it is interesting to note that this difference in activation energies is roughly 13 to 16 kcal. per mole. This range of values agrees with the 15 kcal. per mole (approximately) calculated for the resonance energy of the tetrazole ring from heats of combustion data.[19]

From a consideration of the change of the equilibrium constants with temperature, one concludes that the thermodynamically more stable 5-arylaminotetrazole should predominate at low temperatures. This is further supported by the heats of combustion data for isomeric pairs of aryl substituted aminotetrazoles.[19] Experimentally, the rapid cyclization of an alkylguanyl azide in aqueous system results in the formation of the thermodynamically stable 1-alkyl-5-aminotetrazole. The rapid cyclization of an aryl-substituted guanyl azide in aqueous system, however, yields the less stable 1-aryl-5-aminotetrazole as the major product.[1,12] This phenomenon is similar to that encountered in examples of Diels–Alder reaction, where the unstable *endo* adduct predominates under rate controlled conditions and the thermodynamically more stable *exo* adduct predominates under equilibrium conditions.[21]

Acknowledgments.—The authors wish to express their thanks to LeMoyne Plischke for his assistance in the kinetic measurements and to Robert Boschan for valuable suggestions relative to this work.

CHINA LAKE, CALIF.

(21) R. B. Woodward and H. Baer, THIS JOURNAL, **166**, 645 (1944).

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

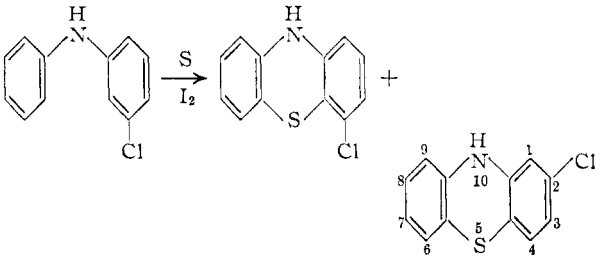
3-Chloro-10-dialkylaminoalkylphenothiazines

BY HARRY L. YALE

RECEIVED NOVEMBER 11, 1954

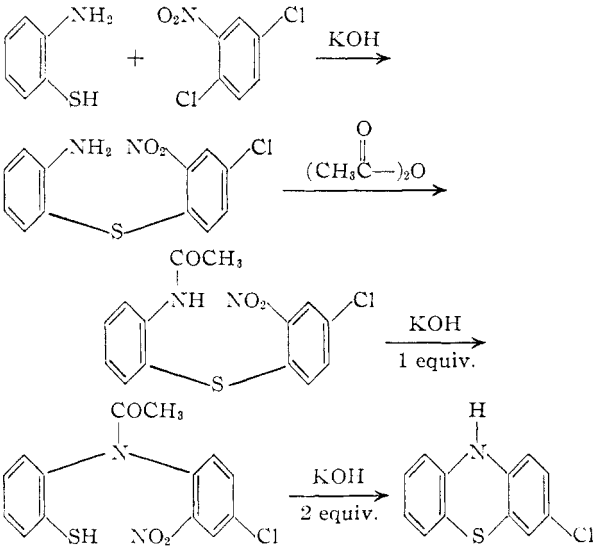
A number of 3-chloro-10-dialkylaminoalkylphenothiazines were prepared by condensing 3-chlorophenothiazine with a variety of dialkylaminoalkyl chlorides in refluxing toluene using sodamide as the condensing agent. These products are oils which can be distilled in high vacuum and form crystalline salts. The preparation of 3-chlorophenothiazine-5-oxide and 3-chlorophenothiazine-5,5-dioxide also is described; the latter compound was condensed with 2-chloro-N,N-dimethylpropylamine to give 3-chloro-10-(2-dimethylamino-1-methylethyl)-phenothiazine-5,5-dioxide.

In recent publications, Charpentier and his associates[1] and Viaud[2] have reported a series of 10-alkylaminoalkyl derivatives of 2- and 4-chlorophenothiazines. The isomeric chlorophenothiazines were obtained as a mixture by the cyclization with sulfur of 3-chlorodiphenylamine and subsequently separated by fractional crystallization.



We have for several years been interested in this class of compounds and wish to report a series of 3-chloro-10-dialkylaminoalkylphenothiazines. One of the compounds described in this paper, 3-chloro-10-(3-dimethylaminopropyl)-phenothiazine was mentioned by Viaud,[2] but no details of the synthesis or the physical properties of the base or its salts were reported.

The classic achievement of Evans and Smiles[3] in affording through the Smiles rearrangement a convenient synthesis of 3-chlorophenothiazine made available to us this nucleus free of any other isomer.



The condensations of 3-chlorophenothiazine with a variety of dialkylaminoalkyl chlorides were carried out in refluxing toluene using sodamide as the condensing agent. The 3-chloro-10-dialkylaminoalkylphenothiazines were obtained as oils which could be distilled in high vacuum without decomposition; they formed crystalline hydrochlorides and acid oxalates.

3-Chlorophenothiazine, by the usual procedures, gave 3-chlorophenothiazine-5-oxide and 3-chlorophenothiazine-5,5-dioxide. The latter compound was condensed with 2-chloro-N,N-dimethylpro-

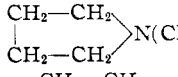
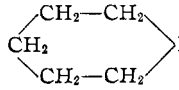
(1) P. Charpentier, P. Gaillot, R. Jacob, J. Gaudechon and J. Buisson, *Compt. rend.*, **235**, 59 (1952); U. S. Patent 2,645,640 (July 14, 1953).

(2) P. Viaud, *J. Pharm. Pharmacol.*, **6**, 361 (1954).

(3) W. J. Evans and S. Smiles, *J. Chem. Soc.*, **181**, 1263 (1935). The limitations of this synthetic method were implied indirectly by these authors; more recently R. Baltzly, M. Harfenist and F. J. Webb, THIS JOURNAL, **68**, 2673 (1946), have reported two unsuccessful attempts to utilize this rearrangement in the synthesis of related phenothiazines.

TABLE I

3-CHLORO-10-DIALKYLAMINOALKYLPHENOTHIAZINES AND THEIR DERIVATIVES

Side chain	Mol. formula	Base: Yield, %	Boiling point °C.	Mm.	Nitrogen, % Calcd.	Found	Chlorine, % Calcd.	Found
$(CH_3)_2N(CH_2)_2$	$C_{16}H_{17}ClN_2S$	57	192–195	0.50	9.19	8.75	11.63	11.89
$(n\text{-}C_3H_7)_2N(CH_2)_2$	$C_{20}H_{25}ClN_2S$	64	195–198	.50	7.76	7.80	9.82	10.13
$(CH_3)_2N(CH_2)_3$	$C_{17}H_{19}ClN_2S$	56	193–195	.30	8.79	8.74	11.10	11.13
$(CH_3)_2NCH(CH_3)CH_2$[h]	$C_{17}H_{19}ClN_2S$	65	178–180	.25	8.79	8.45	11.10	10.70
	$C_{19}H_{21}ClN_2S$	82	202–205	.30	8.12	8.01	10.28	10.63
	$C_{20}H_{23}ClN_2S$	54	235–238	.10	7.81	7.93	9.88	10.33

Mol. formula	Salts: Yield, %	M.p., °C.	Nitrogen, % Calcd.	Found	Chlorine, % Calcd.	Found
$C_{16}H_{17}ClN_2S\cdot C_2H_2O_4$[a]	47	184–185	7.10	7.00	8.98	9.07
$C_{16}H_{17}ClN_2S\cdot HCl$[b]	58	185–187	8.21	8.52	20.77	20.33
$C_{20}H_{25}ClN_2S\cdot C_2H_2O_4$[a]	70	144–146	6.21	6.08	7.86	8.20
$C_{20}H_{25}ClN_2S\cdot HCl$[c]	65	85–87	7.05	7.29	17.85	17.44
$C_{17}H_{19}ClN_2S\cdot C_2H_2O_4$[a]	70	158–160	6.85	6.90	8.67	8.82
$C_{17}H_{19}ClN_2S\cdot HCl$[d]	48	178–179	7.89	7.97	19.96	20.18
$C_{17}H_{19}ClN_2S\cdot C_2H_2O_4$[a]	73	170–172	6.85	7.10	8.67	8.66
$C_{17}H_{19}ClN_2S\cdot HCl$[e]	60	144–146	7.89	7.79	19.96	20.37
$C_{19}H_{21}ClN_2S\cdot C_2H_2O_4$[a]	62	195–196[g]	6.44	6.66	8.15	8.49
$C_{20}H_{23}ClN_2S\cdot C_2H_2O_4$[a]	47	173–175	7.90	7.63	6.24	6.43
$C_{20}H_{23}ClN_2S\cdot HCl$[f]	60	155–157	7.09	7.13	17.94	18.19

[a] Recrystallized from acetonitrile. [b] Recrystallized from chlorobenzene. [c] Recrystallized from benzene–hexane. [d] Recrystallized from methyl ethyl ketone. [e] Recrystallized from methyl ethyl ketone–hexane. [f] Recrystallized from ethyl acetate. [g] With decomposition. [h] One of an unresolved mixture of two isomeric side chains; the other isomer would have the side chain $(CH_3)_2NCH_2CH(CH_3)$.

pylamine as described above; the crude base,[4] since it could not be distilled or crystallized, was converted directly to the oxalate. It was of interest that, in this instance, only the neutral oxalate was isolated.

Acknowledgment.—The author is indebted to Mr. W. A. Lott for his advice and coöperation during this investigation. The microanalyses were carried out by Mr. Joseph F. Alicino and his associates.

Experimental Part

All temperatures are uncorrected.

3-Chlorophenothiazine.—Since large amounts of this compound were required, certain modifications of the original procedure of Evans and Smiles[3] were necessary. The following is a typical preparation. To a solution of 576 g. (3.0 moles) of 2,5-dichloronitrobenzene and 375 g. (3.0 moles) of 2-aminobenzenethiol in 10 l. of 2-propanol was added dropwise, with stirring, a solution of 198 g. (3.0 moles) of 85% potassium hydroxide in 400 ml. of 95% ethanol. Subsequently, the mixture was stirred and refluxed for three hours, and then concentrated to dryness. The residual solid was stirred with 1 l. of water, filtered and air-dried. The yield of crude **2-aminophenyl 4-chloro-2-nitrophenyl sulfide**, suitable for the next step, was 531 g. (97%). The crude *sulfide*, 3 l. of acetic anhydride, 150 ml. of pyridine and 20 g. of Darco were heated for two hours on the steam-bath and filtered hot. The filtrate was concentrated to about 500 ml. and cooled. The solid which separated was filtered and air-dried to give 528 g. (84% yield) of crude **2-acetamidophenyl 4-chloro-2-nitrophenyl sulfide.** To 12 l. of acetone was added a solution of 88 g. (1.32 moles) of 85% potassium hydroxide in 700 ml. of 95% ethanol. The mixture was stirred and diffused with nitrogen for about 15 minutes, 214 g. (0.66 mole) of the crude **acetamido derivative** was added and the mixture distilled from the steam-bath as rapidly as possible under nitrogen. The residue was stirred with 1 l. of water, the solid was filtered and dried to give 130 g. (84% yield) of crude 3-chlorophenothiazine. One recrystallization from xylene gave 100 g. of pure product, m.p. 199–200°. Evans and Smiles[3] report a m.p. of 199°.

The 3-chloro-10-dialkylaminoalkylphenothiazines and their derivatives were all prepared as described in the following example. Physical properties, yields, solvents of recrystallization and analyses will be found in Table I.

3-Chloro-10-(3-dimethylaminopropyl)-phenothiazine.—A mixture of 80 g. (0.35 mole) of 3-chlorophenothiazine, 15 g. (0.4 mole) of sodamide and 2 l. of dry toluene was stirred and refluxed for six hours. A slow stream of dry nitrogen gas was used to sweep out the ammonia as formed. The mixture was cooled and 360 ml. of a 1 *M* solution of 3-dimethylaminopropyl chloride in toluene was added dropwise, with stirring. Subsequently, the mixture was stirred and refluxed for six hours, cooled, and concentrated *in vacuo*. The viscous residue was refluxed with 500 ml. of chloroform and filtered hot. The chloroform filtrate was treated with Darco and again filtered. The filtrate was concentrated and the residue distilled to give 61 g. (56% yield) of product, pale yellow oil, b.p. 193–195° (0.3 mm.).

3-Chloro-10-(3-dimethylaminopropyl)-phenothiazine Hydrochloride.—A solution of 43.5 g. (0.14 mole) of the above *base* in 300 ml. of dry ether was cooled in ice and treated, dropwise, with 25.5 ml. of 5.3 *N* ethereal HCl. A gum separated which soon became granular. This solid was filtered and recrystallized from methyl ethyl ketone to give 23.3 g. (48% yield) of product, m.p. 178–179°.

3-Chloro-10-(3-dimethylaminopropyl)-phenothiazine Acid Oxalate.—A solution of the base (18 g., 0.056 mole) in 180 ml. of warm acetonitrile was treated all at once with a solution of 5.1 g. (0.056 mole) of anhydrous oxalic acid in 50 ml. of acetonitrile. An exothermic reaction occurred as the solutions mixed and almost immediately crystals of the acid oxalate separated. The solid was filtered and recrystallized from acetonitrile to give 16.0 g. (70% yield) of product, m.p. 170–172°.

3-Chlorophenothiazine-5-oxide.—A mixture of 10 g. (0.043 mole) of 3-chlorophenothiazine, 30 ml. of acetic

(4) This product consists presumably of a mixture of two isomers: 3-chloro-10-(2-dimethylaminopropyl)-phenothiazine-5,5-dioxide and 3-chloro-10-(2-dimethylamino-1-methylethyl)-phenothiazine-5,5-dioxide. No attempt was made to separate the mixture.

anhydride and 25 ml. of acetyl chloride was refluxed gently for four hours, and then concentrated *in vacuo*. **The 10-acetyl-3-chlorophenothiazine** was obtained as a non-crystalline gum. **The crude acetyl derivative**, 50 ml. of acetic acid and 10 g. of 30% hydrogen peroxide were refluxed for four hours, and then concentrated *in vacuo*. The residual gum, **10-acetyl-3-chlorophenothiazine-5-oxide**, was again non-crystalline. When this derivative, 25 ml. of 95% ethanol and 5 ml. of concentrated hydrochloric acid were refluxed for one hour, cooled and the solid filtered, there was obtained 8 g. (74% yield) of crude product, m.p. 270–273° dec.; pure 3-chlorophenothiazine-5-oxide, m.p. 280–281° dec., was obtained by recrystallization from aqueous dimethylformamide.

Anal. Calcd. for $C_{12}H_8ClNOS$: N, 5.61; Cl, 14.20. Found: N, 5.62; Cl, 14.26.

3-Chlorophenothiazine-5,5-dioxide.—Crude 10-acetyl-3-chlorophenothiazine, obtained as above from 24 g. of 3-chlorophenothiazine, was refluxed for four hours with 50 ml. of glacial acetic acid and 40 g. of 30% hydrogen peroxide. When the mixture was cooled, an oil separated which soon solidified. The solid was filtered and dried; it weighed 28 g. It consisted of a mixture of acetylated and deacetylated products. For identification a small portion of the crude material was extracted with boiling 95% ethanol and filtered hot; on cooling, the filtrate deposited crystals of 10-acetyl-3-chlorophenothiazine-5,5-dioxide, m.p. 167–168°.

Anal. Calcd. for $C_{14}H_{10}ClNO_3S$: C, 54.70; H, 3.61; N, 4.56. Found: C, 54.83; H, 3.50; N, 4.82.

The crude mixture was then hydrolyzed by refluxing for one hour with 24 ml. of concentrated hydrochloric acid and 500 ml. of 95% ethanol. The mixture was cooled, the solid filtered and recrystallized from aqueous dimethylformamide to give 22 g. (80% yield) of 3-chlorophenothiazine-5,5-dioxane, m.p. 295–297°.

Anal. Calcd. for $C_{12}H_8ClNO_2S$: C, 54.25; H, 3.04; N, 5.27. Found: C, 54.23; H, 3.23; N, 5.53.

3-Chloro-10-(2-dimethylamino-1-methylethyl)-phenothiazine-5,5-dioxide Oxalate.—A condensation was carried out as described above between 22 g. (0.066 mole) of 3-chlorophenothiazine-5,5-dioxide, 2.8 g. (0.07 mole) of sodamide in 500 ml. of dry toluene and 80 ml. of 1 *M* solution of 2-chloro-N,N-dimethylpropylamine in toluene. The crude *base*, 30.5 g., was dissolved in 300 ml. of warm acetonitrile and treated with 7 g. of anhydrous oxalic acid in 70 ml. of warm acetonitrile. A gum separated from the cooled mixture. The acetonitrile was decanted, the gum was dissolved in 150 ml. of boiling water, the solution was decolorized with Darco, and filtered. The cooled filtrate deposited a solid which was filtered and recrystallized from acetonitrile to give 3.5 g. (10% yield), of product, m.p. 96–97° dec.

Anal. Calcd. for $(C_{17}H_{19}ClN_2O_2S)_2 \cdot C_2H_2O_4$: Cl, 8.96; N, 7.08. Found: Cl, 8.99; N, 7.09.

3-(1-Pyrrolidyl)-propyl Chloride.—No reference could be found to the preparation of this intermediate. To 250 g. (1.0 mole) of trimethylene chlorobromide in 250 ml. of dry ether was added, with stirring and ice cooling, 142 g. (2.0 moles) of pyrrolidine; an oil separated. The mixture stood overnight, the oil was separated and discarded; the ether layer was diluted with 250 ml. of ether, cooled in ice and extracted with three 250-ml. portions of ice-cold 10% hydrochloric acid. The hydrochloric acid extracts were cooled and made alkaline with 40% potassium hydroxide solution. The oil which separated was extracted with four 200-ml. portions of ether, the ether extracts were dried over anhydrous potassium carbonate, filtered, concentrated and distilled to give 97 g. (66% yield) of product, b.p. 103° (45 mm.).

Anal. Calcd. for $C_7H_{14}ClN$: N, 9.49; Cl, 24.01. Found: N, 9.29; Cl, 23.99.

NEW BRUNSWICK, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

The Benzidine Rearrangement. VI. The Rearrangement of 3,3′,5,5′-Tetrafluorohydrazobenzene in 2:1 Sulfuric Acid[1]

BY ROBERT B. CARLIN AND S. ALLEN HEININGER[2]

RECEIVED SEPTEMBER 30, 1954

When treated with 2:1 sulfuric acid at 85–90°, 3,3′,5,5′-tetrafluorohydrazobenzene (I) yields the rearrangement products 2,2′,6,6′-tetrafluorobenzidine (II), 2,2′,4,6′-tetrafluorodiphenyline (III) and 2,2′-diamino-4,4′,6,6′-tetrafluorobiphenyl (IV), plus the disproportionation products 3,5-difluoroaniline (V) and 3,3′,5,5′-tetrafluoroazobenzene (VI). The relative amounts in which these products were formed are much less closely comparable with those in which analogous products were formed from 3,3′,5,5′-tetrachloro-, -tetrabromo- and -tetramethylhydrazobenzenes than they are with the relative amounts in which corresponding products were formed from the rearrangement of unsubstituted hydrazobenzene under identical conditions. Since covalent fluorine is more like hydrogen than like chlorine in steric character, and more like chlorine than like hydrogen in its polar nature, the results of this investigation suggest that steric factors exert the major influence over product ratios when 3,3′,5,5′-tetrasubstituted-hydrazobenzenes are rearranged, although other influences are also operative.

A comparison of the rearrangements of three 3,3′,5,5′-tetrasubstituted-hydrazobenzenes in 2:1 sulfuric acid at 85–90° disclosed the fact that steric size of the substituent is a major but not the only factor which influences the ratio in which the three isomeric rearrangement products (benzidine, diphenyline and 2,2′-diaminobiphenyl) are formed.[3] In order to gather additional information on the effects of 3,3′,5,5′-tetrasubstitution on the ease of rearrangement, product ratios, extent of occurrence of the accompanying disproportionation ($2ArNHNHAr \rightarrow 2ArNH_2 + ArN{=}NAr$), and extent of formation of semidines, if any, the reactions of 3,3′,5,5′-tetrafluorohydrazobenzene in 2:1 sulfuric acid have been studied and are reported in this article. The effects of the substituent fluorine were deemed likely to be especially significant in the effort to distinguish polar and steric effects of substituents; for in polar character fluorine more closely resembles the other halogens than it does hydrogen, whereas in steric size fluorine (van der Waals radius 1.35 Å.[4,5]) more closely approaches hydrogen (1.2 Å.[4]) than it does the smallest of the other halogens (chlorine, 1.80 Å.[4]). Therefore, should the steric size of fluorine be the dominant factor governing the comparative behavior of 3,3′,5,5′-tetrafluorohy-

(1) From the D.Sc. Thesis by S. Allen Heininger.

(2) Plaskon Fellow, 1951–1952.

(3) R. B. Carlin and W. O. Forshey, Jr., THIS JOURNAL, **72**, 793 (1950).

(4) W. A. Waters, "Physical Aspects of Organic Chemistry," Fourth Ed., D. Van Nostrand Co., Inc., New York, N. Y., 1950, p. 58.

(5) H. P. Lemaire and R. L. Livingston, *J. Chem. Phys.*, **18**, 569 (1950).