1,2-Benzothiazines. II. The Preparation and Sodium Borohydride Reduction of 3-Acyl-2H-1,2-benzothiazin-4(3H)-one 1,1-Dioxides[1]

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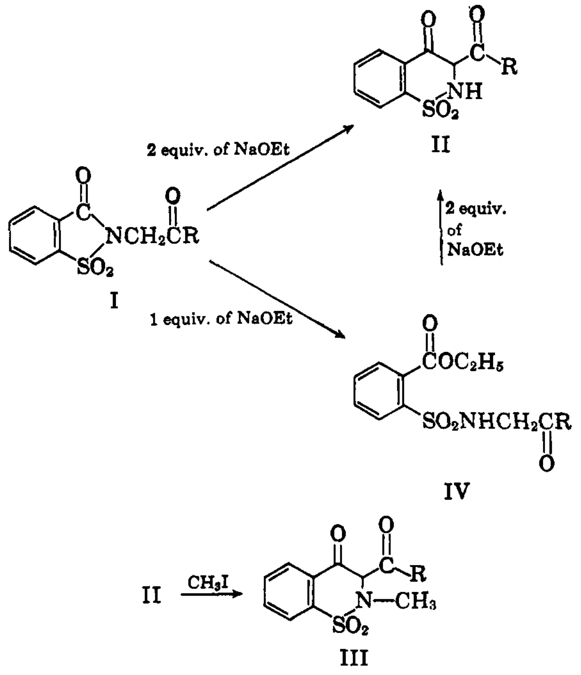
3-Acetyl-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (IIb) was prepared by treatment of N-acetonylsaccharin (Ib) with 2 equiv. of sodium ethoxide. Evidence is presented which supports a mechanism involving ethanolysis of Ib followed by a Dieckmann ring closure. Alkylation of IIb took place preferentially on the nitrogen to give the series of N-substituted derivatives listed in Table I. 3-Ethylidene- and 3-benzylidene-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxides (XVII) were prepared by sodium borohydride reduction of the corresponding 3-acetyl- and 3-benzoyl-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxides. This represents the first reported conversion of β-diketones to α,β-unsaturated ketones by the use of sodium borohydride. A mechanism involving a thermolabile enolate complex (XXII or XXIV) is discussed.

The 1,2-benzothiazines represent a fairly simple heterocyclic system which has remained practically unexplored. The literature gives two references[2,3] to the preparation of compounds of this class but studies of their chemistry were not reported. In one of these, Abe[3] and co-workers have reported the reaction of N-phenacylsaccharin (Ia) with 2 equiv. of sodium ethoxide to give 3-benzoyl-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (IIa) as well as the methylation of the latter to form IIIa[4] (See Chart I).

Chart I



I-IVa, $R = C_6H_5$
b, $R = CH_3$

Employing the same conditions with N-acetonylsaccharin (Ib), we have obtained the 3-acetyl analog IIb in 80% yield. With only 1 equiv. of sodium ethoxide no IIb was formed, but instead there was obtained the crystalline ethanolysis product IVb. This compound was readily converted to IIb on reaction with 2 equiv. of sodium ethoxide, but with 1 equiv. no conversion took place. The foregoing is evidence which supports our earlier suggestion[1] that the rearrangement of I to II takes place by ethanolysis of the carboxamide linkage followed by a Dieckmann cyclization.[5]

The N-methyl derivative IIIb was readily obtained by reaction of the sodium salt of IIb with methyl iodide at room temperature in either an aqueous or nonaqueous solvent. Under these conditions there was no evidence for C- or O-alkylation. Even when 2 equiv. of sodium hydride were used with an excess of methyl iodide in dimethylformamide, the only product isolated (in 77% yield) was IIIb. Compounds IIIa, IIIb, and V-IX, listed in Table I, were similarly prepared, whereas the acid X was obtained by saponification of the corresponding ester VIII.

As completely enolized β-diketones, these compounds (in the absence of carbonyl substituents) showed no band in the carbonyl region above 1640 cm.$^{-1}$; there were three partially fused bands of moderate intensity (relative to the strong sulfonamide band at 1180 cm.$^{-1}$) in the 1640–1530-cm.$^{-1}$ region.[6] They are more acidic than the usual β-diketone as was shown by their solubility in aqueous sodium bicarbonate. This increased acidity can be attributed to the electronegative sulfonamide group. The strong electron-withdrawing property of this system was also reflected in the abnormally high carbonyl stretching frequencies of the ketone groups in VI and VII (1742 and 1708 cm.$^{-1}$, respectively) and the ester groups in VIII and IX (1768 and 1758 cm.$^{-1}$, respectively).

O-Alkylation was achieved by refluxing IIIb with isopropyl iodide and potassium carbonate in acetone,[7] the resulting enol ether XI showing a strong carbonyl band at 1666 cm.$^{-1}$. The product from the same reaction with IIb could not be recrystallized but it was apparent from spectral and other properties that substitution on

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[1] H. Zinnes, R. A. Comes, and J. Shavel, Jr., *J. Org. Chem.*, **29**, 2068 (1964), should be considered as the first paper in this series.

[2] J. von Braun, *Ber.*, **56**, 2332 (1923).

[3] K. Abe, S. Yamamoto, and K. Matsui, *J. Pharm. Soc. Japan*, **76**, 1058 (1956); *Chem. Abstr.*, **51**, 3499 (1957).

[4] The experimental method for the methylation reaction was not described.

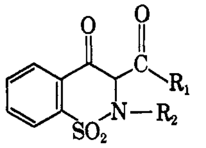
[5] The same mechanism had been suggested by W. J. Gensler ("Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 378) for the related reaction of phthalimide analogs of I which is known as the Gabriel–Colman rearrangement. Kinetic evidence that this is indeed the case has recently been presented by J. H. M. Hill [*J. Org. Chem.*, **30**, 620 (1965)], who showed that ring closure is the rate-determining step. Another mechanism, involving initial removal of a proton from the α-carbon followed by direct attack on the carbonyl by the resulting carbanion, had been postulated by C. R. Hauser and S. W. Kantor [*J. Am. Chem. Soc.*, **73**, 1437 (1951)].

[6] They gave the expected positive ferric chloride test as well as a bathochromic shift in the ultraviolet spectrum in going from a neutral or slightly acidic solvent to one which was basic.

[7] This method has been employed in the steroid series by G. E. Arth, G. I. Poos, and L. H. Sarett, [*J. Am. Chem. Soc.*, **77**, 3834 (1955).]

TABLE I

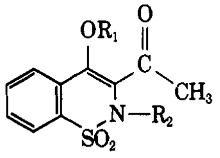
ALKYLATED 3-ACYL-2H-1,2-BENZOTHIAZIN-4(3H)-ONE 1,1-DIOXIDES



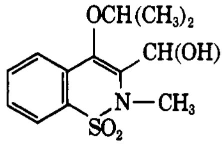
Compd.	R_1	R_2	M.p.,ª °C.	Formula	Anal., % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found	S Calcd.	S Found	Alkylating agent	Method	Yield, %
IIIa	C_6H_5	CH_3	160–161ᵇ	$C_{16}H_{13}NO_4S$									CH_3I	A	86ᶜ
IIIb	CH_3	CH_3	155–156	$C_{11}H_{11}NO_4S$	52.16	52.29	4.38	4.55	5.33	5.62	12.66	12.94	CH_3I	A	80ᶜ
														B	77
V	CH_3	CH_2CN	207–209	$C_{12}H_{10}N_2O_4S$	51.79	51.62	3.62	3.88	10.07	10.33	11.52	11.40	$ClCH_2CN$	B	76ᵈ
VI	CH_3	CH_2COMe	154–155	$C_{13}H_{13}NO_5S$	52.87	52.78	4.44	4.36	4.74	5.00	10.86	10.75	$ClCH_2COMe$	A	61ᶜ
VII	CH_3	CH_2COPh	136–137	$C_{18}H_{15}NO_5S$	60.49	60.69	4.23	4.25	3.92	3.64	8.97	8.94	$BrCH_2COPh$	A	82ᵈ
VIII	CH_3	CH_2CO_2Me	129–130	$C_{13}H_{13}NO_6S$	50.16	49.96	4.21	4.05	4.50	4.42	10.30	10.07	$BrCH_2CO_2Me$	A	87ᶜ
IX	CH_3	CH_2CO_2Et	100–101	$C_{14}H_{15}NO_6S$	51.69	51.45	4.65	4.48	4.30	4.38	9.86	9.95	$BrCH_2CO_2Et$	A	69ᶜ
X	CH_3	CH_2CO_2H	178–180	$C_{12}H_{11}NO_6S$	48.48	48.34	3.73	3.81	4.71	4.65	10.79	10.94			68ᵈ

ª Compounds IIIa, IIIb, VI, and IX were recrystallized from ethanol, compounds V and VII from dichloromethane–ethanol, compound VIII from methanol, and compound X from acetonitrile. ᵇ Reference 3 gives m.p. 159–160. ᶜ Yield refers to the product which crystallized from the reaction mixture; this was sufficiently pure to be used in subsequent reactions. ᵈ Yield refers to recrystallized material which was analytically pure.

the nitrogen had also taken place to give XII. Assignment of the structure of XI was based on its reduction to XIV by sodium borohydride. The n.m.r. spectrum favored structure XIV over its isomer XV in that it showed the terminal C-methyl hydrogens as a doublet (J = 7 c.p.s.) at 1.55 and the adjacent hydrogen as a quartet (J = 7 c.p.s.) at 5.30 p.p.m.

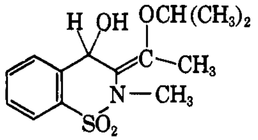


XI, $R_1 = CH(CH_3)_2$; $R_2 = CH_3$
XII, $R_1 = R_2 = CH(CH_3)_2$
XIII, $R_1 = CH_3CO$; $R_2 = CH_3$

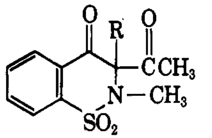


XIV

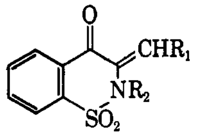
The enol acetate XIII,[8] obtained by treatment of the sodium salt of IIIb with acetyl chloride in dimethylformamide, had carbonyl bands at 1764 and 1693 cm.⁻¹. N-Bromosuccinimide reacted with IIIb in dichloromethane to give an unstable bromo derivative XVIa which on dissolving in methanol afforded the ether XVIb. This was characterized by strong carbonyl bands at 1734 and 1704 cm.⁻¹.



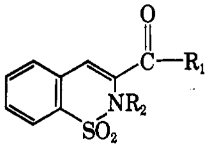
XV



XVIa, R = Br
b, R = OCH_3



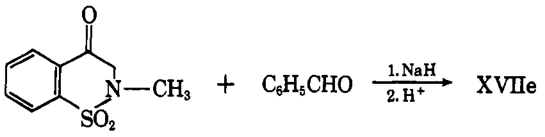
XVII



XVIII

a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = CH_3$; $R_2 = CH_3$
c, $R_1 = CH_3$; $R_2 = CH_2CO_2CH_3$
d, $R_1 = C_6H_5$; $R_2 = H$
e, $R_1 = C_6H_5$; $R_2 = CH_3$

Sodium borohydride reduction of the 3-acyl-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxides IIa, IIb, IIIa, IIIb, and VIII gave the corresponding 3-ethylidene or 3-benzylidene derivatives XVII in yields of 57–72% (see Table II). The procedure consisted of stirring the reactants at −5° in isopropyl alcohol–1,2-dimethoxyethane (1:2) and quenching the reaction mixture by pouring into cold aqueous acid. The 3-ethylidene derivatives XVIIa, XVIIb, and XVIIc were characterized by their respective carbonyl bands at 1679, 1687, and 1688 cm.⁻¹ as well as by prominent olefinic and aromatic absorption. The assignment of these structures rather than the alternative structures XVIII was based on the n.m.r. spectrum of XVIIb which showed the C-methyl hydrogens as a doublet centered at 2.06 and the olefinic hydrogens as a quartet centered at 7.25 p.p.m. (J = 7 c.p.s.). With the benzylidene derivatives XVIId and XVIIe the carbonyl bands were found at 1652 and 1667 cm.⁻¹, respectively, and in the n.m.r. spectrum the olefinic proton signal was hidden among those of the aromatic hydrogens. The structural assignment was confirmed through the synthesis of XVIIe by a sodium hydride catalyzed condensation of XIX[9] with benzaldehyde. In the latter reaction, XVIIe was isolated from a mixture of *cis–trans* isomers, the components of which could be distinguished by the use of thin layer chromatography. In contrast, chromatograms of the crude product from the sodium borohydride reduction of IIIa failed to give the spot corresponding to the other isomer.



XIX

The selective formation of the ethylidene and benzylidene derivatives XVII could result from an initial

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[8] This structure has not been rigorously proven, the assignment being based on analogy with XI. The enol acetate was unaffected by hydrogenation in acetic acid, using platinum oxide or Raney nickel catalysts. Sodium borohydride reduction under the same conditions used with XI was of no use as a structure proof since the only product was XVIIb and this could have arisen through prior alcoholysis of the acetoxy group.

[9] The preparation of XIX will be described in a forthcoming publication.

TABLE II

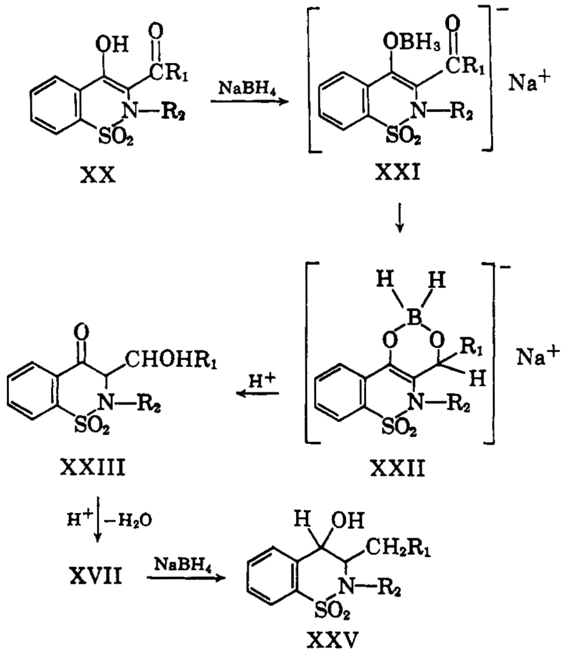
3-ETHYLIDENE- AND 3-BENZYLIDENE-2H-1,2-BENZOTHIAZIN-4(3H)-ONE 1,1-DIOXIDES

Compd.	Yield, %[a] (M.p., °C.)	M.p.,[b] °C.	Formula	Anal., % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found	S Calcd.	S Found	ν_{max}, cm.$^{-1}$	λ_{max}, mμ (ε)
XVIIa	56 (136–138)	138–139	$C_{10}H_9NO_3S$	53.80	53.88	4.06	3.94	6.27	6.46	14.36	14.31	3180, 1679, 1624, 1590, 1570	262 (12,000), 301 sh (4420)
XVIIb	64 (116–119)	120–121	$C_{11}H_{11}NO_3S$	55.68	55.85	4.67	4.88	5.90	5.63	13.51	13.70	1687, 1626, 1592, 1572	263 (13,000), 301 sh (3500)
XVIIc	71 (108–110)	108.5–110	$C_{13}H_{13}NO_5S$	52.87	53.13	4.44	4.47	4.74	4.68	10.86	10.96	1758, 1740, 1685, 1632, 1620, 1593, 1576[c]	262 (12,300), 300 sh (3000)
XVIId	72 (220–224)[d]	220–224[d]	$C_{15}H_{11}NO_3S$	63.14	63.27	3.88	4.13	4.91	4.83	11.24	11.45	3080, 1652, 1590, 1563	235 (10,750), 262 (9900), 335 (16,500)
XVIIe	70 (163–164)	163–164	$C_{16}H_{13}NO_3S$	64.20	64.24	4.38	4.67	4.68	4.74	10.71	10.52	1668, 1592, 1572	234 (12,500), 264 (8750), 331 (20,300)

[a] See the general procedure. [b] Refers to recrystallized analytical samples. Compounds XVIIa, XVIIb, XVIId, and XVIIe were recrystallized from acetonitrile and compound XVIIc from methanol. [c] The doublets observed at 1758, 1740, and 1632, 1620 are apparently due to intermolecular forces since only single bands are observed in solution: $\nu_{max}^{CH_2Cl_2}$ 1752, 1688, 1626, 1594, 1578 cm.$^{-1}$. [d] Decomposes.

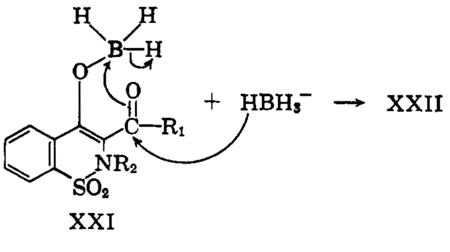
Zerewitinov-like reaction between sodium borohydride and the more acidic (XX) of the two possible enolic forms of the β-diketone to give a structure such as XXI (see Chart II). Reduction of the aliphatic ketone could then take place intramolecularly or by reaction with another mole of sodium borohydride[10] to give the cyclic structure XXII in which the aromatic ketone is protected from reduction. This complex would then be destroyed by acid treatment which could also cause dehydration of the resulting β-keto alcohol XXIII (Chart II).

CHART II



XX-XXVa, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = R_2 = CH_3$
c, $R_1 = CH_3$; $R_2 = CH_2CO_2CH_3$
d, $R_1 = C_6H_5$; $R_2 = H$
e, $R_1 = C_6H_5$; $R_2 = CH_3$

An alternative to the cyclic mechanism is one involving reduction of XXI with a second mole of sodium borohydride to give XXIV. We have shown that under the same conditions XVIIb is reduced to the saturated alcohol XXVb. The formation of the latter undoubtedly involves 1,4-addition of hydride to give the enolate XXVI ($R_1 = R_2 = CH_3$) which must be sufficiently unstable to permit further reduction to the alcohol. If it could be assumed that XXIV and XXVI have comparable stabilities under these reaction conditions, this would be evidence for the cyclic mechanism. However, stabilization of XXIV through hydrogen bonding with the hydroxyl must also be considered. The structure of XXVb was assigned from the absence



XXI

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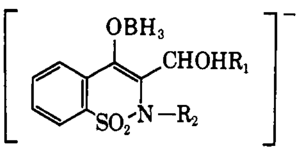
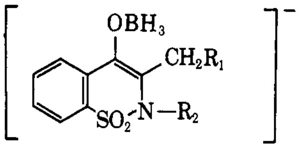
[10] We are indebted to a referee for pointing out the possibility of the intermolecular mechanism.



XXIV



XXVI

of an olefinic proton signal in the n.m.r. spectrum which showed the C-methyl hydrogens as a triplet at 1.12, the methylene hydrogens as a quartet at 1.90,[11] the 3-hydrogen as a sextet at 3.98, and the 4-hydrogen as a quartet at 4.92 p.p.m. The corresponding phenyl derivative XXVc was obtained in a similar manner by sodium borohydride reduction of XVIIe.

Temperature must be a factor in the stability of the enolate complex (XXII or XXIV) since at room temperature the reduction of IIb afforded XVIIb in only 10% yield (as compared to 64% at −5°); the greater part of the reaction product consisted of an oil which showed a strong hydroxyl band at 3500 cm.$^{-1}$ and only trace absorption in the 1800–1500-cm.$^{-1}$ region. The oil, which resisted attempts at purification, was shown by thin layer chromatography to consist of at least four components.

To our knowledge, the application of sodium borohydride reduction for the direct conversion of a β-diketone to its corresponding α,β-unsaturated ketone has not been previously described. The only other report of the preparative use of sodium borohydride with β-diketones is that of Dale[12] who observed complete reduction to give the corresponding 1,3-diols. Lithium aluminum hydride reduction of β-diketones has been reported by Dreiding and Hartman[13a] who found the product to consist mainly of the unsaturated monoalcohol with a small amount of the corresponding 1,3-diol. These authors as well as Stork and Clarke[13b] have also described cases in which the major product was the saturated monoalcohol. While α,β-unsaturated ketones were postulated as possible intermediates, they were not isolated from these reactions.[14]

Experimental

Melting points were determined using the Thomas–Hoover capillary melting point apparatus which was calibrated against known standards. The ultraviolet and infrared spectra were obtained, respectively, with a Beckman DKI spectrophotometer and a Baird Model 455 double-beam instrument. Unless otherwise stated, the former were determined as solutions in 95% ethanol and the latter as Nujol mulls. The n.m.r. spectra were determined in deuterated chloroform using the Varian A-60 spectrometer with tetramethylsilane as an internal standard. Thin layer chromatography was carried out on silica gel G (Stahl) using a 50:50 mixture of *n*-heptane and acetone as the eluent, the chromatograms being developed by placing them in a closed vessel containing iodine crystals. The drying agent used throughout was sodium sulfate.

3-Acetyl-2H-1,2-benzothiazin-4(3H)-one 1,1-Dioxide (IIb).—A solution of sodium ethoxide, prepared from 20.7 g. (0.9 mole) of sodium and 400 ml. of ethanol,[15] was heated to 40° and 100 g. (0.45 mole) of 2-acetonylsaccharin (Ib)[16] was added all at once as the powder. The mixture was quickly heated to 50–55° and maintained at this temperature for 5 min. It was then quickly cooled to 25° and 450 ml. of 9% hydrochloric acid was added as rapidly as possible while maintaining the temperature at 30–35°. The crystals which separated from solution were collected by filtration, washed with 50% aqueous ethanol, and dried *in vacuo* at 60° for 1 hr. to yield 80 g. of product, m.p. 156–158°. Recrystallization from 50% aqueous ethanol gave material: m.p. 158–159°; $\nu_{\max}$ 3240, 1636, 1584, and 1544 cm.$^{-1}$; $\nu_{\max}^{\mathrm{CH_2Cl_2}}$ 3270, 1632, 1593, and 1552 cm.$^{-1}$; $\lambda_{\max}$ 244 mμ (ε 7300) and 324 mμ (ε 11,000); $\lambda_{\min}$ 230 mμ (ε 5100) and 273 mμ (ε 2600); $\lambda_{\max}^{\mathrm{alkali}}$ 252 mμ (ε 5640) and 425 mμ (ε 3440); $\lambda_{\min}$ 240 mμ (ε 5400) and 334 mμ (ε 800).[17]

Anal. Calcd. for $C_{10}H_9NO_4S$: C, 50.20; H, 3.79; N, 5.85; S, 13.40. Found: C, 50.07; H, 4.07; N, 5.96; S, 13.55.

N-Acetonyl-*o*-carbethoxybenzenesulfonamide (IVb).—The reaction was carried out as in the previous example using 0.04 mole of sodium ethoxide and 9.6 g. (0.04 mole) of Ib in 50 ml. of ethanol. After acidification, the reaction mixture was diluted with 2 vol. of water and extracted with dichloromethane, and the dried organic layer was evaporated *in vacuo* to give a dark oil. This was triturated with petroleum ether and allowed to stand overnight at room temperature, whereupon it partially crystallized. It was recrystallized from 30 ml. of ethanol to give 4.5 g. of product, m.p. 85–87°, which gave a negative ferric chloride test. In addition there was obtained 1.4 g. of a second crop, m.p. 83–85°. Recrystallization of the first crop from ethanol gave material: m.p. 89–89.5°; $\nu_{\max}$ 3250, 1730 and 1720 cm.$^{-1}$; $\lambda_{\max}$ 225 mμ (ε 7000) and 276 mμ (ε 1400); $\lambda_{\min}$ 222 mμ (ε 6800) and 259 mμ (ε 1000).

Anal. Calcd. for $C_{12}H_{15}NO_5S$: C, 50.52; H, 5.30; N, 4.91; S, 11.24. Found: C, 50.82; H, 5.48; N, 4.81; S, 11.36.

Reaction of N-Acetonyl-*o*-carbethoxybenzenesulfonamide (IVb) with 1 Equiv. of Sodium Ethoxide.—A solution of 3.5 g. (0.125 mole) of IVb in 20 ml of ethanol was heated to 45° and a solution of 0.125 mole of sodium ethoxide in 15 ml. of ethanol was added all at once.[18] The reaction mixture was quickly heated to 50–55° and maintained at this temperature for 5 min. It was then quickly cooled to 25° and 16 ml. of 9% hydrochloric acid was added as rapidly as possible while maintaining the temperature at 30–35°. Addition of an equal volume of water followed by refrigeration gave 1.4 g. of IVb, m.p. 85–88°. No IIb could be isolated from the mother liquor.

Reaction of N-Acetonyl-*o*-carbethoxybenzenesulfonamide (IVb) with 2 Equiv. of Sodium Ethoxide.—A solution of 0.05 mole of sodium ethoxide in 50 ml. of ethanol was heated to 40° and 7.1 g. (0.025 mole) of IVb was added all at once as a powder. The mixture was quickly heated to 50–55° and maintained at this temperature for 5 min. It was then rapidly cooled to 25° and 60 ml. of 9% hydrochloric acid was added as rapidly as possible while maintaining the temperature at 30–35°. The reaction mixture was diluted with an equal volume of water and refrigerated overnight. The resulting crystals were washed with 50%

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[11] An octet is to be expected. The individual peaks of the observed quartet are somewhat broadened, suggesting that further splitting is present.

[12] J. Dale [*J. Chem. Soc.*, 910 (1961)] obtained 1,3-diols from acetylacetone, 2,2,6,6-tetramethylheptane-3,5-dione, and dibenzoylmethane whereas, with cyclic ketones such as cyclohexane-1,3-dione and dimedone, the starting materials were recovered completely. The latter result was attributed to the greater acidity of the cyclic ketones which caused decomposition of the sodium borohydride. These reactions were carried out in either methanol or aqueous methanol at temperatures ranging from 5 to 20°. It was not made clear whether or not an insoluble complex separated from solution though it was reported that refluxing the sodium salts of the cyclic diketones with sodium borohydride gave no reaction. In the present investigation, our reaction mixtures were homogeneous until they were quenched with acid.

[13] (a) A. S. Dreiding and J. A. Hartman, *J. Am. Chem. Soc.*, **75**, 3723 (1953); (b) G. Stork and F. H. Clarke, Jr., *ibid.*, **83**, 3114 (1961).

[14] An example of the conversion of a β-diketone to the corresponding α,β-unsaturated ketone by lithium aluminum hydride reduction of the enol ether followed by acid hydrolysis is given by R. C. Banerjee [*J. Indian Chem. Soc.*, **39**, 756 (1962)].

[15] The same results were also obtained by the use of the commercially available sodium methoxide in the same volume of ethanol.

[16] H. Eckenroth and K. Klein, *Ber.*, **29**, 329 (1896).

[17] The solvent was prepared by diluting 5 ml. of 1 *N* aqueous sodium hydroxide to a volume of 50 ml. with 95% ethanol. On neutralization with dilute hydrochloric acid there was obtained essentially the same spectrum as observed initially with 95% ethanol.

[18] The inverse addition was employed to ensure that an excess of ethoxide ion was never present.

aqueous ethanol and dried to give 3.5 g. of material, m.p. 155–157°, which was shown by the infrared and ultraviolet spectra to be identical with IIb, prepared as described above.

3-Acetyl-2-methyl-2H-1,2-benzothiazin-4(3H)-one 1,1-Dioxide (IIIb).—The following procedures are illustrative of the two general methods employed in the preparation of the N-substituted 3-acetyl-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxides listed in Table I. When method A was used with chlorides it was necessary to add 1 equiv. of potassium iodide.

A. Aqueous Method.—To a solution of 36 g. (0.15 mole) of 3-acetyl-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (IIb) in a mixture of 150 ml. of 1 *N* sodium hydroxide, 100 ml. of water, and 500 ml. of ethanol was added 25 ml. of methyl iodide. After standing at room temperature for 3 days, there was obtained 30.7 g. of crystals, m.p. 148–151°. Recrystallization from 75 ml. of ethanol gave 24 g. of material: m.p. 155–156°; ν_{max} 1620, 1592, and 1548 cm.$^{-1}$; $\nu_{max}^{CH_2Cl_2}$ 1620, 1595, and 1551 cm.$^{-1}$; λ_{max} 245–248 mμ (ε 6100) and 320 mμ (ε 11,000); λ_{min} 232 mμ (ε 5600) and 274 mμ (ε 2500); λ_{max}^{alkali} 242 mμ (ε 11,400), and 354 mμ (ε 11,200); λ_{min} 222 mμ (ε 7100) and 283 mμ (ε 2200).[17]

B. Nonaqueous Method.—To a slurry of 1.6 g. (0.03 mole NaH) of a 53.4% mineral oil dispersion of sodium hydride in 50 ml. of dimethylformamide was added a solution of 3.6 g. (0.015 mole) of 3-acetyl-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (IIb) in 50 ml. of dimethylformamide, the temperature being maintained at 0–10° during the addition. The solution was allowed to stir at room temperature for 2 hr. and 15 ml. of methyl iodide was added with sufficient cooling to maintain the temperature below 25°. After stirring at room temperature for 1 hr., the reaction mixture was poured into 500 ml. of ice–water, filtered, and acidified with dilute hydrochloric acid. The resulting solid was filtered off and dissolved in methylene chloride, and the dried solution was evaporated. Trituration of the residue with petroleum ether (b.p. 30–60°) gave 2.9 g. of product, m.p. 150–155°. Recrystallization from ethanol gave material, m.p. 155–156°, which was identical with the product obtained using procedure A.

3-Acetyl-2-carboxymethyl-2H-1,2-benzothiazin-4(3H)-one 1,1-Dioxide (X).—A solution of 21.8 g. (0.07 mole) of 3-acetyl-2-carbomethoxymethyl-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (VIII) in a mixture of 140 ml. of 1 *N* sodium hydroxide and 500 ml. of water was allowed to stand at room temperature for 20 hr. The reaction mixture was made strongly acidic by the addition of dilute hydrochloric acid and the resulting white precipitate was collected, washed with water, and sucked dry. Recrystallization from a small volume of acetonitrile gave 14.1 g. of product: m.p. 178–180°; ν_{max} 1725–1710 (doublet), 1618, 1595, and 1545 cm.$^{-1}$; λ_{max} 250–253 mμ (ε 6000) and 320 mμ (ε 9800); λ_{min} 234 mμ (ε 5400) and 276 mμ (ε 2900).

Anal. Calcd. for $C_{12}H_{11}NO_6S$: C, 48.48; H, 3.73; N, 4.71; S, 10.79. Found: C, 48.34; H, 3.81; N, 4.65; S, 10.94.

3-Acetyl-4-isopropoxy-2-methyl-2H-1,2-benzothiazine 1,1-Dioxide (XI).—A mixture of 8.8 g. (0.035 mole) of IIIb, 29.8 g. (0.175 mole) of isopropyl iodide, 29.8 g. of anhydrous potassium carbonate, and 350 ml. of acetone was refluxed with stirring for 48 hr. The acetone was distilled off and the residue was partitioned between water and dichloromethane. The residue from evaporation of the dried organic layer was triturated with petroleum ether (b.p. 30–60°) to give 7.9 g. of solid product, m.p. 117–118°, which gave a negative ferric chloride test; on thin layer chromatography it showed predominantly one spot with a small amount of material remaining at the origin. Recrystallization from isopropyl ether gave 5.8 g. of material: m.p. 121–123°; ν_{max} 1666 and 1585 cm.$^{-1}$; λ_{max} 235 mμ sh (ε 6600), 296 (10,100), and 312 (10,700); λ_{min} 253 mμ (ε 4700) and 301 mμ (ε 10,000).

Anal. Calcd. for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74; S, 10.86. Found: C, 56.87; H, 5.80; N, 4.93; S, 10.84.[19]

3-(1-Hydroxyethyl)-4-isopropoxy-2-methyl-2H-1,2-benzothiazine 1,1-Dioxide (XIV).—A mixture of 1.48 g. (0.005 mole) of XI, 0.38 g. (0.01 mole) of sodium borohydride, 40 ml. of 1,2-dimethoxyethane, and 20 ml. of isopropyl alcohol was stirred at 0 to −10° for 6 hr. It was poured into ice–water containing excess hydrochloric acid and extracted with dichloromethane. Evaporation of the dried organic layer gave a residue which was triturated with petroleum ether (b.p. 30–60°) and then recrystallized from Skellysolve C to give 0.5 g. of product, m.p. 105–106°. Recrystallization gave material: m.p 107–108°, ν_{max} 3520 cm.$^{-1}$, λ_{max} 272 mμ (ε 7640) and 298 mμ (ε 5700), λ_{min} 249 mμ (ε 4840) and 289 mμ (ε 5475).

Anal. Calcd. for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71; S, 10.78. Found: C, 56.74; H, 6.34; N, 4.74; S, 11.01.

4-Acetoxy-3-acetyl-2-methyl-2H-1,2-benzothiazine 1,1-Dioxide (XIII).—To a slurry of 1.8 g. (0.04 mole) of a 53.4% mineral oil dispersion of sodium hydride in 110 ml. of dimethylformamide was added a solution of 9.6 g. (0.038 mole) of IIIb in 120 ml. of dimethylformamide, the temperature being maintained at 0–10° during the addition. The solution was allowed to stir at room temperature for 1 hr. and a solution of 3.14 g. (0.04 mole) of acetyl chloride in 15 ml. of dimethylformamide was added with sufficient cooling to maintain the temperature below 25°. After stirring at room temperature for 18 hr., the reaction mixture was poured into ice–water containing excess hydrochloric acid and was extracted with dichloromethane. The organic layer was distilled *in vacuo* to give a gum which was triturated with several portions of water and redissolved in dichloromethane. The dried organic layer was distilled *in vacuo* to give a gum which on trituration with ether gave 4.8 g. of crystalline product, m.p. 133–135°; it gave a negative ferric chloride test and only one spot on thin layer chromatography. Recrystallization from isopropyl ether gave 3.7 g. of material: m.p. 137–138°; ν_{max} 1780 sh, 1766, 1694, and 1598 cm.$^{-1}$; λ_{max} 293 mμ (ε 10,900) and 305 mμ infl. (ε 10,500); λ_{min} 250 mμ (ε 3800).

Anal. Calcd. for $C_{13}H_{13}NO_5S$: C, 52.87; H, 4.44; N, 4.74; S, 10.86. Found: C, 52.91; H, 4.53; N, 4.75; S, 10.71.

Evaporation of the mother liquor from the ether trituration yielded a semisolid which gave a positive ferric chloride test. Chromatograms showed two spots, one corresponding to the starting material and one to the aforementioned crystalline product.

3-Acetyl-3-methoxy-2-methyl-2H-1,2-benzothiazin-4-(3H)-one 1,1-Dioxide (XVIb).—To a suspension of 21.3 g. (0.13 mole) of N-bromosuccinimide in 200 ml. of dichloromethane was added a solution of 30.3 g. (0.12 mole) of IIIb in 200 ml. of dichloromethane and the mixture was stirred at room temperature for 1 hr. It was then washed successively with two 120-ml. portions of cold 1 *N* sodium hydroxide and two 200-ml. portions of water. The dried organic layer was distilled *in vacuo* to give an oil which solidified on trituration with ether. This was collected and washed successively with ether and petroleum ether to give 23.7 g. of an off-white solid (XVIa), m.p. 104–105°, ν_{max} 1755 and 1690 cm.$^{-1}$, which gave off fumes when exposed to the air and which gave a positive Beilstein test. To a solution of this solid in 150 ml. of dichloromethane was added 6 ml. of methanol, the temperature being maintained below 20° by cooling with an ice bath. The solution was allowed to stand at room temperature for 5 min. and was washed successively with two 50-ml. portions of saturated sodium bicarbonate solution and two 100-ml. portions of water. The dried organic layer was distilled *in vacuo* to dryness to give an oil. Trituration with 25 ml. of methanol and refrigeration gave 11.9 g. of crystals, m.p. 105–108°. Recrystallization from methanol gave material: m.p. 113–114°, ν_{max} 1732 and 1704 cm.$^{-1}$, λ_{max} 250 mμ (ε 7800), λ_{min} 236 mμ (ε 6400).

Anal. Calcd. for $C_{12}H_{13}NO_5S$: C, 50.88; H, 4.63; N, 4.94; S, 11.32; methoxyl, 10.95; N-methyl, 5.31; C-methyl, 5.31. Found: C, 51.07; H, 4.60; N, 5.01; S, 11.41; methoxyl, 10.93; N-methyl, 4.73; C-methyl, 5.45.

General Procedure for the Preparation of 3-Ethylidene- and 3-Benzylidene-2H-1,2-benzothiazin-4(3H)-one 1,1-Dioxides (XVII, Table II).—A solution of 0.1 mole of the 3-acetyl- or 3-benzoyl-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide[3] in a mixture of 450 ml. of 1,2-dimethoxyethane and 150 ml. of isopropyl alcohol was cooled to −5° and 0.3 mole of sodium borohydride was added. The mixture was stirred at −5° for 12 hr.[20] and was poured into 1000 ml. of ice–water to which an excess of hydrochloric acid had previously been added. With all of the compounds except XVIId the resulting precipitate was collected, washed well with water, and dissolved in dichloromethane. The dried organic layer was distilled *in vacuo* and the residue was crystallized by trituration with cold ethanol (XVIIa and XVIIb), methanol (XVIIc and XVIId), or acetonitrile (XVIIe). The tabulated yields and associated melting points refer to material obtained in this manner. With the N-substituted derivatives (XVIIb, XVIIc, and XVIIe)

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[19] The same reaction conditions with IIb gave a gum (XII) which could not be purified. It was insoluble in aqueous alkali and gave a negative ferric chloride test. The infrared spectrum showed a strong band at 1680 cm.$^{-1}$ and the absence of NH absorption.

[20] When it was necessary to interrupt the reaction, the solution was stored overnight in a freezer at −20° and then rewarmed to −5°. Very little reaction seemed to take place at −20°.

the dichloromethane solution was washed successively with 20 ml. of cold 1 *N* sodium hydroxide and 50 ml. of water before removing the solvent. With XVIId, the precipitate obtained from the acidic solution was insoluble in dichloromethane so that it was purified directly.

Preparation of 3-Benzylidene-2-methyl-2H-1,2-benzothiazin-4(3H)-one 1,1-Dioxide (XVIIe) from 2-Methyl-2H-1,2-benzothiazin-4(3H)-one 1,1-Dioxide (XIX).—A slurry of 0.72 g. (0.0165 mole) of a 55% mineral oil dispersion of sodium hydride in 75 ml. of dimethylformamide was cooled to −20° and a solution of 3.2 g. (0.015 mole) of XIX[9] in 75 ml. of dimethylformamide was added. The mixture was stirred at −20° for 1 hr. and a solution of 3.2 g. (0.03 mole) of benzaldehyde in 30 ml. of dimethylformamide was added. Stirring at −20° was continued for 2.5 hr. and the reaction mixture was poured into 1200 ml. of ice–water to which 6 ml. of concentrated hydrochloric acid had previously been added. The resulting yellow precipitate was collected by filtration, washed well with water, and dissolved in dichloromethane. The dried solution was filtered and distilled *in vacuo* to dryness. The residue was triturated with filtered petroleum ether (b.p. 30–60°) and dried *in vacuo* at 80° to give 3.2 g. of material, m.p. 155–160°. The infrared and ultraviolet spectra were practically identical with those of XVIIe, prepared by sodium borohydride reduction of IIIa, but the thin layer chromatogram showed two spots whose relative sizes were estimated to be approximately 60:40; the larger and faster spot corresponded to that given by XVIIe.[21]

Anal. Calcd. for $C_{16}H_{13}NO_3S$: C, 64.20; H, 4.38; N, 4.68; S, 10.71. Found: C, 63.94; H, 4.44; N, 4.66; S, 10.90.

Recrystallization from acetonitrile gave 1.6 g. of material, m.p. 163–164°, whose chromatogram showed only the faster spot.[22] Mixture melting point and spectral data showed it to be identical with XVIIe prepared by the other method.

Anal. Found: C, 64.25; H, 4.27; N, 4.60; S, 10.95.

Attempts to isolate the other component were unsuccessful. Chromatograms of the acetonitrile mother liquor showed the same two spots in approximately the same proportions as in the crude product, suggesting that the slower moving material might be converted to the faster one during purification.

3-Ethyl-3,4-dihydro-2-methyl-2H-1,2-benzothiazin-4-ol 1,1-Dioxide (XXVb).—A solution of 2.4 g. (0.01 mole) of 3-ethylidene-2-methyl-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (XVIIb) in a mixture of 60 ml. of 1,2-dimethoxyethane and 20 ml. of isopropyl alcohol was cooled to −5° and 1.0 g. of sodium borohydride was added. The mixture was stirred at −5° for 7 hr. and was poured into an excess of ice-cold 2% hydrochloric acid. The reaction mixture was extracted with methylene chloride and the dried organic layer was evaporated *in vacuo* to give an oil which was dissolved in ether. Concentration of the ether solution gave 0.75 g. of crystalline material, m.p. 110–113°, which no longer showed carbonyl absorption. Recrystallization from isopropyl ether–dichloromethane gave material, m.p. 114–115°, ν_{max} 3470 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27; N, 5.80; S, 13.29. Found: C, 54.78; H, 6.39; N, 5.68; S, 13.19.

3-Benzyl-3,4-dihydro-2-methyl-2H-1,2-benzothiazin-4-ol 1,1-Dioxide (XXVe).—A mixture of 6 g. (0.02 mole) of 3-benzylidene-2-methyl-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (XVIIe), 3 g. (0.076 mole) of sodium borohydride, and 500 ml. of isopropyl alcohol was stirred at room temperature for 24 hr. and was poured into an excess of ice-cold 2% hydrochloric acid. The mixture was extracted with methylene chloride and the organic layer was dried and evaporated to give an oil which was triturated with petroleum ether to remove the residual isopropyl alcohol. The resulting gum was dissolved in 10 ml. of ethanol, whereupon it began to crystallize. On refrigeration, there was obtained 2.8 g. of material, m.p. 116–117.5°, which was free of carbonyl absorption. Recrystallization from ethanol gave material, m.p. 125–126°, ν_{max} 3450 cm.$^{-1}$; n.m.r. showed a singlet at 2.87 (NCH_3), a doublet at 3.27 (CH_2), and complex absorption centered at 4.17 and 4.50 (2 tertiary hydrogens) p.p.m.

Anal. Calcd. for $C_{16}H_{17}NO_3S$: C, 63.35; H, 5.65; N, 4.62; S, 10.57. Found: C, 63.49; H, 5.78; N, 4.80; S, 10.81.

Reaction of 3-Acetyl-2-methyl-2H-1,2-benzothiazin-4(3H)-one 1,1-Dioxide (IIIb) with Sodium Borohydride at Room Temperature.—Sodium borohydride reduction of 5.1 g. (0.02 mole) of IIIb was carried out and worked up as described above except that the reactants were stirred at room temperature rather than −5°. The crude product (0.56 g.) was triturated with cold ethanol to give 0.47 g. of crystalline XVIIb, m.p. 116–118°, which was identified by its chromatographic and spectral properties.

The acidic filtrate from the original precipitation was extracted with dichloromethane and the dried organic layer was evaporated *in vacuo* to give 3.2 g. of a thick oil which resisted attempts at purification. The infrared spectrum showed a strong band at 3500 and very weak bands at 1687, 1626, and 1592 cm.$^{-1}$. A chromatogram showed four spots, one of which corresponded to XVIIb.

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[21] The faster spot also coincided with that given by XIX in the same chromatographic system.

[22] Recrystallization from ethanol gave a product, m.p. 161–163°, whose chromatogram was practically identical with that of the unrecrystallized material.