	6.50
4-Aminoantipyrine	C_2H_5	C_2H_5	H	$C_{22}H_{26}N_4O$	98	220–221	72.90	7.23	72.71	7.06
4-Aminoantipyrine	CH_2CH_2Cl	CH_2CH_2Cl	CH_3	$C_{23}H_{26}N_4OCl_2$	81	112–113	62.02	5.88	62.05	5.94
o-Aminobiphenyl	CH_2CH_2Cl	CH_2CH_2Cl	CH_3	$C_{24}H_{24}N_2Cl_2$	88	116–117	70.07	5.88	69.76	6.01
1-Aminoanthracene	CH_2CH_2Cl	CH_2CH_2Cl	CH_3	$C_{26}H_{24}N_2Cl_2$	88	174–175	71.72	5.56	71.53	5.75

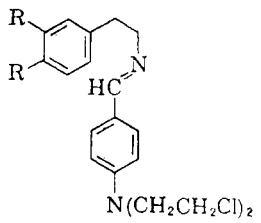
[a] Spang Microanalytical Laboratory, Ann Arbor, Mich.

terest to note that 3-aminopyridine, 2-aminobiphenyl, and cyclopentylamine, which gave oils or gums with I, all gave crystalline products with *m*-tolualdehyde nitrogen mustard (III).

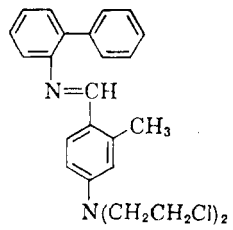
It was hoped to make use of some of these Schiff bases in attempts to introduce the alkylating agent function into heterocyclic compounds. Attempts to apply the Pictet-Spengler synthesis[9] to V and VI[10] failed, however, to yield any isoquinoline. Both V and VI underwent hydrolysis

(9) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **6**, 151 (1951).

(10) Compounds V and VI were first prepared by R. C. Elderfield and F. D. Popp at the University of Michigan; thanks go to Dr. Elderfield for permission to include them in this paper.



V. R = H
VI. R = OCH_3



VII

with 24% hydrochloric acid[11] to yield I. Polyphosphoric acid[12] also led to the hydrolysis of V. The attempted condensation of I or III with aminoacetal gave an oil which could not be induced to crystallize and which decomposed on attempted distillation. An attempted Pomeranz-Fritsch reaction[13] on these oils gave only tarry material from which no picrate could be obtained.

The conversion of 2-benzylideneaminodiphenyl into 9-phenylphenanthridine by stannic chloride in boiling *o*-dichlorobenzene has been reported.[14] It was hoped that this might provide a convenient route to a phenanthridine containing the nitrogen mustard function. However, treatment of N-(4-[bis-(2-chloroethyl)amino]-2-methylbenzylidine)-2-biphenylamine (VII) or the crude gum from the reaction of 2-aminobiphenyl and I under the above conditions yielded only tarry materials. Treatment of acetone or ethanol solutions of these tars with picric acid led only to the recovery of picric acid and tars.

EXPERIMENTAL[15]

Reagents. The amines used were all prepared by reported procedures or obtained from commercial sources.[16] The preparation of benzaldehyde nitrogen mustard (I) has been previously described.[8]

4-[Bis(2-chloroethyl)amino]-o-tolualdehyde (III). To 91.8 g. (0.6 mole) of phosphorus oxychloride chilled in an ice bath 58.5 g. (0.3 mole) of *m*-tolyldiethanolamine was slowly added. After the addition was complete, the mixture was warmed at 95° for 1 hr. and then mixed with 250 ml. of benzene and 250 ml. of ice. The aqueous layer was extracted with additional benzene and the combined benzene layers concentrated *in vacuo*. Treatment of the residue with a small volume of hot methanol gave 52.9 g. (76%) of solid. A solution of 42.7 g. of this crude solid in 125 ml. of dimethylformamide was added slowly with stirring and cooling in ice to a solution of 28.6 g. of phosphorus oxychloride in 125 ml. of dimethylformamide. After the addition was complete, the solution was held in the ice bath for 15 min. and then warmed to 40° for 2 hr. The mixture was poured into about 400 g. of ice and water and filtered after standing for a few minutes. Filtration gave 43.7 g (91%) of the desired aldehyde which could be used without purification. Several recrystallizations from absolute ethanol gave a white solid, m.p. 86.5–87.5°.

Anal. Calcd. for $C_{12}H_{15}NOCl_2$: C, 55.40; H, 5.81. Found. C, 55.67, 55.43; H, 6.06, 6.01.

Treatment of this aldehyde with 2,4-dinitrophenylhydrazine gave a *2,4-dinitrophenylhydrazone,* m.p. 230–232°.

Anal. Calcd. for $C_{18}H_{19}N_5O_4Cl_2$: C, 49.10; H, 4.35. Found: C, 48.95; H, 4.72.

p-[N-Ethyl-N-(2-chloroethyl)amino]benzaldehyde. N-Phenyl-*N*-ethylethanolamine (165 g., 1 mole) and 170 g. (1.1 moles) of phosphorus oxychloride was reacted as described above. After the heating was complete, the solution was made basic and extracted with ether. Concentration of the ether gave 176 g. of liquid. A solution of 83.1 g. (0.45 mole) of this crude liquid in 150 ml. of dimethylformamide was treated with 70 g. of phosphorus oxychloride and 250 ml. of dimethylformamide as described above. In this case treatment with ice and water did not yield a solid. Extraction with ether and concentration of the ether gave 75.2 g. (80%) of a blue liquid, which was used without further purification. This liquid yielded a *2,4-dinitrophenylhydrazone,* m.p. 217–218°.

Anal. Calcd. for $C_{17}H_{18}N_5O_4Cl$: C, 52.11; H, 4.63. Found: C, 52.27; H, 4.70.

Schiff bases formation. A mixture of 0.01 mole of aldehyde and 0.01 mole of amine in a minimum of absolute ethanol (at least 25 ml.) was refluxed for 30 min. on a steam bath. In most cases the product crystallized on cooling, although in a few cases it was necessary to concentrate partially the ethanol. The products of this reaction are shown in Tables I and II. In all cases recrystallization was from absolute ethanol.

Acknowledgment. We acknowledge the assistance of S. Kotzen, P. Melvin, and H. Swarz in the preparation of some of the benzaldehyde and tolualdehyde nitrogen mustard used in this work.

CORAL GABLES, FLA.

(11) E. C. Weinbach and W. H. Hartung, *J. Org. Chem.*, **15**, 676 (1950).

(12) F. D. Popp and W. E. McEwen, *Chem. Revs.*, **58**, 321 (1958); *Trans. Kans. Acad. Science*, **63**, 169 (1960).

(13) W. J. Gensler, *Org. Reactions*, **6**, 191 (1951).

(14) C. A. Bartram, D. Harrison, and W. F. Short, *J. Chem. Soc.*, 1158 (1958).

(15) All melting points are uncorrected. Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(16) The author would like to thank the many companies who have donated amines for this project. They are too numerous to list individually.