an open flask for 15 min. The excess solvent was removed *in vacuo* and the resulting oil was recrystallized from hot *n*-heptane to give needles, m.p. 127–131°.

Anal. Calcd. for $C_{12}H_9FN_4$: C, 63.1; H, 4.0; F, 8.3; N, 24.6. Found: C, 62.7; H, 4.0; F, 8.1; N, 24.6.

Method B.—A solution of 5 g. of 9-benzyl-6-chloropurine[17] in 100 ml. of reagent toluene was refluxed and stirred with 25 g. of silver fluoride (AgF, Harshaw Chemical Company) for 1.5 hr. The silver salts were filtered. Evaporation of the toluene filtrate gave 3.5 g. of solid which was recrystallized from benzene–*n*-heptane to give 3.0 g. of needles, m.p. 124–126°. This product was identical to 9-benzyl-6-fluoropurine prepared by method A.

2-Fluoro-9-methylpurine.—To a solution of 2 g. of 2-chloro-9-methylpurine in 80 ml. of reagent xylene (b.p. 137–140°) was added 20 g. of silver fluoride, and the mixture was refluxed with stirring for 0.75 hr. The silver salts were filtered. The filtrate was returned to the reaction flask; 20 g. of fresh silver fluoride was added; and the mixture refluxed with stirring for 0.5 hr. The silver salts were removed by filtration and the xylene allowed to evaporate to give 0.6 g. of crude product which was purified by crystallization from boiling benzene to give crystals, m.p. 151–151.5°.

Anal. Calcd. for $C_6H_5FN_4$: C, 47.4; H, 3.3; F, 12.5; N, 36.8. Found: C, 47.6; H, 3.6; F, 12.3; N, 36.6.

6-Fluoro-9-methylpurine (II).—To a solution of 3 g. of 6-chloro-9-methylpurine (I)[16] in 75 ml. of reagent toluene was added 21 g. of silver fluoride, and the mixture was stirred and refluxed for 1.5 hr. The silver salts were filtered and the toluene evaporated to give 1.55 g. of crystalline solid. This was recrystallized from 1:1 (v./v.) benzene–*n*-heptane to give 1.40 g. of needles, m.p. 125–127°. The product was identical to the 6-fluoro-9-methylpurine prepared from 5-amino-6-fluoro-4-methylaminopyrimidine.[7]

8-Fluoro-9-methylpurine.—To a solution of 0.55 g. of 8-chloro-9-methylpurine in 75 ml. of reagent toluene was added 6 g. of finely divided silver fluoride, and the mixture was stirred and refluxed for 1.5 hr. The silver salts were removed by filtration and the toluene filtrate allowed to evaporate slowly to a small volume to give 0.3 g. of prisms, m.p. 111–112°.

Anal. Calcd. for $C_6H_5FN_4$: C, 47.4; H, 3.3; F, 12.5; N, 36.8. Found: C, 47.2; H, 3.7; F, 12.7; N, 36.9.

2,6-Difluoro-7-methylpurine (VI).—To a solution of 3.0 g. of 2,6-dichloro-7-methylpurine (VII)[28] in 100 ml. of reagent xylene (b.p. 137–140°) was added 30 g. of silver fluoride. The mixture was refluxed and stirred for 1 hr. and the silver salts were removed by filtration. The filtrate was returned to the reaction flask; 30 g. of fresh silver fluoride was added; and the mixture refluxed and stirred for 1.5 hr. The silver salts were filtered and the filtrate allowed to evaporate to give 0.34 g. of crystalline solid, which was recrystallized from benzene to give needles, m.p. 154–161°.

Anal. Calcd. for $C_6H_4F_2N_4$: C, 42.4; H, 2.4; F, 22.3; N, 32.9. Found: C, 41.9; H, 2.7; F, 22.3; N, 32.4.

Reaction of 7-Methyl-2,6,8-trichloropurine and Silver Fluoride.—To a solution of 4 g. of 7-methyl-2,6,8-trichloropurine[18,19] in 100 ml. of reagent xylene was added 40 g. of silver fluoride. The mixture was refluxed and stirred for 0.75 hr. and the silver salts were removed by filtration. The filtrate was returned to the reaction flask; 30 g. of fresh silver fluoride was added; and the mixture refluxed and stirred for 0.75 hr. The silver salts were filtered and the filtrate allowed to evaporate. The crude product was washed with three 3-ml. portions of benzene to give 1.5 g. of crystalline solid, which was recrystallized first from benzene and then from ethyl acetate to give crystals, m.p. 228–233°. The analyses showed the product to be a difluorohydroxy-7-methylpurine; presumably the hydroxy group is at position 8.

Anal. Calcd. for $C_6H_4F_2N_4O$: C, 38.7; H, 2.2; F, 20.4; N, 30.1. Found: C, 38.4; H, 2.0; F, 20.0; N, 29.7.

3,4-Dihydro-3-imino-2*H*-1,2,4-benzothiadiazine 1,1-Dioxides

JOHN G. TOPLISS AND LEROY M. KONZELMAN

Medicinal Chemical Research Department, Schering Corporation, Bloomfield, New Jersey

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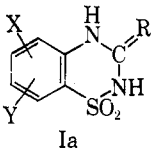
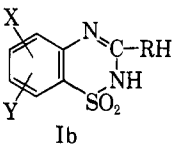
A number of 3,4-dihydro-3-imino-2*H*-1,2,4-benzothiadiazine 1,1-dioxides have been prepared by fusion of substituted *o*-aminobenzenesulfonamides with guanidine carbonate. The properties and reactions of these compounds have been investigated and certain comparisons made with the corresponding 3-oxo compounds. Possible distinction between the alternate tautomeric forms of certain compounds is discussed in the light of spectral evidence.

3,4-Dihydro-3-oxo-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (I, R = O, X = Y = H) was first synthesized by Schräder[1] in 1917. Parke and Williams[2] prepared this compound and others of the same type bearing substituents in the phenyl ring by utilizing the reaction of a substituted *o*-aminobenzenesulfonamide with urea at high temperatures. The properties and reactions of the ring system were examined briefly by Parke and Williams[2] and more extensively in a number of papers by Raffa.[3] Other publications[4] have also recently appeared which describe the synthesis of sulfamoyl substituted 3,4-dihydro-3-oxo-2*H*-1,2,4-benzothiadiazine 1,1-dioxides.

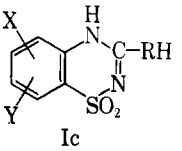
We became interested in the possible synthesis of compounds of the ring system (I) where R = NH[5] and



Ia



Ib



Ic

investigated the condensation of guanidine with orthanilamide. The fusion of orthanilamide with guanidine carbonate at 180–200° gave *ca.* a 50% yield of 3,4-dihydro-3-imino-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (I, R = NH, X = Y = H). The same compound was obtained when cyanamide was substituted for guanidine carbonate, but in much lower yield. With aminoguanidine bicarbonate under similar reaction conditions, I (R = NH, X = Y = H) was isolated in very poor yield. A number of other 3,4-dihydro-3-imino-2*H*-1,2,4-benzothiadiazine 1,1-dioxides containing halogen and alkyl substituents in the phenyl por-

(1) E. Schräder, *J. prakt. Chem.*, (2) **95**, 392 (1917).

(2) D. O. Parke and R. T. Williams, *J. Chem. Soc.*, 1760 (1950).

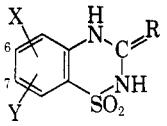
(3) (a) L. Raffa, *Farmaco* (Pavia) *Ed. sci.*, **12**, 293 (1957); (b) p. 400; (c) p. 495; (d) p. 502; (e) L. Raffa, M. DiBella, and A. Monzani, *ibid.*, **15**, 716 (1960); (f) L. Raffa, M. DiBella, M. Melegari, and G. Vampa, *ibid.*, **16**, 3 (1961). (g) L. Raffa and A. Monzani, *ibid.*, **16**, 14 (1961); (h) L. Raffa, A. Monzani, and M. DiBella, *ibid.*, **17**, 234 (1962).

(4) W. J. Close, L. R. Swett, L. E. Brady, J. H. Short, and M. Vernsten, *J. Am. Chem. Soc.*, **82**, 1132 (1960); F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. Sprague, *J. Org. Chem.*, **25**, 970 (1960).

(5) At the outset of our investigations no mention of these compounds had appeared in the literature. Since then reports of their synthesis have been published: ref. 3a; ref. 3g. (a) E. Angeletti, *Gazzetta*, **90**, 841 (1960); (b) U. M. Testino and G. Maffii, British Patent 847,176 (1960); (c) L. Raffa, M. DiBella, M. Melegari, and G. Vampa, *Farmaco* (Pavia) *Ed sci.*, **17**, 331 (1962).

TABLE I

3,4-DIHYDRO-3-IMINO(OXO)-2*H*-1,2,4-BENZOTHIADIAZINE 1,1-DIOXIDES



No.	X	Y	R	M.p., °C.[a]	Formula	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
1	H	H	NH	344–345[b]	$C_7H_7N_3O_2S$			21.31	20.89	16.24	16.36
2	6Cl	H	NH	339–340 dec.[c]	$C_7H_6ClN_3O_2S$	15.30	14.91	18.14	18.27		
3	H	7Cl	NH	>360[d]	$C_7H_6ClN_3O_2S$	15.30	15.39			13.84	13.72
4	6Cl	7Cl	NH	>360[e]	$C_7H_5Cl_2N_3O_2S$	26.65	26.92	15.75	15.93		
5	6Cl	8Cl	NH	316–317 dec.	$C_7H_6ClN_3O_2S$	26.65	26.27			12.05	11.83
6	$6CF_3$	H	NH	342–344 dec.	$C_8H_6F_3N_3O_2S$	21.59	21.72[f]	15.84	15.65		
7	$6CH_3$	H	NH	326–328 dec.	$C_8H_9N_3O_2S$			19.89	20.03	15.18	15.38
8[g]	6Cl	H	O	322–324 dec.[h]	$C_7H_5ClN_2O_3S$	15.24	15.44	12.04	12.25		
9	H	7Cl	O	333–335 dec.[i]	$C_7H_5ClN_2O_3S$	15.24	15.17	12.04	11.87		
10	6Cl	7Cl	O	289–291 dec.[j]	$C_7H_4Cl_2N_2O_3S$	26.55	26.99	10.49	10.76		

[a] All melting points are uncorrected. [b] Ref. 3a reports m.p. 339–340°. [c] Ref. 5c reports m.p. 329–330°. [d] Ref. 5c reports m.p >360°. [e] Ref. 5c reports m.p. >360°. [f] Fluorine. [g] We are indebted to B. W. Pettersen for the preparation of this compound [h] Ref. 3e reports m.p. 304°. [i] Ref. 3h reports m.p. 314–315°. [j] Ref. 3h reports m.p. 280–282°.

TABLE II

SPECTRAL AND TITRATION DATA OF 3,4-DIHYDRO-3-IMINO(OXO)-2*H*-1,2,4-BENZOTHIADIAZINE 1,1-DIOXIDES

No.[a]	pK_a'[b]	>C=R Absorption λ_{max}^{Nujol}	Ultraviolet absorption spectra in methanol: λ_{max} mμ	ϵ	λ_{max} mμ	ϵ	Ultraviolet absorption spectra in 0.1 *N* methanolic NaOH: λ_{max} mμ	ϵ[c]	λ_{max} mμ	ϵ[c]
1	11.1	6.05	243	11,400	285	1900	268	16,000	302	3600
2	9.7	6.02	248	8,950	276	2200	278	17,900	305	3150
3	10.1	5.98	250	15,500	297	1750	278	21,300	318	2550
4	9.0	6.02	256	13,400	280[d]	2400	283	22,100		
5	9.0	5.98	255	8,100	295, 304	2100	281	16,300	320	2950
6	9.4	5.96, 6.03	246	10,100	295	2300	277	17,700	321	2800
7	11.0	6.04	255	8,750	295	1900	272	13,800	300	3000
8	3.4	5.92	245	9,350	295	2000	247	9,500	295	2150
9	3.3	5.78, 5.92	247	17,000	298	2100	251	16,400	305	2100
10	3.2	5.80	253	14,600	304	2250	256	14,200	307	2450

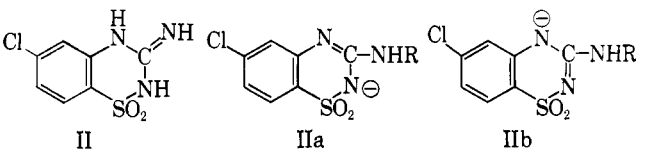
[a] Compound no. refers to those given in Table I. [b] Determined in 66% dimethylformamide solution. [c] Extinction coefficients calculated using molecular weight of free acids. [d] Shows an additional absorption maximum at 300 mμ (ϵ 2300).

tion of the nucleus were prepared by the fusion of substituted *o*-aminobenzenesulfonamides with guanidine carbonate. These are listed in Table I. Attempts to prepare 2- or 4-methyl derivatives of 6-chloro-3,4-dihydro-3-imino-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (I, R = NH, X = 6Cl, Y = H) by fusion of guanidine carbonate with 2-amino-4-chloro-N-methylbenzene sulfonamide and 4-chloro-2-methylaminobenzenesulfonamide, respectively, were unsuccessful.

3,4-Dihydro-3-imino-2*H*-1,2,4-benzothiadiazine 1,1-dioxides are weak acids, the pK_a' values of the compounds ranging from 9.0 to 11.0. They are not titratable as bases under standard conditions. The corresponding 3-oxo compounds are much stronger acids with pK_a' values of 3.0 to 4.0. In structures of type I, where R = NH or O, three tautomeric forms, Ia, Ib, and Ic, are possible. The infrared spectra (Nujol mulls) of the imino compounds (I, R = NH) show a strong band at about 6.0 μ, which is indicative of the C=NH function.[6] On this evidence they may be considered to exist in the tautomeric form Ia in the solid state. Similarly, the 3-oxo compounds show a strong infrared band at about 5.9 μ, indicative of the >C=O function, and, therefore, may be considered to exist in the tautomeric form Ia (R = O). Spectral and titration data pertaining to the 3,4-dihydro-3-imino-(oxo)-2*H*-1,2,4-benzothiadiazine 1,1-dioxides prepared are given in Table II.

The detailed examination of the chemistry of the 3,4-dihydro-3-imino-2*H*-1,2,4-benzothiadiazine 1,1-dioxide structure was carried out using the 6-chloro derivative (II). This compound was found to be remarkably stable to hydrolysis. Thus it was recovered unchanged after prolonged refluxing with base of various strengths or with acid. Equally stable to hydrolysis was the 3-N-*n*-butyl derivative (XVI, R = *n*-C_4H_9) However, the 4-methyl compound (III) (Scheme I) could be hydrolyzed with 10% aqueous sodium hydroxide to 6-chloro-3,4-dihydro-4-methyl-3-oxo-2*H*-1,2-4-benzothiadiazine 1,1-dioxide (IV) in 80% yield and to 4-chloro-2-methylaminobenzenesulfonamide (V) in 80% yield under more vigorous hydrolytic conditions.

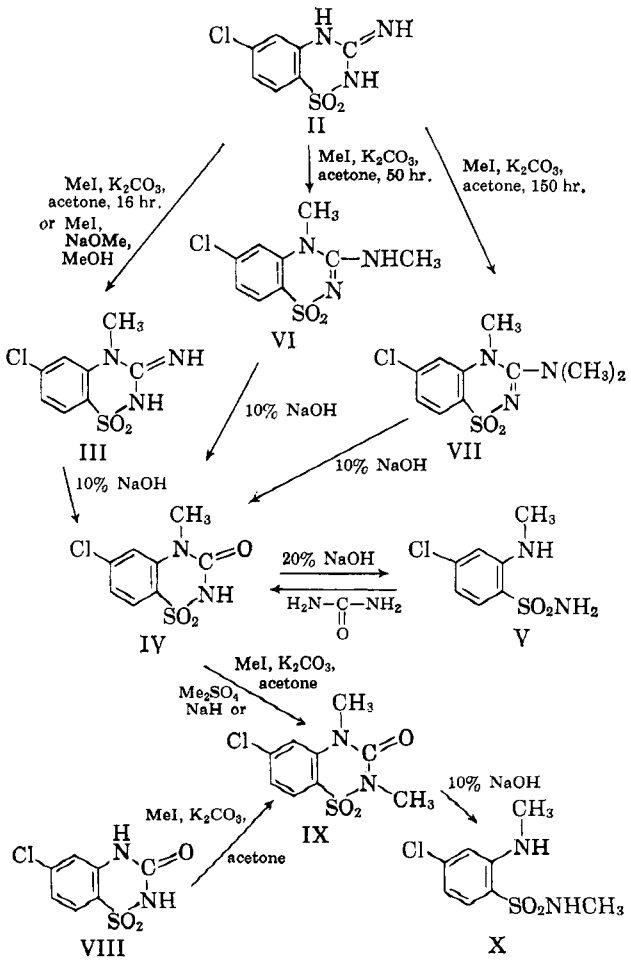
The stability of II and XVI (R = *n*-C_4H_9) towards base relative to IV may be rationalized on the basis of



II IIa IIb

(6) (a) B. Witkop, *Experientia*, **10**, 420 (1954); *J. Am. Chem. Soc.*, **78**, 2873 (1956). (b) There is evidence that when the C=N bond is in the 2,3-position (compound VII) or in the 3,4-position (**10**) the absorption appears at a higher wave length and is not so sharp and strong.

SCHEME I



resonance stabilization of the anions (IIa ↔ IIb, etc.)[7] of II and XVI (R = *n*-C_4H_9). Because of the blocking effect of the methyl group at position 4, the anion of III is less well stabilized by resonance and should be more susceptible to nucleophilic attack. This view is in accord with the pK_a' data: the pK_a' of II is 9.7, whereas III is too weakly acidic to titrate with base under standard conditions. The 6-chloro-3,4-dihydro-3-oxo-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (VIII) behaved analogously to its 3-imino counterpart (II) in resisting hydrolysis under a variety of conditions. The 4-methyl-3-oxo compound (IV) was degraded with aqueous alkali to V as already noted. A rationalization equivalent to that used in the imino series, however, is not well supported by the pK_a' data since VIII and IV have practically the same pK_a' value (3.4).

The products of successive methylation of II are shown in Scheme I. With methyl iodide and sodium methoxide in methanol solution only the 4-methyl compound (III) could be obtained irrespective of the reaction time and the quantities of reagents. However, methyl iodide and anhydrous potassium carbonate in acetone resulted in the introduction of one, two, or three methyl groups depending on the reaction time (Scheme I). The structures of the methylation products, III, VI, and VII follow from their elemental composition and the fact that alkaline hydrolysis furnished in each case the 3-keto-4-methyl compound (IV).

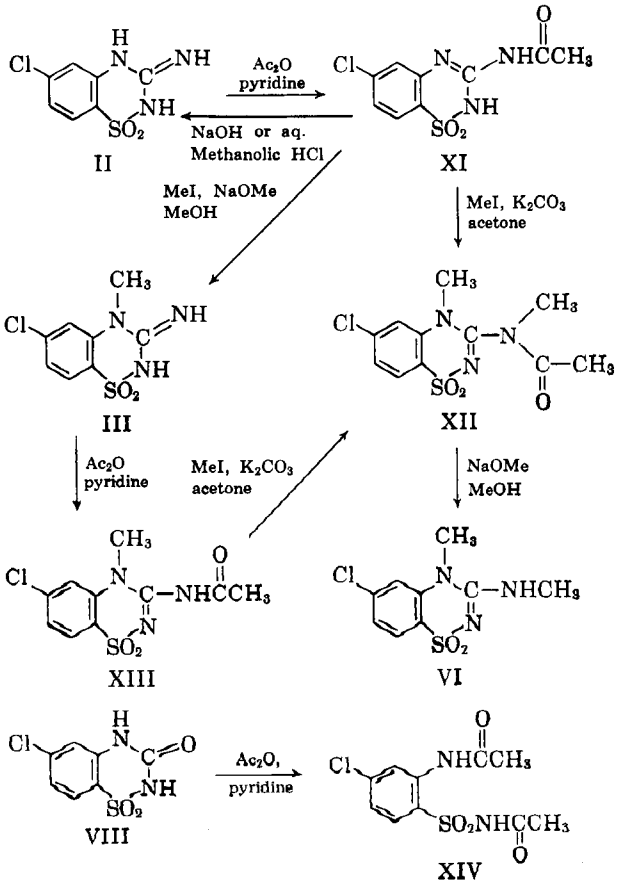
(7) These are resonance forms of the anion of the tautomeric structures Ib or Ic.

The assignment of the double bond position as shown for the monomethyl compound III, rather than in the alternate tautomeric position, is based on the strong infrared bond at 6.05 μ, indicative of the >C=NH function. The infrared spectrum of VII, where the double bond is unequivocally in the 2,3-position, does not show any band at this wave length. The >C=N— grouping in this compound appears to absorb at 6.3 to 6.4 μ as a summation band with phenyl ring absorptions. The absorption pattern of the dimethyl compound (VI) in the 6.2- to 6.5-μ region is almost identical with that of the trimethyl compound (VII) and the medium intensity band at 3.00 μ in the spectrum of VI fits much better the N–H of a secondary amine than the N–H of a sulfonamide. Thus the double bond assignment for the dimethyl compound as shown in VI is adequately supported.

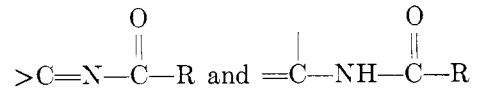
In contrast to the 3-imino compound (II), 6-chloro-3,4-dihydro-3-oxo-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (VIII) could not be methylated with methyl iodide and sodium methoxide in methanol or sodium hydride (1 mole) in dimethylformamide, presumably because of the greater stability of the anion. With methyl iodide and potassium carbonate in acetone, VIII gave only the 2,4-dimethyl-3-keto compound (IX); no monomethyl compound could be isolated. The 4-methyl-3-keto compound (IV) was obtained by fusion of V with urea. IV was unreactive to methyl iodide and sodium methoxide in methanol but could be methylated to give IX using either dimethyl sulfate and sodium hydride in dimethylformamide or methyl iodide and potassium carbonate in acetone. IX was degraded with refluxing 10% sodium hydroxide solution giving 4-chloro-2-methylamino-*N*-methylbenzenesulfonamide (X). Evidence for IV existing in the keto form is provided by the strong infrared band at 5.95 μ.

Acetylation of 6-chloro-3,4-dihydro-3-imino-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (II) with acetic anhydride in refluxing pyridine afforded a monoacetyl derivative (XI) in high yield. Transformations involving XI and related compounds are shown in Scheme II. Attempts to prepare a diacetyl derivative using a large excess of acetic anhydride at reflux temperature in the presence of pyridine or a catalytic amount of perchloric acid were unsuccessful. XI was a much stronger acid (pK_a' 8.05) than the starting material (pK_a' 9.73), and, therefore, it seems highly unlikely that the acetyl group in XI is located at the 2-position. The compound was readily hydrolyzed by refluxing 5% aqueous sodium hydroxide or hydrochloric acid to give II. Methylation of XI with methyl iodide and sodium methoxide in methanol gave 6-chloro-3,4-dihydro-3-imino-4-methyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (III), with loss of the acetyl group. However, methylation of XI using methyl iodide and potassium carbonate in acetone afforded a monoacetyl-dimethyl derivative (XII) which upon removal of the acetyl group with methanolic sodium methoxide furnished 6-chloro-4-methyl-3-methylamino-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (VI). Thus, the acetyl group in XI cannot be at position 4 and, therefore, must be attached to the nitrogen atom at position 3. The 4-methyl-3-imino compound (III) also was acetylated under the same conditions as II giving XIII. The latter compound was converted to XII on methyla-

SCHEME II



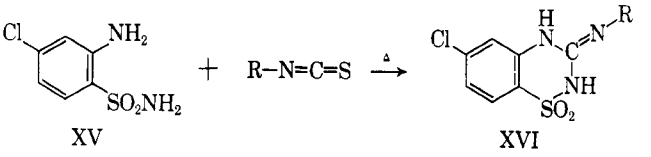
tion with methyl iodide and potassium carbonate in acetone. The most probable position for the double bond in XI is at 3,4 based on the infrared absorption of the >C=N function at 6.10 μ. This absorption occurs at a slightly lower wave length than might have been predicted considering the nature of the substituents attached to the >C=N function. However, each of the three possible tautomeric forms contains a differently substituted >C=N system and, of these, the 3,4 system would be expected to absorb at the lowest wave length. In XII where the >C=N function must of necessity be 2,3, the band appears at 6.32 μ as a summation band with phenyl ring absorptions. For compound XIII it was not possible to distinguish between the 2,3 double bond position as shown and the alternative *exo* position from a comparison of the infrared absorption spectra of compounds XI, XII, and XIII. The position of the >C=O absorption in the systems



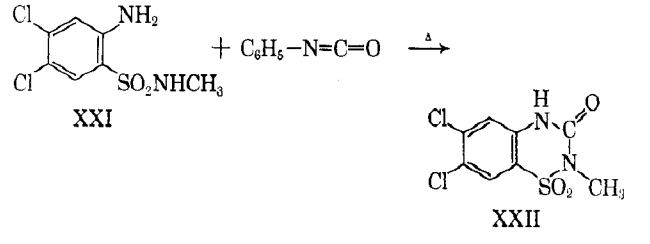
does not appear to differ appreciably.[8]

In the 3-oxo series, VIII, upon acetylation under the same conditions employed for II, yielded 3-chloro-6-acetylsulfamoylacetanilide (XIV). Ring opening of this type of compound upon acetylation has also been observed by Raffa.[3d] Under less vigorous conditions no acetylation was observed.

The synthesis of compounds substituted only on the imino nitrogen atom was carried out by condensing XV with isothiocyanates. In this manner 3-ethyl-, 3-*n*-butyl-, and 3-phenylimino-6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxides (XVI, R = C_2H_5, n-C_4H_9, and C_6H_5, respectively) were obtained. Each of these three compounds showed a strong infrared band in the 6.12- to 6.15-μ region (>C=N—) supporting dou-



ble bond position given in XVI. An attempt was made to utilize the reaction for the synthesis of compounds of this series bearing substituents both on the imino nitrogen atom and the nitrogen atom at position 2. However, no recognizable product could be isolated from the attempted reaction of 2-amino-4-chloro-*N*-methylbenzenesulfonamide and *n*-butyl isothiocyanate either under the usual conditions or in the presence of a base (sodium hydride). Similarly, the attempted condensation of the N,N′-dimethyl intermediate (X) with *n*-butyl isothiocyanate was unsuccessful, except that in this case most of XI was recovered unchanged. When phenyl isocyanate, instead of phenyl isothiocyanate was condensed with XV, the reaction took a different course with formation of the 3-oxo-3,4-dihydro compound (VIII) in high yield. Condensation of the N-methylsulfonamide (XXI) with phenyl isocyanate gave a low yield of the 2-methyl-3-oxo-3,4-dihydro compound (XXII). In this connection it may be noted that we were not able to obtain the 2-methyl derivative of VIII by direct alkylation.

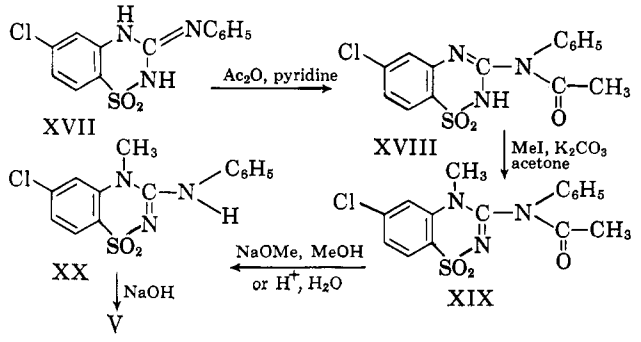


6-Chloro-3,4-dihydro-3-phenylimino-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (XVII) was acetylated with refluxing acetic anhydride in pyridine furnishing a monoacetyl derivative which was shown by subsequent transformations to be XVIII (Scheme III). Methylation of XVIII with methyl iodide and potassium carbonate in acetone afforded the monomethyl monoacetyl

(8) K. Tsuda and R. Hayatsu, *J. Am. Chem. Soc.*, **78**, 4107 (1956), report infrared bands at 5.98 μ for both 15-aza-16-keto-Δ^{14}-D-homocholesten-3β-ol benzoate (a) and 15-aza-16-keto-$\Delta^{8(14)}$-D-homocholesten-3β-ol benzoate (b)

corresponding to amide carbonyl absorptions. E. Schipper and E. Chinery, *J. Org. Chem.*, **26**, 4480 (1961), report infrared bands at 5.75–5.80 μ and 5.85–5.90 μ for amide carbonyl absorptions in compounds of types c and d, respectively.

SCHEME III



compound XIX. Treatment of XIX with sodium methoxide in methanol or with aqueous acid removed the acetyl group yielding XX which was then degraded with alkali to V. This establishes the position of the methyl group as 4 in compounds XIX and XX. Since the amide >C=O absorption in the infrared spectrum of XVIII appears at 5.90 μ, it is highly unlikely that the acetyl group is located on the nitrogen at position 2; thus, it must be attached to the external nitrogen atom as depicted in XVIII (and XIX). The remaining uncertainties are the position of the double bonds in XVIII and XX. We were unable to distinguish between the double bond positions as shown and those of the corresponding tautomeric forms by means of infrared or ultraviolet absorption spectral data.

Experimental[9]

3,4-Dihydro-3-imino-2*H*-1,2,4-benzothiadiazine 1,1-Dioxides (I, R = NH). (**A**).—An intimate mixture of the substituted *o*-aminobenzenesulfonamide[10] (0.07 mole) and guanidine carbonate (0.14 mole) was heated at 180° for 2 hr. The brown reaction mass was dissolved in boiling water (charcoal), the solution carefully acidified to pH 6, and rapidly filtered free of an orange gum. The pH of the filtrate was further adjusted to congo red and the solution chilled. The crude product was filtered off and recrystallized from methanol–water. Yields varied between 18 and 53%. Larger scale runs usually resulted in lower yields (Tables I and II).

(**B**).—An intimate mixture of *o*-aminobenzenesulfonamide (3.0 g.) and cyanamide (1.5 g.) was heated at 180–190° for 2 hr. The crude reaction mass was dissolved in hot water (charcoal) and the solution acidified, chilled, and filtered free of a small quantity of low melting solid. Concentration of the filtrate gave crude product (1.6 g.), m.p. 250–270°. Two recrystallizations from methanol gave 3,4-dihydro-3-imino-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (0.5 g., 14.5%), m.p. 335–337°.

(**C**).—An intimate mixture of *o*-aminobenzenesulfonamide (3.0 g.) and aminoguanidine bicarbonate was heated for 2 hr. at 180–190°. The crude reaction mass was dissolved in hot water (charcoal) and the resulting solution acidified and chilled giving 3,4-dihydro-3-imino-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (0.1 g., 3%), m.p. 328–330°. No further product was obtained.

3,4-Dihydro-3-oxo-2*H*-1,2,4-benzothiadiazine 1,1-Dioxides (I, R = O).—An intimate mixture of the substituted *o*-aminobenzenesulfonamide (0.07 mole) and urea (0.14 mole) was heated at 180–190° for 1 hr. The reaction mixture melted and resolidified within 0.5 hr. The reaction mass was dissolved in hot water (charcoal) and the solution acidified, chilled, and filtered giving crude product often in yields in excess of 90%. The crude products usually melted within 5° of the pure products. Recrystallization from aqueous methanol gave yields of between 77 and 85% (Tables I and II).

(9) All melting points are uncorrected; ultraviolet absorption spectra were determined in methanol solution, infrared absorption spectra as Nujol mulls, and pK_a' values in 66% dimethylformamide, unless otherwise stated.

(10) J. G. Topliss, M. H. Sherlock, H. Reimann, L. M. Konzelman, E. P. Shapiro, B. W. Pettersen, H. Schneider, and N. Sperber, *J. Med. Chem.*, **6**, 122 (1963).

Attempted Hydrolysis of 6-Chloro-3,4-dihydro-3-imino-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (II). (**A**).—A solution of II (0.5 g.) in concentrated hydrochloric acid (25 ml.) was refluxed for 5 hr. and then chilled. Filtration gave a 95% recovery of II.

(**B**).—A solution of II (0.5 g.) in 10% sodium hydroxide (50 ml.) was refluxed for 24 hr. Acidification of the cooled solution followed by recrystallization of the collected solid gave an 80% recovery of starting material.

(**C**).—A solution of II (0.5 g.) in 25% sodium hydroxide was refluxed for 6 hr. and then kept at room temperature for 16 hr. A work-up similar to that described in section B resulted in an 80% recovery of starting material.

(**D**).—A solution of II (1.0 g.) in 10% potassium carbonate (50 ml.) was refluxed for 6 hr. and then acidified affording a virtually quantitative recovery of starting material.

6-Chloro-3,4-dihydro-3-imino-4-methyl-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (III). (**A**).—Methyl iodide (90.0 g.) was added in one portion to a solution of II (30.0 g.) and sodium methoxide (10.5 g.) in methanol (350 ml.) and the reaction mixture refluxed for 16 hr. Chilling of the solution gave III (19.3 g., 60%), m.p. 275–278° dec. A sample recrystallized from ethanol–water had m.p. 276–278° dec.; λ_{max} 250 mμ (ϵ 8200); 290 mμ (ϵ 1100); $\lambda_{max}^{0.1\ N\ NaOH\ (MeOH)}$ 249 mμ (ϵ 10,700); λ_{max} 293 mμ (ϵ 2100); λ_{max} 6.05 μ (s).

Anal. Calcd. for $C_8H_8ClN_3O_2S$: Cl, 14.43; N, 17.10; S, 13.05. Found: Cl, 14.03; N, 17.16; S, 12.80.

(**B**).—A mixture of II (1.0 g.), anhydrous potassium carbonate (1.15 g.), and methyl iodide (0.48 g.) in dry acetone (35 ml.) was refluxed with stirring for 16 hr. The potassium carbonate was filtered off from the cooled reaction mixture and washed with acetone (30 ml.). The combined filtrates were concentrated to dryness and the residue recrystallized twice from ethanol–water giving III (0.15 g.), m.p. 276–278° dec.

4-Chloro-2-methylaminobenzenesulfonamide (V).—6-Chloro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide[11] (50.9 g.) was added to a solution of sodium methoxide (15.5 g.) in methanol (300 ml.) and stirred until solution was complete. Methyl iodide (51.0 g.) was added in one portion and the resulting solution refluxed for 16 hr. On chilling 6-chloro-4-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (46.2 g., 85%), m.p. 287–289°, was obtained. Recrystallization from methanol–water gave 40.5 g., m.p. 288–289°; λ_{max} 222 mμ (ϵ 30,600); 275 mμ (ϵ 7700).

Anal. Calcd. for $C_8H_7ClN_2O_2S$: Cl, 15.37; N, 12.15. Found: Cl, 15.41; N, 12.49.

6-Chloro-4-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (43.2 g.) in 10% sodium hydroxide solution (600 ml.) was refluxed for 16 hr. Acidification of the reaction mixture with concentrated hydrochloric acid and chilling gave V (40.0 g., 96%), m.p. 178–181°. Recrystallization from methanol–water yielded 4-chloro-2-methylaminobenzenesulfonamide (35.4 g.), m.p. 179–181°; λ_{max} 254 mμ (ϵ 12,200); 321 mμ (ϵ 4700) (2-amino-4-chloro-N-methylbenzenesulfonamide[10] has m.p. 112–114°).

Anal. Calcd. for $C_7H_9ClN_2O_2S$: Cl, 16.07; N, 12.70; S, 14.70. Found: Cl, 15.87; N, 12.87; S, 15.05.

6-Chloro-3,4-dihydro-4-methyl-3-oxo-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (IV).—An intimate mixture of 4-chloro-2-methylaminobenzenesulfonamide (10.0 g.) and urea (5.5 g.) was heated at 180–190° for 1 hr. The reaction mass was dissolved in warm water and the solution acidified with concentrated hydrochloric acid and chilled giving a product (9.6 g., 86%), m.p. 289–291° dec. Recrystallization from ethanol–water gave IV (8.5 g.), m.p. 291–293° dec.; λ_{max} 248 mμ (ϵ 10,500); 295 mμ (ϵ 2100); $\lambda_{max}^{0.1\ N\ NaOH\ (MeOH)}$ 253 mμ (ϵ 9900); 296 mμ (ϵ 2200); λ_{max} 5.98 μ (vs); pK_a' 3.4.

Anal. Calcd. for $C_8H_7ClN_2O_3S$: Cl, 14.37; N, 11.36. Found: Cl, 14.36; N, 11.13.

Hydrolysis of 6-Chloro-3,4-dihydro-3-imino-4-methyl-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (III). (**A**).—A solution of III (0.4 g.) in 10% sodium hydroxide solution (25 ml.) was refluxed for 6 hr. Acidification of the chilled reaction mixture gave a crude hydrolysis product (0.3 g.), m.p. 225–240°. Two recrystallizations from methanol–water gave IV (0.1 g.), m.p. 290–292° dec., identified by comparison with an authentic specimen.

(**B**).—A solution of III (0.3 g.) in 20% sodium hydroxide solution (25 ml.) was refluxed for 16 hr. Acidification of the chilled reaction mixture gave crude hydrolysis product (0.22 g.),

(11) J. H. Short and U. Biermacher, *J. Am. Chem. Soc.*, **82**, 1135 (1960).

m.p. 176–200°. Recrystallization from methanol–water gave V (0.1 g.), m.p. 179–181°, identified by comparison with an authentic specimen.

(C).—A solution of III (0.5 g.) in 10% potassium carbonate solution (50 ml.) was refluxed for 2.5 hr. and then allowed to stand at room temperature for 16 hr. Filtration gave product (0.35 g.), m.p. 180–230°. No additional product was obtained by acidification of the filtrate. The crude product (0.35 g.) was dissolved in hot methanol and the solution concentrated to a volume of 8 ml. and chilled giving IV (0.06 g.), m.p. 287–289° dec. The addition of water (25 ml.) to the filtrate gave V (0.23 g.), m.p. 180–183°.

6-Chloro-4-methyl-3-methylamino-4*H*-1,2,4-benzothiadiazine 1,1-Dioxide (VI).[12]—A mixture of II (1.0 g.), anhydrous potassium carbonate (2.30 g.), methyl iodide (7.0 g.), and acetone (50 ml.) was refluxed for 48 hr. The reaction mixture was filtered, the filter cake washed with acetone, and the combined filtrates concentrated to dryness. The residue, on trituration with 5% sodium hydroxide (20 ml.), yielded a gum, which after being kept under ether (50 ml.) for 48 hr., gave crude product (0.50 g.), m.p. 293–310° dec. Traces of II were removed by washing with 5% sodium hydroxide and then two recrystallizations from ethanol–water gave VI (0.20 g.), m.p. 326–329° dec.; λ_{max} 250 mμ (ε 9800); 290 mμ (ε 2000); λ_{max} 3.00 μ (m); 6.25 μ (s); 6.32 μ (s); 6.40 μ (vs).

Anal. Calcd. for $C_9H_{10}ClN_3O_2S$: Cl, 13.36; N, 16.18. Found: Cl, 13.80; N, 16.24.

Hydrolysis of VI.—A solution of VI (0.5 g.) in 10% sodium hydroxide (30 ml.) was refluxed for 16 hr. Acidification and chilling gave IV (0.4 g.), m.p. 265–270° dec., identified by comparison with an authentic specimen.

6-Chloro-3-dimethylamino-4-methyl-4*H*-1,2,4-benzothiadiazine 1,1-Dioxide (VII).—A mixture of II (5.0 g.), anhydrous potassium carbonate (25.0 g.) methyl iodide (75 g.), and acetone (250 ml.) was refluxed with stirring for 7 days. The reaction mixture was filtered, the filter cake washed with acetone, and the combined filtrates concentrated to dryness. The residue (8.2 g.) was boiled with chloroform (500 ml.) and filtered free of potassium iodide (2.0 g.). The chloroform solution was concentrated to 15–20 ml., petroleum ether (200 ml.) added, and the solution chilled giving crude product (4.9 g.), m.p. 220–223°. Recrystallization from methanol gave VII (3.9 g.), m.p. 227–229°; λ_{max} 223 mμ (ε 30,900); 250 mμ (ε 9500); 284 mμ (ε 1600); λ_{max} 6.25 μ (s); 6.32 μ (s); 6.42 μ (vs).

Anal. Calcd. for $C_{10}H_{12}ClN_3O_2S$: Cl, 12.95; N, 15.35; S, 11.71. Found: Cl, 13.17; N, 15.19; S, 11.69.

Hydrolysis of VII.—A solution of VII (0.5 g.) in 10% sodium hydroxide solution (40 ml.) was refluxed 16 hr., acidified, and chilled giving IV (0.4 g.), m.p. 291–293° dec., identified by comparison with an authentic specimen.

6-Chloro-3,4-dihydro-2,4-dimethyl-3-oxo-1,2,4-benzothiadiazine 1,1-Dioxide (IX).—A mixture of VIII (1.0 g.), anhydrous potassium carbonate (2.3 g.), methyl iodide (7.0 g.), and acetone (60 ml.) was refluxed for 3 days when additional methyl iodide (7.0 g.) and anhydrous potassium carbonate (2.3 g.) were added and refluxing continued for 3 more days. The reaction mixture was filtered, the filter cake washed with acetone, and the combined filtrates concentrated to dryness. The residue was triturated successively with petroleum ether (100 ml.) and water (30 ml.) yielding IX (1.0 g.), m.p. 171–174°. Recrystallization from methanol gave 0.9 g., m.p. 172–174°; λ_{max} 248 mμ (ε 10,100); 291 mμ (ε 2200); λ_{max} 5.92 μ (vs) (broad).

Anal. Calcd. for $C_9H_9ClN_2O_3S$: Cl, 13.60; N, 10.75; S, 12.30. Found: Cl, 13.64; N, 10.75; S, 12.22.

Methylation of IV.—A 52.7% suspension of sodium hydride in mineral oil (2.70 g.) was added to a stirred solution of IV (12.0 g.) in dimethylformamide (150 ml.) at 120°. After 0.5 hr. dimethyl sulfate (9.2 g.) was added dropwise with stirring and the solution heated at 120° for 6 hr. The reaction mixture was concentrated *in vacuo* almost to dryness and the gummy residue crystallized from methanol giving IX (9.0 g., 71%), m.p. 172–174°.

4-Chloro-2-methylamino-N-methylbenzenesulfonamide (X).—A mixture of IX (3.0 g.) and 10% sodium hydroxide (60 ml.) was refluxed for 16 hr. The cooled solution was acidified giving crude product (2.6 g.). Two recrystallizations from methanol–water gave X (1.4 g., 52%), m.p. 89–90°; λ_{max} 255 mμ (ε 12,400); 323 mμ (ε 5100).

Anal. Calcd. for $C_8H_{11}ClN_2O_2S$: Cl, 15.11; N, 11.94. Found: Cl, 15.23; N, 12.09.

3-Acetylamino-6-chloro-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (XI).—A mixture of II (4.5 g.), acetic anhydride (8.4 g.), and pyridine (75 ml.) was refluxed for 4 hr. The solution was concentrated to *ca.* 10–20 ml., poured into cold water (200 ml.), and chilled giving XI (5.0 g., 95%), m.p. 279–282°. Recrystallization from ethanol–water gave 3.9 g., m.p. 282–284°; λ_{max} 222 mμ (ε 41,900); 264 μ (ε 7600); 294 mμ (ε 1600); $\lambda_{max}^{0.1\ N\ NaOH\ (MeOH)}$ 285 mμ (ε 14,400); λ_{max} 3.10 μ (ms); 3.28 μ (w); 5.86 μ (s); 6.10 μ (vs); 6.26 μ (vs); 6.48 μ (ms); pK_a' 8.05.

Anal. Calcd. for $C_9H_8ClN_3O_3S$: Cl, 12.95; N, 15.35; S, 11.71. Found: Cl, 13.32; N, 15.04; S, 11.75.

Hydrolysis of XI. (A).—A solution of XI (9.5 g.) in 5% sodium hydroxide (100 ml.) was heated on a steam bath for 1.5 hr. and the cooled solution acidified giving II (6.2 g., 78%), m.p. 340–342° dec.

(B).—A solution of XI (1.0 g.) in methanol (30 ml.), water (10 ml.), and concentrated hydrochloric acid (10 ml.) was refluxed for 1.5 hr. and then chilled. Filtration gave II (0.8 g., 94%), m.p. 339–341° dec.

Methylation of XI.—Methyl iodide (2.5 g.) was added portionwise to a refluxing solution of XI (1.0 g.) and sodium methoxide (0.3 g.) in methanol (25 ml.) and the resulting solution refluxed for 16 hr. and chilled yielding III (0.25 g.), m.p. 275–277°. The filtrate was evaporated to dryness giving 0.45 g. of material, m.p. 248–255°, which after one recrystallization from methanol yielded III (0.25 g.), m.p. 274–277°.

3-*N*-Methylacetylamino-4-methyl-6-chloro-4*H*-1,2,4-benzothiadiazine 1,1-Dioxide (XII).—A mixture of XI (1.0 g.), anhydrous potassium carbonate (2.5 g.), and methyl iodide (6.0 g.) in acetone (60 ml.) was refluxed with stirring for 16 hr. The reaction mixture was filtered and the filter cake washed with acetone. The combined filtrates were evaporated almost to dryness, petroleum ether (100 ml.) added, and the chilled solution filtered giving 1.5 g. of material which was triturated with water (30 ml.) giving XII (0.9 g., 82%), m.p. 194–196°. Recrystallization from methanol gave 0.8 g., m.p. 196–197°; λ_{max} 223 mμ (ε 31,700); 272 mμ (ε 7500); λ_{max} 3.25 μ (w); 5.85 μ (vs); 6.25 μ (s); 6.32 μ (vs); 6.50 μ (ms).

Anal. Calcd. for $C_{11}H_{12}ClN_3O_3S$: Cl, 11.75; N, 13.92; S, 10.62. Found: Cl, 11.80; N, 13.53; S, 10.66.

Hydrolysis of XII. (A).—A solution of XII (1.0 g.) and sodium methoxide (0.19 g.) in methanol (70 ml.) was refluxed for 16 hr. and then concentrated until crystallization began. Chilling then gave VI (0.8 g., 93%), m.p. 327–329°.

(B).—A solution of XII (1.0 g.) in methanol (30 ml.), water (10 ml.), and concentrated hydrochloric acid (10 ml.) was refluxed for 1.5 hr. (product began to separate after 10 min.). The chilled reaction mixture was filtered giving VI (0.8 g., 93%), m.p. 332–334°.

3-Acetylamino-4-methyl-6-chloro-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (XIII).—A solution of III (19.3 g.), acetic anhydride (32.0 g.), and pyridine (300 ml.) was refluxed for 4 hr. The reaction mixture was concentrated *in vacuo* to *ca.* 40 ml., poured into cold water (400 ml.), and the solid which separated collected (20.5 g., 91%), m.p. 228–230° dec. Recrystallization from methanol–water gave XIII (15.2 g.), m.p. 233–235°; λ_{max} 224 mμ (ε 19,500); 267 mμ (ε 8600); $\lambda_{max}^{0.1\ N\ NaOH\ (MeOH)}$ 224 mμ (ε 27,200) 270 mμ (ε 2200); λ_{max} 3.09 μ (m–w); 3.16 μ (m–w); 5.90 μ (s); 6.25 μ (s); 6.45 μ (m); pK_a' 8.4.

Anal. Calcd. for $C_{10}H_{10}ClN_3O_3S$: Cl, 12.32; N, 14.60. Found: Cl, 12.31; N, 14.56.

Methylation of XIII.—The method employed for the methylation of XIII was identical to that used in the preparation of XII by the methylation of XI. The yield of recrystallized XII was about 75%.

Acetylation of VIII.—A solution of VIII (2.0 g.), acetic anhydride (3.6 g.), and pyridine (30 ml.) was refluxed for 4 hr. The reaction mixture was concentrated and poured into cold water (200 ml.) giving XIV (1.8 g., 72%), m.p. 200–203°. Recrystallization from methanol gave XIV (1.1 g.), m.p. 202–204°; λ_{max} 222 mμ (ε 31,100); 250 mμ (ε 13,100); 294 mμ (ε 3100); λ_{max} 2.96 μ (m); 3.26 μ (s); 5.82 μ (s); 5.95 μ (s).

Anal. Calcd. for $C_{10}H_{11}ClN_2O_4S$: Cl, 12.20; N, 9.64. Found: Cl, 12.38; N, 9.54.

6-Chloro-3,4-dihydro-3-ethylimino-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (XVI, R = C_2H_5).—A mixture of 2-amino-4-chloro-

(12) Compound VI can be conveniently prepared by the route II → XI → XII → VI (Scheme II), all steps of which proceed in high yield.

benzenesulfonamide (3.0 g.) and ethyl isothiocyanate (6 ml.) was heated at 140° for 2 hr. The cooled reaction mixture was dissolved in acetone, the solution concentrated, and methanol added. Further concentration and cooling gave the product (1.4 g., 38%), m.p. 274–278°. Recrystallization from methanol–acetone gave 1.0 g., m.p. 284–285°; λ_{max} 250 mμ (ε 11,900); 290 mμ (ε 2000); $\lambda_{max}^{0.1\ N\ NaOH\ (MeOH)}$ 280 mμ (ε 23,400); sh 310 mμ (ε 2100); λ_{max} 6.15 μ (s); pK_a' 10.1.

Anal. Calcd. for $C_9H_{16}ClN_3O_2S$: Cl, 13.65; S, 12.34. Found: Cl, 13.53; S, 12.68.

3-*n*-Butyl-6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (XVI, R = *n*-C_4H_9).—A mixture of 2-amino-4-chlorobenzenesulfonamide (3.0 g.) and *n*-butyl isothiocyanate (6 ml.) was heated at 170° for 1 hr. The reaction mixture was triturated with hexane, the solvent decanted, and the residue crystallized from acetone–methanol giving crude product (2.4 g., 58%), m.p. 252–256°. Recrystallization from the same solvent pair gave the pure product (1.6 g.), m.p. 264–265°; λ_{max} 250 mμ (ε 11,400); 290 mμ (ε 2100); $\lambda_{max}^{0.1\ N\ NaOH\ (MeOH)}$ 222 mμ (ε 26,500); 280 mμ (ε 22,600); sh 310 mμ (ε 2800); λ_{max} 6.12 μ (vs); pK_a' 9.8.

Anal. Calcd. for $C_{11}H_{14}ClN_3O_2S$: Cl, 12.32; N, 14.60; S, 11.40. Found: Cl, 12.23; N, 14.62; S, 11.39.

The compound was recovered unchanged on attempted hydrolysis for 16 hr. with 10% and 20% sodium hydroxide or 10% aqueous-methanolic hydrogen chloride.

6-Chloro-3,4-dihydro-3-phenylimino-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (XVI, R = C_6H_5).—A mixture of 2-amino-4-chlorobenzenesulfonamide (40 g.) and phenyl isothiocyanate (80 ml.) was heated at 190–200° for 1.5 hr. The mixture melted and resolidified within 0.5 hr. The reaction mass was washed with ether leaving crude product (53.0 g., 90%), m.p. 345–347° dec. Recrystallization from dimethylformamide–water gave the pure product (44.5 g.), m.p. 353–354° dec.; λ_{max} 263 mμ (ε 24,200); $\lambda_{max}^{0.1\ N\ NaOH\ (MeOH)}$ 220 mμ (ε 26,400); 245 mμ (ε 11,800); 294 mμ (ε 30,400); λ_{max} 6.15 μ (s); pK_a' 8.8.

Anal. Calcd. for $C_{13}H_{10}ClN_3O_2S$: Cl, 11.52; S, 10.42. Found: Cl, 11.90; S, 10.33.

The compound was recovered unchanged after being refluxed for 16 hr. with 25% sodium hydroxide solution.

Reaction of 2-Amino-4-chlorobenzenesulfonamide with Phenyl Isocyanate.—A mixture of 2-amino-4-chlorobenzenesulfonamide (3.0 g.) and phenyl isocyanate (6.0 ml.) was refluxed for 5 min. At this point a solid mass formed. An additional quantity (3 ml.) of phenyl isocyanate was added and the reaction mixture refluxed for 1 hr. The mixture was cooled and the resulting reaction mass washed with ether affording VIII (3.0 g., 89%), m.p. 317–319° dec. Recrystallization from methanol–chloroform gave VIII (2.3 g.), m.p. 320–322° dec.

2-Amino-4,5-dichloro-*N*-methylbenzenesulfonamide (XXI).—2-Amino-4,5-dichlorobenzenesulfonyl chloride[13] (48.0 g.) was added, portionwise, to 40% aqueous methylamine. The solution was heated to remove excess of methylamine, acidified with hydrochloric acid, and the crude product collected by filtration, washed with water, and air dried. Recrystallization from methanol–water gave XXI (30.0 g., 61%). A sample recrystallized from the same solvent system had m.p. 138–140°; λ_{max} 257 mμ (ε 12,100); 328 mμ (ε 4000).

Anal. Calcd. for $C_7H_8Cl_2N_2O_2S$: Cl, 27.79; N, 10.98. Found: Cl, 27.41; N, 10.71.

(13) The crude sulfonyl chloride was prepared from 3,4-dichloroaniline according to the procedure of J. H. Short and U. Biermacher, ref. 11, and recrystallized from chloroform–hexane, m.p. 127–129°.

6,7-Dichloro-3,4-dihydro-2-methyl-3-oxo-4*H*-1,2,4-benzothiadiazine 1,1-Dioxide (XXII).—A mixture of XXI (3.0 g.) and phenyl isocyanate was heated at 180° for 2 hr. On trituration of the cold gummy reaction mixture with chloroform, XXII (1.2 g., 36.5%), m.p. 232–235°, was obtained. Recrystallization from methanol gave 0.8 g., m.p. 233–235°; λ_{max} 254 mμ (ε 15,200); 305 mμ (ε 2200); $\lambda_{max}^{0.1\ N\ NaOH\ (MeOH)}$ 223 mμ (ε 27,800); 279 mμ (ε 24,900); 327 mμ (ε 3000); λ_{max} 5.90 μ (vs); pK_a' 9.7.

Anal. Calcd. for $C_8H_6Cl_2N_2O_3S$: Cl, 25.22; N, 9.97; S, 11.40. Found: Cl, 25.22; N, 10.10; S, 11.63.

The over-all results from this reaction were found to vary considerably from run to run.

6-Chloro-3-*N*-phenylacetylamino-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (XVIII).—A solution of XVII (5.0 g.) in acetic anhydride (6.7 g.) and pyridine (100 ml.) was refluxed for 4 hr. and then concentrated to dryness *in vacuo*. The residue was washed with ether (100 ml.) affording crude XVIII (10.2 g., 93%), m.p. 242–245°. Recrystallization from methanol–acetone gave XVIII (8.7 g.), m.p. 251–252°; λ_{max} 220 mμ (ε 33,900); 266 mμ (ε 10,300); $\lambda_{max}^{0.1\ N\ NaOH\ (MeOH)}$ 221 mμ (ε 29,100); 289 mμ (ε 15,600); λ_{max} 3.29 μ (w); 5.93 μ (m); 6.22 μ (m); 6.28 μ (m); 6.37 μ (w); pK_a' 5.6.

Anal. Calcd. for $C_{15}H_{12}ClN_3O_3S$: Cl, 10.14; N, 12.02. Found: Cl, 9.99; N, 11.89.

6-Chloro-4-methyl-3-*N*-phenylacetylamino-4*H*-1,2,4-benzothiadiazine 1,1-Dioxide (XIX).—A mixture of XVIII (8.5 g.), methyl iodide (34.5 g.), anhydrous potassium carbonate (14.1 g.), and acetone (350 ml.) was treated as in the preparation of XII giving XIX (6.0 g., 68%), m.p. 199–200°, after recrystallization from methanol. λ_{max} 221 mμ (ε 35,800); 270 mμ (ε 10,200); λ_{max} 3.25 μ (m–w); 5.84 μ (s); 6.25 μ (m–s); 6.32 μ (m–s); 6.49 μ (m).

Anal. Calcd. for $C_{16}H_{14}ClN_3O_3S$: Cl, 9.75; N, 11.55; S, 8.81. Found: Cl, 9.98; N, 11.32; S, 8.68.

3-Anilino-6-chloro-4-methyl-4*H*-1,2,4-benzothiadiazine 1,1-Dioxide (XX). (A).—A solution of XIX (5.0 g.) in methanol (200 ml.), water (40 ml.), and concentrated hydrochloric acid (10 ml.) was refluxed for 1.5 hr., concentrated to *ca.* 100 ml., and then chilled yielding XX (4.1 g., 93%), m.p. 245–250°. Recrystallization from methanol–water gave XX (3.1 g.), m.p. 262–263°; λ_{max} 220 mμ (ε 35,800); 260 mμ (ε 22,300); λ_{max} 3.03 μ (m); 6.22 μ (m); 6.34 μ (m–s); 6.43 μ (vs).

Anal. Calcd. for $C_{14}H_{12}ClN_3O_2S$: Cl, 11.02; N, 13.06. Found: Cl, 10.84; N, 12.96.

(B).—A solution of XIX (4.2 g.) and sodium methoxide (0.62 g.) in methanol (100 ml.) was refluxed for 16 hr. and then concentrated to dryness. The residue was triturated with ether and the resulting crude solid product recrystallized from methanol–water giving XX (1.9 g., 51%), m.p. 262–264°.

Hydrolysis of XX.—A solution of XX (0.4 g.) in 10% sodium hydroxide (25 ml.) was refluxed for 16 hr. and the cooled reaction mixture diluted with water (25 ml.) and acidified with hydrochloric acid. The crude product was filtered off and recrystallized from methanol–water affording V (0.15 g.), m.p. 179–181°.

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