Acidification of Dipotassio Salt VI to Form Dihydrobenzalacetophenone (VII).—To a stirred solution of 0.1 mole of dipotassiobenzalacetophenone (VI) was added cautiously in small portions 12 g. of solid ammonium chloride (black color discharged), and the liquid ammonia was replaced with ether (steam-bath). The resulting ether suspension was cooled, and 100 ml. of water was added with stirring. The ether layer was separated, dried over Drierite, and the solvent evaporated on the steam-bath. The residual yellow oil was dissolved in 25 ml. of hot ethanol, and the solution was cooled in an ice-bath to precipitate 20.4 g. (98%) of slightly yellow ketone VII, m.p. 70–72°. One recrystallization from 95% ethanol raised the melting point to the reported[11] value 72–73°.

Monobenzylation of Dipotassium Salt VI to Form β,γ-Diphenylbutyrophenone (VIII).—To a stirred solution of 0.1 mole of dipotassiobenzalacetophenone (VI) in 250 ml. of anhydrous liquid ammonia was added a solution of 12.66 g. (0.1 mole) of benzyl chloride in 100 ml. of dry ether. The black solution turned red when all the halide had been added. After five minutes the liquid ammonia was replaced with 200 ml. of ether (steam-bath). The resulting suspension in ether was cooled, and 100 ml. of water was added with caution. After stirring to dissolve the suspended solid, the ether layer was separated and dried over Drierite. The solution was concentrated on the steam-bath, and the resulting white solid was taken up in hot 95% ethanol. The hot solution was filtered with suction (Büchner funnel) and cooled to deposit 22 g. (73%) of ketone VIII, m.p. 111–112°. Recrystallization from 95% ethanol gave a white powder, m.p. 112–113°.

Anal. Calcd. for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C, 88.51; H, 6.72.

This compound was independently synthesized from 0.1 mole each of benzalacetophenone and benzylmagnesium chloride in ether. The mixture was stirred and refluxed for one hour, then cooled and neutralized with aqueous ammonium chloride to give a 95% yield of crude ketone VIII. After two recrystallizations from 95% ethanol, the ketone melted at 112–113°. This product showed no melting point depression on admixture with a sample of the product prepared as described above. Both samples gave a positive test for the carbonyl function with 2,4-dinitrophenylhydrazine reagent.

Dibenzylation of Dipotassio Salt VI to Form α-Benzyl-β,γ-diphenylbutyrophenone (IX).—To a stirred solution of 0.1 mole of dipotassiobenzalacetophenone (VI) was added a solution of 25.32 g. (0.2 mole) of benzyl chloride in 100 ml. of ether. The red color observed in the monobenzylation (see above) was noticed when approximately half of the halide was added. This became light yellow when the remainder of the halide was added and the mixture was stirred for about 20 minutes. Solid ammonium chloride was then added, and the ammonia removed on the steam-bath. After adding ether, the suspension was cooled and 100 ml. of water added. The solid that failed to dissolve was collected on a funnel, and recrystallized from a 1:1 mixture of 95% ethanol and ethyl acetate to give 30 g. (76%) of ketone IX (white cubic crystals), m.p. 162–163°.

Anal. Calcd. for $C_{29}H_{26}O$: C, 89.35; H, 6.40. Found: C, 89.37; H, 6.26.

Benzylation of Ketone VIII to Form Ketone IX.—To a solution of 0.0334 mole of potassium amide in 250 ml. of liquid ammonia was added a solution of 10 g. of β,γ-diphenylbutyrophenone (VIII) in 100 ml. of ether. The resulting green solution deposited a tan colored precipitate within 10 minutes. To the stirred suspension was added 4.22 g. (0.0334 mole) of benzyl chloride in 50 ml. of ether. A red color was produced which soon faded to yellow. After stirring for one hour, the liquid ammonia was replaced with ether, and the product isolated essentially, as described in the preceding experiment. There was obtained 9.7 g. (75%) of the ketone IX, m.p. 162–163°. This product was shown to be identical with the product obtained in the preceding experiment by mixed melting point and by comparison of their infrared spectra.

Dibenzylation of Dipotassio Salt VI in Ether.—Dipotassio salt VI (0.1 mole) was prepared in liquid ammonia as described above, and the ammonia then replaced with ether. The resulting suspension was cooled, and the mixture treated with a solution of 25.33 g. of benzyl chloride (0.2 mole) in 100 ml. of dry ether. After refluxing for one hour, the reaction mixture was treated with cold aqueous ammonium chloride solution (5 g. in 100 ml. of water). There was obtained 11.9 g. (30%) of ketone IX, m.p. and mixed m.p. 161–162°. Also, an oil was isolated from the ether layer which solidified on cooling in a Dry-Ice acetone-bath but melted on warming to room temperatures. This product appeared to be the second diastereoisomer of ketone IX, but this was not established.

Addition Reaction of Dipotassiobenzalacetophenone (VI) with Benzophenone to Form Hydroxy-ketone V.—To a stirred liquid ammonia solution of 0.1 mole of dipotassiobenzalacetophenone was added 18.2 g. (0.1 mole) of benzophenone in 100 ml. of dry ether. A precipitate formed immediately. After stirring 15 minutes a solution of 12 g. of ammonium chloride in 200 ml. of liquid ammonia was added with stirring. The liquid ammonia was then replaced with ether (steam-bath), and the resulting suspension was shaken with water. The remaining solid was collected on a funnel and dissolved in excess benzene. The solvent was distilled until the condensate was no longer cloudy (water was assumed to be removed), and the clear solution was then cooled to deposit 18.3 g. (47%) of the hydroxy-ketone V, m.p. 222–223°. This melting point was not depressed on admixture with a sample prepared as described above from benzalacetophenone and disodiobenzophenone. The infrared spectra of the two samples were identical.

DURHAM, N. C.

(11) See ref. 10, Vol. I, p. 139.

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

Synthesis of 7-(Dialkylaminoalkyl)-benzo[c]phenothiazines

BY DAVID A. SHIRLEY AND W. EARL TATUM

RECEIVED JUNE 11, 1958

The preparation of a series of 7-(dialkylaminoalkyl)-benzo[c]phenothiazines is described. Of particular interest is the synthesis of 7-(3-dimethylaminopropyl)-9-chlorobenzo[c]phenothiazine, which is closely related to chlorpromazine (III).

The pharmacological importance of 10-dialkylaminoalkyl derivatives of phenothiazine is well established. Since 1946, when Halpern[1] introduced 10-(2-dimethylaminoethyl)-phenothiazine-HCl (I) and 10-(2-dimethylamino-1-propyl) phenothiazine-HCl or Phenergan (II) as potent antihistamines, the list of useful phenothiazine derivatives has been growing.[2] Phenergan, in addition to its antihistaminic activity, has twice the local anesthetic activity of cocaine.[1] Chloropromazine or 10-(3-dimethylaminopropyl)-2-chlorophenothiazine-HCl (III) has been found effective in suppressing nausea[3] and in the treatment of neuropsychiatric disorders.[4] The tranquilizing activity of Vesprin or 10-(3-dimethylaminopropyl)-2-trifluoromethyl-

(1) B. N. Halpern, *Compt. rend. soc. biol.*, **140**, 361 (1946).
(2) S. P. Massie, *Chem. Revs.*, **54**, 822 (1954).
(3) D. G. Friend and J. F. Cummins, *J. Am. Med. Assoc.*, **153**, 480 (1953).
(4) J. H. Moyer, *et al.*, *Arch. Internal Med.*, **95**, 202 (1955).

TABLE I

7H BENZO[c]PHENOTHIAZINES

R in structure VII				Molecular formula	Yield, %	M.p., °C.	Carbon, %		Hydrogen, %		Nitrogen, %	
R_1	R_2	R_3	R_4				Calcd.	Found	Calcd.	Found	Calcd.	Found
H	H	CH_3	H	$C_{17}H_{13}NS$	60	192[a]	77.55	77.20, 77.26	4.98	4.81, 5.11	5.32	5.08, 5.12
H	H	OCH_3	H	$C_{17}H_{13}NOS$	52	167	73.09	73.01, 72.30	4.69	4.72, 4.86	5.01	5.01, 4.69
H	Cl	H	H	$C_{16}H_{10}ClNS$	56	163[b]	67.72	68.15, 68.53	3.55	3.75, 3.93	4.94	4.95, 5.02
CH_3	H	H	CH_3	$C_{18}H_{13}NS$	75	180[c]	77 94	77.85, 77.99	5.45	5.51, 5.22	5 05	4.74, 4.86

[a] Previously reported[11] by F. Ackermann, m.p. 182°. [b] Previously reported[9] by Knoevenagel, m.p. 163°. [c] Previously reported[10] by Buu Hoï, m.p. 170°.

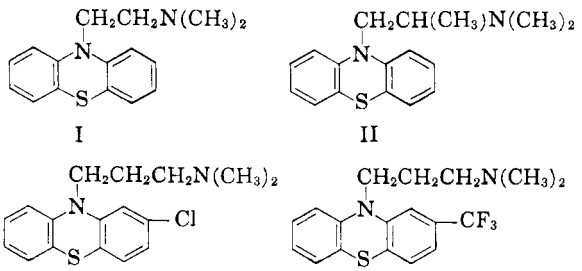
TABLE II

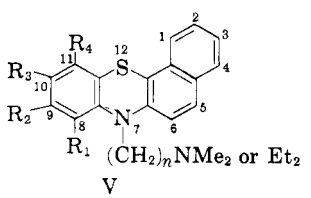
7-(DIALKYLAMINOALKYL)-BENZO[c]PHENOTHIAZINES

7-(Dialkylamino-alkyl group	R in structure VIII				Yield, %	B.p., °C.	Mm.	Molecular formula	Carbon, %		Hydrogen, %		Nitrogen, %	
	R_1	R_2	R_3	R_4					Calcd.	Found	Calcd.	Found	Calcd.	Found
$-(CH_2)_2N(CH_3)_2$[a]	H	H	H	H	43	212–214	0.2	$C_{20}H_{20}N_2S$	74.96	75.09	8.74	8.80	6.29	6.10
$-(CH_2)_2N(C_2H_5)_2$[b]	H	H	H	H	60	210–212	.08	$C_{22}H_{24}N_2S$	75.82	75.88	6.94	6.56	8.04	7.85
										75.49		6.46		7.61
$-(CH_2)_3N(CH_3)_2$[b]	H	H	H	H	40	219–221	.2	$C_{21}H_{22}N_2S$	75.41	75.53	8.38	8.30	6.63	6.61
$-(CH_2)_3N(CH_3)_2$[b]	H	H	CH_3	H	63	248–250	1.75	$C_{22}H_{24}N_2S$	75.82	75.65	6.94	6.93	8.04	8 08
										76.02		7.04		8.20
$-(CH_2)_3N(CH_3)_2$[b]	H	Cl	H	H	44	253–256	1.3	$C_{21}H_{21}ClN_2S$	68.37	68.27	5.74	5 53	7.59	7.32
										68.76		5.43		7.36
$-(CH_2)_3N(CH_3)_2$[b]	H	H	OCH_3	H	43	245–247	1.45	$C_{22}H_{24}N_2OS$	72.49	72.27	6.64	6.49	7.69	7.20
										72.72		6.51		7.42
$-(CH_2)_3N(CH_3)_2$[b]	CH_3	H	H	CH_3	55	236–238	1.25	$C_{23}H_{26}N_2S$	76.20	75 81	7.23	6.99	7 73	8.07
										75.70		6.84		8.24

[a] Toluene employed as solvent for reaction. [b] Xylene employed as solvent for reaction.

phenothiazine-HCl (IV) was recently reported.[5] In view of such a wide spectrum of pharmacological activity, closely related phenothiazine derivatives should be examined. This paper reports the synthesis of a series of 7-(dialkylaminoalkyl)-benzo[c]phenothiazines (V).

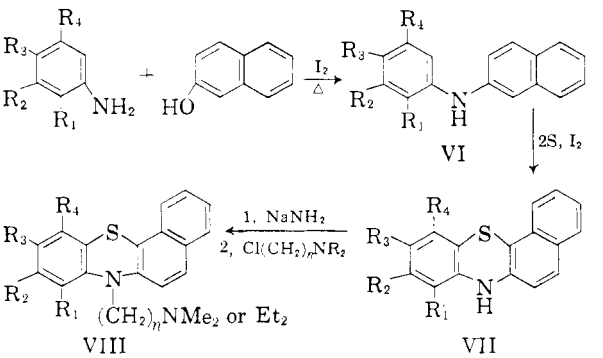




A recent paper[6] from this Laboratory describing the preparation of a series of 12-(dialkylaminoalkyl)-benzo[a]phenothiazines is apparently the first record in the literature of benzophenothiazines substituted by dialkylaminoalkyl groups.

Badger and co-workers[7] have demonstrated tumor growth inhibition with some simple benzophenothiazine types.

Syntheses of 7-(dialkylaminoalkyl-)benzo[c]phenothiazines were accomplished by the sequence of reactions



The 7H-benzo[c]phenothiazines (Table I) were prepared by thionation[8,9] of various N-phenyl-β-naphthylamines (VI), using iodine as catalyst. The structures of the substituted benzo[c]phenothiazines are indicated by the method of preparation in all cases except the 9-chloro derivative. Thionation of N-(*m*-chlorophenyl)-β-napthylamine could lead to either the 9- or the 11-chlorobenzo-[c]phenothiazine and Knoevenagel[9] does not assign a structure to the reaction product. It has been rather well established, however (see reference 6 for leading references), in similar cases that the thionation ring closure occurs predominately *para* to a chlorine atom, which would lead to 9-chlorobenzo[c]phenothiazine.

Reaction of 7H-benzo[c]phenothiazines with various dialkylaminoalkyl chlorides in xylene or

(5) H. L. Yale, F. Sowinski and J. Bernstein, THIS JOURNAL, **79**, 4375 (1957).

(6) P. B. Talukdar and D. A. Shirley, *ibid.*, **80**, 3462 (1958).

(7) G. M. Badger, *et al.*, *Proc. Roy. Soc.* (*London*), **B130**, 255 (1942).

(8) F. Kehrman and J. H. Dardel, *Ber.*, **55 II**, 2350 (1922).

(9) E. Knoevenagel, *J. prakt. chem.*, **89**, 1 (1914).

(10) Ng. Ph. Buu-Hoï, *J. Chem. Soc.*, 1146 (1950).

(11) F. Ackermann, German Patent 224,348 (July 9, 1909); *Chem. Zentr.*, **81, II**, 608 (1910).

TABLE III

DERIVATIVES OF 7-(DIALKYLAMINOALKYL)-BENZO[c]PHENOTHIAZINES

7-(Dialkylamino-alkyl group	—R in structure VIII— R_1	R_2	R_3	R_4	Derivative	M.p., °C.	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$-(CH_2)_2N(CH_3)_2$	H	H	H	H	Methiodide[b]	231–233	$C_{21}H_{29}IN_2S$	54.54	54.50	5.01	4.84	6.06	5.95
									54.49		5.23		5.70
$-(CH_2)_2N(CH_3)_2$	H	H	H	H	Picrate[c]	222–224	$C_{26}H_{28}N_8O_7S$					12.74	12.60
													12.95
$-(CH_2)_2N(C_2H_5)_2$	H	H	H	H	Picrate[c]	152.5–153.5	$C_{28}H_{27}N_8O_7S$					12.13	12.05
													12.20
$-(CH_2)_3N(CH_3)_2$	H	H	H	H	Methiodide[b]	238.5–240	$C_{22}H_{28}IN_2S$	55.46	55.31	5.29	5.66	5.88	5.61
$-(CH_2)_3N(CH_3)_2$	H	H	H	H	Picrate[c]	177–178	$C_{27}H_{26}N_8O_7S$					12.43	12.35
													12.60
$-(CH_2)_3N(CH_3)_2$	H	H	CH_3	H	Methiodide[b]	243–244	$C_{23}H_{27}IN_2S$	56.32	56.24	5.55	5.26	5.71	5.50
									56.21		5.56		5.60
$-(CH_2)_3N(CH_2)_2$	H	Cl	H	H	Methiodide[b]	217–218.5	$C_{22}H_{24}ClIN_2S$	51.72	51.87	4.74	4.81	5.48	5.46
									51.58		4.61		5.54
$-(CH_2)_3N(CH_3)_2$	CH_3	H	H	CH_3	Methiodide[a]	237–238.5	$C_{24}H_{29}IN_2S$	57.14	56.88	5.79	5.61	5.55	5.44
									57.03		5.65		5.72

[a] This compound when simply washed with ether gave the above m.p. and analysis. When recrystallized twice from 95% ethanol–ether the methiodide melted at 251–252.5° and gave the analysis: Calcd. for $C_{24}H_{29}IN_2S$: C, 57.14; H, 5.79; N, 5.55. Found: C, 57.78; H, 5.95; N, 5.19. [b] Recrystallization was from 95% ethanol–ether mixture. [c] Recrystallization was from 95% ethanol.

toluene in the presence of freshly-prepared sodamide gave the desired 7-(dialkylaminoalkyl)-benzo[c]phenothiazines (VIII) in yields of 40–63% (Table II). The N-alkylated benzophenothiazines are highly viscous yellow or yellow-orange oils with a green fluorescence. Picrate derivatives or quaternary salts with methyl iodide were prepared for further characterization and are listed in Table III.

The compounds prepared in this investigation are currently being tested by the Eli Lilly Co. of Indianapolis, Ind., for central nervous system effects and by the National Cancer Institute for anticancer activity. Significant results of these tests will be reported elsewhere.

Experimental

All melting and boiling point temperatures are uncorrected. Elemental microanalyses are by Drs. G. Weiler and F. B. Strauss, Oxford, England.

Preparation of N-Phenyl-β-naphthylamines (VI).—The secondary amines used as intermediates in this investigation were prepared using conventional condensation methods[9] with minor modifications. In general, a mixture of 1 mole of β-naphthol, 1.3 moles of the appropriately substituted aniline, and a catalytic amount of iodine was heated under reflux for 15–40 hours. The dark reaction mixture obtained was then fractionated *in vacuo* and the product recrystallized from an appropriate solvent.

Preparation of 7H-Benzo[c]phenothiazines (VII).—A mixture of the appropriate secondary amine (0.5 mole), sulfur (1.0 g. atom) and a small amount of iodine was heated at approximately 180° until the evolution of H_2S ceased (8 to 20 minutes). The dark sticky mass was recrystallized several times from benzene. In some instances chromatography of the dark reaction mixture in benzene solution on a 2 × 50 cm. column of Florisil adsorbent followed by elution with benzene aided in the purification. The 7H-benzo[c]-phenothiazines prepared in this manner are listed in Table I.

Preparation of 7-(Dialkylaminoalkyl)-benzo[c]phenothiazines (VIII).—A general procedure employed in preparation of these compounds will be described. Sodamide (0.55 mole) (freshly prepared from sodium and liquid ammonia using a trace of ferric nitrate as catalyst) was covered with about 50 ml. of dry xylene or toluene. To this solution was added the appropriate benzo[c]phenothiazine (0.5 mole) and the resulting wine or red-colored solution was refluxed for one hour. To this refluxing solution was added the dialkylaminoalkyl chloride (0.7 mole) in 25 ml. of xylene or toluene over a period of 45 minutes. After complete addition of the chloride, the mixture was refluxed for a further period of 1–4 hours, the reaction mixture cooled, the product extracted with 4% HCl or 10% HOAc, the acid extracts combined, basified with NaOH pellets, and the dark oil which separated was extracted several times with ether. The combined ethereal extracts were dried over anhydrous Na_2SO_4, the ether removed, and the product vacuum distilled using a short Vigreux column. The 7-(dialkylaminoalkyl)-benzo[c]phenothiazines prepared in this manner are listed in Table II.

Acknowledgment.—The financial assistance of the National Institute of Mental Health (Grant M-1239) is gratefully acknowledged. The authors also wish to thank the Eli Lilly Co. for pharmacological evaluation of the compounds prepared in this investigation.

KNOXVILLE, TENN.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Organoboron Compounds. IX. 8-Quinolineboronic Acid, its Preparation and Influence on Reactions of Chlorohydrins[1]

BY ROBERT L. LETSINGER AND S. H. DANDEGAONKER

RECEIVED JULY 9, 1958

8-Quinolineboronic acid and several of its derivatives are described An unusual effect of 8-quinolineboronic on the rate of liberation of chloride ion from chlorohydrins is reported.

Organoboronic acids with basic functional groups located in the vicinity of the boron atom would be of particular interest since they might serve as selective catalysts for certain base-catalyzed reactions. As part of a general program concerned with catalytic properties of organoboron compounds we have therefore undertaken a study of hetero-

(1) This work was supported by the National Science Foundation. For the previous paper in this series see R. L. Letsinger and S. B. Hamilton, THIS JOURNAL, **80**, 5411 (1958).