Sulfamoylquinoxalines, 1,2,4,5-Benzothiatriazepines, and 1,2,5-Benzothiadiazepines

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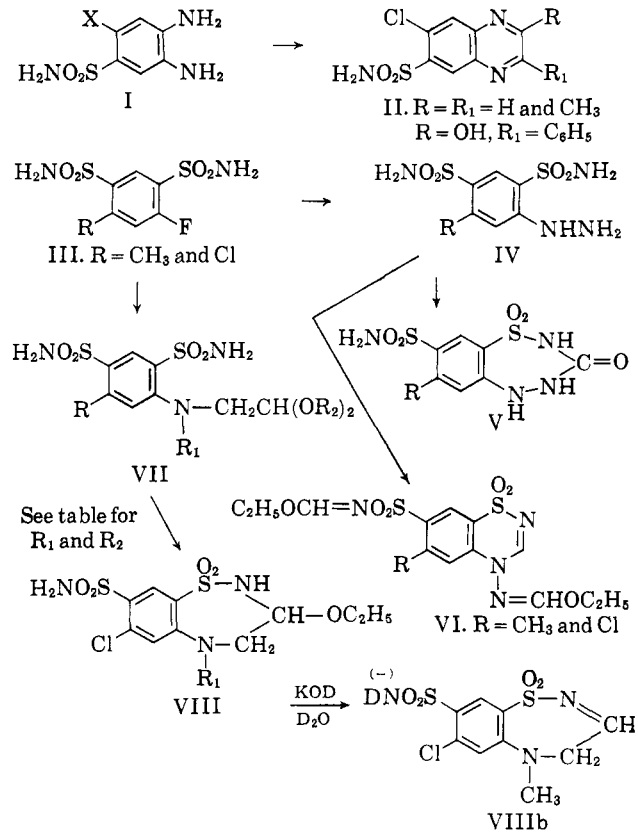
Condensation of 1,2-dicarbonyl compounds with a 3,4-diaminobenzenesulfonamide yielded sulfamoylquinoxalines. Disulfamoylphenylhydrazines were cyclized to 1,2,4,5-benzothiatriazepines, and β,β-dialkoxyethylamino-2,4-disulfamoylbenzenes yielded 1,2,5-benzothiadiazepines.

Since the early publications[1] of the physiologically active benzothiadiazines, reports[2-5] have appeared which describe modifications in the heterocyclic ring. This paper presents our investigations of sulfamoylquinoxalines, benzothiatriazepines, benzothiadiazepines, and benzobisthiadiazoles.

Reactions of glyoxal and of 2,3-butanedione with 6-chloro-3,4-diaminobenzenesulfonamide (I) yielded, respectively, 6-chloro-7-sulfamoylquinoxaline and 6-chloro-2,3-dimethyl-7-sulfamoylquinoxaline. Ethyl phenylglyoxalate condensed with I to give only one of two possible products. This product was assigned the structure 6-chloro-3-hydroxy-2-phenyl-7-sulfamoylquinoxaline because of the difference in the basicity of the two amino groups. The 4-amino group of I is less basic than the 3-amino group due to the electromeric effect of the sulfonamide. Condensation of the keto group of ethyl phenylglyoxalate would occur more readily with the basic 3-amino group followed by cyclization of the carbethoxy with the less basic 4-amino group.

The fluorine atoms of 5-chloro-2,4-disulfamoylfluorobenzene (III, R = Cl)[6] and of 5-methyl-2,4-disulfamoylfluorobenzene (III, R = CH_3)[6] were displaced with hydrazine in the manner described by Jackman[7] and co-workers. Cyclization of 5-chloro-2,4-disulfamoylphenylhydrazine (IV, R = Cl) with urea yielded $C_7H_7ClN_4O_5S_2$ having one of two possible structures: 7-chloro-3-keto-8-sulfamoyltetrahydro-1,2,4,5-benzothiatriazepine 1,1-dioxide (V) or 4-amino-6-chloro-3-keto-7-sulfamoyldihydro-1,2,4-benzothiadiazine 1,1-dioxide. The product showed two titratable groups, the very acidic —SO_2—NH—C=O— with a pK_a' below 3 and the weakly acidic SO_2NH_2 with a pK_a' of 12.0. This confirms structure V, the benzothiatriazepine. If the alternate 4-amino-1,2,4-benzothiadiazine 1,1-dioxide had been obtained it would have a third titratable group, the strongly basic extranuclear amine.

Hydrazides were prepared from IV and formic acid, acetic acid, propionic acid, succinic acid and cyclohexylacetic acid. All attempts to cyclize these hydrazides in base yielded only the unchanged hydrazides and acid treatment resulted in hydrolysis. Triethyl orthoformate and IV gave 7-N-ethoxymethylenesulfamoyl-1,2,4-benzothiadiazine 1,1-dioxides, VI, (R = Cl and CH_3). The structures of VI were verified by the absence of NH absorption in the infrared and by the instability of the hetero ring in base, since base cleavage is characteristic[6] of 4-substituted 1,2,4-benzothiadiazine 1,1-dioxides.



Displacement of the fluorine atoms of III with β,β-dialkoxyethylamines yielded 2,4-disulfamoyl-N-β,β-dialkoxyethylanilines, VII. Acid treatment of 5-chloro-2,4-disulfamoyl-N-β,β-diethoxyethylaniline yielded a polymeric substance having an apparent molecular weight of 936. Substitution of the aromatic amino group prevented polymerization of VII. Treatment of 5-chloro-2,4-disulfamoyl-N-β,β-diethoxyethyl-N-methylaniline (VII, R_1 = CH_3) and of 5-chloro-2,4-disulfamoyl-N-β,β-diethoxy-N-benzylaniline (VII, R_1 = $CH_2C_6H_5$) with acid resulted in an intramolecular elimination of ethanol in each case. This was demonstrated both by elemental analysis and by molecular weight determinations of the products (VIII). The nuclear magnetic resonance (n.m.r.) of VIII (R_1 = CH_3) was obtained by the Varian Model HR-60 after converting the compound to the 2-ion with potassium deuteroxide in deuterium oxide, Figure 1. Assignment of the aryl and alkyl protons with proof of the presence of only one ethoxy group requires a bicyclic structure having a benzene ring fused to a seven-membered 1,2,5-thiadiazepine ring as

(1) F. C. Novello and J. M. Sprague, *J. Am. Chem. Soc.*, **79**, 2028 (1957).
(2) U. M. Teotino and G. Cignarella, *ibid.*, **81**, 4935 (1959); **82**, 1594 (1960).
(3) S. M. Gadikor and J. L. Frederick, *J. Org. Chem.*, **27**, 1383 (1962).
(4) F. C. Novello, U. S. Patent 2,957,883 (1957); U. S. Patent 2,952,680 (1958).
(5) E. Cohen, B. Klasberg, and J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **82**, 2731 (1960).
(6) C. W. Whitehead and J. J. Traverso, *J. Org. Chem.*, **27**, 951 (1962).
(7) G. B. Jackman, V. Petrow, O. Stephenson, and A. M. Wild, *J. Pharm. Pharmacol.*, **12**, 648 (1960).

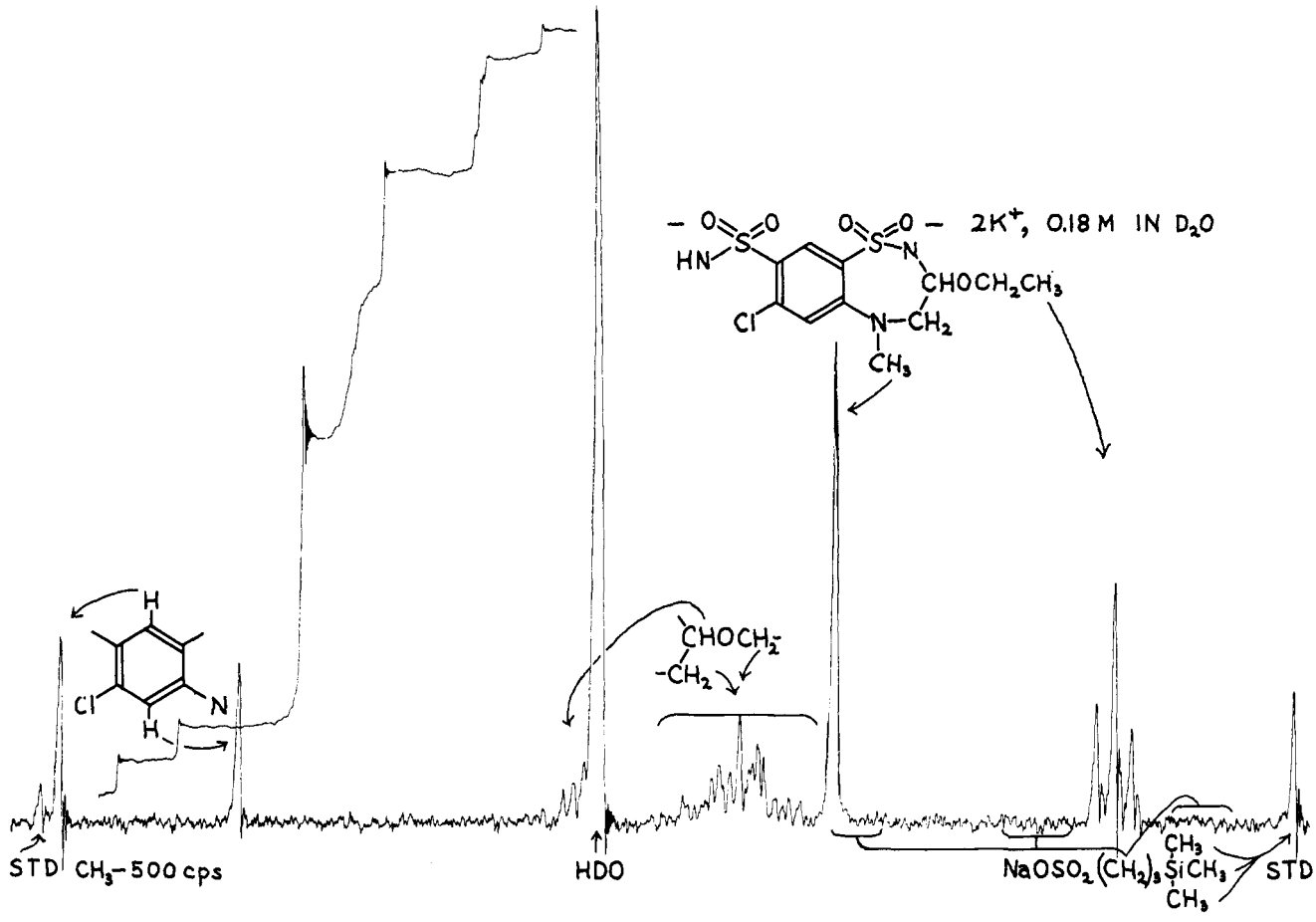


Figure 1

shown. The titration data is consistent with this structure with pK_a' values of 11.3 and 12.7, giving an apparent molecular weight of 366 compared to the theory of 368.5. The structure of VIII, $R_1 = CH_2C_6H_5$ was also confirmed by n.m.r. in an analogous manner. When VIII ($R_1 = CH_3$) is allowed to remain in the ionic form there is a gradual elimination of a second mole of ethanol. The spectrum in Figure 1 taken within ten minutes shows the methyl triplet of the ethyl group divided about 90:10 between the structure shown and $DOCH_2CH_3$. After two and one-half hours there was a 50:50 ratio, and after twelve hours the methyl triplet existed completely as $DOCH_2CH_3$ resulting in the total conversion of VIII ($R_1 = CH_3$) to the dihydro-1,2,5-benzothiadiazepine VIIIb ($R_1 = CH_3$).

Experimental

6-Chloro-7-sulfamoylquinoxaline, II, R = R₁ = H.—A solution containing 2.21 g. (0.01 mole) of 6-chloro-3,4-diaminobenzenesulfonamide,[3] 1.93 g. (0.01 mole) of 30% aqueous glyoxal and 1.08 g. (0.01 mole) of sodium bisulfite in 50 ml. of alcohol was boiled under reflux for 3 hr. The solution was filtered and concentrated and the resulting product was recrystallized from dilute alcohol, yield 1.5 g. (62%), m.p. 254°.

Anal. Calcd. for $C_8H_6ClN_3O_2S$: C, 39.55; H, 2.49; N, 17.30. Found: C, 39.35; H, 2.50; N, 17.19.

6-Chloro-2,3-dimethyl-7-sulfamoylquinoxaline, II, R = R₁ = CH₃.—A solution of 0.86 g. (0.01 mole) of 2,3-butanedione and 2.2 g. (0.01 mole) of 6-chloro-3,4-diaminobenzenesulfonamide in 100 ml. of alcohol was boiled under reflux for 2 hr. The solution was concentrated and the product was collected and recrystallized from dilute alcohol, yield 0.3 g. (11%), m.p. 260°.

Anal. Calcd. for $C_{10}H_{10}ClN_3O_3O_2S$: C, 44.30; H, 3.72; N, 15.52. Found: C, 44.86; H, 3.69; N, 15.21.

6-Chloro-3-hydroxy-2-phenyl-7-sulfamoylquinoxaline, II, R = OH, R₁ = C₆H₅.—A solution of 2.22 g. (0.01 mole) of 6-chloro-3,4-diaminobenzenesulfonamide and 1.8 g. (0.01 mole) of ethyl phenylglyoxalate in 50 ml. of ethanol was boiled under reflux for 4 hr. The solution was concentrated and the product that separated was recrystallized from dilute alcohol, yield 3 g. (89%), m.p. 270°.

Anal. Calcd. for $C_{14}H_{10}ClN_3O_3S$: C, 50.08; H, 3.00; N, 12.52. Found: C, 50.24; H, 3.07; N, 12.24.

1-Formyl- and 1-Acyl-2(2,4-disulfamoyl)phenylhydrazines, Table I, No. 7–13.—A solution of 5-chloro-2,4-disulfamoylphenylhydrazine (Table I, no. 6) or of 5-methyl-2,4-disulfamoylphenylhydrazine[7] in excess formic acid or in dioxane containing one mole equivalent of the appropriate carboylic acid anhydride was boiled under reflux for 5 hr. The solution was concentrated by reduced pressure distillation and the product recrystallized from dilute alcohol.

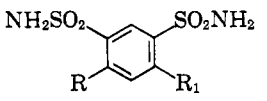
Attempted cyclization of these derivatives with aqueous ammonium hydroxide or with sodium ethoxide in ethanol yielded unchanged starting materials. Acid treatment resulted in hydrolysis of the acyl group.

7-Chloro-3-keto-8-sulfamoyl-2,3,4,5-tetrahydro-1,2,4,5-benzothiatriazepine 1,1-Dioxide, V, R = Cl.—A finely ground mixture of 15 g. of 5-chloro-2,4-disulfamoylphenylhydrazine and 7 g. of urea was heated in an oil bath at 190–195° for 3 hr. The residue was extracted with hot dilute alcohol. After the solution was filtered and concentrated the product crystallized, yield 14 g. (86%), m.p. 260° dec.

Anal. Calcd. for $C_7H_7ClN_4O_5S$: C, 25.73; H, 2.16, N, 17.15. Found: C, 25.93; H, 2.29; N, 17.00.

6-Chloro- and 6-Methyl-7-ethoxymethylenesulfamoyl-4-ethoxymethyleneamino-1,2,4-benzothiadiazine 1,1-Dioxide, VI.—Ten grams of 5-chloro-2,4-disulfamoylphenylhydrazine or of 5-methyl-2,4-disulfamoylphenylhydrazine was boiled in excess redistilled ethyl orthoformate (b.p. 145°) for 4 hr. The excess orthoformate was removed under reduced pressure and the residue was washed with ether. The products were recrystallized from alcohol. The 6-chloro derivative (compound A), m.p. 220°,

TABLE I



No.	R	R_1	Formula	Yield, %	M.p., °C.	Analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	Cl	$NHCH_2CH(OC_2H_5)_2$	$C_{12}H_{20}ClN_3O_6S_2$	50	170	35.80	5.02	10.45	35.99	5.17	10.49
2	Cl	$N(CH_3)CH_2CH(OCH_3)_2$	$C_{11}H_{18}ClN_3O_6S_2$	41	200	34.10	4.68	10.83	34.34	5.00	10.31
3	CH_3	$N(CH_3)CH_2CH(OCH_3)_2$	$C_{12}H_{21}N_3O_6S_2$	50	192			11.44			11.39
4	Cl	$N(C_3H_7)CH_2CH(OCH_3)_2$	$C_{13}H_{22}ClN_3O_6S_2$	55	176	37.58	5.33	10.10	37.62	5.54	9.97
5	Cl	$N(CH_2C_6H_5)CH_2CH(OC_2H_5)_2$	$C_{19}H_{26}ClN_3O_6S_2$	32	192 dec.	46.42	5.12	8.58	46.39	5.29	8.08
6	Cl	$NHNH_2$	$C_6H_9ClN_4O_4S_2$	86	230 dec.	23.96	3.02	18.63	23.95	3.20	18.37
7	Cl	NHNHCHO	$C_7H_9ClN_4O_5S_2$	91	260 dec.	25.57	2.76	17.04	25.92	2.89	17.10
8	Cl	$NHNHCOCH_3$	$C_8H_{11}ClN_4O_5S_2$	88	275 dec.	28.03	3.23	16.35	28.25	3.16	16.41
9	CH_3	NHNHCHO	$C_8H_{12}N_4O_5S_2$	90	251 dec.	31.16	3.92	18.55	31.29	4.29	18.17
10	CH_3	$NHNHCOCH_3$	$C_9H_{11}N_4O_5S_2$	85	265 dec.	33.53	4.38	17.38	33.61	4.42	17.05
11	Cl	$NHNHCO(CH_2)_2CO_2H$	$C_{10}H_{13}ClN_4O_7S_2$	32	225 dec.	29.96	3.27	13.98	30.08	3.17	13.95
12	CH_3	$NHNHCOC_2H_5$	$C_{10}H_{16}N_4O_5S_2$	80	285 dec.	35.70	4.79	16.66	36.11	5.26	16.71
13	CH_3	$NHNHCOCH_2C_6H_{11}$	$C_{15}H_{24}N_4O_5S_2$	80	215			13.96			13.94

was obtained in 21% yield, and the 6-methyl derivative (compound B), m.p. 225° was obtained in 28.5% yield.

The infrared spectra of both compounds did not show NH absorption.

Anal. of A. Calcd. for $C_{13}H_{15}ClN_4O_6S_2$: C, 36.92; H, 3.57; N, 13.25. Found: C, 37.02; H, 3.71; N, 13.03.

Anal. of B. Calcd. for $C_{14}H_{18}N_4O_6S_2$: C, 41.78; H, 4.51; N, 13.92. Found: C, 41.61; H, 4.62; N, 13.77.

2,4-Disulfamoyl-N-(β,β-dialkoxyethyl)anilines, Table I, No. 1–5).—A solution of 0.1 mole of the appropriate β,β-dialkoxyethylamine, 0.1 mole of triethylamine and 28.8 g. (0.1 mole) of 5-chloro-2,4-disulfamoylfluorobenzene or 26.8 g. (0.1 mole) of 5-methyl-2,4-disulfamoylfluorobenzene in 80 ml. of ethanol and 20 ml. of dioxane was boiled under reflux for 6 hr. The solution was concentrated, diluted with water and the product allowed to crystallize. The products were purified by recrystallization from dilute alcohol.

7-Chloro-3-ethoxy-5-methyl-8-sulfamoyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, VIII, R_1 = CH_3.—Five grams of 5-chloro-2,4-disulfamoyl-N-(β,β-diethoxyethyl)-N-methylaniline was added to 50 ml. of 95% alcohol and 6 ml. of 6N hydrochloric acid. The mixture was warmed on the steam bath. After a few minutes the solid dissolved and the product crystallized from solution. It was recrystallized from dilute alcohol, yield 4 g. (91%), m.p. 205°. The product is much less soluble (*ca.* 3–4 g./l.) than the starting material (*ca.* 15 g./100 ml.) in alcohol, and the melting point of a mixture of the two is depressed below that of either one alone.

Titration of the product in 66% N,N-dimethylformamide showed it to have pK_a' values of 11.4 and 13.0. The molecular weight was observed to be 366.0 (theory 368.5). The assigned structure is consistent with the infrared spectrum, having NH bands at 3.00, 3.09, and 3.22 μ; aryl ring absorption at 6.25 and 6.5 μ; a NH_2 deformation band at 6.32 μ; SO_2 bands at 7.59 and 8.7 μ; and an ether band at 9.26 μ.

Anal. Calcd. for $C_{11}H_{16}ClN_3O_5S_2$: C, 35.78; H, 4.36; N, 11.36; S, 17.35. Found: C, 35.76; H, 4.56; N, 11.36; S, 16.92.

7-Chloro-5-benzyl-3-ethoxy-8-sulfamoyl-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine, VIII, R_1 = $CH_2C_6H_5$.—Two grams of 5-chloro-2,4-disulfamoyl-N-benzyl-N-(β,β-diethoxyethyl)aniline was treated with 75 ml. of alcohol and 8.5 ml. of 6 *N* hydrochloric acid in the manner described for the preparation of VIII, R_1 = CH_3, yield 1.5 g. (86%), m.p. 198°.

The benzothiadiazepine structure is consistent with the nuclear magnetic resonance data. Maxima for the two *para* protons of the aromatic ring and the three protons of the methyl of the ethoxy group were identified.

Anal. Calcd. for $C_{17}H_{20}ClN_3O_4S_2$: C, 45.60; H, 4.67; N, 9.81; S, 14.38; Cl, 7.95. Found: C, 45.80; H, 4.82; N, 10.05; S, 14.64; Cl, 7.74.

Stereospecific Syntheses of Some Optically Active 5-Substituted 3-Aralkylideneamino-2-oxazolidinones

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The dextrorotatory 3,5-disubstituted 2-oxazolidinones IXa–d were prepared by a stereospecific synthesis that established their absolute configuration. The enantiomorph of IXd, XVI, was also prepared from the same starting material.

In a study made to determine whether the preparation of (−)-3(5-nitrofurfurylideneamino)-5-morpholinomethyl-2-oxazolidinone[1] from D-mannitol was feasible and to determine its absolute configuration, the compounds reported in this paper were prepared. The syntheses that were used are shown in the Flow Diagram.

The synthetic route V → IX was chosen so that none of the reactions used to make the series of 3,5-disubstituted 2-oxazolidinones, IXa–d, occurred at the asymmetric carbon atom. Thus no choice had to be made between alternate mechanisms in any of the steps and the absolute configuration of the products was elucidated.

(1) The partial resolution of the racemic compound, Furaltadone, was reported in 1960: G. Gever, J. G. Michels, B. F. Stevenson, F. F. Ebetino, E. A. Bellamy, and G. D. Drake, Abstracts of Papers, 137th National Meeting American Chemical Society, Cleveland, Ohio, April, 1960, p. 30 N.