Experimental[14]

Alkylation of Pyridine Derivatives. (a) Reaction of 2-Picoline with β-Dimethylaminoethyl Chloride Using Phenylsodium as the Condensing Agent.—The previously described procedure[1] for the alkylation of 3-picoline using sodium diisopropylamide as the condensing agent was employed except that phenylsodium was used in place of sodium diisopropylamide. Thus, from the reaction of a benzene suspension of phenylsodium (0.6 mole), 2-picoline (0.6 mole, 55.8 g.) and β-dimethylaminoethyl chloride (0.6 mole, 64.2 g.) there was obtained 62.9 g. (64%) of 1-(2-pyridyl)-3-dimethylaminopropane, b.p. 97–99° at 6.0 mm.[6]

(b) Reaction of 2-Benzylpyridine with β-Dimethylaminoethyl Chloride and N-(2-Chloroethyl)-pyrrolidine Using Phenyllithium as the Condensing Agent.—The previously described[15] procedure for alkylating 2-picoline was followed. Thus, from the reaction of an ether solution of phenyllithium (1.0 mole), 2-benzylpyridine (1.0 mole, 169 g.) and β-dimethylaminoethyl chloride (1.0 mole) there was isolated 188.9 g. (79%) of 1-(2-pyridyl)-1-phenyl-3-dimethylaminopropane, b.p. 128–129° at 0.85 mm.[6]; picrate, m.p. 201–202°[6] (from 95% ethanol).

Similarly, from the interaction of one mole each of phenyllithium, 2-benzylpyridine and N-(2-chloroethyl)-pyrrolidine there was isolated 183 g. (68%) of 1-(2-pyridyl)-1-phenyl-3-(N-pyrrolidino)-propane, b.p. 136–138° at 0.18 mm.

Anal. Calcd. for $C_{18}H_{22}N_2$: C, 81.15; H, 8.33. Found: C, 80.68; H, 8.25.

This compound formed a dipicrate, m.p. 170–171° (from 95% ethanol).

Anal. Calcd. for $C_{30}H_{28}N_8O_{14}$: C, 49.72; H, 3.89. Found: C, 50.04; H, 4.02.

Acylation of 1-(2-Pyridyl)-3-dimethylaminopropane (I), 1-(2-Pyridyl)-1-phenyl-3-(dimethylamino)-propane (II) and 1-(2-Pyridyl)-1-phenyl-3-(N-pyrrolidino)-propane (XIII).—These compounds were acylated using phenylsodium and/or phenyllithium as the condensing agents using the procedures for similar reactions which were previously described.[1,5] The properties of the ketones which were obtained by acylating I and II appear in Tables I and II, respectively. From the reaction of XIII (0.2 mole, 54.3 g.), phenyllithium (0.2 mole) and ethyl propionate (0.1 mole), there was obtained 18.3 g. (57%) of 1-(N-pyrrolidino)-3-phenyl-(2-pyridyl)-hexanone-4, b.p. 190–195° at 1 mm. (literature value[10] b.p. 165–170° at 0.15 mm.). The ketone forms a succinate salt, m.p. 149.0–149.8° (from ethyl acetate, literature value,[10] m.p. 144–146°).

PITTSBURGH 13, PENNA.

(14) The 2-picoline and 2-benzylpyridine were supplied through the courtesy of Dr. F. E. Cislak, Reilly Tar and Chemical Corp.

(15) C. Osuch and R. Levine, THIS JOURNAL, **78**, 1723 (1956).

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

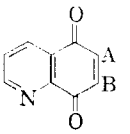
Quinolinequinones. V. 6-Chloro- and 7-Chloro-5,8-quinolinequinones[1a]

BY YOLANDA T. PRATT WITH NATHAN L. DRAKE[1b]

RECEIVED JULY 6, 1959

6-Chloro- and 7-chloro-5,8-quinolinequinone (II and III) were prepared and aryl groups were introduced at the unsubstituted positions of the quinone rings by reaction with diazonium salts; alkyl groups were introduced by peroxide alkylation. The 7-aryl-6-chloro- and 6-aryl-7-chloro-5,8-quinolinequinones were readily hydrolyzed to the corresponding hydroxyl derivatives. The parent compound, 5,8-quinolinequinone, adds hydrogen chloride at the 6,8-positions exclusively to yield 6-chloro-5,8-dihydroxyquinoline under anhydrous conditions.

Several of the derivatives of 5,8-quinolinequinone[2] described in preceding papers of this series have displayed significant amebicidal activity in preliminary tests. One of the most effective of these was 7-undecyl-6-hydroxy-5,8-quinolinequinone (I).[3] Since the well-known amebicides Vioform and Diodoquin are halogenated quinolines, it was of interest to investigate the activity of some halogenated quinolinequinones as well as certain other hydroxyquinolinequinones. In the



I, A = OH, B = n-$C_{11}H_{23}$
II, A = Cl, B = H
III, A = H, B = Cl

present work a variety of potential parasiticides have been prepared from 6-chloro- and 7-chloro-5,8-quinolinequinone (II and III) as shown in the table. The first two compounds, IV and V, are modifications of I and its isomer, 6-undecyl-7-hydroxy-5,8-quinolinequinone, in which the hydroxyl groups are replaced by chlorine. A second type of derivative is represented by the 7-aryl-6-chloro- and 6-aryl-7-chloro-5,8-quinolinequinones, VI–XIII, with various p-substituents in the aryl groups. In compounds XIV–XX the alkyl group of I and its isomer are replaced by p-substituted aryl groups.

The parent 6-chloro-5,8-quinolinequinone (II) was synthesized by oxidation of 6-chloro-5,8-diaminoquinoline obtained from 6-chloro-8-aminoquinoline[4] by diazonium coupling and subsequent reduction. The yield of the diamine (32%) was very poor in contrast to the high yield of the positively substituted 6-methoxy-5,8-diaminoquinoline previously prepared by the same procedure.[3] The over-all yield of the chloroquinone II from 6-chloro-8-aminoquinoline was 24%. The 7-chloroquinone III was readily obtained in 42% over-all yield from 5-nitro-8-hydroxyquinoline by chlorination at the 7-position followed by reduction to the 5-amino compound and oxidation of the latter. This procedure is an adaptation of Petrow and Sturgeon's synthesis of 7-bromo-5,8-quinolinequinone.[5]

The undecyl derivatives (IV and V) of the two chloroquinolinequinones were prepared by alkylation of the parent chloroquinones with dilauroyl

(1) (a) This research was supported by a research grant (PHS E-665 and continuation grants) from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, Public Health Service. (b) Deceased.

(2) "Chemical Abstracts" indexes list this compound as 5,8-quinolinedione.

(3) Y. T. Pratt with N. L. Drake, THIS JOURNAL, **77**, 4664 (1955).

(4) H. Gilman, *et al.*, *ibid.*, **68**, 1577 (1946).

(5) V. Petrow and B. Sturgeon, *J. Chem. Soc.*, 570 (1954).

TABLE I

5,8-QUINOLINEQUINONES

Cmpd.	A (6-substituent)	B (7-substituent)	M.p., °C.	Yield,[a] %	Recrystn. solvent	Carbon, % Calcd.	Carbon, % Found[b]	Hydrogen, % Calcd.	Hydrogen, % Found
IV	Cl	*n*-$C_{11}H_{23}$	94.5–95.5	45	Skelly C	69.05	69.33	7.53	7.83
V	*n*-$C_{11}H_{23}$	Cl	140–141	41	Skelly C	69.05	69.29	7.53	7.73
VI	Cl	*p*-$C_6H_4NO_2$	300.0–301.5[c]	50	$CHCl_3$–P. E.	57.25	57.13	2.24	2.39
VII	Cl	*p*-$C_6H_4SO_2NH_2$	300[d]	43	Acetone[e]	51.65	52.11	2.60	2.92
VIII	Cl	*p*-C_6H_4Cl	222–223	72	$CHCl_3$–P. E.	59.24	59.37	2.32	2.44
IX	Cl	*p*-$C_6H_4CH_3$	240–243[c]	42	$CHCl_3$–P. E.	67.73	67.86	3.55	3.60
X	Cl	*p*-$C_6H_4OCH_3$	183.5–185.0	28	Skelly C	64.11	64.29	3.43	3.36
XI	*p*-$C_6H_4NO_2$	Cl	318.0–319.5[c]	52	$CHCl_3$–P. E.[f]	57.25	57.01	2.24	2.39
XII	*p*-C_6H_4Cl	Cl	204–205[c]	33	C_6H_6–P. E.	59.24	59.44	2.32	2.56
XIII	*p*-$C_6H_4CH_3$	Cl	211–212	20	$CHCl_3$–P. E.	67.73	67.75	3.55	3.57
XIV	OH	*p*-$C_6H_4NO_2$	329.5–330.0[c]	53	Acetone[e]	60.81	60.92	2.72	2.76
XV	OH	*p*-$C_6H_4SO_2NH_2$	Dec. 331	65	Acetone[e]	54.54	54.57	3.05	2.95
XVI	OH	*p*-C_6H_4Cl	287–288[c]	60	Acetone	63.06	62.91	2.82	3.06
XVII	OH	*p*-$C_6H_4CH_3$	174.5–175.5[g]	67	C_6H_6–P. E.	76.95	77.09[g]	4.99	5.10
XVIII	*p*-$C_6H_4NO_2$	OH	246.5–248.5[c]	78	Acetone	60.81	60.90	2.72	3.01
XIX	*p*-C_6H_4Cl	OH	205.5–207.0[h]	65	$CHCl_3$-P. E.[h]	63.06	63.09	2.82	3.06
XX	*p*-$C_6H_4CH_3$	OH	269–271[c]	80	C_6H_6–P. E.	72.44	72.81	4.18	4.22

[a] Yield of recrystallized product, see Experimental. [b] Averages of duplicate determinations. [c] Melts with decomposition; placed in melting point both at about 10° below the recorded temperature and heated at the rate of approximately 3 to 4° per minute. [d] Gradually decomposes when placed in melting point bath at 295°. [e] Recrystallized by continuous extraction. [f] After a preliminary recrystallization from acetic acid and water. [g] Contains benzene of crystallization, removed by brief preliminary heating at 95–100°. A second allotropic form melts at 152.5–154.0° (see Experimental). [h] Crystallizes well from benzene–P. E. or dilute acetic acid with solvent of crystallization and higher melting point (see Experimental).

peroxide in the usual manner.[3,6] The yield of the 6-chloro derivative IV was about the same as that of the corresponding hydroxyl compound I and that of the 7-chloro derivative V was 7% higher than that of the 7-hydroxyl compound.[7]

p-Substituted aromatic groups were introduced at the unsubstituted positions of the quinone rings of the chloroquinones II and III to give products VI–XIII by the method of Kvalnes.[8] An acetic acid solution of the quinone buffered with sodium acetate was treated with a 20% excess of the desired diazonium salt and reaction was allowed to proceed at room temperature until all of the diazonium compound was consumed by reaction with the quinone or by decomposition. Reaction periods varied from overnight to four days, depending upon the quinone as well as the *p*-substituent of the diazonium salt. The reactions were most rapid and the yields highest with negatively substituted diazonium compounds such as those from *p*-nitroaniline and sulfanilamide. The fact that reaction periods for 7-chloroquinolinequinone (III) were much shorter than those for 6-chloroquinolinequinone (II) shows that these periods were not merely an indication of the relative stabilities of the diazonium salts but were a partial measure of reaction rates with the quinones. Diazotized *p*-toluidine and *p*-chloroaniline gave much lower yields with III than with II, despite the faster reaction rates. Although these lower yields may, in part, be a result of the greater solubility of the 7-chloro derivatives which makes separation from the numerous by-products more difficult, it is probable that a rapid side-reaction involving 7-chloroquinolinequinone (III) interferes with the formation of the desired products.

The feasibility of preparing 6-aryl-7-hydroxy- and 7-aryl-6-hydroxy-5,8-quinolinequinones by hydrolysis of the corresponding chloroquinones was suggested by the rapid development of a red color when these halogen compounds were treated with weak alkali. This was of particular interest since the direct synthesis of the analogous 3-aryl-2-hydroxy-1,4-naphthoquinones by the action of diazonium salts on 2-hydroxy-1,4-naphthoquinone has been shown by Fieser and co-workers to be rather unsatisfactory.[9] It was found that most of the arylated chloroquinolinequinones (VI–VIII and XI–XIII) were readily hydrolyzed by dilute alkali and satisfactory yields of XIV–XVI and of XVII–XX were obtained in this way. The yields of Table I do not reflect exclusively the efficiency of the hydrolysis since the crude arylated chloroquinones rather than the pure compounds were hydrolyzed to conserve material; the hydroxyl compounds in the form of their potassium salts could be more easily separated from the by-products of the arylation reaction. One of the chloroquinones, 7-*p*-tolyl-6-chloro-5,8-quinolinequinone (IX), gave only low yields of impure product when hydrolyzed by the standard method. The pure compound IX was therefore converted to the hydroxyl derivative XVII by heating with a methanol solution of sodium hydroxide according to the procedure of Fieser for hydrolyzing 3-cyclohexyl-2-bromo-1,4-naphthoquinone.[10]

Since the above synthesis of the parent 6-chloro-5,8-quinolinequinone (II), involving a coupling reaction with 6-chloro-8-aminoquinoline, was not very satisfactory and since it has been reported[4] that 6-iodo-5-aminoquinaldine failed to couple with diazonium salts, it seemed worthwhile to investigate a different type of synthesis for the 6-

(6) L. F. Fieser, M. T. Leffler, *et al.*, THIS JOURNAL, **70**, 3174 (1948).

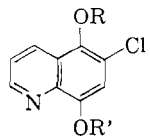
(7) Y. T. Pratt with N. L. Drake, *ibid.*, **79**, 5024 (1957).

(8) D. E. Kvalnes, *ibid.*, **56**, 2478 (1934).

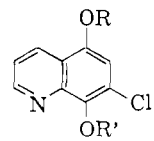
(9) L. F. Fieser, M. T. Leffler and co-workers, *ibid.*, **70**, 3203 (1948).

(10) L. F. Fieser, *ibid.*, **70**, 3173 (1948).

halogenated 5,8-quinolinequinones. One possibility was that introduction of halogen into the quinone nucleus by the addition of halogen acids to 5,8-quinolinequinone to form halogenated hydroquinones such as XXI or XXV might result in a satisfactory yield of the 6-halo isomer XXI which could be oxidized to the desired quinone.



XXI, R, R′ = H
XXII, R, R′ = $COCH_3$
XXIII, R = H; R′ = $COCH_3$
XXIV, R = $COCH_3$; R′ = H



XXV, R, R′ = H
XXVI, R, R′ = $COCH_3$
XXVII, R = H; R′ = $COCH_3$
XXVIII, R = $COCH_3$; R′ = H

In this connection Long and Schofield[11] have reported that 5,8-quinolinequinone reacts with boiling aqueous hydrochloric acid to give a mixture of the two possible hydroquinones XXI and XXV. In the absence of hydrolytic solvents, however, quinolinequinone, an extremely weak base, would exist exclusively in the form of its salt in which the directive influence of the nitrogen is considerably enhanced. A preponderance of a single isomer would, therefore, be more likely under anhydrous conditions.

In our studies of the addition of hydrogen chloride to 5,8-quinolinequinone, reference compounds of known structure were first obtained by reducing and acetylating 6-chloro-and 7-chloro-5,8-quinolinequinone (II and III). The 6-chloroquinone II yielded a hydroquinone,[12] XXI, melting at 167° which formed a diacetate, XXII, melting at 138°. The hydroquinone, XXV, from 7-chloroquinolinequinone (III) melted at 179° and formed a diacetate XXVI, which melted at 131°. The melting points of these diacetates are not in complete accord with those reported by the English workers for the acetates obtained from the addition products of aqueous hydrogen chloride and 5,8-quinolinequinone.[11] They isolated a hydroquinone melting at 164° which formed a diacetate melting at 131°. The correct carbon, hydrogen and halogen analyses for the diacetate were reported and these melting points correspond approximately to those for the 6-chloro derivatives XXI and XXII. After acetylation of the hydroquinone mixture they separated a second acetate which consisted of feathery needles melting at 159–161° for which only carbon and hydrogen analyses were reported. As will be shown below, however, unless this higher melting acetate is another allotropic form of one of the diacetates, it is apparently an impure sample of 5-acetoxy-7-chloro-8-hydroxyquinoline (XXVIII), which melts at 179° and has almost the same carbon and hydrogen content as the diacetate XXVI. This compound could have been formed when excess acetic anhydride was hydrolyzed in working up the reaction mixture. None of the other possible acetates melts that high.

(11) R. Long and K. Schofield, *J. Chem. Soc.*, 3919 (1953).

(12) Since the hydroquinones are somewhat unstable the melting points given for XXI and XXV may not be the maximum obtainable.

In a related project we had found that 5,6,8-triacetoxyquinoline prepared from 6-hydroxy-5,8-quinolinequinone[13] was hydrolyzed by brief treatment with boiling water to a higher melting diacetoxyquinolinol with only a slightly different carbon and hydrogen content than the original triacetoxyquinoline. Since this observation seemed to be a clue to the English workers' chlorodihydroxyquinoline acetate melting at 161°, the diacetates of 6-chloro- and 7-chloro-5,8-quinolinequinone (XXII and XVI) were treated with boiling water. There were obtained feathery needles melting at 145 and 179°, respectively, with analytical data for carbon, hydrogen and chlorine corresponding to those required for chloromonoacetoxy-monohydroxyquinolines (XXIII or XXIV and XXVII or XXVIII). The presence of an intramolecularly bonded hydroxyl group in each compound was shown by the infrared spectra in carbon tetrachloride solution.[14] The absorption peak at 3450 $cm.^{-1}$ displayed by the 7-chloro derivative and that at 3430 $cm.^{-1}$ by the 6-chloro derivative are both in the range of the hydroxyl band (3419 $cm.^{-1}$) reported for 8-hydroxyquinoline in the same solvent[15] and were unchanged on tenfold dilution. Since intramolecular hydrogen bonding can occur in the 7-chloro isomer only if the hydroxyl group occupies the 8-position, this compound must be 5-acetoxy-7-chloro-8-hydroxyquinoline (XXVIII) rather than the isomer XXVII. One of the two alternative structures for the 6-chloro compound, XXIII would show hydrogen bonding with chlorine, but in *o*-chlorophenol[16] (in carbon tetrachloride solution) the OH-stretching absorption appears at 3542 $cm.^{-1}$, over 100 $cm.^{-1}$ higher than that of the monoacetate. It is therefore evident that the hydroxyl group in the 6-chloro isomer is also at the 8-position and the correct structure is XXIV.

With the identities of the diacetates of the expected addition products established, 5,8-quinolinequinone in dry benzene solution was treated with anhydrous hydrogen chloride. The product precipitated as the salt of the hydroquinone. Since the free hydroquinones are somewhat unstable and decompose below the melting point, complete characterization was not attempted at this stage, but a sample of the free base after one recrystallization melted at 163–164°, the approximate melting point of 6-chloro-5,8-dihydroxyquinoline (XXI). For more extensive examination of the product, the crude hydroquinone hydrochloride was heated directly with acetic anhydride and found to give a high yield (92% from quinolinequinone) of 6-chloro-5,8-diacetoxyquinoline (XXII) and the presence of none of the 7-chloro isomer XXVI could be detected by infrared analysis. It therefore appears that under anhydrous conditions hydrogen chloride adds to 5,8-quinolinequinone at the 6-position exclusively and that 6-bromo-5,8-quinolinequinone might be available by an analogous procedure.

(13) Y. T. Pratt and N. L. Drake, THIS JOURNAL, **77**, 37 (1955).

(14) The authors thank Professor Ellis R. Lippincott of these laboratories for aid in interpreting infrared data.

(15) F. J. C. Rossotti and H. S. Rossotti, *J. Chem. Soc.*, 1304 (1958).

(16) A. W. Baker, THIS JOURNAL, **80**, 3598 (1958).

The mode of addition of various reagents to unsymmetrically substituted naphthoquinones has been investigated by Thomson and Lyons[17] and the addition of hydrogen chloride to 5,8-quinolinequinone appears to be consistent with their work. It is hoped that additional studies now in progress on the relative reactivities at the 6- and 7-positions of 5,8-quinolinequinone will furnish sufficient information to interpret such results on the basis of the various reaction mechanisms involved.

This work has been facilitated by developing standardized procedures for synthesizing the parent 5,8-quinolinequinone. Although the preparation of this compound from 5-amino-8-hydroxyquinoline has been described in several papers since Fischer and Renouf's original publication,[5,11,18] few details are available. More satisfactory yields have been obtained by oxidizing this amine with ferric chloride as well as with dichromate under carefully defined conditions.

Experimental[19]

6-Chloro-5,8-quinolinequinone (II).—A suspension of 0.3 mole (62.5 g.) of pure 6-chloro-8-nitroquinoline[4,20] in 550 ml. of acetic acid and 550 ml. of water was heated on a steam-bath with vigorous stirring while 53 g. of iron powder (100 mesh) was added at a rate to maintain gentle refluxing over 15 min.[21] The mixture was then heated 75 min. longer. It was cooled in an ice-bath to precipitate any unreduced starting material and the solid was separated by filtration and washed well with cold 50% (by volume) acetic acid. The filtrate was diluted with water to precipitate crude **6-chloro-8-aminoquinoline** as a gray solid. The dried product was dissolved in anhydrous ether, decolorized with Darco and separated from a dark insoluble impurity by filtration. Evaporation of the ether solution yielded 43.5 g. of the amine as a pale yellow solid which melted at 69.0–70.5°. (The pure compound is colorless and melts at 72–73°.[4])

The above product was dissolved in 200 ml. of acetic acid, mixed with a solution of 62 g. of potassium acetate in 50 ml. of water and at room temperature added to one equivalent of diazotized sulfanilic acid[22] cooled in an ice-bath. After 10 min. the mixture was removed from the bath and allowed to stand with occasional stirring until after a negative test was obtained with α-naphthylamine[23] (about 2 hr.). It was then cooled in an ice-bath and the solid was separated by filtration through canvas and washed with saturated sodium chloride solution. The moist coupling product was suspended in 480 ml. of water after it had first been stirred into a paste with a portion of the water to prevent lumping. After the addition of 170 ml. of 8 *N* potassium hydroxide solution the mixture was warmed to 70°, treated with 135 g. of sodium dithionite and further heated at 95° for 15 min. The yellow precipitate, **5,8-diamino-6-chloroquinoline,** weighed 20.0 g. Upon continuous extraction with 300 ml. of dry benzene and precipitation with Skellysolve F there was obtained 15.1 g. of bright yellow crystals which melted at 156.5–158.0°. The analytical sample (m.p. 157.5–159.0°) was recrystallized from the same solvent mixture.

Anal. Calcd. for $C_9H_8N_3Cl$: C, 55.82; H, 4.16. Found: C, 56.04, 56.09; H, 3.89, 4.09.

From the mother liquors of the product there was obtained a trace of an orange by-product which melted at 139–140° after recrystallization from Skellysolve C. According to the analytical data it is isomeric with the above product and is presumed to be **6-chloro-7,8-diaminoquinoline.**

Anal. Calcd. for $C_9H_8N_3Cl$: C, 55.82; H, 4.16; N, 21.70; Cl, 18.31. Found: C, 56.06, 55.91; H, 4.37, 4.03; N, 21.34, 21.33; Cl, 18.27, 18.43.

The purified 6-chloro-5,8-diaminoquinoline (15.1 g.) was well dispersed in 400 ml. of water, treated with 15 ml. of 12 *N* sulfuric acid and cooled to 5°. After the addition of 100 g. of ice, the mixture was vigorously shaken while an ice-cold solution of 60 ml. of 12 *N* sulfuric acid in 85 ml. of approximately 2 *N* potassium dichromate solution[24] was added rapidly. The mixture was then stirred in an ice-bath for 15 min. and the precipitate was collected on a cold funnel and washed with ice-water. The red-brown solid thus obtained weighed 13.3 g. It was dissolved in 400 ml. of chloroform and the solution was filtered and washed with 70 ml. of 1 *N* sulfuric acid containing 3 ml. of 2 *N* dichromate solution, then with two more 70-ml. portions of 1 *N* sulfuric acid, and finally with saturated sodium chloride solution. The chloroform solution was shaken with Drierite and Norite and evaporated to about 50 ml. under reduced pressure. On the addition of Skellysolve F there was obtained 11.3 g. of bright yellow **6-chloro-5,8-quinolinequinone.** It had no definite melting point, but the analytical sample (from benzene and Skellysolve F) gradually darkened when placed in the bath at 180° and only partly melted at 187°.

Anal. Calcd. for $C_9H_4NO_2Cl$: C, 55.83; H, 2.08. Found: C, 56.09, 55.95; H, 2.09, 1.99.

7-Chloro-5,8-quinolinequinone (II).—The oxidation of 5-nitroso-8-hydroxyquinoline to **5-nitro-8-hydroxyquinoline** was carried out according to the procedure of Petrow and Sturgeon[5] except that the acid mixture was neutralized directly with sodium acetate. In our experiments, however, there was invariably obtained a considerable quantity of the alcohol-insoluble 5,7-dinitro derivative and the yields of mononitro compound which melted at 179.5–181.5° after recrystallization from alcohol were 62–67% of theory.

The above product (40 g.), suspended in 4 l. of water and 1 equivalent (213 ml.) of 1 *N* potassium hydroxide solution, was vigorously stirred while 285 ml. (5% excess) of Clorox[25] was added over about 90 min. During the course of the addition all of the starting material dissolved and soon the salt of **5-nitro-7-chloro-8-hydroxyquinoline** began to precipitate. Two hours after the addition was complete, the mixture was neutralized with acetic acid and stirred to permit complete conversion of the precipitate to the free quinolinol before the product was filtered off and washed with water. The crude material (42.3 g.) on recrystallization from 1200 ml. of ethyl acetate by continuous extraction yielded 35.0 g. of the bright orange chloro compound which melted at 239.0–240.5° dec. (lit.[26] 235°).

One-tenth mole (22.4 g.) of the chlorinated nitro compound was ground in a mortar with 110 ml. of 1 *N* potassium hydroxide to ensure complete reduction of the insoluble potassium salt. The suspension was transferred to an Erlenmeyer flask equipped with a long magnetic stirring bar with the aid of 280 ml. of water. After the mixture had been heated in a water-bath with vigorous stirring, 70 ml. of 8 *N* potassium hydroxide was added and at 50° it was treated with 70 g. of sodium dithionite. The mixture was then reheated and maintained at 80° for 10 min. with rapid stirring while a stream of nitrogen was passed into the flask. Ten grams more of dithionite was added and the reaction was allowed to continue 10 min. longer. The resulting suspension was cooled in ice under nitrogen and the precipitate was filtered off, washed with cold water containing a trace of dithionite and dried rapidly in a vacuum oven. There was thus obtained 17.9 g. of **5-amino-7-chloro-8-hydroxyquinoline** as a gold-yellow solid which melted at 172–173° dec. (lit.[26] 173–174° dec.)

(17) J. H. Thomson, *J. Org. Chem.*, **16**, 1082 (1951); J. M. Lyons and J. H. Thomson, *J. Chem. Soc.*, 2910 (1953).

(18) O. Fischer and E. Renouf, *Ber.*, **17**, 1644 (1884); T. Urbański and S. Krzyżanowski, *Roczniki Chem.*, **27**, 390 (1953) [*C. A.*, **49**, 1041b (1955)].

(19) The authors thank Professor Katherine Gerdeman and Miss Jane Swan for the microanalyses and Mr. William Fearheller and Mr. Charles White for the infrared spectra. Melting points are corrected.

(20) F. Richter and G. F. Smith, THIS JOURNAL, **66**, 396 (1944).

(21) This procedure is based on that of C. C. Price and D. B. Guthrie, *ibid.*, **68**, 1592 (1946) for 7-chloro-8-aminoquinoline.

(22) L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., Boston, Mass., 1941, p. 208.

(23) H. J. Lucas and D. Pressman, "Principles and Practice in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 388.

(24) The solution contained 100 g. of potassium dichromate per liter.

(25) The Clorox solution used contained 0.792 mole of sodium hypochlorite per liter.

(26) F. X. Wiederkehr and E. Hofstetter, *Helv. Chim. Acta*, **35**, 468 (1952), obtained 5-nitro-7-chloro-8-hydroxyquinoline directly by a Skraup reaction.

A fine suspension of the above amine in 600 ml. of water was prepared in an Erlenmeyer flask with a long magnetic stirring bar. One equivalent (18 ml.) of 12 *N* sulfuric acid was added to dissolve the amine and vigorous stirring continued while the solution was cooled to 2° and the salt precipitated in a finely divided form. An ice-cold solution made up of 103 ml. of 2 *N* potassium dichromate solution[24] and 71 ml. of 12 *N* sulfuric acid was then added all at once. The mixture was stirred and cooled in an ice-bath for 15 min. The precipitated **7-chloro-5,8-quinolinequinone** was filtered off on a cold Büchner funnel containing ice and washed with cold water. The light tan product weighed 12.5 g. It was dissolved in chloroform and treated with a small amount of decolorizing carbon; the solution was boiled down until crystallization began and the product was finally precipitated with Skellysolve F to yield 11.0 g. of bright yellow crystals. The quinone melted with preliminary decomposition at 173.5–174.5° when placed in the bath at 166° and heated at the rate of 3–4° per min. The melting point was unchanged after recrystallization.

Anal. Calcd. for $C_9H_4O_2NCl$: C, 55.83; H, 2.08. Found: C, 55.70, 55.97; H, 2.26, 2.26.

Peroxide Alkylations.—A solution of 2.32 g. (0.012 mole) of the chloroquinone in 35 ml. of acetic acid was treated with a 10% excess of dilauroyl peroxide according to the method of Fieser and co-workers.[3,6] The product precipitated from solution and was separated by filtration and washed with a little acetic acid. One recrystallization from Skellysolve C yielded the pure products IV and V. The mother liquors contained a small quantity of additional product which was not isolated.

Arylations with Diazonium Salts.—A solution of 20% excess of the diazonium salt[27] was added all at once to 0.02 mole of the chloroquinolinequinone in 140 ml. of acetic acid, followed by 20 ml. of concentrated potassium acetate solution (containing 14–15 g. of potassium acetate). Stirring was continued at 24–26° to help redissolve any traces of starting material that might have precipitated. Generally the product began to precipitate within an hour. Tests for the presence of unreacted diazonium compound[23] were made only during the day so most of the time periods below represent only very rough limits of the times required for disappearance of the diazonium salts in the synthesis of the compounds given: compound VI, 24–40 hr.; VII, 6–24 hr.; VIII, 3–4 days; IX, 2–3 days; X, 3–4 days; XI, 6–18 hr.; XII, 6–19 hr.; XIII, 27–29 hr.

When the reactions were complete, the mixture was cooled in ice and the product was separated by filtration and washed with 50% acetic acid. Except for the *p*-anisyl derivative X, which was orange, the products were yellow. After separation of the crude precipitates of the 7-chloro derivatives, considerable quantities of solid material could be obtained upon dilution of the mother liquors with an equal volume of water, but only in the preparation of XII could a significant amount (5%) of pure product be isolated from this material by recrystallization. The yields given in Table I are those of the recrystallized products which, except for VI (m.p. 293–301° dec.) and VIII (m.p. 219.0–221.5° dec.), melted no more than 1.5° below the melting points of the purest samples.

In exploratory reactions between 6-chloro-5,8-quinolinequinone (II) and diazotized sulfanilamide, no advantage was found in adding hydroquinone or 6-chloro-5,8-dihydroxyquinoline as a promoter.[28] When copper powder was used, the product, which precipitated only after dilution, was very dark colored.

Hydrolysis of Chloroquinones to Hydroxyquinones.—In the general procedure 2 g. of the crude arylated chloroquinolinequinone was suspended in 20 to 25 ml. of methanol and stirred with a magnetic stirrer for 10 min. after the addition of 50 ml. of 1 *N* potassium hydroxide. Sufficient boiling water (100–300 ml.) was added to dissolve all of the precipitated potassium salt of the product and the red solution was filtered. The filtrate was then made acid to congo red to precipitate the product. The yields given in the table are those of the recrystallized material, which melted within 1° of the melting points of the purest samples. Except for XVIII, which was orange, and XVII and XIX (see below), these products were yellow.

The sulfonamide derivative VII was hydrolyzed merely by dissolving it at room temperature in a solution of 20 ml. of 1 *N* potassium hydroxide in 50 ml. of water. After acidification, alcohol was added to coagulate the partly colloidal precipitate.

Compound XIX was recrystallized by pouring its chloroform solution into boiling Skellysolve C and boiling off excess chloroform. It separated as an orange solvent-free product with a melting point of 205.5–207.0°, unchanged on further recrystallization. It could be more easily purified by recrystallization from dilute acetic acid or from benzene–Skellysolve F, but the product contained solvent of crystallization. The material from acetic acid was red and when placed in the melting point apparatus at 155° and heated slowly changed to orange before melting at 209–210°. It contained one molecule of acetic acid per molecule of quinone.

Anal. Calcd. for $C_{15}H_8O_3NCl \cdot C_2H_4O_2$: C, 59.05; H, 3.50; Cl, 10.25. Found: C, 59.36, 59.36; H, 3.55, 3.66; Cl, 10.16, 9.99.

The crystals from benzene were bright yellow and changed to orange when dried in a vacuum oven at 90–95°. The weight loss (a 0.400 g. sample weighed 0.315 g. after heating) corresponded to that calculated for one molecule of benzene per molecule of quinone.

Anal. Calcd. for $C_{15}H_8NO_3Cl \cdot C_6H_6$: Cl, 9.74. Found: Cl, 9.42, 9.47.

One gram of pure 7-*p*-tolyl-6-chloro-5,8-quinolinequinone was hydrolyzed by heating under reflux with a solution of sodium hydroxide in methanol according to Fieser's procedure.[10] The product did not precipitate on acidification and dilution with 50 ml. of water, so the solution was evaporated under reduced pressure until the methanol had been removed. There was obtained 0.81 g. of crude product XVII. After recrystallization from benzene–Skellysolve F the yield of orange hexagonal plates containing benzene of crystallization was 0.81 g. (67%). After 10 min. at about 95° to remove benzene, this material melted at 152.5–154.0°. The melting point was unchanged on recrystallization although a previous sample prepared in the same way had crystallized as orange needles which melted at 174.5–175.5° after removal of the benzene of crystallization. A mixture of the two products containing only 5–15% of the higher melting material melted at 173.5–174.5° (after preliminary heating at 95°) indicating that the lower melting product was a second allotropic form of the higher melting one and was easily transformed to the latter during the removal of the solvent of crystallization. Conversion of each form to the other by cross-seeding their benzene solutions confirmed this observation.

6-Chloro-5,8-diacetoxyquinoline (XXII).—A suspension of 1.2 g. of 6-chloro-5,8-quinolinequinone (II) in 50 ml. of ethyl acetate was shaken in a separatory funnel with 2.5 g. of sodium dithionite and 7 ml. of water. After reduction was complete the clear organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were shaken with Drierite, boiled down to a low volume and treated with Skellysolve F to precipitate the product. The yield of almost colorless hydroquinone (XXI) melting at 167–169° dec. was 1.05 g. After recrystallization from ether–Skellysolve F colorless needles with the same melting point were obtained.

A sample of the crude hydroquinone (0.5 g.) was acetylated by boiling for 5 min. with excess acetic anhydride. After the excess reagent was hydrolyzed by stirring below room temperature with dilute sodium acetate solution, 0.70 g. of crude colorless material (m.p. 136.5–138.0°) was obtained. Recrystallization from ether–Skellysolve F and from ethyl acetate–Skellysolve F yielded the pure diacetate XXII which melted at 138–139°.

Anal. Calcd. for $C_{13}H_{10}O_4NCl$: C, 55.83; H, 3.60; Cl, 12.68. Found: C, 55.88, 55.78; H, 3.47, 3.50; Cl, 12.44, 12.45.

6-Chloro-5,8-dihydroxyquinoline Monoacetate (XXIV).—An alcohol solution of the above diacetyl compound (once-recrystallized) was poured into a large volume of boiling water. Vigorous boiling was continued for about 10 min. to complete hydrolysis and remove most of the alcohol. Upon cooling there were obtained soft, pale yellow needles of the monoacetyl derivative, which after recrystallization

(27) H. E. Fierz-David and L. Blangey, "Fundamental Processes of Dye Chemistry," Interscience Publishers, Inc., New York, N. Y., 1949, pp. 241–246.

(28) K. Schimmelschmidt, *Ann.*, **516**, 184 (1950).

from chloroform–Skellysolve F melted at 144.5–146.0°. The melting point was 145.5–146.5° after further recrystallization from alcohol and water.

Anal. Calcd. for $C_{11}H_8O_3NCl$: C, 55.59; H, 3.39; Cl, 14.92. Found: C, 55.50, 55.65; H, 3.48, 3.37; Cl, 14.84, 14.94.

7-Chloro-5,8-diacetoxyquinoline (XXVI).—Reduction of 1.2 g. of 7-chloro-5,8-quinolinequinone (III) as described above for the 6-chloro isomer yielded 1.0 g. of crude, yellow hydroquinone XXV which melted at 174.5–175.5° dec. After recrystallization from ether–Skellysolve F the product melted at 178.5–179.5° dec. The yield of crude, yellow diacetyl derivative XXVI, obtained on acetylation of 0.8 g. of this material, was 0.95 g. (m.p. 129.5–131.0°). Recrystallization from ether–Skellysolve F and from benzene–Skellysolve F (Norite) yielded the essentially colorless diacetate XXVI, whose melting point was 131–132°.

Anal. Calcd. for $C_{13}H_{10}O_4NCl$: C, 55.83; H, 3.60; Cl, 12.68. Found: C, 55.87, 55.69; H, 3.43, 3.47; Cl, 12.66, 12.50.

7-Chloro-5,8-dihydroxyquinoline Monoacetate (XXVIII).—Hydrolysis of the diacetate XXVI as described above for the 6-chloro isomer yielded pale yellow, soft, feathery needles which melted at 177.5–179.0°. The melting point of a mixture of this product with 7-chloro-5,8-dihydroxyquinoline (XXV) (m.p. 177.5–179.0°) was 160–165°. On recrystallization from ether–Skellysolve F (Norite) there were obtained colorless, feathery needles of the pure monoacetyl compound XXVIII melting at 179.5–180.5°.

Anal. Calcd. for $C_{11}H_8O_3NCl$: C, 55.59; H, 3.39; Cl, 14.92. Found: C, 55.69, 55.81; H, 3.34, 3.58; Cl, 14.90, 14.65.

5,6,8-Triacetoxyquinoline.—Five millimoles (0.88 g.) of 6-hydroxy-5,8-quinolinequinone[18] dissolved in 15 ml. of water and 1.9 ml. of 8 *N* potassium hydroxide was heated under nitrogen on a steam-bath for 2 or 3 min. with 1.35 g. of sodium dithionite. Addition of 5 ml. of acetic acid and 1.4 g. of anhydrous sodium sulfate to the cooled solution caused precipitation of the sulfate of the hydroquinone. Sulfur dioxide was removed by a stream of nitrogen, the suspension was cooled and the solid was filtered off and washed with cold water. There was obtained 0.96 g. of brick-red product.

When 0.3 g. of this salt was heated in acetic anhydride to the boiling point it dissolved completely, and after 5 min. refluxing the solution was worked up as described above yielding 0.34 g. of colorless crystals which melted at 148.5–150.0°. The purest sample of 5,6,8-triacetoxyquinoline prepared by recrystallization from benzene–Skellysolve F melted at 150–151°.

Anal. Calcd. for $C_{15}H_{13}O_6N$: C, 59.40; H, 4.32; N, 4.62. Found: C, 59.59, 59.46; H, 4.37, 4.39; N, 4.80, 4.66.

5,6,8-Trihydroxyquinoline Diacetate.—A sample of 5,6,8-triacetoxyquinoline was recrystallized from water by boiling the suspension a few minutes until all had dissolved. Upon cooling, an essentially colorless product crystallized out. It melted at 159.0–159.5° and further recrystallization from benzene–petroleum ether did not change the melting point.

Anal. Calcd. for $C_{13}H_{11}O_5N$: C, 59.77; H, 4.25; N, 5.36. Found: C, 59.91, 59.63; H, 4.28, 4.20; N, 5.59, 5.30.

5,8-Quinolinequinone.—To a solution of 0.4 mole (58 g.) of 8-hydroxyquinoline in 200 ml. of water, 75 ml. of concentrated hydrochloric acid and 200 g. of ice was added a solution of 30 g. of sodium nitrite in 100 ml. of water in portions with vigorous shaking over 1 hr. at 0 to 4°. The mixture was allowed to stand overnight at 0° before the product was filtered off and washed with cold water. A yield of 80 g. (air-dried) of the hydrochloride of **5-nitroso-8-hydroxyquinoline** was obtained.[29]

In a 2-liter, round-bottomed flask 40 g. of this freshly prepared salt was dissolved in 160 ml. of water and 260 ml. of 5 *N* sodium hydroxide solution. When the solution was warmed to 40° and treated with 95 g. of sodium dithionite the temperature rose spontaneously to 75–80°. A rapid stream of nitrogen was introduced and the orange solution was allowed to cool slowly to about 50°; 250 ml. of 12 *N* sulfuric acid was then added and when the evolution of sulfur dioxide had subsided, the solution was maintained under diminished pressure with magnetic stirring until most of the dissolved gases had been removed. The resulting precipitate of the sulfate of **5-amino-8-hydroxyquinoline** was filtered off without washing after the mixture had been cooled in an ice-bath. It contained some sulfur and weighed 34 g.

Oxidation of this salt to 5,8-quinolinequinone may be carried out with potassium dichromate or ferric chloride. Best results were obtained with freshly prepared intermediates.

Twenty grams of the above crude salt was partially dissolved in 200 ml. of water, an equal volume of ice and 70 ml. of 12 *N* sulfuric acid. The mixture was placed in an ice-bath and vigorously stirred while 60 ml. of approximately 2 *N* potassium dichromate solution,[24] diluted to 80 ml. with ice, was added in about 30 sec. Five hundred milliliters of ice-cold chloroform was immediately added and after 3 min. the layers were allowed to settle briefly and the chloroform was drawn off by means of suction. A second 500-ml. portion of cold chloroform was quickly added and stirring resumed until 7 min. after the addition of the dichromate. An additional extraction with 250 ml. of cold chloroform was completed 5 min. later. The combined extracts were washed with saturated sodium chloride solution, shaken with Drierite and then a little Norite and concentrated under diminished pressure to about 60 ml. After the addition of about 400 ml. of Skellysolve F there was obtained 6.7 g. of bright yellow **5,8-quinolinequinone**. The quinone gradually decomposed above 116° when placed in the melting point bath at 110°, and melted at 120–121°.

Oxidation of crude 5-amino-8-hydroxyquinoline sulfate with ferric chloride was conducted in a separatory funnel at room temperature. Twenty-three grams of the salt suspended in 200 ml. of water and 300 ml. of chloroform was vigorously shaken for 1 min. with a solution of 70 g. of ferric chloride hexahydrate in 125 ml. of water and 25 ml. of concentrated hydrochloric acid. The chloroform was quickly removed and successive extractions with two 250-ml. and two 150-ml. portions of chloroform were completed within about 12 min. after the beginning of the reaction. After the combined chloroform extracts had been washed twice with saturated sodium chloride, the **5,8-quinolinequinone** was isolated as above in two fractions: 5.3 g. (m.p. 121–122° dec.) and 1.4 g. (m.p. 116.5–118.0° dec.).

A sample of the reductive acetylation product **5,8-diacetoxyquinoline**, was prepared as a derivative. One millimole of the quinone in 2 ml. of 2 *N* hydrochloric acid was treated with 0.3 g. of anhydrous sodium sulfite. Ice was added and the mixture was shaken with a large excess of acetic anhydride and 2 ml. of 8 *N* potassium hydroxide. The colorless crystalline precipitate thus obtained melted at 195–196° after two recrystallizations from alcohol.

Anal. Calcd. for $C_{13}H_{11}O_4N$: C, 63.67; H, 4.52. Found: C, 63.70, 63.89; H, 4.47, 4.74.

Addition of Hydrogen Chloride to 5,8-Quinolinequinone.—Two grams of 5,8-quinolinequinone was dissolved in 150 ml. of dry benzene in a 250-ml., round-bottomed flask containing an egg-shaped magnetic stirring bar to break up particles of precipitated salt formed as the reaction proceeded. After a rapid stream of dry hydrogen chloride had passed into the solution for 30 min. the stream of gas was slowed and vigorous stirring continued for 3 hr. longer. The precipitated salt of the addition product thus obtained weighed 2.84 g. A sample of this salt was converted to the free base in aqueous solution by treatment with sodium acetate. The melting point of this crude product was about 157° dec. and rose to 163–164° after recrystallization from ether–Skellysolve F. When one gram of the hydrochloride of the hydroquinone was acetylated by treatment with excess acetic anhydride for 5 min. at the boiling point, there was obtained 1.15 g. (95%) of crude diacetate which melted at 133.0–134.5°. The melting point was not depressed by admixture with 6-chloro-5,8-diacetoxyquinoline (XXII), but was lowered about 15° by admixture with a roughly equal amount of 7-chloro-5,8-diacetoxyquinoline (XXVI).

The infrared absorption spectrum of the latter compound, XXVI in a Nujol mull shows strong peaks at 1275 and 858

(29) This procedure has been described, without details, by St. v. Kostanecki, *Ber.*, **24**, 150 (1891).

cm.$^{-1}$ which are absent in 6-chloro-5,8-diacetoxyquinoline (XXI). There was no evidence of these bands in the spectrum of the above crude diacetyl derivative obtained from the hydrogen chloride addition product or of that of the second crop of crystals obtained on recrystallization.

COLLEGE PARK, MD.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

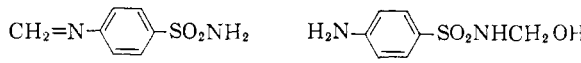
Dihydrobenzothiadiazine 1,1-Dioxides and their Diuretic Properties

BY L. H. WERNER, A. HALAMANDARIS, S. RICCA, JR., LOUIS DORFMAN AND GEORGE DESTEVENS

RECEIVED JUNE 12, 1959

A wide variety of 3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxides has been prepared by different methods. The nature of each of these reactions has been explored. The most promising procedure consists in condensing the appropriate *o*-aminobenzenesulfonamide with an aldehyde or acetal. Alkylation studies on 6-chloro-3,4-dihydro-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (VIIIa) have also led to some interesting products, the nature of which has been elucidated by chemical and physical means. The unique infrared absorption characteristics of this class of compounds have been studied. Some of these compounds were found to exhibit unusually high diuretic activity.

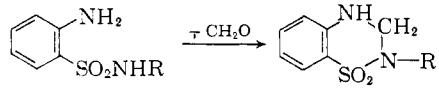
In the course of our studies on the chemotherapeutic properties of sulfonamides, it became of interest to determine the nature of the products derived from the condensation of sulfonamides with aldehydes. The literature[1] records that such condensations lead to resins or trimers. With regard to the *p*-aminobenzenesulfonamide–formaldehyde condensation, Wood and Battye[2] reported that products with the formulas I and II were obtained along with some polymer. A similar type of con-



I II

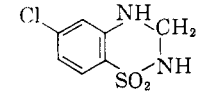
densation leading to a high molecular weight product has been suggested by Druey[3] for the reaction of formaldehyde with sulfathiazole.

However, it has been reported[4] that substituted *o*-aminobenzenesulfonamides react with formaldehyde in alkaline alcoholic solution to yield dihydrobenzothiadiazine 1,1-dioxides.



R = phenyl and substituted phenyl

We have carried out this reaction with unsubstituted *o*-aminobenzenesulfonamide[5] and various aldehydes in non-polar solvents with catalytic amounts of hydrogen chloride and have obtained analogous compounds. When the condensation was carried out with 2-amino-4-chlorobenzenesulfonamide and paraformaldehyde, the yield of 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide (III) dropped off markedly concomitant with the formation of an amorphous powder. It thus appeared that the polar chloro group on the



III

benzene ring modified the reactivity of the amino and sulfamyl functions. Since our interest in these heterocycles was influenced primarily by the inherent diuretic effect of disulfonamides and related substances,[6] we now turned our attention to the condensation of 6-substituted-4-amino-*m*-benzenedisulfonamides with various aldehydes. On the basis of previous experience, the possible formation of a polymer could not be discounted.

One of the first reactions explored was condensation of formaldehyde under acidic conditions with 4-amino-6-chloro-*m*-benzenedisulfonamide Va (see Scheme I). It was of interest to note that only cyclization had occurred to yield 6-chloro-3,4-dihydro-7-sulfamyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (VIIIa). The structure of this compound was confirmed by sodium borohydride reduction of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (VI).[7]

A large number of dihydrobenzothiadiazine 1,1-dioxides was prepared and selected representative examples are given in Tables I, II and III.

The methylation and acetylation of 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (VI) and of the corresponding dihydro compound VIIIa were studied and interesting differences in the reactivity of these two compounds were noticed.

The methylation of VIIIa with dimethyl sulfate yielded a monomethyl and dimethyl derivative. The latter was found to be identical with VIIIb which was obtained by condensing the N,N′-dimethyl-*m*-benzenedisulfonamide Vb with formaldehyde. Moreover, the infrared spectrum of this compound did not show NH_2 bands. Its diacetyl derivative XIb was devoid of NH bands (*vide infra*). However, the infrared spectrum of the monomethyl derivative *did* exhibit the bands characteristic of NH_2 absorption suggesting structures X or XIII. Nevertheless, the 7-methylsulfamyl derivative XVa could not be discounted

(1) A. Magnus-Levy, *Ber.*, **26**, 2148 (1893); E. Hug, *Bull. soc. chim.*, **5**, 1, 990 (1934); L. McMaster, THIS JOURNAL, **56**, 204 (1934); O. Albrecht, *Rev. gen. mat. plastiques*, **15**, 135 (1939); for a brief but concise review of this subject see also C. M. Suter, "The Organic Chemistry of Sulfur," J. Wiley and Sons, Inc., New York, N. Y., 1944, pp. 855–857.

(2) F. C. Wood and A. E. Battye, *J. Soc. Chem. Ind.*, **52**, 346 (1933).

(3) J. Druey, *Helv. Chim. Acta*, **31**, 179 (1948).

(4) J. H. Freeman and E. C. Wagner, *J. Org. Chem.*, **16**, 815 (1951).

(5) This compound was prepared according to the procedure outlined by H. E. Fierz-David, E. Schlittler and H. Waldman, *Helv. Chim. Acta*, **12**, 663 (1929).

(6) J. M. Sprague, N. Y. Acad. Sci., Biol. Sect., November 8, 1957.

(7) F. C. Novello and J. M. Sprague, THIS JOURNAL, **79**, 2028 (1957).