TABLE II

TESTS FOR AZIDE GROUP

Pyrimidine	Sample, wt.	Sodium ethoxide test Hydrazoic acid, meq. Found	Calcd.	Theory, %	Sample, wt.	Tetralin test Nitrogen, ml. Found	Calcd.	Theory, %
2,4-Diazido	1.00	12.8	12.4	103	1.00	245	276	88
2,4-Diazido-6-methyl	0.50	3.6	5.7	63	1.00	249[a]	254	98
2,4-Diazido-6-phenyl	0.50	3.5	4.2	82	0.44	78	83	94
2,4-Diazido-6-furyl	0.50	5.6	4.4	127[b]	0.35	70	69	101

[a] The first 150 ml. was collected in 10 minutes, the remainder in 6 hours, compared to a total of about 15 minutes for the other samples. The slow rate of decomposition may account for the low results in the sodium ethoxide test. [b] The furyl ring is opened by dilute acids and the resulting hydroxyl group oxidized to an acid under oxidizing conditions. Such formation of acid and its steam distillation would account for the high results.

was treated with dilute sulfuric acid followed by steam distillation of the hydrazoic acid formed; collection of the distillate was made in excess 0.1 *N* NaOH, which was then back titrated with 0.1 *N* HCl. The distillates were tested qualitatively with ferric chloride and in all cases were found to contain azide.

Decomposition of Diazides in Tetralin.—The samples were heated in tetralin (about 25 ml./g.) to 200°, and held there until no appreciable amount of gas was given off. In a blank run 5 ml. of gas was collected and this was subtracted from all results.

Attempts to Convert Diazides to Ditetrazoles (2,4-Diazidopyrimidine Was Used in All Experiments).—Diazide (0.8 g.) was refluxed in 30 ml. absolute alcohol overnight. On evaporation of the alcohol only the unchanged diazide was recovered.

Diazide (1.0 g.) was refluxed in 30 ml. of *t*-amyl alcohol for 8 hours; no gas was given off. On evaporation of the alcohol only the diazide was obtained.

Diazide (1.0 g.) was refluxed in *n*-butyl alcohol for 6 hours. On evaporation of the alcohol only the diazide was recovered.

About 0.1 g. of diazide and 2 g. of $NaHCO_3$ in 40 ml. of water refluxed for 3 hours. A very slight dark brown precipitate formed. The mixture was filtered and the filtrate evaporated to dryness. All efforts to isolate azide from this residue were unsuccessful. Similar results were obtained when pyridine was used.

All absorption spectra were determined using a Model DU Beckman spectrophotometer. The following list tabulates the concentrations used for each wave length region. The absorption spectra were determined in 95% ethanol.

Compound	Concn., moles/l.	Wave length, mμ
m-Diazidobenzene	2.2×10^{-5}	210–270
	1.8×10^{-4}	270–310
2,4-Diazidopyrimidine	8.3×10^{-5}	265–310
	4.1×10^{-5}	210–310
2,4-Diazido-6-methyl-pyrimidine	3.4×10^{-5}	215–290
	6.8×10^{-5}	215–225 and 255–300
2,4-Diazido-6-phenyl-pyrimidine	2.45×10^{-5}	215–325
	4.9×10^{-5}	270–330
2,4-Diazido-6-furylpyrimidine	2.4×10^{-5}	215–340

SOUTH NORWALK, CONNECTICUT

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF IRWIN, NEISLER & COMPANY]

Bis-ammonium Salts. Derivatives of Fluorene, Carbazole and Phenothiazine

BY CHESTER J. CAVALLITO, ALLAN P. GRAY AND ERNEST E. SPINNER

RECEIVED NOVEMBER 27, 1953

A series of bis-quaternary salts of the type, $R'-\overset{R}{\underset{R}{\overset{|\oplus}{N}}}-(CH_2)_x-\overset{R}{\underset{R}{\overset{|\oplus}{N}}}-R'\ 2Br^{\ominus}$, in which x = 6 or 10, R = methyl or ethyl and R′ is benzhydryl, 9-fluorenyl, 2-fluorenyl, 9-fluorenylethyl, 9-carbazylethyl, or 10-phenothiazinylethyl has been prepared. Quaternization of bis-(dialkylamino)-alkanes with benzhydryl bromide and 9-bromofluorene proceeded in excellent yield provided that solvolytic conditions were avoided. The compounds have been examined for neuromuscular blocking action, and several found to possess considerable activity. In particular, the bis-9-fluorene derivatives, IV and VI, in which x is 6, were unusually potent. The biological data are interpreted in terms of possible structure–activity relationships, and the enhancing effect of the large, planar, lipophilic 9-fluorenyl group on the neuromuscular blocking activity of bis salts is indicated.

During the past five years, a very large number of synthetic neuromuscular blocking agents have been reported and excellent reviews of the subject are available.[1–4] With very few exceptions, the most active compounds contain two quaternary nitrogen atoms situated at a maximum distance from one another of approximately 15 Å. Compounds with more than two quaternary groups appear to depend for high activity upon an optimum steric relationship between two of these groups.[5] With monoquaternaries, only in a series of quinone derivatives have compounds as active as the related bis quaternaries been reported.[6]

In the present report, a series of α,ω-bis-quaternary substituted alkanes is described in which the groups bound to each of the quaternary nitrogen atoms consist of two methyl or ethyl groups and one larger substituent of lipophilic character.

(1) L. E. Craig, *Chem. Revs.*, **42**, 285 (1948).

(2) F. F. Foldes, T. S. Machaj, R. D. Hunt, P. G. McNall and P. C. Carberry, *J. Am. Med. Assoc.*, **150**, 1559 (1952).

(3) D. Bovet and P. Viaud, *Anesthèse et Analgésie*, **8**, 1 (1951); D. Bovet, *Ann. N. Y. Acad. Sci.*, **54**, 407 (1951).

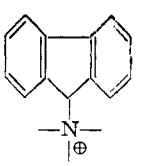
(4) W. F. Riker, *Am. J. Med.*, **15**, 231 (1953).

(5) E. W. Pelikan and K. R. Unna, *J. Pharmacol. Exptl. Therap.*, **104**, 354 (1952).

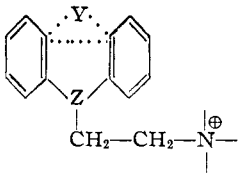
(6) C. J. Cavallito, A. E. Soria and J. O. Hoppe, THIS JOURNAL, **72**, 2661 (1950).

Variations in planarity, polarity and steric hindrance about the ammonium nitrogens are involved. A summary of the data obtained, including neuromuscular blocking activity,[7] is presented in Table I. Results of the dog experiments are a better criterion of activity. Some unique structure–activity relationships are evident among these compounds. In homologous series of bis-ammonium alkanes from simple "hexamethonium" and "decamethonium" types to those with larger terminal substituents, such as isoquinolines[8] or atropine,[9] the much greater curare-like activity of derivatives with a C_{10} as compared with the C_5 or C_6 chain (or equivalent distance between "onium" centers) has invariably been in evidence. The bis-9-fluorene derivatives, IV and VI, of the present series are not only unusually active C_6 homologs, but are actually more active in dogs than the corresponding C_{10} derivatives, V and VII. That the activity of the bis-9-fluorenyl salts is not the result of molecular size or lipophilic properties alone is evident upon comparison with the bis-benzhydryl C_6 derivative, III, which is only a tenth as active as IV. The flat 9-fluorenyl group, capable of strong van der Waals bonding, markedly increased activity. It is interesting that increasing the lipophilic character of the molecule without increased planarity (I *vs.* III) did not increase activity. Although much less active than the analogous 9-fluorene compounds, even with the benzyl derivatives the C_6 homolog I is more active in dogs than the C_{10} member, II. In light of the marked potency of the C_6 bis-9-fluorenyl derivative, IV, the relatively inert nature of the corresponding C_6-bis-2-fluorenyl derivative, VIII, is most unusual. Compounds IX through XIII are bis-9-fluorenylethyl, bis-9-carbazylethyl and bis-10-phenothiazinylethyl C_6 analogs. These are less active than IV or VI and the less planar and more polar phenothiazine derivatives are least active. The 9-fluorenyl monoquaternary, XIV, and the bis-tertiary-fluorenylamino derivative, XV, were relatively inactive. The C_6 derivatives showed no significant ganglionic blocking properties and had no effect on blood pressure; the C_{10} homologs V and VII produced a transient hypotensive reaction somewhat more prolonged than that given by *d*-tubocurarine.

It appears from the present series of bis-ammonium neuromuscular blocking agents that (1) the presence of planar structures can markedly increase activity and change optimal distance relationships between "onium" centers; (2) a high degree of specificity is associated with position of attachment of the planar structure; (3) the marked difference in activity between the 9- and 2-fluorene substituted derivatives might be related to differences in distribution of the electrostatic field about the "onium" group.



IV–VII, XIV, XV



IX, Z = CH, Y absent
X, XI, Z = N, Y absent
XII, XIII, Z = N, Y = S

The 9-fluorenyl and benzhydryl derivatives were prepared in excellent yield from their respective bromides and the appropriate α,ω-bis-(amino)-alkane. These salts were formed most satisfactorily in acetonitrile solution, either at room temperature or at reflux for periods of from three to five hours. More prolonged refluxing resulted in decomposition of the salt products and the use of alcoholic solvents in solvolysis of the labile diaryl-C–Br and $-C-N^{\oplus}R_3$ bonds. The effect of alcohol is pointed up by the observation that although an 87% yield of the benzhydryl derivative, III, was obtained when the reaction was carried out in acetonitrile, reaction in ethanol afforded 85% of the dihydrobromide of the starting material, 1,6-bis-(dimethylamino)-hexane.

The lability of these $C-N^{\oplus}R_3$ bonds was likewise encountered in attempts to prepare the bis-9-fluorenyl salts from 9-dimethylaminofluorene and α,ω-dibromoalkanes. Although 9-fluorenyltrimethylammonium bromide (XIV) is readily formed from 9-dimethylaminofluorene and methyl bromide, reaction of an excess of this base with the more sluggish dibromoalkanes under necessarily forcing conditions afforded poor yields of difficult-to-purify salt mixtures. Since an excess of the base was used, a base-catalyzed decomposition seems suggested.[10]

To obtain the bis salts, VIII–XIII, hexamethylene bromide was refluxed with an excess of the appropriate tertiary base in a polar solvent. These preparations were unexceptional, although the weak aniline-type base, 2-dimethylaminofluorene, underwent quaternization only in poor yield and under forcing conditions. The bases required for the synthesis of IX–XIII were conveniently prepared by the sodamide alkylation of fluorene, carbazole and phenothiazine with the suitable dialkylaminoethyl chloride. A point of interest with respect to these alkylations is the marked accelerating effect of the alkyl halide on the rate of evolution of ammonia, and, therefore, on the rate of proton exchange between the compound to be alkylated and sodamide. Addition of the alkyl halide during, rather than after, the proton exchange reaction causes ammonia evolution to proceed much more rapidly and seems to drive the reaction to completion. This effect might conceivably be interpreted in terms of a "push–pull" termolecular mechanism.

Experimental[11]

Aminofluorenes.—2-Dimethylaminofluorene, m.p. 178–179°, was prepared from 2-aminofluorene[12] according to the

(7) Detailed pharmacology to be published by Dr. F. J. Macri.

(8) H. O. J. Collier, *Brit. J. Pharmacol.*, **7**, 392 (1952).

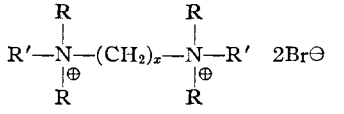
(9) K. K. Kimura and K. R. Unna, *J. Pharmacol. Exptl. Therap.*, **98**, 286 (1950).

(10) The effect of bases on 9-fluorenyl quaternary ammonium salts has been the subject of much study. See for example: W. R. Bamford, T. S. Stevens and J. W. Wright, *J. Chem. Soc.*, 4334 (1952); G. Wittig and G. Felletschin, *Ann.*, **555**, 133 (1944); L. A. Pinck and G. E. Hilbert, THIS JOURNAL, **68**, 2011 (1946).

(11) Microanalyses were performed by the Clark Microanalytical Laboratories, Urbana, Illinois. All melting points are corrected.

(12) Organic Syntheses, Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 447.

TABLE I



No.	R	R′	x	M.p., °C. cor.[a]	Mol. formula	Analyses, % Calcd. C	Calcd. H	Calcd. Br	Found C	Found H	Found Br[b]	Neuromuscular block, mg./kg. Mice, i.v. RD_{50}	Mice, i.v. LD_{50}	Dogs, i.v. N.M. block[m]
I	CH_3	$C_6H_5CH_2$–	6	[c]								2.9	3.4	2.5
II	CH_3	$C_6H_5CH_2$–	10	[c]								1.95	3.9	>5
III	CH_3	$(C_6H_5)_2CH$–	6	193–203	$C_{36}H_{46}Br_2N_2$	64.87	6.97	23.98	64.21	6.81	24.37	2	2.8	2
IV	CH_3	9-$C_{13}H_9$–[d]	6	188–189	$C_{26}H_{42}Br_2N_2$	65.26	6.39	24.12	64.99	6.59	23.82	1.26	1.76	0.21
V	CH_3	9-$C_{13}H_9$–[d]	10	155–156	$C_{40}H_{50}Br_2N_2 \cdot C_2H_5OH$[e]	65.96	7.38	20.90	66.08	7.56	21.05	0.95	1.27	0.5
									66.04	7.39	20.45			
VI	C_2H_5	9-$C_{13}H_9$–[d]	6	243–245	$C_{40}H_{50}Br_2N_2 \cdot 0.5H_2O$	66.03	7.06	22.24	66.05	6.96	21.96	0.72	1.16	0.21
						N, 3.84; H_2O, 1.23			N, 3.63; H_2O, 1.58[j]					
VII	C_2H_5	9-$C_{13}H_9$–[d]	10	171–172	$C_{44}H_{58}Br_2N_2 \cdot 0.5H_2O$[e]	67.42	7.59	20.39	66.98	7.56	20.31	0.70	0.75	0.66
									67.22	7.68	20.35			
							N, 3.58			N, 3.71				
VIII	CH_3	2-$C_{13}H_9$–[f]	6	218–223	$C_{36}H_{42}Br_2N_2$	65.26	6.39	N, 4.23	65.65	6.51	N, 4.05	...	...	None at 8
IX	CH_3	9-$C_{13}H_9CH_2CH_2$–[g]	6	Above 125	$C_{40}H_{50}Br_2N_2 \cdot 1.5H_2O$	64.42	7.18	21.43	64.18	7.04	21.72	0.5	0.7	1
						N, 3.75; H_2O, 3.62			N, 4.31; H_2O, 4.30[j]					
X	CH_3	9-$C_{12}H_8NCH_2CH_2$–[h]	6	172–175	$C_{38}H_{48}Br_2N_4$	63.32	6.73	22.18	62.92	6.83	22.20	3	5	1.4
XI	C_2H_5	9-$C_{12}H_8NCH_2CH_2$–[h]	6	193–195	$C_{42}H_{56}Br_2N_4 \cdot H_2O$[e]	63.47	7.36	20.11	63.53	7.16	20.31	...	...	2.5
									63.53	7.67	19.69			
XII	CH_3	10-$C_{12}H_8SNCH_2CH_2$–[i]	6	Shrinks 190 Melts 229[k]	$C_{38}H_{48}Br_2N_4S_2$	58.16	6.18	20.37	58.33	5.99	21.12	6.5	7.5	None at 4
XIII	C_2H_5	10-$C_{12}H_8SNCH_2CH_2$–[i]	6	158–160[l]	$C_{42}H_{56}Br_2N_4S_2$	59.99	6.71	19.01	60.16	6.73	19.09	10	11	None at 4

[a] Many of the salts melted with decomposition. [b] Bromine analyses reported are for ionic bromine, excepting in the case of VII, which was analyzed for both ionic and total bromine. [c] See D. R. Smith and C. J. Cavallito, THIS JOURNAL, **75**, 3303 (1953). [d] 9-Fluorenyl [e] The compound was prepared several times and repeatedly recrystallized with no change in melting point. Analytical results were consistent and indicated the presence of solvent of crystallization. Representative analytical data are given in the table. [f] 2-Fluorenyl. [g] 9-Fluorenylethyl. [h] 9-Carbazylethyl. [i] 10-Phenothiazinylethyl. [j] Water was determined by the Karl Fischer method. [k] This compound, m.p. 185–186°, has been reported by P. Charpentier, French Patent, 942,366 (1949) (*C. A.*, **45**, 3427*g* (1951)). [l] This compound, without details of preparation or properties, has been referred to by D. Bovet and P. Viaud, Proc. XI, Internl. Congr. Pure and Appl. Chem. pp. 29–40 (1947). [m] Comparable results from: *d*-tubocurarine chloride, 0.24; decamethonium iodide, 0.2; hexamethonium iodide, 40 ±.

published procedure.[13] 9-Bromofluorene, m.p. 100–102° (Wittig and Felletschin, ref. 10), afforded 9-dimethylaminofluorene, m.p. 48–50°,[14] on treatment with dimethylamine.

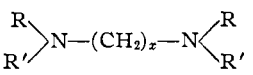
With methyl bromide this yielded **9-fluorenyltrimethylammonium bromide** (XIV), m.p. 185–187°.[14]

Anal. Calcd. for $C_{16}H_{18}BrN$: Br, 26.27. Found: Br (ionic), 26.72.

α,ω-Bis-(amino)-alkanes.—The diamines were prepared in fair yield essentially as described for 1,6-bis-(dimethylamino)-hexane.

A mixture of 67.5 g. (1.5 moles) of dimethylamine and 61 g. (0.25 mole) of 1,6-dibromohexane in 150 ml. of 50% ethanol was heated in a pressure bottle at about 70° for 16 hours. The resultant clear solution was acidified with concentrated hydrochloric acid and evaporated almost to dryness under vacuum. The solid residue was treated with 20% sodium hydroxide and the product extracted into ether. After drying and removal of the ether, the residual oil was distilled to yield 27.7 g. (65%) of the diamine. Properties of the α,ω-bis-(amino)-alkanes are listed in Table II.

TABLE II



R	R′	x	B.p. °C.	Mm.	Basic N, % Calcd.	Found
CH_3	CH_3	6	87–89	15[a]	...	...
CH_3	CH_3	10	106–108	0.5[b]	...	...
CH_3	H	6	75–80	10[a]	...	...
C_2H_5	C_2H_5	6	90–92	1	12.27	11.78
C_2H_5	C_2H_5	10	130–135	0.7	9.85	9.42

[a] *Cf.* S. v. Braun, *Ber.*, **43**, 2853 (1910). [b] *Cf.* S. v. Braun, *Ann.*, **386**, 280.

Reaction of Benzhydryl Bromide with 1,6-Bis-(dimethylamino)-hexane. A. In Ethanol.—A solution of 2.6 g. (0.015 mole) of 1,6-bis-(dimethylamino)-hexane and 11.1 g. (0.045 mole) of benzhydryl bromide in absolute ethanol was refluxed on the steam-bath for 4 hours. The precipitate which separated on cooling was recrystallized from alcohol and ether to yield 4.3 g. (85%) of 1,6-bis-(dimethylamino)-hexane dihydrobromide, m.p. 224–225°.

Anal. Calcd. for $C_{10}H_{26}Br_2N_2$: Br, 47.82. Found: Br (ionic), 47.33.

B. In Acetonitrile.—Hexamethylenebis-(benzhydryldimethylammonium) dibromide (III) was obtained in 87% yield when the reactants were allowed to stand for two days at room temperature in acetonitrile solution.

1,6-Bis-(9-fluorenylmethylamino)-hexane Dihydrobromide (XV).—To a solution of 5.17 g. (0.022 mole) of 9-bromofluorene in 50 ml. of acetonitrile was added 1.44 g. (0.01 mole) of 1,6-bis-(methylamino)-hexane. After the initial reaction had subsided, the reaction mixture was refluxed for 2 hours, cooled and the collected precipitate twice recrystallized from aqueous ethanol. There was obtained 0.96 g. of XV, m.p. 245–247°, with preliminary darkening.

Anal. Calcd. for $C_{34}H_{38}Br_2N_2$: C, 64.36; H, 6.04; Br, 25.19. Found: C, 64.16; H, 6.24; Br, 24.75.

Hexamethylenebis-(2-fluorenyldimethylammonium) Dibromide (VIII).—A mixture of 4.18 g. (0.02 mole) of 2-dimethylaminofluorene and 1.22 g. (0.005 mole) of 1,6-dibromohexane was heated at 115° (bath temperature) for 24 hours, 10 ml. of dry dioxane added and the mixture refluxed (oil-bath) for an additional 37 hours. The solid was filtered off, washed with hot solvent and twice recrystallized from *n*-propyl alcohol to yield 0.45 g. of analytically satisfactory product.

Hexamethylenebis-(9-fluorenylethyldimethylammonium) Dibromide (IX).—An acetonitrile solution of 5.0 g. (0.021 mole) of 9-(dimethylaminoethyl)-fluorene and 1.7 g. (0.007 mole) of 1,6-dibromohexane was refluxed for 24 hours. The solid that had formed was collected and the mother liquor diluted with ether to yield additional precipitate. Recrystallization of the combined precipitates from alcohol and ether yielded 4.2 g. (84%) of analytically pure IX.

TABLE III

$R—CH_2CH_2—NR'_2$

R	R′	Salt	Physical properties	Analyses, % Calcd.	Found
9-$C_{13}H_9$[a]	CH_3	...	B.p. 126–129° (1.5 mm.) $n^{24}D$ 1.5987	N, 5.90	N,[b] 6.52
9-$C_{12}H_8N$[c]	CH_3	...	B.p. 142–144° (0.7 mm.) M.p. 34–35°	N, 5.87(basic)	N,[b] 5.67
9-$C_{12}H_8N$[c]	C_2H_5	...	B.p. 196° (3 mm.)[d] $n^{24}D$ 1.6097		
9-$C_{12}H_8N$[c]	C_2H_5	HCl	M.p. 115–116°	Cl, 11.71	Cl,[e] 11.23
9-$C_{12}H_8N$[c]	C_2H_5	CH_3I	M.p. 195–196°	I, 31.08	I,[e] 31.33
10-$C_{12}H_8SN$[f]	CH_3	...	B.p. 171–175° (1.7 mm.)[g] M.p. 42–44.5°	N, 5.18(basic)	N,[b] 5.52
10-$C_{12}H_8SN$[f]	C_2H_5	...	B.p. 178–180° (0.7 mm.)[g,h]		
10-$C_{12}H_8SN$[f]	C_2H_5	HCl	M.p. 184.5–186.5°[g]	Cl, 10.59	Cl,[e] 10.60

[a] 9-Fluorenyl. [b] Basic nitrogen determination. [c] 9-Carbazyl. [d] *Cf.* ref. 15. [e] Ionic halogen determination. [f] 10-Phenothiazinyl. [g] *Cf.* S. Nishijo and A. Nishimura, Japanese Patent 1134 (1950), *C. A.*, 47, 2217e (1953). [h] *Cf.* H. Gilman and D. A. Shirley, THIS JOURNAL, 66, 888 (1944).

Dialkylaminoalkyl Derivatives.—Alkylation with sodamide, essentially according to the methods described by Eisleb,[15] was satisfactory for the preparation of the dialkylaminoalkyl derivatives of fluorene, carbazole and phenothiazine. In general, alkylation with dimethylaminoethyl chloride went in poorer yield than with the diethyl analog, owing to the greater propensity of the former chloro base for self-condensation. Properties of the compounds and a few of their salts are given in Table III.

Hexamethylenebis-(9-fluorenyldimethylammonium) Dibromide (IV).—To a solution of 13.2 g. (0.054 mole) of 9-bromofluorene in 200 ml. of acetonitrile was added 3.1 g. (0.018 mole) of 1,6-bis-(dimethylamino)-hexane. Heat was evolved and solid began to precipitate immediately. After the initial reaction had subsided, the mixture was refluxed for 3.5 hours on the steam-bath. The solid was collected and recrystallized three times from *n*-propyl alcohol to give 10.7 g. (89% yield) of analytically pure product.

Biological Tests.—Preliminary tests for curare-like activity were carried out with mice and dogs. Mice were tested by the inclined screen technique[6] but the drug was given by the intravenous rather than subcutaneous route as it was observed that some of these compounds were poorly absorbed when given subcutaneously to mice.[7] Anesthetized dogs were administered compound intravenously and the dose which blocked contraction of the gastrocnemius muscle after electrical stimulation of the sectioned tibial nerve was determined.[7] Activity was of a curare-like or competitive (polarizing) rather than "decamethonium" type.[16]

(13) F. Bell and D. B. Mulholland, *J. Chem. Soc.*, 2020 (1949).

(14) C. K. Ingold and J. A. Jessop, *ibid.*, 2357 (1929).

(15) O. Eisleb, *Ber.*, **74**, 1433 (1941).

(16) Successive replacement of methyl by larger groups on the nitrogens appears to change a depolarizing mechanism into a polarizing one, although recent studies may indicate that these differences are more apparent than real (see E. Zaimis, *Nature*, **170**, 617 (1952); M. I. Gluckman, *Arch. Int. Pharmacodyn.*, **94**, 320 (1953).

Acknowledgment.—The authors wish to express their appreciation to Mrs. Dorothy Schlieper for help with the synthetic work and to Mr. Donald L. Miller of these laboratories for carrying out the ionic halogen, basic nitrogen and water determinations.

DECATUR, ILL.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Reaction of α-Cyanobenzyl Benzenesulfonate with Thioureas[1a,b]

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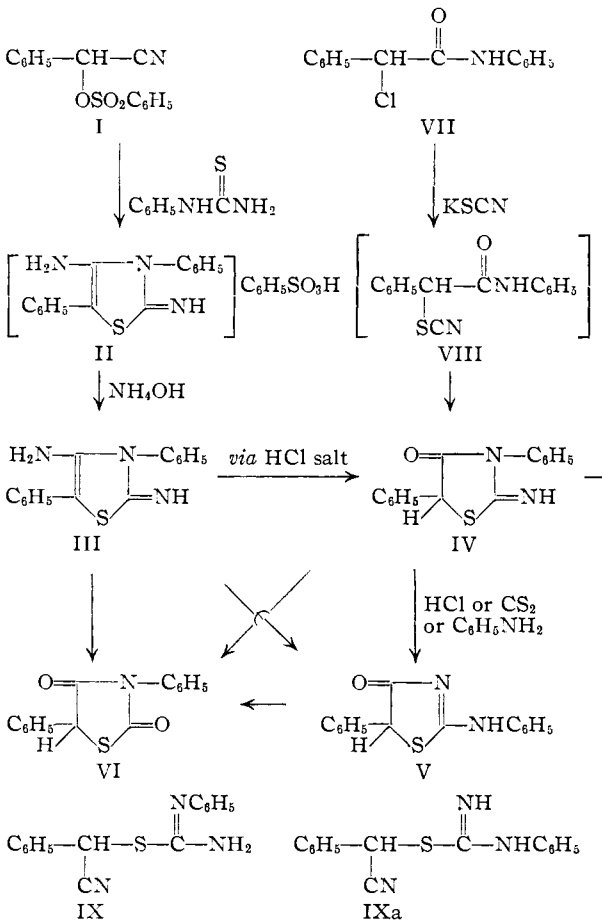
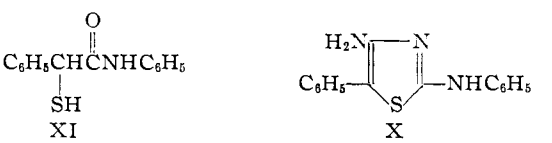
The condensation of α-cyanobenzyl benzenesulfonate (I) with phenylthiourea gave 2(3)-imino-3,5-diphenyl-4-aminothiazoline benzenesulfonate (II). Prolonged heating of the free base III with dilute acid gave 3,5-diphenyl-2,4-thiazolidinedione (VI), while short heating with dilute acid gave 2-anilino-5-phenyl-4(5)-thiazolone (V). Stirring the hydrochloride of III with water gave 2-imino-3,5-diphenyl-4-thiazolidone (IV), the structure of which was established by independent synthesis from α-chloro-α-phenylacetanilide and potassium thiocyanate and by alkaline hydrolysis to α-mercapto-α-phenylacetanilide. IV rearranged to V on heating with acid, carbon disulfide or aniline; V is known to rearrange to VI under hydrolytic conditions. Thus, the observed conversion of III to VI involves hydrolysis with concomitant twofold rearrangement. Similar results were obtained in the condensation of I with alkylthioureas. The significance of the observed rearrangement of IV to V in the interpretation of some reactions of related thiazoles is discussed.

The condensation of benzaldehyde, potassium cyanide and benzenesulfonyl chloride to give α-cyanobenzyl benzenesulfonate (I) and the reaction of this latter compound with thiourea to give 2,4-diamino-5-phenylthiazole has been described recently.[2] As a result of an expanding program on the chemistry of heterocyclic amides and amidines, we became interested in the reactions of 4-aminothiazoles and as a consequence have been led to an investigation of extensions of the above condensation reaction. The reactions of α-cyanobenzyl benzenesulfonate (I) with some aryl and alkylthioureas and some explorations of the chemistry of the products provide the subject for this paper.





α-Cyanobenzyl benzenesulfonate (I) condensed smoothly in acetone solution with phenylthiourea to give the benzenesulfonic acid salt of 2(3)-imino-3,5-diphenyl-4-aminothiazoline (II). The structure of II (and of the derived free base III) was established as follows. The most likely alternative structures for the condensation product were IX (or IXa) and X (both as the benzenesulfonic acid salts). The open-chain isomer IX (or IXa) was eliminated on the basis of the absence of a cyano band at 2140–2160 cm.$^{-1}$ in the infrared spectrum of the product (Fig. 1A). A decision between II and X was made as follows: When the condensation product of I and phenylthiourea was dissolved in water and the solution made faintly alkaline with ammonium hydroxide, the free base (III or X) separated. The infrared spectrum of a freshly prepared sample (Fig. 1B) was similar to that of the benzenesulfonate from which it was prepared, indicating, *vide infra*, that no rearrangement had taken place during neutralization. The free base so prepared rapidly turned pink on exposure to air and was destroyed by alkali, but it was converted by short heating with dilute acid to 2-anilino-5-phenyl-4(5)-thiazolone (V) and by prolonged heating with dilute acid to 3,5-diphenyl-2,4-thiazolidinedione (VI), both known compounds. However, when the free base (III or X) was dissolved in dry benzene

(1) (a) Taken in part from theses presented by Joseph Wolinsky and Hiok-Huang Lee to the University of Illinois in partial fulfillment of the degree of Bachelor of Science in Chemistry. (b) Presented before the Division of Organic Chemistry at the 124th National Meeting of the American Chemical Society, September, 1953, Chicago, Ill.

(2) R. M. Dodson and H. W. Turner, THIS JOURNAL, **73**, 4517 (1951).