crude product (22.4 g., 92%) melted at 160–176°. Recrystallization from methanol brought the m.p. to 178–181°.

4-Amino-2-chloro-5-(methylsulfamyl)-benzenesulfonamide (No. 13).—6-Chloro-3-keto-2-methyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide (9 g.) was dissolved in 90 cc. of 20% sodium hydroxide solution and refluxed overnight. The solution was filtered, cooled, and acidified with hydrochloric acid. The precipitate was filtered and washed with water to yield 7.8 g. (94%) of product, m.p. 168–170°.

4-Amino-2-chloro-5-(ethylsulfamyl)-benzenesulfonamide (No. 14) was obtained in a manner similar to that described above. The yield was 71%, m.p. 145–148°.

4-Amino-2-chloro-5-(isopropylsulfamyl)-benzenesulfonamide (no. 15) was obtained in a similar manner. The yield was 92%, m.p. 155–157°.

Preparation of 7-Sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxides.—All of these products are given in Table II. With the exception of a few compounds (*vide infra*) they were prepared by the condensation of aldehydes with the disulfonamides, usually in aqueous solution. Occasionally a non-aqueous solvent (acetone or dimethylformamide) gave better results. The yields were good (70–97%) in nearly all cases, but no attempt was made to find optimum conditions for all preparations. Several typical preparations are described in detail below.

Compound 17 was prepared by catalytic dehalogenation. Compound 37 was prepared by alkylation, as well as by cyclization. These experiments are described.

6-Chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide (No. 19).—A suspension of 287 g. of 4-amino-6-chloro-1,3-benzenedisulfonamide in five liters of water was brought to reflux. To this was added a solution of 95 cc. of formalin and 60 g. of ammonium chloride in 100 cc. of water. Refluxing was continued for 90 minutes. The reaction mixture was cooled and filtered. The yield was 283 g. (95%), m.p. 268–271° dec. Recrystallization from water brought the m.p. to 270–272° dec.

6-Chloro-3-ethyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide (No. 31).—A solution of 5.7 g. of 4-amino-6-chloro-1,3-benzenedisulfonamide and 5.8 g. of propionaldehyde in 75 cc. of acetone was refluxed for two hours. Removal of the acetone and treatment of the residue with chloroform precipitated 6.3 g. (96%) of crude product, m.p. 258–260° dec. Recrystallization from alcohol–water brought the m.p. to 266–267° dec.

6-Chloro-3-(chloromethyl)-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide (No. 34).—A solution of 7.9 g. of 45% aqueous chloroacetaldehyde and 1.2 g. of ammonium chloride in 10 cc. of water was added to 5.7 g. of 4-amino-6-chloro-1,3-benzenedisulfonamide in 25 cc. of dimethylformamide. The reaction mixture was heated for 30 minutes on the steam-bath, cooled, and poured into water. Filtration gave 6.0 g., (87%) m.p. 226–228° dec. The product was purified by dissolving in dimethylformamide and reprecipitating with water. The pure material decomposed at 235–236°.

6-Chloro-2-methyl-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide (No. 37). A. By Cyclization with Formalin.—A solution of 3.0 g. of 4-amino-2-chloro-5-(methylsulfamyl)-benzenesulfonamide in 70 cc. of boiling water was prepared in a round-bottom flask fitted with a reflux condenser. The solution was refluxed while 1.5 g. of formalin was added through the condenser. Refluxing was continued for 90 minutes. After standing overnight, the solution deposited 2.8 g. (90%) of product which was recrystallized from water. The analytical sample melted at 248° dec.

B. By Alkylation of 6-Chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide.—Sodium hydride (0.48 g.) was added, with stirring, to a solution of 5.96 g. of 6-chloro-7 sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide in 30 cc. of dimethylformamide. The mixture was stirred at 70° for 30 minutes, after which 2.84 g. of methyl iodide in 3 cc. of dimethylformamide was added dropwise. Stirring was continued for one hour at 70°.

The reaction mixture was poured into 800 cc. of water. The supernatant liquid was decanted from the gummy precipitate and allowed to stand overnight. The product (2.4 g., m.p. 237–240° dec.) crystallized from the aqueous solution. Recrystallization from water brought the m.p. to 242–243° dec. Although the higher m.p. obtained in the alternate method of preparation was not achieved here, a melting point of the mixture was not depressed. Identity was confirmed by infrared spectra and elemental analyses.

Anal. Calcd. for $C_9H_{10}ClN_3O_4S_2$: C, 30.8; H, 3.2; N, 13.5. Found: C, 31.2; H, 3.5; N, 13.5.

7-Sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-Dioxide (No. 17).—6-Chloro-7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide (6 g.) was dissolved in 100 cc. of water containing 3.2 g. of sodium hydroxide. The material was hydrogenated under two atmospheres of pressure with 1.2 g. of 5% palladium-on-carbon as a catalyst. When the uptake was complete (less than 1 hr.) the catalyst was removed by filtration. Acidification precipitated 4.2 g. (80%), m.p. 218° dec.

The material was found to cling tenaciously to water of crystallization. Recrystallization from water and prolonged drying under vacuum gave an analytical sample melting at 219–220° dec.

NORTH CHICAGO, ILL.

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

Synthesis of Potential Diuretic Agents. II. Dichloro Derivatives of 1,2,4-Benzothiadiazine 1,1-Dioxide[1]

BY JAMES H. SHORT AND URSULA BIERMACHER

RECEIVED JUNE 11, 1959

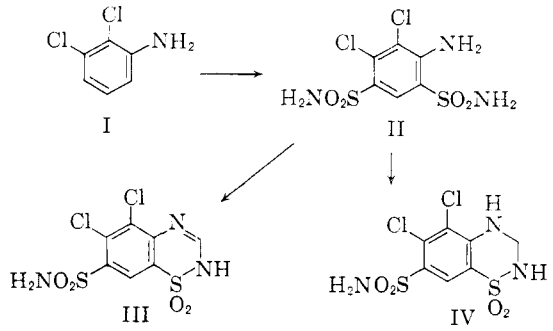
The following were allowed to react with chlorosulfonic acid, and the resulting sulfonyl chlorides converted to the corresponding sulfonamides: 2,3-dichloro-, 2,5-dichloro-, 3,4-dichloro- and 3,5-dichloroaniline. Except for 2,5-dichloroaniline, which did not sulfonate in the position *ortho* to the amino group, the sulfonamides were cyclized with formic acid, and also with formaldehyde, to obtain substituted 1,2,4-benzothiadiazine 1,1-dioxides. Further, 2-aminobenzenesulfonamide and 2-amino-4-chlorobenzenesulfonamide were prepared by a known procedure not involving the use of chlorosulfonic acid. These, also, were cyclized with formic acid and formaldehyde. The diuretic potency of the compounds described was compared with chlorothiazide and dihydrochlorothiazide.

In our continuing investigation of potential diuretic agents related to chlorothiazide and dihydrochlorothiazide, we have turned our attention to dichlorobenzothiadiazines. The latter seemed a logical group to investigate since the necessary isomeric dichloroanilines are readily available.

The chlorosulfonation of 2,3-dichloroaniline (I), followed by treatment with ammonia, gave the desired 4 - amino - 5,6 - dichloro - 1,3 - benzenedisulfonamide (II). Refluxing II with 98% formic acid gave 5,6-dichloro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (III). With formalin II gave rise to the dihydro derivative IV.

The chlorosulfonation of 2,5-dichloroaniline,

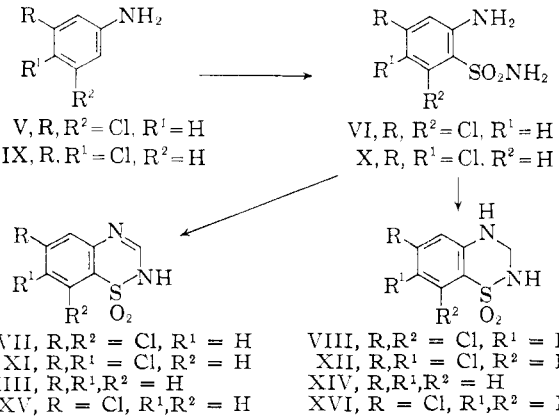
(1) For paper I in this series see W. J. Close, *et al.*, THIS JOURNAL, **82**, 1132 (1960).



followed by ammonolysis, yielded a substance which contained only one sulfonamide group. Catalytic dehalogenation produced a substance identical to *p*-aminobenzenesulfonamide but different from *o*-aminobenzenesulfonamide. The original sulfonamide, therefore, was 4-amino-2,5-dichlorobenzenesulfonamide. No disulfonyl chloride was obtained from 2,5-dichloroaniline or its monosulfonamide even at the temperature of refluxing chlorosulfonic acid.

When 2,5-dichloroaniline was subjected to the action of sulfuryl chloride in the presence of aluminum chloride, the only product isolated was 2,3,4,6-tetrachloroaniline.

From 3,5-dichloroaniline (V) we obtained, again, only a monosulfonamide. Dehalogenation gave rise to *o*-aminobenzenesulfonamide. The material in question, therefore, was 2-amino-4,6-dichlorobenzenesulfonamide (VI).



Reaction of VI with formic acid or formaldehyde gave, respectively, 6,8-dichloro-1,2,4-benzothiadiazine 1,1-dioxide (VII) and 6,8-dichloro-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide (VIII).

From 3,4-dichloroaniline (IX) we hoped to obtain a disulfonamide in which both sulfonamide groups were *ortho* to the amino group. Again, however, only a monosulfonamide (X) could be obtained. From X the benzothiadiazines XI and XII were obtained.

We had hoped to obtain disulfonamides from all four of the dichloroanilines in order to prepare benzothiadiazines with a sulfamyl substituent on the benzene ring. However, cyclization of the two monosulfonamides VI and X allowed us to determine if the 7-sulfamyl group was essential for diuretic activity in this series.

In order to elaborate this point further, we have also prepared, from 2-aminobenzenesulfonamide the completely unsubstituted analogs, namely, 1,2,4-benzothiadiazine 1,1-dioxide (XIII) and 3,4-dihydro - 1,2,4 - benzothiadiazine 1,1 - dioxide (XIV).

Cyclization of 2-amino-4-chlorobenzenesulfonamide with formic acid and with formaldehyde gave, respectively, 6-chloro-1,2,4-benzothiadiazine 1,1-dioxide (XV) and 6-chloro-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxide (XVI). The latter two substances differ from chlorothiazide and dihydrochlorothiazide by lacking the 7-sulfamyl group.

Pharmacological Results

All of the substances reported here which are derivatives of 1,2,4-benzothiadiazine 1,1-dioxide have been tested for diuretic potency.[2]

The dichlorobenzothiadiazines VII, VIII, XI and XII obtained from monosulfonamides lacked significant diuretic activity. The remaining two dichlorobenzothiadiazines, which also contain a 7-sulfamyl group, were active. Compound III is as potent as, or slightly more potent than, chlorothiazide. The material represented by structure IV was more active than chlorothiazide, but not so active as dihydrochlorothiazide. The 6-chloro derivatives XV and XVI and also the completely unsubstituted analogs XIII and XIV were inactive.

No conclusions could be drawn concerning the relative diuretic activity of dichlorobenzothiadiazines. Not all of them could be obtained with a sulfamyl group on the benzene ring, and the latter group appears to be absolutely essential for significant activity.

Experimental

4-Amino-5,6-dichloro-1,3-benzenedisulfonamide (II).—To 120 ml. of chlorosulfonic acid was added dropwise 20 g. (0.125 mole) of 2,3-dichloroaniline. The resulting solution was heated at 110° for 48 hours. After cooling, the solution was poured onto ice, and the sulfonyl chloride was collected on a filter. It was added, in small portions, to liquid ammonia. After the ammonia had evaporated, the residue was dissolved in hot, dilute ammonia water, and the product precipitated with acetic acid. After a second such treatment, this time with the aid of charcoal, 10.8 g. (27%) of white solid was obtained, m.p. 293–294°.

Anal. Calcd. for $C_6H_7Cl_2N_3O_4S_2$: C, 22.51; H, 2.21. Found: C, 22.41; H, 2.20.

When the reaction was carried out at 150° for 4 hours, or overnight at 120°, comparable yields were obtained. At steam-bath temperature for 4 hours or overnight, yields were considerably lower.

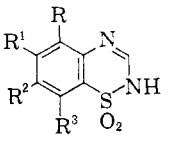
4-Amino-2,5-dichlorobenzenesulfonamide (2,5-Dichlorosulfanilamide).—A solution of 10 g. (0.06 mole) of 2,5-dichloroaniline in 60 ml. of chlorosulfonic acid was heated at 125° for four hours. The crude product, obtained after hydrolysis and treatment with ammonia, was recrystallized from ethanol with the aid of charcoal to give 7.8 g. (54%) of thick, white needles, m.p. 258–259°.

Anal. Calcd. for $C_6H_6Cl_2N_2O_2S$: C, 29.88; H, 2.51; N, 11.62; S, 13.30. Found: C, 29.87; H, 2.62; N, 11.90; S, 13.50.

Attempts to obtain a disulfonamide from 2,5-dichloroaniline failed. At 170° for 0.5 hour the product obtained was the monosulfonamide. When the monosulfonamide itself was refluxed in chlorosulfonic acid for 2 hours, followed by hydrolysis and treatment with ammonia, no pure product was isolated.

(2) The diuretic studies were carried out in the Pharmacology Department, Abbott Laboratories, by Doctors Kao Hwang and Morton Goldberg. The results will be reported in greater detail elsewhere.

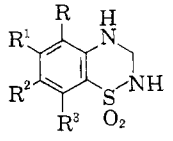
TABLE I



							Analyses, %							
							Calcd.				Found			
Cpd.	R	R^1	R^2	R^3	M.p., °C.	Formula	C	H	Cl	N	C	H	Cl	N
III	Cl	Cl	SO_2NH_2	H	314–315	$C_7H_5Cl_2N_3O_4S_2$	25.46	1.53	21.48		25.55	1.69	21.58	
VII	H	Cl	H	Cl	309–310	$C_7H_4Cl_2N_2O_2S$	33.48	1.61	28.24		33.48	1.75	28.30	
XI	H	Cl	Cl	H	310–311[a]	$C_7H_4Cl_2N_2O_2S$	33.48	1.61	28.24		33.52	1.44	28.27	
XIII	H	H	H	H	221–222[a,b]	$C_7H_6N_2O_2S$	46.14	3.32		15.38	46.24	3.30		15.49
XV	H	Cl	H	H	255–256[a]	$C_7H_5ClN_2O_2S$[c]	38.81	2.32		12.93	38.94	2.30		13.12

[a] Recrystallized from isopropyl alcohol. [b] The recorded melting point is 222°; D. O. Parke and R. T. Williams, *J. Chem. Soc.*, 1763 (1950). [c] Calcd.: S, 14.77. Found: S, 14.66.

TABLE II



							Analyses, %							
							Calcd.				Found			
Cpd.	R	R^1	R^2	R^3	M.p., °C.	Formula	C	H	Cl	N	C	H	Cl	N
IV	Cl	Cl	SO_2NH_2	H	302–303	$C_7H_7Cl_2N_3O_4S_2$[a]	25.31	2.13		12.65	25.29	2.23		12.60
VIII	H	Cl	H	Cl	249–250	$C_7H_6Cl_2N_2O_2S$	33.21	2.39	28.02	11.07	32.99	2.58	28.03	10.96
XII	H	Cl	Cl	H	207–209	$C_7H_6Cl_2N_2O_2S$	33.21	2.39	28.02	11.07	33.27	2.42	28.08	10.87
XIV	H	H	H	H	171–172[b]	$C_7H_8N_2O_2S$	45.64	4.38		15.21	45.62	4.38		15.36
XVI	H	Cl	H	H	172–173	$C_7H_7ClN_2O_2S$	38.45	3.22	16.22	12.81	38.49	3.29	16.37	12.82

[a] Calcd.: S, 19.31. Found: S, 19.27. [b] Recrystallized from water or isopropyl alcohol.

Dehalogenation of the Monosulfonamide from 2,5 Dichloroaniline.—A mixture of 5.8 g. (0.024 mole) of the monosulfonamide from 2,5-dichloroaniline, 1.0 g. of 5% palladium-on-charcoal, 20 ml. of 5 *N* sodium hydroxide solution and 100 ml. of water was subjected to hydrogenation at two atmospheres pressure. The theoretical amount of hydrogen was absorbed in 15 minutes. The catalyst was removed, and the filtrate was acidified to obtain 3 g. (72%) of white solid, m.p. 163–164°. A mixed melting point with an authentic sample of *p*-aminobenzenesulfonamide showed no depression, but with an authentic sample of *o*-aminobenzenesulfonamide a depression was observed. The recorded melting point of *p*-aminobenzenesulfonamide is 166°.[3]

2-Amino-4,6-dichlorobenzenesulfonamide (VI).—A solution of 20 g. (0.12 mole) of 3,5-dichloroaniline in 120 ml. of chlorosulfonic acid was heated at 105° for 24 hours. The solution was hydrolyzed and treated with ammonia in the usual manner. The product was recrystallized twice from water, once with the aid of charcoal, to give 12.5 g. (42%) of white needles, m.p. 161–162°.

Anal. Calcd. for $C_6H_6Cl_2N_2O_2S$: C, 29.88; H, 2.51; N, 11.62. Found: C, 30.15; H, 2.72; N, 11.44.

Attempts to obtain a disulfonamide from 3,5-dichloroaniline failed. At 130° the yield of VI was greatly reduced, while at 150° no product was isolated at all. When VI itself was refluxed in chlorosulfonic acid for four hours and then treated with ammonia, a small amount of material was obtained which appeared to be a mixture of VI and the desired disulfonamide. Anhydrous aluminum chloride had no effect on the course of the latter reaction.

Dehalogenation of the Monosulfonamide from 3,5-Dichloroaniline.—Catalytic dehalogenation of 5.7 g. (0.024 mole) of the monosulfonamide from 3,5-dichloroaniline was carried out as described above for the monosulfonamide from 2,5-dichloroaniline. The product was a white solid and the yield was 2.35 g. (59%), m.p. 153–154.5°. A mixture with an authentic sample of *o*-aminobenzenesulfonamide showed no depression, but with an authentic sample of *p*-aminobenzenesulfonamide a depression was observed. The recorded[3] melting point of *o*-aminobenzenesulfonamide is 153°.

2-Amino-4,5-dichlorobenzenesulfonamide (X).—A solution of 10 g. (0.06 mole) of 3,4-dichloroaniline in 60 ml. of chlorosulfonic acid was heated at 125° for four hours. The crude product, obtained after hydrolysis and treatment with ammonia, was recrystallized twice from aqueous acetone to give 5.5 g. (38%) of white, crystalline solid, m.p. 175.5–176.5°.

Anal. Calcd. for $C_6H_6Cl_2N_2O_2S$: C, 29.88; H, 2.51; N, 11.62. Found: C, 29.86; H, 2.47; N, 11.47.

2-Amino-4-chlorobenzenesulfonamide.—Reduction of 19 g. (0.08 mole) of 4-chloro-2-nitrobenzenesulfonamide[4,5] was accomplished at low pressure in ethanol over palladium-on-charcoal to give 12.2 g. (72%) of white solid, m.p. 144–146°.

Anal. Calcd. for $C_6H_7ClN_2O_2S$: C, 34.87; H, 3.41; N, 13.55. Found: C, 34.88; H, 3.36; N, 13.63.

Preparation of 1,2,4-Benzothiadiazine 1,1-Dioxides.—A solution of the sulfonamide in 98% formic acid was heated under reflux for two hours, and then poured into water. The crude product could, if necessary, be purified by dissolving it in dilute ammonia water and precipitating with acetic acid or by recrystallization from a suitable solvent. The products were white, crystalline solids, and the yields varied between 73 and 94%. These compounds are described in Table I.

Preparation of 3,4-Dihydro-1,2,4-benzothiadiazine 1,1-Dioxides.—A solution of the sulfonamide in water, acetone or aqueous acetone containing formalin was heated under reflux for two hours. The product usually precipitated on chilling. When acetone was used as the solvent, dilution with water was necessary. The crude products could be purified, when necessary, by precipitation from dilute ammonia water, or by recrystallization from a suitable solvent. The substances were white, crystalline solids, and the yields varied between 83 and 97%. They are described in Table II. In some cases excess formaldehyde gave less pure materials than when only an equivalent quantity was used.

Acknowledgments.—We wish to thank Dr. Warren J. Close for valuable discussions during the course of this work. Microanalyses are due to Mr. Elmer Shelberg and his staff of the Abbott

(3) W. J. C. Dyke, *Quart. J. Pharm. Pharmacol.*, **10**, 320 (1937).

(4) J. N. Elgersma, *Rec. trav. chim.*, **48**, 757 (1929).

(5) E. Riesz, *Monatsh.*, **50**, 263 (1928).

Microanalytical Laboratory to whom we are grateful. We are indebted to Miss Evelyn Schuber for preparation of 4,4′-dichloro-2,2′-dinitrodiphenyl disulfide. We wish to thank B. L. Lemke and Co., Inc., Lodi, N. J., for a generous sample of 2,2′-dinitrodiphenyl disulfide. Finally, we wish to acknowledge our debt to Mr. Morris Freifelder and Mr. George Stone for carrying out the catalytic hydrogenations described herein.

NORTH CHICAGO, ILL.

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Benzacridines. III.[1] Synthesis and Chemistry of 6,6-Dimethyl-6,11-dihydrobenz[b]-acridine and Derivatives[2]

BY NORMAN H. CROMWELL AND JOHN C. DAVID

RECEIVED JULY 31, 1959

6,6-Dimethyl-6,11-dihydrobenz[b]acridine (III) was synthesized in two ways starting with 1,1-dimethyl-2-tetralone *via* (a) 1,1-dimethyl-3-(*o*-nitrobenzal)-2-tetralone (I) by a reductive ring closure and (b) *via* 6,6-dimethyl-12-carboxy-6,11-dihydrobenz[b]acridine (II) by decarboxylation. The 11-morpholino- (V), 11-ethoxy- (VI) and 11-methoxy- (VII) derivatives of III were obtained from the very reactive 11-bromo-(IV) derivative of III. The 11-keto derivative VIII was obtained by the direct oxidation of III and by a hydrolytic oxidation of the 11-bromo-derivative IV. The expected tertiary carbinol X resulted from the reaction of VIII with methylmagnesium iodide. The ultraviolet spectra of III and its derivatives showed some interesting features and were useful in confirming these structures. These are the first syntheses of 6,11-dihydrobenz[b]acridines.

The benz[a]acridines and benz[c]acridines have been extensively studied, particularly in terms of the biological activity of their derivatives.[3] The linear benz[b]acridines, lacking the "K-region" to which the carcinogenic properties of the (a) and (c) series have been ascribed,[3,4] have received much less attention. The relatively limited synthetic approaches and reactions of the (b) series have been reviewed.[5] The Pfitzinger–Borsche reaction[6] has been used extensively for the synthesis of benz[c]-acridine derivatives.[1,3,5,7] Using isatin and *cis*-*β*-decalone, Buu-Hoi and co-workers obtained a mixture of the carboxyoctahydrobenz[b]- and benz-[a]acridines.[8]

In connection with a general program involving the synthesis of polycyclic nitrogen heterocyclic compounds for testing as carcinogenic and anti-tumor agents, it was of interest to investigate the two methods used in the synthesis of 5,5-dimethyl-5,6-dihydrobenz(c)acridines[1,7] from 4,4-dimethyl-1-tetralone, for the preparation of 6,6-dimethyl-6,11-dihydrobenz(b)acridine(III) from the isomeric and available 1,1-dimethyl-2-tetralone.[9]

An application of a method of precedent[8] for the synthesis of III consisted of the condensation of 1,1-dimethyl-2-tetralone[9] with isatin in aqueous alcoholic potassium hydroxide to give 6,6-dimethyl-12-carboxy-6,11-dihydrobenz(b)acridine (II), followed by thermal decarboxylation. The alternative method, superior in terms of yield, consisted of condensation of 1,1-dimethyl-2-tetralone with *o*-nitrobenzaldehyde in acetic–sulfuric acid mixture[1,7] to give 1,1-dimethyl-3-(*o*-nitrobenzal)-2-tetralone (I), followed by an iron–acetic acid reduction of the nitro group and an *in situ* ring closure of the amine (A) to form III.

The intermediate amine A underwent ring closure, possibly for steric reasons, much more readily than did the corresponding 2-(*o*-aminobenzal)-4,4-dimethyl-1-tetralones in forming the 5,5-dimethyl-5,6-dihydrobenz(c)acridines.[1,7] Catalytic hydrogenation of I produced only very small amounts of III and most of the starting material was recovered.

Since the preparation of 11-substituted derivatives of III was one objective of this investigation, the reactivity of the methylene group of this dihydrobenz(b)acridine was of primary interest. The recent successful preparation of 5,5-dimethyl-6-bromo-5,6-dihydrobenz(c)acridines[1,7] using N-bromosuccinimide suggested that III might be converted to the corresponding bromo derivative IV. The reaction of III with N-bromosuccinimide proceeded with great rapidity in the presence of benzoyl peroxide, but all attempts to isolate IV led to decomposition or reaction with the recrystallizing solvents. Consequently, solutions of IV were prepared and its further rapid reaction with alcohols and amines carried out without isolating the bromo intermediate.

By way of comparison of the reactivity of IV, 9-bromofluorene reacts with dimethylamine in dilute alcohol at 80° with no competition from the solvent.[10] Bromide IV is apparently rapidly hydrolyzed in carbon tetrachloride solution on contact with water to produce the alcohol IX which in turn is rapidly oxidized in air to the keto acridine VIII.

(1) For paper II see, V. L. Bell and N. H. Cromwell, *J. Org. Chem.*, **24**, 1077 (1959).

(2) Presented in part at 133rd Meeting of the American Chemical Society, San Francisco, Calif., April, 1958.

(3) For an excellent review entitled, "The Relation between Carcinogenic Activity and the Physical and Chemical Properties of Angular Benzacridines," see A. Lacassagne, N. P. Buu-Hoi, R. Daudel and F. Zajdela, "Advances in Cancer Research," Academic Press, Inc., New York, N. Y., 1956, Vol. IV, pp. 316–369.

(4) See C. A. Coulson, "Advances in Cancer Research," Academic Press, Inc., New York, N. Y., 1953, Vol. I, pp. 1–56.

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