take the results of the product analyses as a measure of this contribution and compute an estimated second-order rate constant from the experimental rate constant. A similar though smaller correction may be applied to the hydrolysis of III, using the results of the fractional distillation as a measure of the SN1 contribution. In the case of the hydrolysis of III the amounts of the isomeric aminoalcohols would not be expected to be as good a measure of SN1 contribution since the steric effect of the single ethyl group would be less effective in blocking direct nucleophilic attack on the more substituted carbon than the steric effect of the two methyl groups in IV. On the other hand there seems to be a small amount of polymer formed during the hydrolysis reaction and this concurrent polymerization would require an additional correction, which would tend to offset the above-mentioned difficulty in the interpretation of the aminoalcohol analysis. The final corrected values of the second-order hydrolysis rate constants, computed from experimental data, are listed in Table V. It will be observed that these

TABLE V

COMPARISON OF SECOND-ORDER HYDROLYSIS RATE CONSTANTS

Imine	pK (H_2O)	pk_2 (corr.)	pk_0 (E)[c]	pk_0 (SS)[c]
2,2-Dimethylethylen-	7.179	7.703[a]	7.412	7.642
2-Ethylethylen-	8.083	8.216[b]	7.858	8.182
Ethylen-	7.898	7.898	7.560	7.812

[a] Corrected using product analysis by potentiometric method. [b] Corrected using product analysis by fraction distillation. [c] See data in Table III.

values, for all three hydrolyses, are below the corresponding values of k_0 from either correlation equation, computed from the rates of the faster reactions. The k_0 values using the equation of Swain and Scott[9] are closer to the experimental values than are those from the equation of Edwards.[10]

Several explanations might be advanced for this behavior, perhaps the most obvious being that the nucleophilic constant (E_n) for water is somewhat high (*i.e.*, water is not as strong a nucleophile as predicted). If the value of this constant were -0.14 for water, the estimated values would all agree within experimental error with the computed values of k_0. This small effect might be due to the fact that the species being attacked in these reactions are cations, while uncharged substrates were used in the evaluation of the nucleophilicity constants. Although the deviation certainly seems real, it is not large enough to invalidate the correlation equations.

The values of the activation thermodynamic quantities for these three hydrolyses, the product analyses and the relationship between the rates of imine hydrolysis and the rates of the faster reactions all point to the conclusion that the acid hydrolysis of 2,2-dimethylethylenimine is primarily an SN1 reaction although there is a small SN2 contribution. The acid hydrolysis of 2-ethylethylenimine is primarily SN2 with a possible small SN1 contribution. The comparable reaction of ethylenimine is probably exclusively SN2.[13]

Our results also indicate that the equations which have been presented[9,10] for the correlation of nucleophilic displacements, can be used to estimate amounts of SN1 and SN2 character in certain solvolysis reactions. When combined with data on activation entropies, etc.,[12] this method shows promise of giving satisfactory answers to solvolytic mechanism problems.

(13) Compare G. J. Buist and H. J. Lucas, THIS JOURNAL, **79**, 6157 (1957), a paper published while this one was in preparation.

PROVIDENCE 12, R. I.

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

Synthesis of 12-(Dialkylaminoalkyl)-benzo[a]phenothiazines

BY PURNENDU B. TALUKDAR[1] AND DAVID A. SHIRLEY[2]

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A series of 12-(dialkylaminoalkyl)-benzo[a]phenothiazines has been synthesized for pharmacological evaluation. These compounds were obtained by thionation of various N-phenyl-α-naphthylamines and condensation of the resulting benzo[a]-phenothiazines with dialkylaminoalkyl chlorides using sodamide. Several N-acyl and sulfone derivatives of the benzo[a]-phenothiazines also were prepared.

The past decade has seen considerable work on phenothiazine chemistry which was initially stimulated by the observations of Halpern[3] and Charpentier[4] on the antihistaminic activity of 10-dialkylaminoalkylphenothiazines. More recently additional stimulus has been provided by the discovery of the effects of these phenothiazine types in treatment of mental illness.

In spite of the large amount of work on phenothiazine derivatives[5] little attention has been given to the benzophenothiazines. We have undertaken in this Laboratory a study of reactions and reaction products of the various benzophenothiazines. The present paper describes the synthesis of some new derivatives of benzo[a]phenothiazine with particular emphasis on the N-dialkylaminoalkyl types. Our initial objective has been the synthesis of compounds related to the therapeutically useful phenothiazine types.

Thionation of N-phenyl-α-naphthylamine in the presence of iodine catalyst leads to benzo[a]-

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(3) B. N. Halpern, *Compt. rend. soc. biol.*, **140**, 363 (1946).

(4) P. Charpentier, *Compt. rend.*, **225**, 306 (1947).

(5) S. P. Massie, *Chem. Revs.*, **54**, 797 (1954).

TABLE I

BENZO[a]PHENOTHIAZINES (I)

Name	Substituents (I) R_1	R_2	R_3	Yield, %	M.p., °C.	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
9-Methyl-12H-	CH_3	H	H	60	151–152	$C_{17}H_{13}NS$	77.51	77.06	4.97	4.71	5.34	4.96
10-Methyl-12H-	H	CH_3	H	[a]	159–160							
11-Methyl-12H	H	H	CH_3	50	145–146	$C_{17}H_{13}NS$	77.51	77.51	4.97	4.78	5.34	5.10
9-Methoxy-12H	OCH_3	H	H	43	117–118	$C_{17}H_{13}NOS$[b]	73.06	73.79	4.68	4.70	5.31	4.78
								73.55		4.93		4.59
10-Chloro-12H	H	Cl	H	[c]	168–170							

[a] Previously reported by Buu-Hoï and Lecocq,[8] m.p. 160°. [b] This compound did not show a completely satisfactory analysis after several crystallizations to constant m.p. and two chromatographic separations over Florisil. Four N-substituted derivatives, however, showed satisfactory analytical values. [c] Previously reported by Knoevenagel,[6] m.p. 172°.

TABLE II

DERIVATIVES OF 12-CHLOROACETYLBENZO[a]PHENOTHIAZINE (IV)

Name	M.p., °C.	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
12-Piperidinoacetyl-	176–176.5[a]	$C_{23}H_{22}N_2OS$	73.74	73.57	5.92	6.14	7.52	7.85
12-Morpholinoacetyl	172–173[b]	$C_{22}H_{20}N_2O_2S$	70.18	70.25, 70.46	5.31	5.50, 5.07	7.43	7.50, 7.64

[a] Hydrochloride, m.p. 245–247°. [b] Hydrochloride, m.p. 213–215° dec.

phenothiazine in good yield[6,7] and a few substituted types have been prepared by the same route.[6,8] In our hands better yields could be obtained by much shorter reaction times than those given in the literature. Another improvement was the use of chromatography over Florisil adsorbent in the purification procedure. This was especially effective in eliminating oxidation products of benzophenothazine formed during the thionation process or during subsequent work up of the reaction mixture.

Thionation of N-phenyl-α-naphthylamines substituted in the *m*-position in the N-phenyl group can lead to two products since thionation can occur either *ortho* or *para* to the substituent. This situation has been examined rather carefully in the phenothiazine series, and it has been demonstrated that thionation *para* to the substituent occurs to a greater degree.[9–12] Infrared spectra have been useful for assignment of structure to the isomers formed. Thus the compound showing a band at about 12.2 μ (1,2,4-trisubstituted benzene) was stated to be the 2-isomer and the compound showing a band at 12.7 μ (1,2,3-trisubstituted benzene) was the 4-isomer.[10–12]

Thionation of both N-(*m*-tolyl)- and N-(*m*-chlorophenyl)-α-naphthylamine has been reported[6,8] to give only one product in each case. The original workers assigned the chloro and methyl groups to the 10-position (I; $R_1 = R_3 = H$, $R_2 =$ Cl or CH_3) but offer no experimental evidence for these structures. We have obtained the same products, that is, 10-methyl- and 10-chlorobenzo[a]phenothiazine, as indicated by comparison of melting points with the literature values, and these were the only products isolated from the thionation reaction. We determined the infrared spectra of these products but unfortunately the spectra did not provide an unequivocal answer to the structural problem. Benzo[a]phenothiazine itself shows a strong rather sharp band at 12.53 μ, which simply broadens in both the chloro- and the methyl-substituted derivatives mentioned above with no new bands appearing in the 12–13 μ region. Consequently, we are unable to present any evidence from infrared spectra for the structure of the supposed 10-chloro and 10-methylbenzo[a]phenothiazine. It seems rather likely that these compounds have the structure indicated, but the assignments should be regarded as tentative.

9-Methylbenzo[a]phenothiazine and 11-methylbenzo[a]phenothiazine were prepared by thionation of N-(*p*-tolyl)-α-naphthylamine and N-(*o*-tolyl)-α-naphthylamine, respectively. 9-Methoxybenzo[a]phenothiazine was also prepared from N-(*p*-anisyl)-α-naphthylamine. This product was extremely difficult to purify and completely satisfactory elementary analyses could not be obtained. However, N-substituted derivatives were obtained in pure form.

Benzo[a]phenothiazine and the five nuclearly substituted derivatives were converted to the 12-acyl and 12-aroyl derivatives as indicated in Table III. Some of these were then oxidized[13] to the corresponding sulfones (III) with hydrogen peroxide as indicated in Table IV. 12-Acetylbenzo[a]-phenothiazine-7-dioxide was hydrolyzed to 12H-benzo[a]phenothiazine-7-dioxide.

Substitution of dialkylaminoalkyl groups on nitrogen (12-position) was accomplished in conventional fashion by treatment of the benzo[a]phenothiazine with freshly prepared sodamide in toluene or xylene solvent followed by addition of the dialkylaminoalkyl chloride. The products containing the basic side chain were converted to solid derivatives (usually picrates) for further characterization (Table VI). Of particular importance is compound 9 in Table V. This is analogous to chloropromazine except for the fusion of a benzene ring onto a benzene ring of the phenothiazine nucleus.

(6) E. Knoevenagel, *J. prakt. Chem.*, [2] **89**, 14 (1913).
(7) F. Kehrmann and H. Dardel, *Ber.*, **55B**, 2346 (1922).
(8) Ng. Ph. Buu-Hoï and J. Lecocq, *Compt. rend.*, **218**, 648 (1944).
(9) P. Charpentier, P. Gaillot, R. Jacob, J. Gaudechon and P. Buisson, *Compt. rend.*, **235**, 59 (1952).
(10) H. L. Yale, F. Sowinski and J. Bernstein, THIS JOURNAL, **79**, 4375 (1957).
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(12) A. Roe and W. F. Little, *ibid.*, **20**, 1577 (1955).
(13) H. Gilman and R. D. Nelson, THIS JOURNAL, **75**, 5422 (1953).

TABLE III: 12-ACYL- OR AROYLBENZO[a]PHENOTHIAZINES (II)

No.	Method	R_1	R_2	R_3	R_4	Yield, %	M.p., °C.	Solv. for crystn.	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	A	H	H	H	CH_3CO	..	132–133[a]	Benzene							
2	C	H	H	H	$ClCH_2CO$	90	182.5–183.5	Benzene	$C_{18}H_{12}ClNOS$	66.33	66.52	3.71	3.64	4.32	4.32
3	D	H	H	H	C_6H_5CO	50	159.5-160	Aq. acetone	$C_{23}H_{16}NOS$	77.92	77.84	4.55	4.27	3.97	3.81
4	A	CH_3	H	H	CH_3CO	87	152–153	Acetone–ligroin	$C_{19}H_{15}NOS$	74.70	74.84	4.95	4.75	4.61	4.43
5	A	H	CH_3	H	CH_3CO	91.3	146–147	Ethanol–ligroin	$C_{19}H_{15}NOS$	74.70	74.52	4.95	4.79	4.61	4.55
6	B	H	H	CH_3	CH_3CO	..	151–152[b]	.....	.....				..		
7	B	CH_3O	H	H	CH_3CO	95.6	167–168	Acetone	$C_{19}H_{15}NO_2S$	70.98	71.08	4.69	4.97	4.37	4.54
8	B	H	Cl	H	CH_3CO	91.8	144–146	Acetone–ligroin	$C_{18}H_{12}ClNOS$	66.32	65.97	3.71	3.58	4.03	4.25
															4.22

[a] Kehrmann and Dardel (ref. 7) reported m.p. 132°. [b] Attempted crystallization was unsuccessful.

TABLE IV: 12-ACYL- OR AROYLBENZO[a]PHENOTHIAZINE-7-DIOXIDES (III)

No.	R_1	R_2	R_3	R_4	Yield, %	M.p., °C.	Solv. for crystn.	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	H	H	H	CH_3CO	92	236–237	Acetone	$C_{18}H_{14}NO_3S$	66.13	**66.34**	4.22	4.12	4.21	4.29
2	H	H	H	$ClCH_2CO$	91.4	251–252	Ethanol	$C_{15}H_{12}ClNO_3S$	60.39	**60.50**	3.38	3.43	3.96	4.03
3	H	H	H	C_6H_5CO	82.5	268–269	Acetone–ethanol	$C_{23}H_{15}NO_3S$	71.65	**71.60**	3.92	4.14	3.65	3.65
4	CH_3	H	H	CH_3CO	90.9	188.5–189	95% ethanol	$C_{19}H_{15}NO_3S$	67.62	**67.28**	4.48	4.58	4.17	4.03
5	H	CH_3	H	CH_3CO	99	265–266	Acetone	$C_{19}H_{15}NO_3S$	67.62	**67.50**	4.48	4.62	4.17	4.27
6	H	H	CH_3	CH_3CO	90	264–265	Acetone	$C_{19}H_{15}NO_3S$	67.62	**67.74**	4.48	4.63	4.17	4.12
										67.92		4.59		**4.43**
7	CH_3O	H	H	CH_3CO	75	197–198	Acetone–ligroin	$C_{19}H_{15}NO_4S$	64.56	64.27	4.22	4.25	3.98	3.73

TABLE V

12-DIALKYLAMINOALKYLBENZO[a]PHENOTHIAZINES (II)

No.	Benzo[a]-phenothiazine, mole	Dialkylaminoalkyl chloride, mole	Sodium amide, mole	R_1	R_2	R_3	R_4	B.p., °C.	B.p., Mm.	Yield, %	Molecular formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	0.078	0.110	0.100[c]	H	H	H	$-(CH_2)_2N(CH_3)_2$	196–198	0.7	72	$C_{20}H_{20}N_2S$	75.09	6.21	8.73	74.79	6.11	8.55
2	.094	.120	.110[d]	H	H	H	$-(CH_2)_2N(C_2H_5)_2$[a]	230–232	1.6	50	$C_{22}H_{24}N_2S$	75.81	6.96	8.04	75.90	6.90	8.10
															75.45	6.78	8.15
3	.034	.037	.035[d]	H	H	H	$-(CH_2)_3N(CH_3)_2$[b]	205–207	0.2	69.3	$C_{21}H_{22}N_2S$	75.11	6.63	8.37	74.95	6.45	8.0
															74.83	6.53	8.35
4	.076	.090	.085[d]	CH_3	H	H	$-(CH_2)_2N(C_2H_5)_2$	227–228	1.5	83.6	$C_{23}H_{26}N_2S$	76.16	7.22	7.76	76.30	7.20	7.34
5	.051	.052	.060[d]	H	CH_3	H	$-(CH_2)_2N(C_2H_5)_2$	212–215	0.1	33.3	$C_{23}H_{26}N_2S$	76.16	7.22	7.76	76.09	7.17	7.43
6	.076	.090	.085[c]	H	H	CH_3	$-(CH_2)_2N(C_2H_5)_2$	230–232	0.4	41	$C_{23}H_{26}N_2S$	76.16	7.22	7.76	76.11	6.83	7.35
7	.066	.074	.072[c]	CH_3O	H	H	$-(CH_2)_2N(C_2H_5)_2$	242–243	0.1	53.5	$C_{23}H_{26}NOS$	72.95	6.92	7.43	72.69	6.83	7.18
															72.85	6.86	7.04
8	.100	.120	.110[d]	H	Cl	H	$-(CH_2)_2N(C_2H_5)_2$	234–236	0.4	46.4	$C_{22}H_{23}ClNS$	68.96	6.05	7.35	68.84	5.89	7.50
															69.11	6.19	7.13
9	.124	.156	.139[c]	H	Cl	H	$-(CH_2)_3N(CH_3)_2$	258–260	2	62.4	$C_{21}H_{21}ClN_2S$	68.33	5.73	7.63	68.12	5.86	7.2
															68.21	5.65	7.42

[a] On storing solidified, after crystallization from ligroin (30–60°) product melted at 54-54.5°. [b] On storing solidified, after crystallization from ligroin (60–90°) product melted at 84.5–85°. [c] Toluene solvent used. [d] Xylene solvent used.

TABLE VI

DERIVATIVES OF 12-DIALKYLAMINOALKYLBENZO[a]PHENOTHIAZINES

Compound used (Table III)	Derivative	Solvent for crystn.	M.p., °C.	Molecular formula	Nitrogen, % Calcd.	Found
1	Picrate	95% ethanol	179.5–180	$C_{26}H_{23}N_5O_7S$	12.76	12.75, 12.85
2	Hydrochloride	Ethanol–ether	168–170	.....	...	.....
3	Methiodide	Acetone–ethyl acetate	182–183	$C_{22}H_{25}N_2SI$	5.90	6.02, 6.23
4	Picrate	95% ethanol	151.5–152.5	$C_{29}H_{26}N_5O_7S$	11.89	11.6, 11.6
5	Picrate	95% ethanol	177–178	$C_{29}H_{26}O_5O_7S$	11.89	11.55, 11.75
7	Picrate	95% ethanol	183.5–184	$C_{29}H_{26}N_5O_8S$[a]	11.57	11.2, 11.4
8	Picrate	95% ethanol	185	$C_{28}H_{26}ClN_5O_7S$	11.56	11.8
9	Picrate	95% ethanol	179–180	$C_{27}H_{24}ClN_5O_7S$	11.76	11.4, 11.6

[a] *Anal.* Calcd. for $C_{29}H_{26}N_5O_8S$: C, 57.23; H, 4.81. Found: C, 57.03, 57.38; H, 4.67, 4.91.

Since certain 10-(α-aminoacyl)-phenothiazines are reported[14] to possess marked local anesthetic activity, 12-diethylaminoacetyl-, 12-piperidinoacetyl- and 12-morpholinoacetylbenzo[a]phenothiazine were prepared for evaluation.

We plan to continue a study of potential chemotherapeutic agents in the benzophenothiazine series.

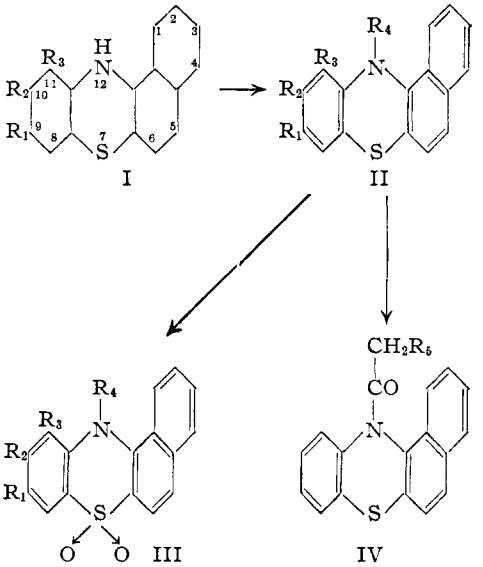
The compounds reported in this paper have been submitted to the Eli Lilly Co. for pharmacological evaluation. Significant results of the screening tests will be reported elsewhere.

Acknowledgment.—The authors wish to express appreciation to the Eli Lilly Co. for the pharmacological testing and to the National Institute of Mental Health for a research grant (M-1239) which is supporting this research program.

Experimental

Boiling points and melting points are uncorrected. Melting points were determined on a Kofler micro hot-stage apparatus. Micro analyses are by Weiler and Strauss, Oxford, England.

12H-Benzo[a]phenothiazine (I, $R_1 = R_2 = R_3 = H$) was prepared essentially by the method of Kehrmann and Dardel[7] with some modifications. Thus 33 g. (0.15 mole) of N-phenyl-α-naphthylamine, 9.6 g. (0.30 g. atom) of sulfur and 1.0 g. of iodine were heated at 180–185° for 20–25



minutes. The warm mass was dissolved in the minimum quantity of acetone. The solution was diluted with sufficient ligroin (b.p. 60–90°) to form a dark layer and this was separated from the clear yellow layer. The dark acetone–ligroin mixture was evaporated and the residue was treated again as described above. The process was repeated twice more and the final tarry residue extracted with boiling ligroin. The ligroin solutions were combined and concentrated to a small volume at room temperature and left in the cold room for crystallization. The yellow product melted at 135–137°, literature[7] m.p. 130.5°. The yield was 30 g. (80%). The product was sufficiently pure for subsequent reactions.

Chromatography of 5 g. of this material in benzene solution on a 2 × 50 cm. column of Florisil adsorbent followed by elution with benzene gave 4.5 g. of bright yellow product, m.p. 136–137°.

Table I gives data on substituted benzo[a]phenothiazine derivatives prepared in similar manner.

12-Acyl- or Aroylbenzo[a]phenothiazines (II).—Acetyl derivatives of the various benzo[a]phenothiazines were prepared either (A) by refluxing the appropriate phenothiazine with excess of acetic anhydride and a few drops of pyridine or (B) by gently warming a mixture of the phenothiazine and acetyl chloride in benzene solution in the presence of anhydrous sodium carbonate.

The chloroacetyl derivatives were prepared (C) by refluxing a mixture of the benzo[a]phenothiazine with chloroacetyl chloride in benzene solution.

The benzoyl derivatives were prepared (D) by refluxing a mixture of the benzo[a]phenothiazine with excess of benzoyl chloride.

The data are summarized in Table III.

12-Acyl- and Aroylbenzo[a]phenothiazine-7-dioxides (III).—The acyl or aroyl derivatives (Table III) were oxidized in glacial acetic acid with excess 30% hydrogen peroxide. After a brief period of warming, the mixture was refluxed for 1 hour and cooled, at which point the sulfone separated. In some cases it was necessary to dilute the reaction mixture with water for complete separation of the sulfone. Most of the sulfones were white, crystalline solids and sparingly soluble in most common organic solvents. The data are summarized in Table IV.

12H-Benzo[a]phenothiazine-7-dioxide (III, $R_1 = R_2 = R_3 = R_4 = H$).—A suspension of 1.0 g. (0.0031 mole) of 12-acetylbenzo[a]phenothiazine-7-dioxide (no. 1, Table IV) in 30 ml. of hot ethanol was treated with 1 ml. of 10% sodium hydroxide solution. The mixture immediately turned yellow and the majority of the suspended solid went into solution with immediate precipitation of yellow solid. After a reflux period of 30 minutes, the mixture was cooled and the yellow solid was collected and washed with ethanol. The yield of the product, m.p. 237°, was 0.85 g. (98%). Two additional crystallizations from acetone gave light yellow solid, m.p. 239.5°.

Anal. Calcd. for $C_{16}H_{11}NO_2S$: C, 68.29; H, 3.94; N, 5.00. Found: C, 68.44; H, 4.06; N, 4.78.

12-Diethylaminoacetylbenzo[a]phenothiazine Hydrochloride, (IV, $R_5 = N(C_2H_5)_2$).—A solution of 5 g. (0.013 mole) of 12-chloroacetylbenzo[a]phenothiazine (no. 2, Table III) in 80 ml. of dry benzene was treated with 6 ml. of diethylamine and the mixture was refluxed on a steam-bath for 4 hours. The mixture was cooled in an ice-bath, filtered and the white residue was washed with more benzene. The filtrate and washings were combined and extracted with four 50-ml. portions of 5% hydrochloric acid. The aqueous solution was neutralized with sodium carbonate solution, and the liberated oil was extracted with ether, dried over sodium sulfate and the ether evaporated. Attempted crystallization of the base was unsuccessful and the

(14) R. Dahlbom and T. Ekstrand, *Acta Chem. Scand.*, **5**, 120 (1951).

base was converted into its hydrochloride, m.p. 227–228° dec. The yield was 5.85 g. (96%). Further crystallization from ethanol–isopropyl alcohol mixture raised the m.p. to 230–231° dec.

Anal. Calcd. for $C_{22}H_{23}ClN_2OS$: C, 66.20; H, 5.81; N, 7.05. Found: C, 66.36; H, 5.81; N, 6.93.

Table III lists two additional derivatives prepared in similar manner.

N-Alkylation of Benzo[a]phenothiazines. General Procedure.—The reactants were used in the following ratio: benzo[a]phenothiazine, 1.0 mole; sodium amide, 1.05 to 1.1 mole; dialkylaminoalkyl chloride, 1.1 to 1.4 mole.

Sodium amide, freshly prepared from an equivalent quantity of sodium and liquid ammonia in the presence of a catalytic amount of ferric nitrate, was suspended in dry toluene or xylene. The appropriate benzophenothiazine was added which caused the development of a deep red to purple color. The mixture was refluxed with stirring for 30 to 60 minutes and the dialkylaminoalkyl chloride, dissolved in an equal volume of toluene or xylene, was added dropwise during 60 to 90 minutes. After completion of addition, refluxing was continued for 3 to 5 hours. The mixture was cooled, decomposed with 5% aqueous acetic acid or 2% aqueous hydrochloric acid. The organic layer was separated and extracted twice more with dilute acid. The combined acid solution was washed once or twice with ether and then neutralized with sodium hydroxide solution. The liberated base was extracted with ether, washed with saline water, dried over sodium sulfate, the solvent evaporated and the residual oil was distilled under vacuum. The products were highly viscous oils, light yellow to orange-yellow in color with a greenish fluorescence.

The relevant data are summarized in Table V and the corresponding derivatives in Table VI.

KNOXVILLE, TENNESSEE

[CONTRIBUTION FROM THE ROHM AND HAAS CO.]

The Reaction of 5-Ethoxymethylenerhodanines with Amines

BY CHIEN-PEN LO

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A number of 5-aminomethylenerhodanines have been prepared by the reaction of 5-ethoxymethylenerhodanines with primary and secondary amines. Certain crystalline amine salts of rhodanine, 2,4-thiazolidinedione and their 5-substituted derivatives are also reported.

In a previous publication,[1] the synthesis of 5-alkoxymethylenerhodanines from rhodanines and alkyl orthoformates and their reaction with rhodanines were reported. At about the same time, Knott[2] published independently his work on the preparation of 5-1′-alkoxyalkylidenerhodanines by a similar method.[3] In his article the reaction of 3-allyl- and 3-carbethoxymethyl-5-1′-alkoxyalkylidenerhodanines with ammonia, primary and secondary amines also were described. The present paper reports our work on the reaction of amines with 5-ethoxymethylenerhodanines and the 3-substituted 5-ethoxymethylenerhodanines other than the two reported by Knott.

3-Substituted 5-ethoxymethylenerhodanines reacted with primary and/or secondary amines to give the corresponding 5-aminomethylenerhodanines as reported by Knott. The reaction of 5-ethoxymethylenerhodanine with amines was found to be dependent upon the nature of the latter. Most amines, primary or secondary, gave the amine salts of the corresponding 5-aminomethylenerhodanines, some of which were isolated as crystalline solids (Table I). These amine salts yielded the free 5-aminomethylenerhodanines when treated with acid. Aniline and diallylamine gave the corresponding 5-aminomethylenerhodanines directly. Dicyclohexylamine yielded the dicyclohexylamine salt of 5-ethoxymethylenerhodanine at room temperature, but at higher temperature the corresponding salt of 5-dicyclohexylaminomethylenerhodanine was formed. The details of these reactions are given in the Experimental part and the data on the 5-aminomethylenerhodanines thus prepared are given in Table II.

In connection with this and related work, we have found that rhodanine, 2,4-thiazolidinedione and their 5-alkylidene derivatives formed crystalline salts (Table III) with certain amines.[4] The amine salts of 2,4-thiazolidinediones appeared to be more stable than those of rhodanines which showed signs of decomposition on storage. As a rule, the amine salts of rhodanines melted with decomposition, whereas those of 2,4-thiazolidinediones melted without decomposition.

Experimental[5]

5-Ethoxymethylenerhodanines.—The 5-ethoxymethylenerhodanines were prepared by the reaction of rhodanines with ethyl orthoformate in acetic anhydride as reported previously.[1] The 5-ethoxymethylene-3-ethylrhodanine was similarly obtained in a 67% yield, m.p. 92–92.5°.

Anal. Calcd. for $C_8H_{11}NO_2S_2$: N, 6.5; S, 29.5. Found: N, 6.1; S, 29.6.

5-Anilinomethylenerhodanine (Method A).—Aniline (20 g.) was added to a solution of 5-ethoxymethylenerhodanine (20 g.) in acetone (100 ml.). The resulting solution was diluted with water (100 ml.). The yellow solid which separated was collected, washed with aqueous acetone (1:1) and air-dried. The product which decomposed at 215–217° weighed 17 g. After recrystallization from acetic acid, the 5-anilinomethylenerhodanine decomposed at 225–226°.

Since Dains and Davis[6] had prepared 5-anilinomethylenerhodanine by the reaction of diphenylformamidine with rhodanine and reported its m.p. as 248°, this compound was made according to the procedure of Dains and Davis. The crude product (m.p. 215° dec., 74% yield) after one recrys-

(1) C. P. Lo and W. J. Croxall, THIS JOURNAL, **76**, 4166 (1954).

(2) E. B. Knott, *J. Chem. Soc.*, 1482 (1954).

(3) It is interesting to note that among the six 5-alkoxymethylenerhodanines reported by us and the four by Knott prepared independently by the same method, only one compound, namely, 5-ethoxymethylene-3-phenylrhodanine, is described in both places. There is a good agreement in the m.p. and yield of this compound from the two sources.

(4) 3-Substituted 5-alkylidene- and 5-aminomethylenerhodanines did not react with amines under the experimental conditions, indicating that the amines do not add to the double bond conjugated to the carbonyl group under these conditions.

(5) All melting points are uncorrected.

(6) F. B. Dains and S. I. Davis, *Kansas Univ. Sci. Bull.*, **15**, 265 (1924).