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1,2,4-BENZOTHIADIAZINE DIOXIDES AND 3,4-DIHYDRO-1,2,4-BENZOTHIADIAZINE DIOXIDES[1,2]

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This paper reports the results of a study of the preparation and some properties of compounds of the types named, and includes a discussion of the courses of the ring closures employed or attempted in their formation. The class of benzothiadiazine dioxides has been represented hitherto by eight compounds, and the dihydro series by five.[4] There are added nine benzothiadiazine dioxides, all with substituents in position 2, and nine dihydrobenzothiadiazine dioxides similarly substituted, as well as twenty-six intermediates or derived compounds. The ultraviolet absorptions of the two types and of some intermediate or related compounds are reported. A case of isomerization involving migration of an acetyl group from one nitrogen atom to another is described.

I. *1,2,4-Benzothiadiazine dioxides.* Ekbom (1) obtained three compounds of this class from orthanilamide. Schrader (2) and Wertheim (3) reported two more, and Tozer and Smiles (4) reported as new a compound identical with one of Ekbom's. Some of these compounds were obtained as unexpected products in studies with other objectives.[5]

1. *Formation of 1,2,4-benzothiadiazine dioxides.* The method of Ekbom (1),

[1] Paper constructed from the Ph.D. dissertation of James H. Freeman, University of Pennsylvania, 1950.

[2] Self-evident numbers to locate the dioxide condition (1- or 1,1-) are omitted as a superfluous complication of names already cumbersome.

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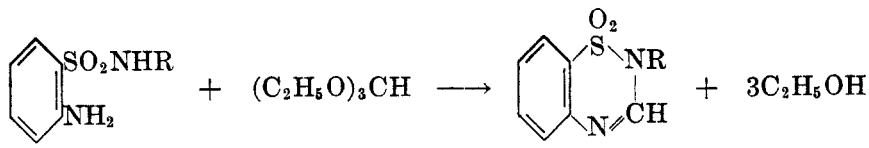
[4] At the time this paper was first written there had been reported five benzothiadiazine dioxides and no dihydrobenzothiadiazine dioxides. The recent paper by Parke and Williams (41) reports preparation of three new compounds of the first class (made from nuclear-substituted orthanilamides by action of formic acid) and five compounds of the dihydro series. These last are all substituted 3-keto compounds made by interaction of substituted orthanilamides and urea.

[5] Shrader (2), while studying Curtius rearrangements, found that *o*-sulfamidobenzoyl azide yielded the benzothiadiazine dioxide instead of the expected orthanilamide. Wertheim (3) obtained 3-phenyl-1,2,4-benzothiadiazine dioxide in the course of attempts to make "diphensaccharin." Tozer and Smiles (4), during the study of *o*-carbamyl derivatives of diphenyl ether, were unable to obtain *o*-aminobenzenesulfonacetamide from the corresponding nitro compound because ring closure accompanied reduction (*cf.* compound XXXIX). Of the meager literature in this field several papers were discovered belatedly owing to the incidental appearance of the compounds, coupled with some vagaries in nomenclature and indexing. Shrader designated 3-hydroxy-1,2,4-benzothiadiazine dioxide as "*o*-sulfamidophenylcarbamic anhydride" and it is so indexed. Wertheim's compounds are indexed under the entry "Benzamide, N-(*o*-aminophenylsulfonyl)." The association of these related matters is overdue, for it appears that the writers of the papers cited were unaware of the disclosures of their predecessors.

an extension of the Ladenburg ring closure, was selected for study. The intermediate *o*-aminobenzenesulfonamides were prepared from *o*-nitrochlorobenzene *via* *o*-nitrobenzenesulfonyl chloride (5), the N-substituted *o*-nitrobenzenesulfonamides (6–10), the corresponding *o*-aminobenzenesulfonamides (7, 11–14), with final ring closure by interposition of a carbon between the two nitrogen atoms. Data for five *o*-nitrobenzenesulfonamides not previously reported appear in Table I. Reduction to the corresponding *o*-aminobenzenesulfonamides was most satisfactorily effected by use of either stannous chloride (7) or of hydrogen in presence of palladium-charcoal (13, 14). Data for seven N-substituted *o*-aminobenzenesulfonamides are collected in Table II.

Ring closure. The familiar reagents for closure of 1,3-diaza-rings by involving —NH_2 with —NH— to yield —N=C(|)—N< include acids, acid anhydrides, acyl chlorides, amides, esters, orthoesters (15b), imino-esters (ethers), amidines (16), and 1,1,1-trihalogeno compounds and alkali (17). Reagents of the first three types (*viz.*, formic acid, acetic anhydride, acetyl chloride) proved in the present case to be ineffective; the resulting acylated *o*-aminobenzenesulfonamides resisted efforts at ring closure, whether by heat alone or in presence of anhydrous zinc chloride or of alkaline reagents. *Ethyl orthoformate* was used with uniform success, as in closure of the pyrimidine ring (of quinazolines) by von Walther and Bamberg (15).



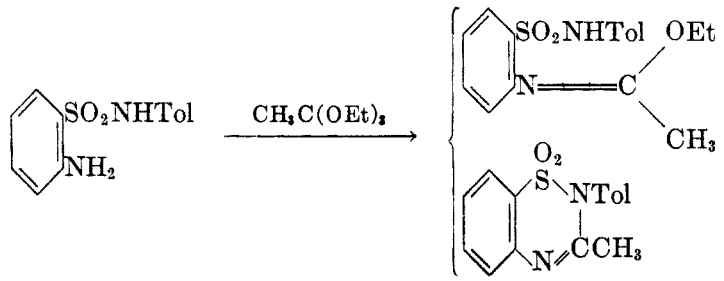
R = C_6H_5, *o*- and *p*-$C_6H_4CH_3$,

o-ClC_6H_4, *o*-$CH_3OC_6H_4$,

2,6-$(CH_3)_2C_6H_3$, α-$C_{10}H_7$

Ring closure was not adversely affected by the presence of an *ortho*-substituent in an N′-aromatic ring, perhaps due to the effect of a group so placed in maintaining the N′-ring in angular orientation with respect to the plane of the fused ring system. During interaction of ethyl orthoformate and the aminosulfonamide the alcohol of reaction was concurrently removed [found advantageous also in the similar preparation of substituted formamidines (18)], as its accumulation may lead to a reversible system in which the corresponding imino-ether may become a prominent product (19, 20, 40). *Ethyl orthoacetate* was used with only qualitative success. The yield of benzothiadiazine dioxide was small, and the principal

product was the imino-ether even though provision was made to remove alcohol as formed:

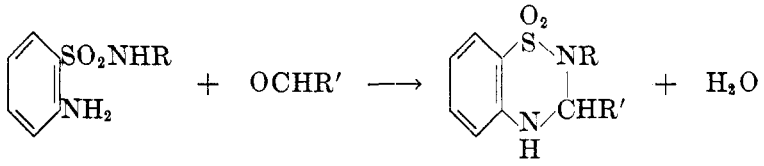


Efforts to force ring-closure in the isolated imino-ether were not successful, suggesting that the imino-ether may not be intermediate in formation of the amidine. In these experiments no evidence was found of the presence of any bis-(benzenesulfamido)acetamidine. Data for seven N′-substituted benzothiadiazine dioxides (made by use of ethyl orthoformate) and for 2-*o*-tolyl-3-methyl-1,2,4-benzothiadiazine dioxide (made by use of ethyl orthoacetate) are presented in Table III.

2. *Some properties of 1,2,4-benzothiadiazine dioxides.* The compounds reported are stable and insoluble in water and in aqueous alkali, facts which, in conjunction with their relationship to the orthanilamide system, make them not obviously promising for therapeutic testing (21). The 3,4-double bond is not affected by bromine, and appears to be not susceptible to satisfactory hydrogenation. Attempted reduction by sodium and alcohol caused ring cleavage with formation of the *o*-aminobenzenesulfonamide, recalling the similar behavior reported for some pyrimidines (22), and contrasting with the ready hydrogenation of the 1,2-double bond of some 3,4-dihydroquinazolines by the same means (23). Attempted catalytic hydrogenation (Pd-charcoal) of 2-*o*-tolyl-1,2,4-benzothiadiazine dioxide (XVIII) in ethanol was without effect, and in acetic acid there was formed only about 10% of the 3,4-dihydro compound; the main product was *o*-formaminobenzenesulfon-*o*-toluide, obtainable also by action of acetic acid alone upon XVIII. The desired product 2-*o*-tolyl-3,4-dihydro-1,2,4-benzothiadiazine dioxide (XXX), made synthetically as described later, was found to be cleaved only partially by sodium and alcohol and not at all by hydrogen and palladium in acetic acid. These facts make it appear that the ring cleavages observed in acetic acid involve the unhydrogenated benzothiadiazine dioxide and may be (over-all) hydrolytic (analogous to cleavages of imidazoles, quinazolines, and some open-chain amidines),[6] proceeding perhaps by a course initiated by addition of acetic acid at the 3,4-double bond and similar to the transacetylation reaction discussed later.

[6] A different cleavage of amidines by slow hydrogenation at low pressures in presence of Pd-C was reported by Kubiczek (24) to yield amine and hydrocarbon. Work in this laboratory with N,N′-diphenylacetamidine and benzimidazole showed both to be unaffected by hydrogen under pressure of 2 to 3 atm. and in presence of either Raney nickel or palladium-charcoal.

II. *3,4-Dihydro-1,2,4-benzothiadiazine dioxides.* Failure to obtain these compounds by hydrogenation of benzothiadiazine dioxides proved to be not a handicap, for it was found that action of aldehydes upon *o*-aminobenzenesulfonamides provided a satisfactory method for their preparation:

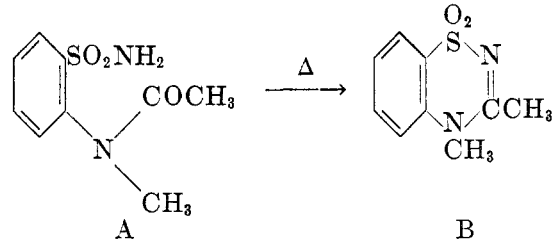


R = C_6H_5, *o*- and *p*-$CH_3C_6H_4$, *o*-ClC_6H_4, R′ = H, CH_3, C_6H_5 *o*-$CH_3OC_6H_4$, 2,6-$(CH_3)_2C_6H_3$, α-$C_{10}H_7$, *n*-C_5H_{11}

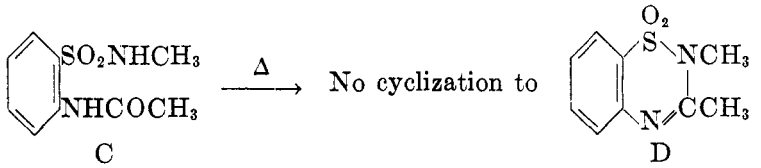
This procedure is based upon that for preparation of open-chain alkylidene-*bis*-amines (25) and of tetrahydroquinazolines (26a). The use of excess aldehyde was not observed to lead to formation of hydroxyalkyl compounds (26). Data for nine dihydrobenzothiadiazine dioxides appear in Table IV.

Catalytic reduction (palladium-charcoal in acetic acid) was without effect upon XXX (R = *o*-tolyl), and action of sodium and alcohol caused partial cleavage to yield the *o*-aminobenzenesulfon-*o*-toluide. Action of permanganate in acetone, in some cases a useful procedure for conversion of —NHCH— to —N=C— (26, 27), and also action of lead tetraacetate (28), failed to dehydrogenate XXX to XVIII.

III. *Course of the cyclization of o-aminobenzenesulfonamides.* A. *1,2,4-Benzothiadiazine dioxides.* Ekbom (1) obtained 1,2,4-benzothiadiazine dioxide from orthanilamide and formic acid, and 3-methyl-1,2,4-benzothiadiazine dioxide from orthanilamide and acetic anhydride. Assuming acylation to precede ring closure, and in an effort to learn the source of the water split out, he prepared the isomeric compounds *o*-(N-methylacetamino)benzenesulfonamide (A) and *o*-acetaminobenzene-N′-methylsulfonamide (C) and attempted ring closures by heat. Only the first compound could be cyclized:



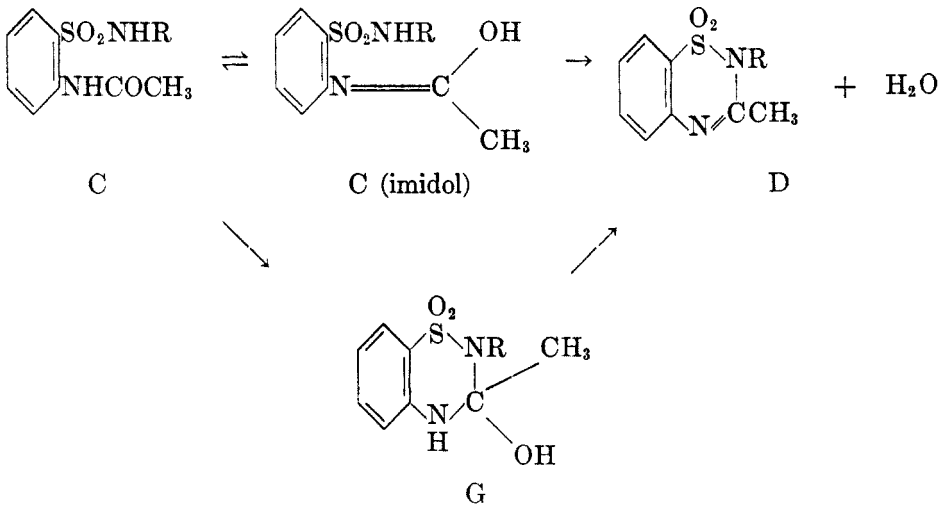
A B



C D

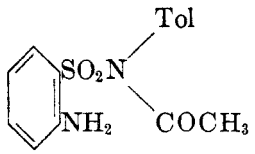
Ekbom concluded that a requisite for ring closure is the presence of two hydrogen atoms on the sulfonamide-nitrogen (as in formula A). This finding is not necessarily relevant to the present study, in which the starting compounds are not of type A. Further Ekbom's cyclized product B, with a fixed 2,3-double bond, is not of the same type (D) as compounds XVII–XXIV (Table III), each of which contains a fixed 3,4-double bond.

The failure of C to undergo ring closure is a matter of interest, for such a reaction appears to be possible by either of two courses:

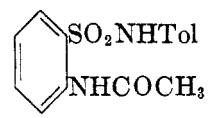


Analogous over-all reactions occur readily in ring closures to yield benzimidazoles and quinazolines. Since in this study treatment of compounds of the type o-$NH_2C_6H_4SO_2NHR$ with formic acid, acetic anhydride, or acetyl chloride, each of which must cause initial acylation, likewise failed to produce benzothiadiazine dioxide, it must be concluded that some unrecognized influence is operative to obstruct ring closure. The view that this influence is the immobilization of a hydrogen atom of the o-amino group by hydrogen bonding with oxygen of the sulfonyl group is considered below and seems tenable.

During attempts to effect ring closure with acetic anhydride and with acetyl chloride it was found that these reagents yielded with o-aminobenzenesulfon-o-toluide (X) not a single product but two isomeric monoacetyl compounds which were identified, by functional tests with corroboration from ultraviolet spectral data, as E and F respectively:



E(XXVIII)

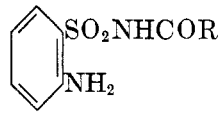


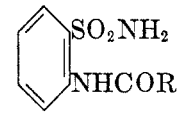
F(XXVI)

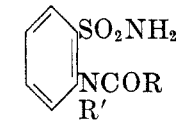
It was found that E is converted to F upon heating (200°), or by action of hot aqueous sodium hydroxide or of warm acetic acid. The reaction could not be reversed, the higher-melting isomer (F) being the more stable. To account for this transacetylation under the conditions mentioned it seems necessary to assume an isomeric but unstable cyclic intermediate G, the probable nature of which is discussed below.

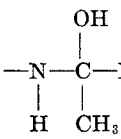
Acylation of *o*-aminobenzenesulfonamides therefore probably occurs on the sulfonamide-nitrogen to yield first a compound of type E which isomerizes to F, so that explanation of the obstruction to ring closure must be sought in the nature of F. By assuming existence of a hydrogen-bond involving *o*-amino hydrogen and sulfonyl oxygen, the existence of which in methyl *o*-aminophenyl sulfone was postulated by Fehnel and Carmack (29), the possibility of isomerization of F to the imidol form is excluded by the immobilization of the hydrogen atom. Any move toward ring closure is further obstructed because chelation results in orientation of the *o*-acetamino group such that the acetyl group is directed away from the sulfonamide nitrogen, an effect perhaps augmented by the repulsive electrochemical characters of the carbonyl and sulfonyl groups and also sterically owing to the bulk of the latter. An alternative path leading from E or F to the benzothiadiazine dioxide *via* hypothetical intermediate G (*cf.* conversion of C to D, above) seems certain to be unproductive even though in such a cyclic compound the chelate binding probably could not survive ring closure, because the instability of this structure to simple cleavage can scarcely be doubted: the structure of G is that of a hydroxylated ethylidine-*bis*-amine, equivalent to a mixed-system hemiacetal or to a mixed-system ortho acid only two-thirds esterified.[7] Its cleavage to yield F should be rapid, unobstructed, and substantially irreversible and is apparently a logical stabilization of the very unstable system in G. It is to be expected that this cleavage will completely anticipate the removal of water from G (by which it could be converted to the benzothiadiazine dioxide), which further is opposed by the rigid orientation of the molecule (so long as it holds together) and by the pull exerted upon the *o*-amino hydrogen by the sulfonyl group.

This hypothesis as to the course of the ring closure leads to the conclusion, which is consistent with observed behaviors, that the following types are eligible to undergo ring closure to yield 1,2,4-benzothiadiazine dioxides:

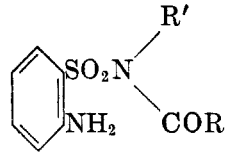


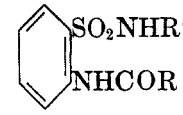




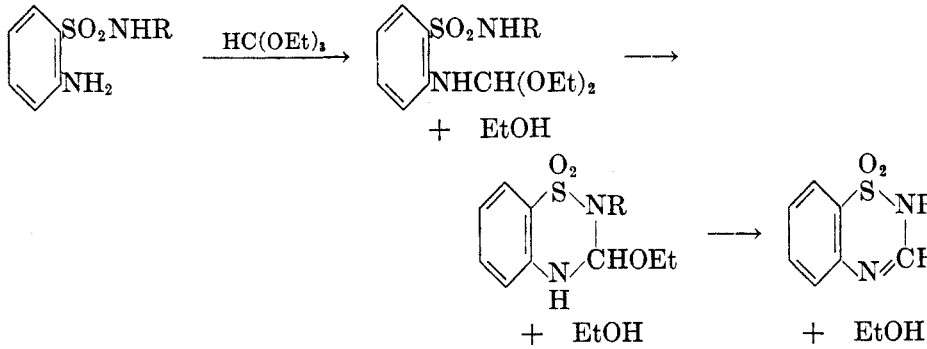
[7] The  grouping in G may be regarded as a nitrogen-system analog of the type of intermediate believed to be involved in transacylations in the carbohydrate series (39).

The following types do not undergo ring closure:



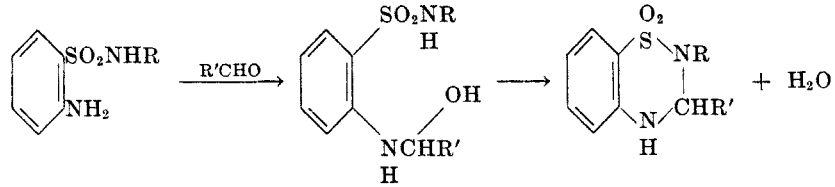


Ring closure by ethyl orthoformate is probably essentially similar to that by aldehydes, for orthoformic ester may be regarded as an acetal and shows a quasi-aldehydic character. Its condensation with *o*-aminobenzenesulfonamides may proceed thus (*cf.* 40):



Loss of alcohol from the assumed cyclic intermediate (which is a mixed-system ortho ester and hence should be more stable than G) would not be strongly impeded, for the hydrogen at position 4 is no longer involved in chelation.

B. *3,4-Dihydro-1,2,4-benzothiadiazine dioxides* (Ring closure). Aldehydes (and ethyl orthoformate) cause cyclizations with precursors not amenable to ring closure by formic acid, acetic anhydride, or acetyl chloride, indicating that the course of ring closure by aldehydes is one not subject to the restrictions discussed above. Aldehydes will react preferentially with the *o*-amino group (rather than with the sulfonamide group) to yield initially hydroxyalkylamine compounds which, in spite of chelate binding of one amino-hydrogen, are free to undergo cyclization:



IV. *Ultraviolet spectral examination.*[8] To extend the descriptions of the types of compounds studied, and to resolve some structural questions, certain of the compounds discussed, and suitable reference compounds, were examined by ultraviolet spectroscopy. Essential data are presented in Table V, and the plotted

[8] Grateful acknowledgment is made to Dr. E. H. Fehnel of Swarthmore College for advice on interpretation of the ultraviolet absorption data.

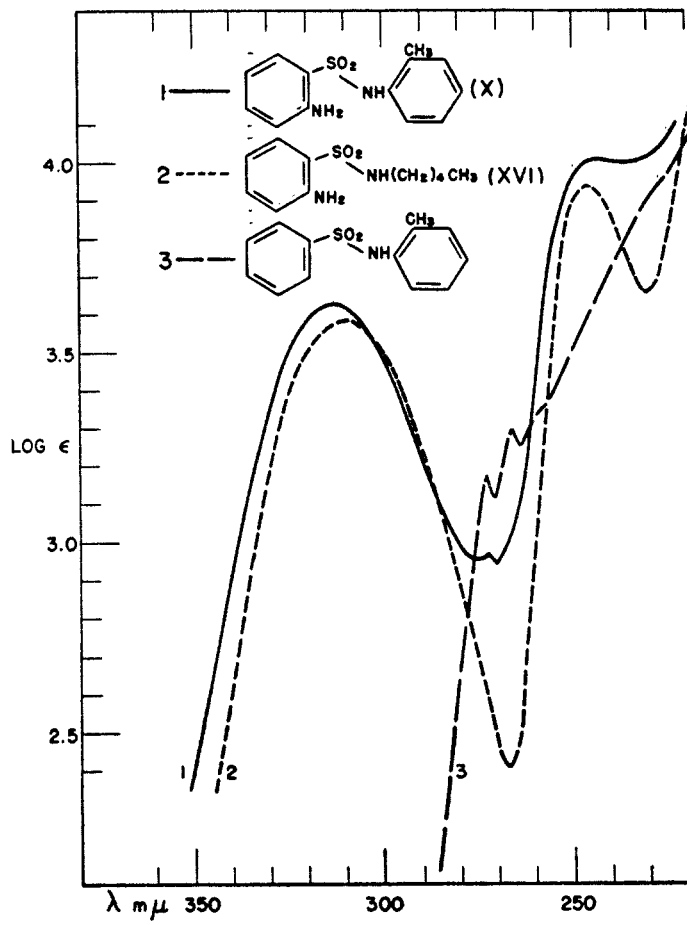
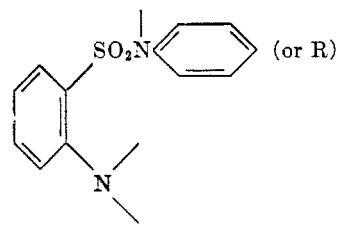


FIGURE 1. ULTRAVIOLET ABSORPTION SPECTRA OF COMPOUNDS X, XVI, AND BENZENESULFON-*o*-TOLUIDE

absorptions are shown in Figures 1 to 5. All the compounds studied represent modifications of a single resonance system in most of which the structure



is present; the curves therefore are modifications of the curve for aniline, showing a bathochromic shift of about 25 mμ and 10 mμ for the prominent bands at longer and shorter wavelengths respectively, attributable to influence of the sulfonyl group upon the resonance within the aniline unit (31).

A primary reference compound is *o*-aminobenzensulfonyl-*o*-toluide (X), the principal features of whose spectrum (curve 1 in Figures 1, 2, 4, and 5) are prominent absorption maxima at 314 mμ and 244 mμ and a small intermediate peak at 272 mμ, probably a modified remnant of the fine structure of benzenoid absorption. The *o*-tolyl group contributes little to the resonating system, owing probably to its inability to maintain a position planar with respect to the *o*-amino-

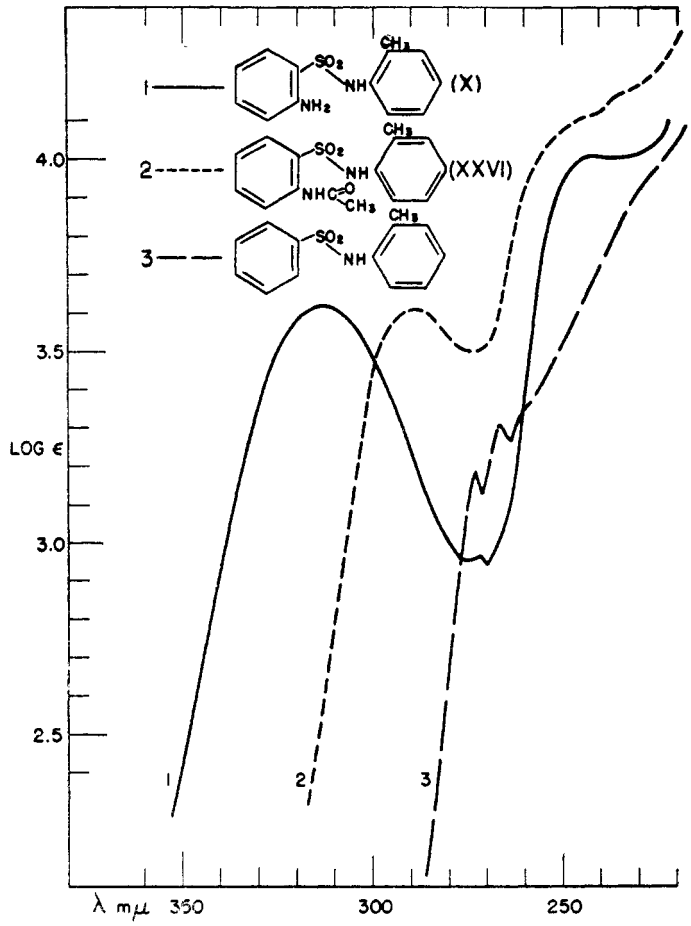


FIGURE 2. ULTRAVIOLET ABSORPTION SPECTRA OF COMPOUNDS X, XXVI, AND BENZENESULFON-*o*-TOLUIDE

benzenesulfonamide system. Replacement of the tolyl group by *n*-amyl (XVI; curve 2, Figure 1) causes only a slight (about 3 mμ) hypsochromic shift, loss of the residual fine structure at 272 mμ, and some sharpening of the maxima, with appearance of a minimum point at 231 mμ. This minimum appears otherwise only in 1,2,4-benzothiadiazine systems in which maximum interference with planarity exists with respect to an N′-aryl group (curves 2 and 3, Figure 5; curve 3, Figure 4). In absence of the *o*-amino group (curve 3, Figure 1) the

prominent absorption in the 310 mμ region due to the aniline chromophore is lacking, and the markedly different absorption is due to superposition of the independent absorptions of the benzenesulfonamide and toluene systems.

Comparison of the absorption of compound F (XXVI) with the absorptions of X and benzenesulfon-*o*-toluide (Figure 2) reveals that the *o*-acetamino group shifts the major peak (of X) from 314 mμ to 290 mμ, obliterating the fine struc-

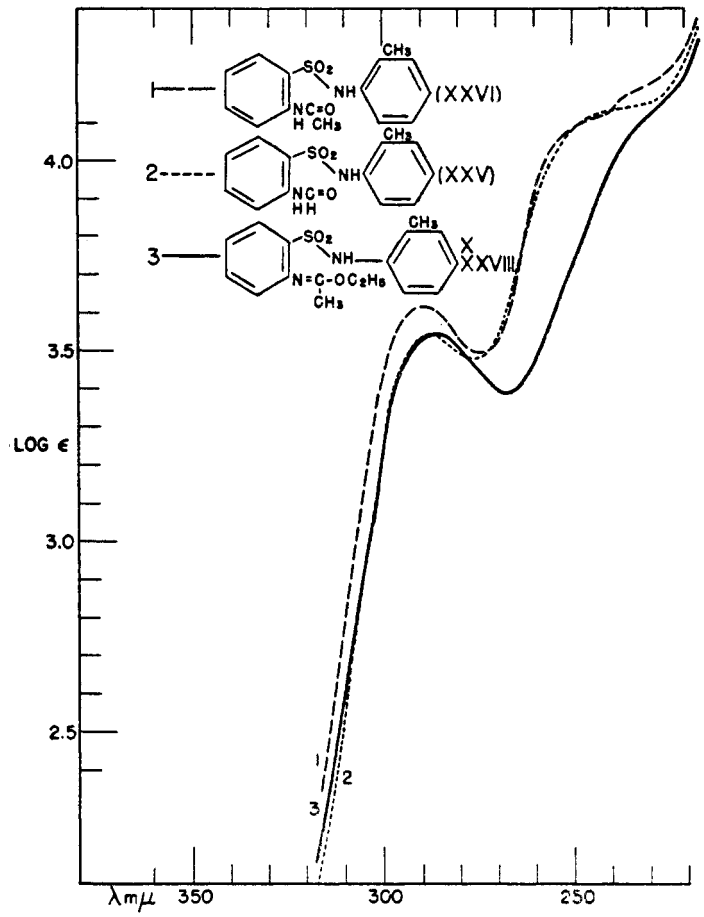


FIGURE 3. ULTRAVIOLET ABSORPTION SPECTRA OF COMPOUNDS XXVI, XXV, AND XXXVIII

ture at 272 mμ in the overlapping feet of the two major bands, and rounding off the shoulder at 244 mμ. It may be concluded that the simultaneous presence of the sulfonyl and the acetyl groups forces the *ortho*-nitrogen atom out of planarity and restricts the resonance of its unshared electron pair with the ring (32). The resonance interference is a matter of degree and does not cancel the aniline characteristics but strongly modifies them. A similar effect due to loss of resonance in substituted dimethylaniline systems was observed by Remington

(30) and by Klevens and Platt (33), and was found to vary in degree with the relative sizes of the groups in the *ortho* position.

The curves for F (XXVI), XXV, and XXXVIII (Figure 3) appear to establish the structure of F (obtained from *o*-aminobenzenesulfon-*o*-toluide by action of acetyl chloride) to be as shown, for these curves show no important differences, and the presence of the formyl group of XXV and of the ester group of XXXVIII

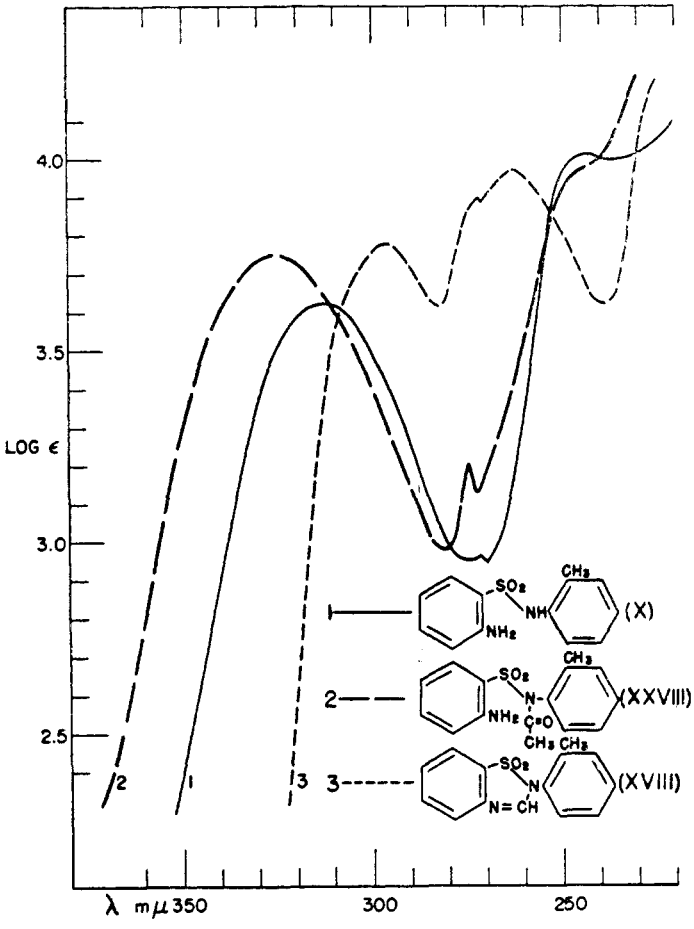


FIGURE 4. ULTRAVIOLET ABSORPTION SPECTRA OF COMPOUNDS X, XXVIII, AND XVIII

on the *ortho*-nitrogen in each case is virtually assured by the manner of preparation and the properties of each. The curve for compound E (XXVIII, obtained from *o*-aminobenzenesulfon-*o*-toluide by action of acetic anhydride, and isomeric with F), shown in Figure 4, is significantly different from that for F (XXVI), showing a pronounced aniline absorption corresponding to that of other compounds with free *ortho*-amino group, though affected by a bathochromic shift from 314 mμ to 325 mμ, attributable to the extended conjugation possible when

the acetyl group is joined to the sulfonamide-nitrogen, in which position it encounters little interference in maintaining planarity. These comparisons suffice to support the identifications of compounds E and F (XXVIII and XXVI), the structures of which are involved in the earlier discussion of the mechanism of ring closure. The absorption of E (Figure 4) much resembles the absorptions of

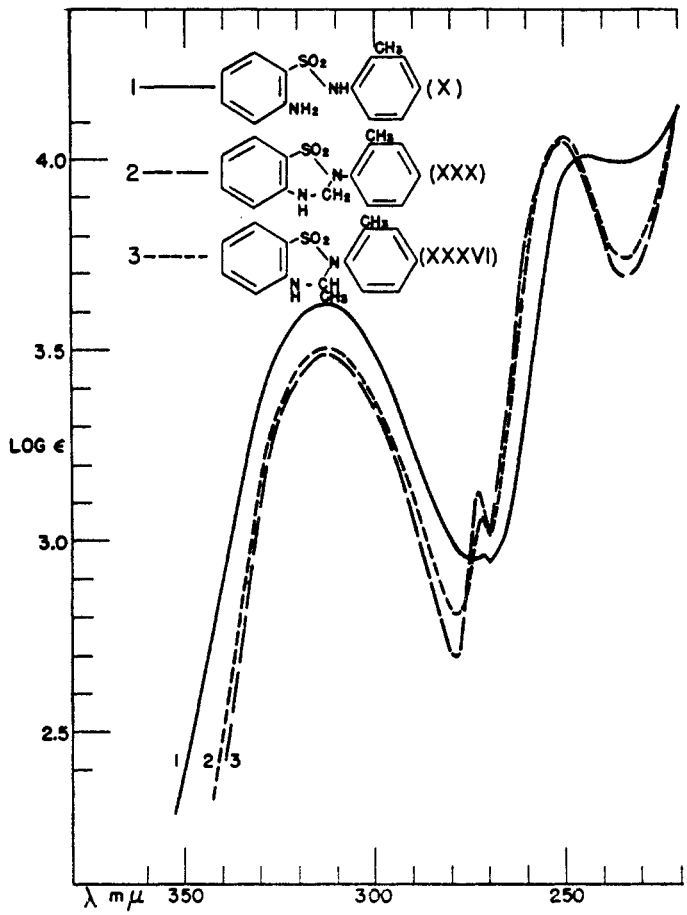


FIGURE 5. ULTRAVIOLET ABSORPTION SPECTRA OF COMPOUNDS X, XXX, AND XXXVI

the dihydrobenzothiadiazine dioxides XXX and XXXVI (Figure 5), as is to be expected since in all there are present similar conditions for resonance.

The absorption of XVIII (a Δ^3-benzothiadiazine dioxide), shown by curve 3 in Figure 4, differs markedly from the absorptions of the non-cyclic compounds and of the dihydro compounds whose absorptions are plotted in Figure 5. In XVIII the presence of the C=N bond results in displacement of the one maximum from 314 mμ to 296 mμ, without obliteration of the small peak at 272 mμ, now a shoulder on the short wavelength band which itself has undergone a bathochromic shift to 263 mμ.

Absorptions of the dihydrobenzothiadiazine systems are plotted in Figure 5. The resemblances to the absorption of X are pronounced, as are the aniline characteristics, due to the fact that the stable ring structure maintains the No. 4 nitrogen in a state of planarity and thus increases the resonance within the phenyl-amino chromophore. The *o*-tolyl group is excluded from contributing to the resonance of the system owing to its enforced orientation almost at right angles to the plane of the main ring systems. As evidence of this condition there reappears the minimum at 235 mμ shown in Figure 1 to be characteristic of a compound (XVI) with an alkyl group attached to the sulfonamide-nitrogen.

It may be added that if either E (XXVIII), obtained by acetylation of X with acetic anhydride, or F (XXVI), obtained either by acetylation of X with acetyl chloride or by transacetylation of E, were the assumed cyclic isomer G instead of the N-acetyl or the N′-acetyl compound, the absorption of this compound should resemble that of the compounds XXX and XXXVI (Figure 5). Comparison of curve for E in Figure 4, the curves for F in Figures 2 and 3, and the curves for the cyclized compounds in Figure 5 reveals lack of identity, and indicates that E and F are acetamino compounds as is to be inferred from the chemical evidence.

EXPERIMENTAL

Compounds for which analyses are given are new. Analyses were made by Sarah M. Woods. nitrogen was determined by the Kjeldahl method, and sulfur by the oxygen bomb (34). Melting points are corrected values. In cases of doubtful identities, especially among intermediates and degradation products, mixture melting point tests were made using all other compounds with which confusion might arise.

Preparation of o-nitrobenzenesulfonamides. To a mixture of 0.22 mole of the amine and 0.2 mole (15.8 g.; 15.6 ml.) of dry pyridine was added 44.3 g. (0.2 mole) of *o*-nitrobenzenesulfonyl chloride (5), with swirling and cooling. After initial reaction subsided the mixture was warmed on a steam-bath for 5 minutes, then cooled and triturated with several 100-ml. portions of 2 *N* hydrochloric acid. The residue was washed with water and then crystallized from ethanol or acetic acid by dilution with water; in some cases the sulfonamide was dissolved in 5% aqueous sodium hydroxide, treated with carbon, and recovered by acidification of the filtrate with 30% acetic acid. Data for the compounds so prepared appear in Table I.

Preparation of o-aminobenzenesulfonamides. Reduction by sodium disulfide (12) or by ferrous hydroxide (11, 12b) gave relatively low yields of products not readily purified. Reduction by stannous chloride and hydrochloric acid in ethanol (7) gave good yields and, in spite of inconveniences in isolation and in removal of final traces of tin, was used in early experiments. Catalytic reduction proved to be the best method, giving good yields of products which in some cases required no further purification.

Reductions by hydrogen and palladium on charcoal (14) were effected in a simple low-pressure outfit (13) provided with a heating jacket wound with chromel wire and asbestos, and using about 0.04 mole of *o*-nitrobenzenesulfonamide in 100–200 ml. of glacial acetic acid, 1 g. of dry catalyst per 0.01 mole of nitro compound, and a temperature of about 55°. Partway through the reduction it was necessary to renew the catalyst (spent catalyst filtered out and 3 g. of fresh catalyst added), and in some cases two replacements were needed. Reduction required about 4 hours and consumed about 3 liters of hydrogen (about 10% in excess of theory owing to manipulative losses). The apparatus was calibrated and the catalyst tested at intervals by hydrogenating cinnamic acid.

The reduction liquid was filtered twice, finally into twice its volume of water. Precipitation of the product was completed by addition of 150–200 g. of sodium bicarbonate. The

product, washed with water and dried, was in many cases pure enough for use. Analtyical samples were taken from material recrystallized from aqueous ethanol. Data for seven new *o*-aminobenzenesulfonamides are presented in Table II. *Hydrochlorides* were prepared by passing hydrogen chloride into solutions of the orthanilamides in dry ethanol, or by adding concentrated hydrochloric acid. Yields generally exceeded 90%. The acid is not firmly held; it is removed by dissolving the salts in ethanol.

Preparation of substituted 1,2,4-benzothiadiazine dioxides.

(a) *Ring-closure by ethyl orthoformate.* To 0.01 mole of pure *o*-aminobenzenesulfonamide in an open Erlenmeyer flask was added 2.2 g. (2.0 ml., 0.015 mole) of ethyl orthoformate (Eastman #1674 redistilled; as received the ester was far from pure), and the mixture was heated in an oil-bath at 110–130° for about 30 minutes or until bubbling ceased and the alcohol of reaction had evaporated; in large runs the alcohol was distilled.[9] The residue was cooled and was ground with 30 ml. of 5% sodium hydroxide to remove unchanged sulfonamide, and was crystallized from methanol.

These compounds are not soluble in water, dilute aqueous sodium hydroxide, hexane, or cyclohexane. To various extents they dissolve in benzene, ether, ethyl acetate, hot

TABLE I

o-NITROBENZENESULFONAMIDES[a]

NUMBER[b]	*o*-NITROBENZENESULFON-	FORMULA	YIELD, %	M.P., °C.	COMPONENT	ANALYSIS	
						Calc'd	Found
II	-*o*-toluide	$C_{13}H_{12}N_2O_4S$	75	137–138	C	53.41	53.40
					H	4.14	4.17
					N	9.59	9.66
IV	-*o*-chloroanilide	$C_{12}H_9ClN_2O_4S$	40	147–148	N	8.96	9.17
V	-*o*-aniside	$C_{13}H_{12}N_2O_5S$	65	91–92	N	9.09	8.80
VI	-2′,6′-dimethylanilide	$C_{14}H_{14}N_2O_4S$	78	163–164	N	9.15	9.11
VII	-α-naphthalide	$C_{16}H_{12}N_2O_4S$	54	166–167	N	8.53	8.68

[a] Some properties of the compounds (appearance, solubilities, etc.) are mentioned in the thesis. [b] Similarly prepared: (I) *o*-nitrobenzenesulfonanilide (7, 8): 72%; m.p. 114–115°; (III) *o*-nitrobenzenesulfon-*p*-toluide (35): 65%; m.p. 114–116°; (VIII) N-(*n*-amyl)-*o*-nitrobenzenesulfonamide: 81%; m.p. 40–43°. Demeny (36) reported m.p. 48° for an undesignated amyl compound identical or isomeric with VIII.

alcohols, carbon tetrachloride, and carbon disulfide. They do not decolorize a solution of bromine in carbon tetrachloride. Some further properties are mentioned later. Essential data for seven benzothiadiazine dioxides thus prepared appear in Table III.

(b) *Ring-closure with ethyl orthoacetate.* When a mixture of 2.62 g. (0.01 mole) of X (Table II) and 2.5 g. (3 ml.; 0.015 mole) of redistilled ethyl orthoacetate (Eastman #P2851) was heated for 25 minutes at 125–145°, the alcohol recovered was two-thirds of that calculated for ring-closure. The isolation procedure yielded only 0.25 g. (9%) of XXIV (Table III). By heating the mixture to 175° for 35 minutes the yield of XXIV was increased to 0.7 g. (25%), but some ester was lost by evaporation. Data for compound XXIV are included in Table III.

The alkaline extract obtained in the first preparation was acidified with dilute acetic acid, and the voluminous colorless precipitate was removed and dried at 75° (2.8 g. decreased to 2.2 g. by crystallization from methanol). The colorless crystals (rectangular

[9] Removal of alcohol seems to be necessary. The reaction failed when attempted in sealed tubes; the starting compounds were recovered.

plates massed into cubes) melted at 110.5–111.5°. This compound appears to be N-(*o*-benzenesulfonyl-*o*-toluidine)acetimino ethyl ether (XXXVIII); if so the yields mentioned are 88% and 70%.

Anal. Calc'd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80.
Found: C, 60.99; H, 5.62; N, 8.52.

No method was found to convert XXXVIII to XXIV by elimination of alcohol. A suspension of 0.5 g. of XXXVIII in 3 ml. of absolute ethanol, treated with 0.1 ml. of conc'd hydrochloric acid, cleared slowly and then suddenly a voluminous precipitate formed, becoming denser and more crystalline on addition of excess acid. This compound melted at 175–176°, and was identified as the hydrochloride of compound X (*o*-aminobenzenesulfon-*o*-toluide). When dissolved in aqueous methanol and crystallized it had m.p. 115–116°, identified as X. A similar cleavage of the acetimino compound by acid is suggested by the facts that it did not dissolve in cold 6 *N* hydrochloric acid, but when the suspension was treated with sodium nitrite and then poured into alkaline β-naphthol a positive coupling test resulted.

TABLE II

o-AMINOBENZENESULFONAMIDES[a]

NUMBER[b]	*o*-AMINOBENZENESULFON-	FORMULA	MADE FROM	YIELD, %	M.P., °C.	COMPONENT	ANALYSIS	
							Calc'd	Found
X	-*o*-toluide	$C_{13}H_{14}N_2O_2S$	II	88	115–116[c]	C	59.52	59.42
						H	5.38	5.45
						N	10.68	10.51
XI	-*p*-toluide	$C_{13}H_{14}N_2O_2S$	III	76	125–126	N	10.68	10.60
XII	-*o*-chloroanilide	$C_{12}H_{11}ClN_2O_2S$	IV	76	82–84	N	9.91	9.83
XIII	-*o*-aniside	$C_{13}H_{14}N_2O_3S$	V	55	102–103	C	56.10	56.21
						H	5.07	5.03
						N	10.07	9.89
XIV	-2′,6′-dimethyl-anilide	$C_{14}H_{16}N_2O_2S$	VI	65	144–145	C	60.84	61.03
						H	5.84	5.65
						N	10.14	9.96
XV	-α-naphthalide	$C_{16}H_{14}N_2O_2S$	VII	90	129–129.5	N	9.39	9.32
XVI	-*n*-amylamide	$C_{11}H_{18}N_2O_2S$	VIII	80	oil[d]	N[f]	10.05	9.93[e]

[a] Footnote *a*, Table I. [b] Similarly prepared: (IX) *o*-aminobenzenesulfonanilide (7): 85%; m.p. 119–120°. [c] X yielded a hydrochloride, m.p. 175–176°. [d] Compound XVI was extracted from the neutralized reduction liquid by ether. The dried extract was taken to residue with aid of a stream of air and then *in vacuo*. The oil was washed with hexane by decantation and dried *in vacuo*. On strong chilling (Dry Ice and acetone) it solidified to a colorless mass with the consistency of petrolatum. It was converted to the hydrochloride, (m.p. 154–155°) which was dried in a vacuum desiccator; drying at 100° caused browning. [e] This weak characterization of XVI is strengthened by the good analytical values obtained for XXXV (Table IV), made from the hydrochloride of XVI by action of formaldehyde, and by the clearcut spectrum obtained. (Figure 1). [f] *Anal.* for hydrochloride, $C_{11}H_{19}ClN_2O_2S$.

Some reactions of 1,2,4-benzothiadiazine dioxides. Attempts to hydrogenate the 3–4 double bond of XVIII and so obtain the corresponding 3,4-dihydro-1,2,4-benzothiadiazine dioxide met with little success. The catalytic procedure outlined earlier led to sparing absorption of hydrogen, even on repeated renewals of the catalyst. After extracting with 5% alkali and recrystallizing the residue from methanol the yield of XXX (Table IV), m.p. 206–207°, was 5 to 7.5%. Acidification of the alkaline filtrate with 20% acetic acid precipitated a compound identified as *o*-formaminobenzenesulfon-*o*-toluide, formed by

TABLE III

SUBSTITUTED 1,2,4-BENZOTHIADIAZINE DIOXIDES[a]

NUMBER	SUBSTITUENT	FORMULA	MADE FROM[b]	YIELD, %	M.P., °C.	ANALYSIS							
						Calc'd				Found			
						C	H	N	S	C	H	N	S
XVII	2-Phenyl[c]	$C_{13}H_{10}N_2O_2S$	IX	43	133–134	60.43	3.88	10.85		60.43	3.87	10.80	
XVIII	2-*o*-Tolyl[c]	$C_{14}H_{12}N_2O_2S$	X	90	167–168	61.73	4.41	10.29	11.77	61.87	4.46	10.19	11.85
XIX	2-*p*-Tolyl[c]	$C_{14}H_{12}N_2O_2S$	XI	22	189–190	61.73	4.41	10.29	11.77	61.76	4.46	10.08	11.51
XX	2-*o*-Chlorophenyl[d]	$C_{13}H_9ClN_2O_2S$	XII	55	185–185.5	53.35	3.08	9.57	10.91	53.48	3.19	9.65	11.07
XXI	2-*o*-Anisyl[c]	$C_{14}H_{12}N_2O_3S$	XIII	90	209–210[g]	58.38	4.19	9.72	11.12	58.42	4.29	9.70	11.07
XXII	2-(2′, 6′-Dimethylphenyl)[c]	$C_{15}H_{14}N_2O_2S$	XIV	85	153–154	62.91	4.93	9.79	11.23	62.89	4.92	9.67	11.16
XXIII	2-*α*-Naphthyl[d]	$C_{17}H_{12}N_2O_2S$	XV	65	165–166	66.21	3.92	9.09		66.33	3.95	8.88	
XXIV	2-*o*-Tolyl-3-methyl	$C_{15}H_{14}N_2O_2S$	X[e]	25	154–155	62.91	4.93	9.78		62.58	5.04	9.68	
	2-*n*-Amyl[f]		XVI·Cl	66	oil								
	PICRATE OF												
	XVII				167–168	46.82	2.69	14.37		47.00	2.60	14.36	
	XVIII				160–161			13.97				14.11	
	XIX				170–171			13.97				13.76	
	XXI				139–140			13.54				13.36	
	XXII				141–142			13.59	6.22			13.59	6.01

[a] Footnote *a*, Table I. [b] Ring closure by ethyl orthoformate unless otherwise indicated. [c] Picrate was prepared either (a) by fusion of benzothiadiazine dioxide with picric acid above 150° and crystallization from benzene or from benzene-hexane mixtures, or (b) by dissolving 0.001 mole of benzothiadiazine dioxide and 0.002 mole of picric acid in 10 ml. of boiling benzene. All picrates obtained were 1:1 salts. Preparation in ethanol (10) was not satisfactory. [d] No satisfactory picrate was obtained. [e] Ring closure by ethyl orthoacetate. The main product was XXXVIII. [f] This compound is probably as represented, but was obtained insufficiently pure for certain characterization. The hydrochloride of XVI was treated with the calculated amount of solid sodium hydroxide, ethyl orthoformate was added, and the mixture was heated. After removal of alcohol and addition of sodium hydroxide the aqueous liquid was decanted from the oily product, which was taken up in ether, dried, and isolated by distillation *in vacuo*; b.p. 174–175° at 0.3 mm. It appeared to be impure and also hydroscopic and on analysis gave erratic values. [g] Recrystallized from butanol.

cleavage of the thiadiazine ring. Identification of this compound required its preparation by the more rational procedure which follows.

o-Formaminobenzenesulfon-o-toluide (XXV). Compound X (2.62 g.; 0.01 mole) was heated under reflux with 10 ml. of 98% formic acid for 2 hours at 105°.[10] The product was precipitated by water and was crystallized by solution in the minimal of methanol and diluting with water while scratching. The yield of colorless product, m.p. 118.5–119.5°, was 85%. The compound is soluble in dilute aqueous sodium hydroxide.

Anal. Calc'd for $C_{14}H_{14}N_2O_3S$: C, 57.91; H, 4.85; N, 9.65.

Found: C, 57.94; H, 4.89; N, 9.74.

In early reduction experiments formation of this compound was overlooked because the alkaline solutions were heated, thus hydrolyzing XXV to X. Later it was found that XXV is obtained when XVIII is heated for a short time in glacial acetic acid. From 0.25 g. of XVIII and 5 ml. of glacial acetic acid kept at 55–60° for 30 minutes and then treated with 10 ml. of cold water and 5 g. of sodium bicarbonate there was obtained, after crystallization from methanol, 0.22 g. (80%) of XXV.

An attempt to hydrogenate XVIII catalytically in ethanol yielded only a trace of XXX, most of the starting compound surviving unchanged.

Sodium and alcohol failed to hydrogenate XVIII but opened the ring: 5.5 g. (0.02 mole) of XVIII, 160 ml. of absolute ethanol, and 2.3 g. (0.1 g.-atom) of sodium yielded, after refluxing for 10 minutes, dilution with water, and acidification with dilute acetic acid, 4.45 g. (85%) of X.

These cleavages of XVIII by hydrogenation, hot acetic acid, and sodium and alcohol, indicate the thiadiazine ring to be only moderately stable; Tozer and Smiles (4) reported that 2-methyl-1,2,4-benzothiadiazine dioxide could not be cleaved by any simple treatment.

Acetyl derivatives of o-aminobenzenesulfon-o-toluide. While studying the unexpected failure of formic acid, acetic anhydride, and acetyl chloride to convert to benzothiadiazine dioxides the *o*-aminobenzenesulfonamides in Table II it was found that by action of acetic anhydride and of acetyl chloride on *o*-aminobenzenesulfon-*o*-toluide (X) there were obtained two different but isomeric monoacetyl derivatives, which must be *o*-acetaminobenzenesulfon-*o*-toluide (XXVI) and N-acetyl-N-(*o*-aminobenzenesulfonyl)-*o*-toluidine (XXVIII). These compounds were prepared and distinguished as follows.

o-Acetaminobenzenesulfon-o-toluide (XXVI). To 2.62 g. (0.01 mole) of X was added, slowly and with cooling, 5 ml. of acetyl chloride, the excess of which was decomposed by cautious addition of 20–25 ml. of 10% aqueous sodium hydroxide so as to leave the mixture barely acid to litmus. The product, twice crystallized in fine needles from methanol by dilution, weighed 1.52 g. (50%), m.p. 178–179°.

Anal. Calc'd for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.24.

Found: C, 59.04; H, 5.42; N, 9.11.

The yield was increased to 65% when reaction occurred in the presence of pyridine, with omission of the treatment with sodium hydroxide. The pyridine was removed by addition of 2 *N* hydrochloric acid, etc.

Designation of this compound as XXVI is based upon the following observations: (a) It is soluble in cold 5% sodium hydroxide and is recovered by acidification with dilute acetic acid. (b) It is insoluble in hydrochloric acid, and gives no characteristic diazotization-coupling test.

Attempts to prepare a diacetyl derivative by the action of excess acetic anhydride in the presence of cold 10% sodium hydroxide or by refluxing with excess acetic anhydride were unsuccessful; XXVI was recovered unchanged.

Compound XXVI was deacetylated by passing dry hydrogen chloride into its solution in absolute alcohol. Heat was evolved, and on dilution with water there was precipitated a compound which, after crystallization from methanol, was found to be X.

[10] These conditions, applied by Ekbom (1) to orthanilamide, led to ring closure with formation of 1,2-4-benzothiadiazine dioxide.

Compound XXVI was obtained also, and in 85% yield, by catalytic reduction of N-acetyl-N-(*o*-nitrobenzenesulfonyl)-*o*-toluidine (XXVII, prepared as described below) in glacial acetic acid (as shown below, reduction in ethanol gives XXVIII) using palladium-charcoal catalyst and the procedure described earlier.

N-Acetyl-N-(o-nitrobenzenesulfonyl)-o-toluidine (XXVII). The method of Oxley and Short (37) (acetyl chloride in presence of pyridine) applied to *o*-nitrobenzenesulfon-*o*-toluide (II) produced a 70% yield of the acetyl compound which, after crystallization from 95% ethanol, melted at 112–113°.

Anal. Calc'd for $C_{15}H_{14}N_2O_5S$: C, 53.89; H, 4.22; N, 8.38.
Found: C, 54.12; H, 4.31; N, 8.51.

A small yield of this compound was obtained by the action of acetic anhydride on the sodium salt of II in xylene. Attempts to make it by interaction of *o*-nitrobenzenesulfonyl chloride and acet-*o*-toluide in pyridine or its sodium salt in xylene (38), or by action of acetic anhydride on II in dilute sodium hydroxide, were all unsuccessful.

N-Acetyl-N-(o-aminobenzenesulfonyl)-o-toluidine (XXVIII). A solution of 2.62 g. (0.01 mole) of X in 20 ml. of cold 20% aqueous sodium hydroxide was treated with enough 95% acetic anhydride (5 to 6 ml.), added in small portions and with swirling and cooling, to leave the reaction mixture slightly acidic. The solid product was crystallized from aqueous methanol and was dried at 110°. The yield of colorless hexagonal platelets was 55%; m.p. 172.5–173.5°. In the presence of sodium acetate instead of sodium hydroxide the reaction failed.

Anal. Calc'd for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.24.
Found: C, 59.00; H, 5.14; N, 9.06.

Designation of this compound as XXVIII is based upon the following observations: (a) it is insoluble in warm 5–10% aqueous sodium hydroxide; (b) it dissolves in hot 3 *N* hydrochloric acid and is precipitated as salt on cooling the solution; (c) it gives a positive diazotization-coupling test.

Compounds XXVI and XXVIII (m.p. 178–179° and 172.5–173.5° respectively) were shown to be not identical by mixture melting point tests, in which depressions of 20–25° were observed. The distinction between XXVI and XXVIII is shown also by the ultraviolet spectral results, which indicate further that neither compound has the cyclic structure represented earlier by formula G.

The hydrochloride of XXVIII was obtained by dissolving XXVIII in ethanol with addition of a drop of conc'd hydrochloric acid, and then adding an excess of conc'd hydrochloric acid or passing in hydrogen chloride. The yield was 91%; m.p. 226–228°. The salt lost hydrochloric acid on standing and failed to give satisfactory analysis; the value for nitrogen was 8.77% instead of the calculated 8.22%.

Compound XXVIII was obtained also by reduction of XXVII by hydrogen and palladium-charcoal in absolute ethanol (as mentioned above, reduction in glacial acetic acid gave XXVI); yield 30%.

Isomerization (transacetylation) of acetyl compounds. Compound XXVIII was isomerized to XXVI by the following means: (a) on boiling with 5% aqueous sodium hydroxide XXVIII dissolved slowly; on cooling and acidifying with dilute acetic acid XXVI precipitated; (b) on heating XXVIII to 200° and crystallizing from methanol; (c) by warming at 55° in glacial acetic acid for 2 hours (probably needlessly long) and neutralization with sodium bicarbonate. In all cases the product was XXVI, identified by crystal form, solubility, m.p. and mixture m.p. tests. The formation of XXVI by reduction of XXVII in glacial acetic acid involves the same isomerization. The isomerization appears to be irreversible, with XXVI the stable isomer.

N-(o-Aminobenzenesulfonyl)acetamide (XXXIX). Results described above made possible the preparation of this compound, which Tozer and Smiles (4) failed to obtain from *o*-nitrobenzenesulfonacetamide by reduction, owing to immediate ring-closure to yield 2-methyl-1,2,4-benzothiadiazine dioxide. This may have been the result of reduction in acetic acid, shown above to induce transacetylation from sulfonamide-nitrogen to amino-

TABLE IV

SUBSTITUTED 3,4-DIHYDRO-1,2,4-BENZOTHIADIAZINE DIOXIDES[a]

NUMBER	SUBSTITUENT	FORMULA	MADE FROM[b]	% YIELD	M.P., °C.	ANALYSIS							
						Calc'd				Found			
						C	H	N	S	C	H	N	S
XXIX	2-Phenyl	$C_{13}H_{12}N_2O_2S$	IX	35	172.5–173	59.98	4.64	10.76		60.21	4.71	10.55	
XXX	2-*o*-Tolyl	$C_{14}H_{14}N_2O_2S$	X	74	208–209	61.31	5.14	10.22	11.69	61.33	5.15	10.23	11.47
XXXI	2-*o*-Chlorophenyl	$C_{13}H_{11}ClN_2O_2S$	XII	32	173–174	52.97	3.76	9.51	10.88	53.04	3.54	9.46	10.90
XXXII	2-*o*-Anisyl	$C_{14}H_{14}N_2O_3S$	XIII	87	200–201[c]	57.91	4.86	9.65	11.04	58.10	4.89	9.69	10.84
XXXIII	2-(2′,6′-Dimethylphenyl)	$C_{15}H_{16}N_2O_2S$	XIV	93	210–211	62.47	5.59	9.72		62.67	5.81	9.55	
XXXIV	2-α-Naphthyl	$C_{17}H_{14}N_2O_2S$	XV	80	233 234[d]	65.78	4.55	9.03		65.82	4.52	8.81	
XXXV	2-*n*-Amyl	$C_{12}H_{18}N_2O_2S$	XVI·HCl[e]	13	[i]	56.66	7.13	11.01		56.54	7.12	11.01	
XXXVI	2-*o*-Tolyl-3-methyl	$C_{15}H_{16}N_2O_2S$	X[f]	72[g]	194–195	62.47	5.59	9.72		62.56	5.69	9.55	
XXXVII	2-*o*-Tolyl-3-phenyl	$C_{20}H_{18}N_2O_2S$	X[h]	32	198.5–199	68.55	5.18	8.00		68.62	5.27	7.92	

[a] Footnote *a*, Table I. [b] Ring closure by formaldehyde unless otherwise indicated. [c] Recrystallized from butanol. [d] Recrystallized from acetic acid by dilution with water, or from dioxane by dilution with hexane. [e] The hydrochloride of XVI was treated with sodium hydroxide in slight excess. The oily product obtained by the action of formaldehyde was extracted in ether, dried, and isolated by distillation *in vacuo*. [f] Ring closure by acetaldehyde. [g] Crude yield; crystallization from 80% methanol involved heavy loss. Concentration of the mother liquor by heating led to turbidity, and cooling caused separation of X (m.p. 115–117°; identified by mixture m.p. test), formed by decomposition of XXXVI. [h] Ring closure by benzaldehyde. The product, though insoluble in ether, was extractable in ether owing to presence of considerable benzaldehyde. The ether solution was washed with sodium bisulfite solution, the ether was evaporated, and the residue was crystallized from acetone. [i] B.p. 204–205°/0.5 mm.

TABLE V

ULTRAVIOLET ABSORPTION SPECTRA OF *o*-AMINOBENZENESULFONAMIDES, 1,2,4-BENZOTHIADIAZINE DIOXIDES, AND RELATED COMPOUNDS, IN ABSOLUTE ETHANOL

COMPOUND	NUMBER	FIGURE	MAXIMA[a]	
			λ(mμ)	Log ε
o-Aminobenzenesulfon-*o*-toluide	X	1, 2 4, 5	314 272 244	3.63 2.97 4.01
o-Aminobenzenesulfonyl-*n*-amylamine[b]	XVI	1	311 276	3.58 3.94
Benzenesulfon-*o*-toluide		1, 2	273 266 (259)	3.18 3.30 3.35
o-Acetaminobenzenesulfon-*o*-toluide	XXVI	2	290 (246) (233)	3.62 4.10 4.18
o-Formaminobenzenesulfon-*o*-toluide	XXV	3	288 (239)	3.54 4.13
N-(*o*-Benzenesulfonyl-*o*-toluide)acetimino ethyl ether	XXXVIII	3	287 (229)	3.54 4.12
2-(*o*-Tolyl)-3,4-dihydro-1,2,4-benzothiadiazine dioxide	XXX	5	313 272 253	3.51 3.07 4.07
2-(*o*-Tolyl)-3-methyl-3,4-dihydro-1,2,4-benzothiadiazine dioxide	XXXVI	5	312.5 273 252	3.50 3.14 4.06
2-(*o*-Tolyl)-1,2,4-benzothiadiazine dioxide	XVIII	4	296 (272) 263	3.78 3.90 3.97
N-acetyl-N-(*o*-aminobenzenesulfonyl)-*o*-toluidine	XXVIII	4	325 275 (244)	3.75 3.21 3.98

[a] Wavelengths in parentheses refer to points of inflection. [b] This compounds was purified, weighed, and dissolved as the hydrochloride, but because of the extent of dilution in ethanol (10^{-4} molar) it was expected that the spectrum obtained would be that of the amino compound. Such was apparently the case.

nitrogen, which in this case would form *o*-acetaminobenzenesulfonamide, a compound subject to easy ring closure. By catalytic reduction in ethanol, using palladium-charcoal catalyst and the procedure outlined above, *o*-nitrobenzenesulfonacetamide, made as described by Tozer and Smiles (4), was converted to XXXIX in 88% yield. After crystallization from aqueous methanol the compound was colorless; m.p. 185–186°.

Anal. Calc'd for $C_8H_{10}N_2O_3S$: N, 13.08. Found: N, 13.37.

The identity of this compound, and the correctness of the above inference, are supported by these observations: (a) the compound gave a positive diazotization-coupling test; (b) on heating to 200° for 5 minutes water was evolved and the residue, crystallized from methanol, yielded a tan solid, m.p. 263–267°. The m.p. of 3-methyl-1,2,4-benzothiadiazine dioxide is given as 264° (1) and 268° (4).

Preparation of substituted 3,4-dihydro-1,2,4-benzothiadiazine dioxides. For ring closure by aldehydes in presence of alkali (26a) the *o*-aminobenzenesulfonamide (0.01 mole) was dissolved in 20 ml. of 90% ethanol containing one pellet of sodium hydroxide, and 5 equivalents of aldehyde (formaldehyde as formalin; acetaldehyde; benzaldehyde) was added. The mixture was warmed on a steam-bath until about half of the alcohol had evaporated. An equal volume of water was added, and the mixture was chilled. The solid product was crystallized from ethanol and dried at 100°. Essential data for nine compounds so made appear in Table IV.

The dihydrobenzothiadiazine dioxides made with formaldehyde (no substituent at position 3) are stable crystalline compounds, insoluble in water, cold or hot 5% aqueous sodium hydroxide, hot dilute hydrochloric acid, hot aqueous ammonia, chloroform, ether, or benzene. They dissolve in acetone or pyridine and in alcohol, and can be recrystallized from ethanol or from glacial acetic acid. Compound XXXVI (2-*o*-tolyl-3-methyl-3,4-dihydro-1,2,4-benzothiadiazine dioxide) appeared to be less stable than compounds XXIX–XXXV (see Table IV, footnote *g*). No compound of this series reported here yielded a satisfactory picrate (*cf.* Table III, footnote *c*).

Attempts to cleave the dihydrobenzothiadiazine ring by reduction were partially successful. Compound XXX in glacial acetic acid in the presence of Pd-C absorbed no appreciable amount of hydrogen and was recovered unaltered. Reduction by sodium and ethanol yielded, with considerable loss, only unchanged XXX and, from the liquors, some X.

Attempts to oxidize XXX to XVIII by potassium permanganate in acetone (27) or by lead tetraacetate in benzene (28) were unsuccessful; only unchanged XXX was isolated.

Ultraviolet absorption spectra. The Beckman model DU spectrophotometer was fitted with quartz cells and with a hydrogen-discharge tube as the light source. Compounds of analytical purity were examined in absolute ethanol, usually in a concentration of 0.0001 molar. The wavelengths and logarithms of the molar extinction coefficients at the absorption maxima and at prominent points of inflection are gathered into Table V. Absorptions are plotted in Figures 1 to 5. The compounds examined were X, XVI, XVIII, XXV, XXVI, XXVIII, XXX, XXXVI, XXXVIII, and benzenesulfon-*o*-toluide (m.p. 124.5–125.5°).

SUMMARY

Nine 2-substituted 1,2,4-benzothiadiazine dioxides were made from substituted orthanilamides by the action of ethyl orthoformate. Formic acid, acetic anhydride, and acetyl chloride caused only acylation and failed to effect ring closure, nor was it possible to effect ring closure using the preformed acyl compounds. It was found that ring closure by the acidic agents named occurs only when there are present on the two nitrogen atoms, after acylation, three hydrogen atoms. Since the necessary removal of the elements of water is apparently possible when only two hydrogen atoms are so present, it is suggested that in orthanilamides one hydrogen atom on the *o*-amino nitrogen is coördinatively bound to an oxygen of the sulfonyl group and that, if removal of this hydrogen is essential to ring closure this will not occur.

Work on the acetylation of *o*-aminobenzenesulfon-*o*-toluide disclosed an instance of amide isomerization by transacetylation.

Nine substituted 3,4-dihydro-1,2,4-benzothiadiazine dioxides were obtained from orthanilamides by action of aldehydes. They could not be made by hy-

drogenation of the Δ^3-benzothiadiazine dioxides, nor were the latter obtained by oxidation of the dihydro compounds.

Some reactions of the two classes including ring cleavage are reported, and the mechanisms of the several ring closures and of the transacetylation are discussed. Ultraviolet absorption spectra of selected end-products and intermediates were determined and compared, yielding evidence useful in discussion of certain structural changes.

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