bath the temperature was maintained during this period at 0°. After addition of the oxime solution stirring was continued at 0° for 30 min. more, and the finely divided precipitate was filtered as quickly as possible through a large Büchner funnel. The precipitate was washed several times with ice–water, then dried thoroughly over KOH *in vacuo*. In the case of tetramethylterephthalobisnitrile oxide (IVd) the crude product consisted to a considerable part of an apparently higher molecular material, from which IVd could be easily extracted with methylene chloride. IVd was then recrystallized from methylene chloride–methanol. Also, the crude anthracene-9-nitrile oxide (IVe) contained some higher molecular impurities. Pure IVe was best obtained by extraction of the crude material with small portions of boiling ligroin (b.p. 60–70°) until no more IVe crystallized out on chilling the extracts in ice.

The nature of these higher molecular by-products is not yet clear. It is certain, however, that they are not the corresponding furoxans; preliminary investigations indicate that they result from a 1,3-dipolar addition of the nitrile oxide to the oximate anion.

Rearrangement of Nitrile Oxides to Isocyanates.—The nitrile oxide (2 mmoles) was refluxed for 5 hr. in dry xylene (20 ml.). To the hot xylene solution, there was added aniline (4.2 mmoles), whereupon the mixed phenylarylureas crystallized out on cooling. A second fraction was obtained on concentration of the mother liquor *in vacuo*. The mixed ureas VIIa–c were recrystallized from aqueous acetic acid. The urea VIId obtained from tetramethylterephthalobisnitrile oxide precipitated already analytically pure; it was extremely difficultly soluble in all common organic solvents, but could be recrystallized from quinoline–ethanol. The nitrile oxides IVa and IVb could also be rearranged by heating without a solvent to 120–125° for 8 hr.; this method, however, failed with the other nitrile oxides. From the melt of IVa, there was isolated 2,4,6-trimethylphenyl isocyanate (VIa), m.p. 45°, and identified with a specimen prepared by known routes.[21] 1-Phenyl-3-(2′,4′,6′-trimethylphenyl)-urea (VIIa) was also identified by mixture melting point with an authentic sample.[22] The anthracenyl-9-nitrile oxide was converted into **ethyl anthracenyl-9-carbamate** by dissolving the crude VIe, remaining after evaporation of the xylene *in vacuo*, in an excess of absolute ethanol: yellow small glistening needles, m.p. 233°, lit.[23] m.p. 236.5–237°.

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.73; H, 5.88; N, 5.36.

Hydroxamic Acid Chlorides (III).—The nitrile oxide (1 mmole) was dissolved in methylene chloride (10 ml.) and ether (5 ml.), and dry hydrogen chloride was passed into the ice-cooled solution until its odor was definitely perceptible. The solvent was then evaporated *in vacuo* and the residue, usually corresponding to the theoretical amount, recrystallized from benzene–petroleum ether.

Aroylanilide Oximes (VIII).—The nitrile oxide (2 mmoles) was dissolved in benzene (30 ml.), a 100% excess of the required amount of aniline was added, and the mixture was heated for 15 min. on the steam bath. The crude amidoxime remaining after evaporation of the solvent *in vacuo* was dissolved in 2 *N* HCl, if necessary filtered from acid-insoluble by-products, and reprecipitated by neutralization with 2 *N* sodium carbonate solution. The anilide oximes were finally purified by recrystallization from aqueous ethanol, with the exception of VIIId, which is quite insoluble in all common organic solvents. The material remaining after successive extraction of the crude product with boiling ethanol and benzene proved to be analytically pure VIIId.

3-Aryl-5-phenylisoxazoles (IX).—The addition of the nitrile oxide (1 mmole) and phenylacetylene (1.1 mmoles) proceeded smoothly on refluxing in benzene (15 ml.) for 15 min. After evaporation of the solvent and excess phenylacetylene, finally at 50° (0.1 mm.), the remaining IX was recrystallized from methanol (IXa–c), acetic acid (IXe), or N-dimethylformamide (IXd).

Acknowledgment.—The research of which this publication forms a part was supported by Public Health Service Research Grant CA 07272-01 and -02 of the National Cancer Institute, Bethesda, Maryland.

(21) R. Dahlbom and L. E. Österberg, *Acta Chem. Scand.*, **9**, 1563 (1955).
(22) P. Grammaticos, *Bull. soc. chim. France*, 761 (1949).
(23) H. J. Creech and W. R. Franks, *J. Am. Chem. Soc.*, **60**, 127 (1938).

A New Type of 1,4-Benzothiazepine Derivatives

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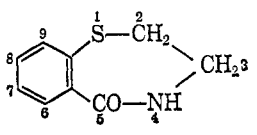
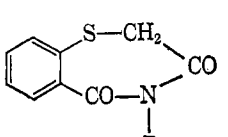
The synthesis of 5-substituted 2,3-dihydro-1,4-benzothiazepines, a hitherto unknown class of heterocyclic compounds, was investigated. Representative compounds were prepared from the appropriate amino ketones I *via* the corresponding mercapto ketones IV. A number of transformations, characteristic for these compounds, are described.

Our interest in the chemistry of 1,4-benzodiazepines led us to investigate other related ring systems. One of these is the little explored group of 1,4-benzothiazepines. Only a few members belonging to this group are known in the literature. These are a tetrahydro-1,4-benzothiazepin-5-one[1] (A) and a few 3,5-



A



B

diones of type B.[2] Compounds bearing a substituent other than oxygen in position 5 were not yet described.

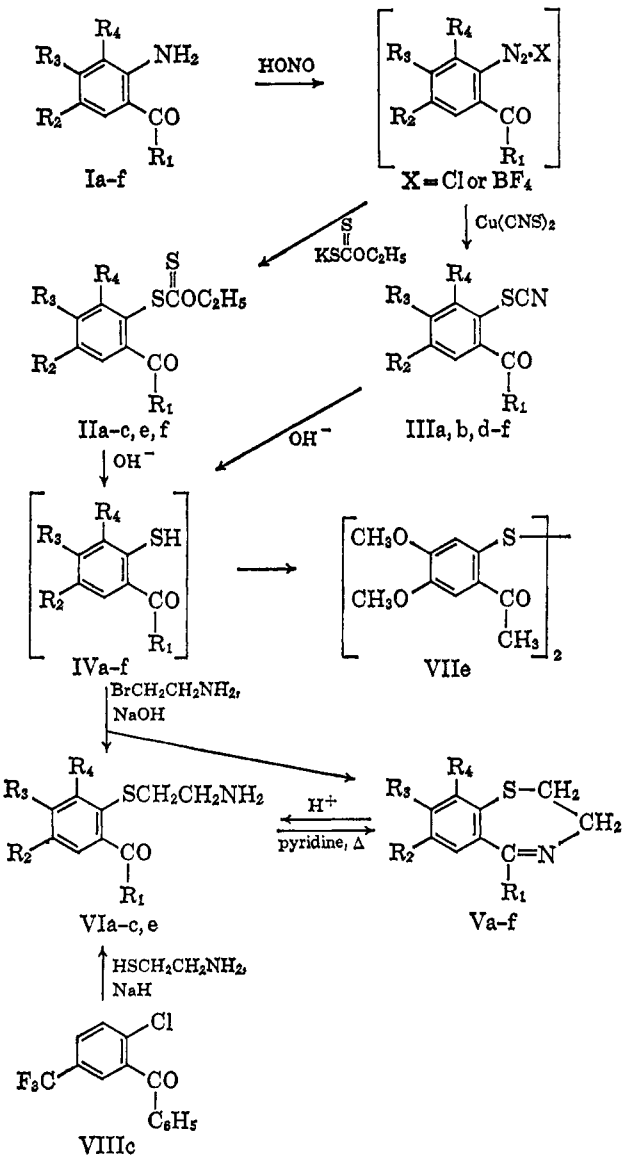
In view of the remarkable pharmacological properties of 5-substituted 1,4-benzodiazepines, we were particularly interested in 2,3-dihydro-1,4-benzothiazepines bearing an alkyl, aryl, or pyridyl substituent in position 5. These compounds were conveniently accessible from *o*-mercapto ketones IV[3] which, when condensed with 2-bromoethylamine, usually yielded a mixture of the desired 2,3-dihydro-1,4-benzothiazepine V with its precursor VI. Complete ring closure was achieved by refluxing the mixture (V + VI) in pyridine.

By an alternate route, condensation of 2-chloro-5-trifluoromethylbenzophenone[4] with 2-mercaptoethylamine yielded VIc which could be cyclized in boiling pyridine to the 2,3-dihydro-1,4-benzothiazepine Vc.

The *o*-mercapto ketones IV were obtained by diazotization of the corresponding *o*-amino ketones I, followed by a Sandmeyer-type reaction using either potassium ethyl xanthate or copper thiocyanate, and

(1) F. Jacob and P. Schlack, *Ber.*, **96**, 88 (1963).
(2) E. W. McClelland, M. J. Rose, and D. W. Stammers, *J. Chem. Soc.*, 81 (1948).
(3) For compounds I–VIII, see Scheme I.
(4) G. Saucy and L. H. Sternbach, *Helv. Chim. Acta*, **45**, 2226 (1962).

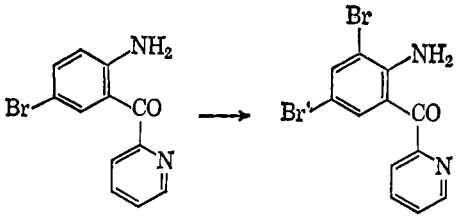
SCHEME I



Ia-f; X = Cl or BF_4; IIa-c, e, f; IIIa, b, d-f; IVa-f; VIIe; VIa-c, e; Va-f; VIIIc

a, R_1 = C_6H_5; R_2 = R_3 = R_4 = H
b, R_1 = C_6H_5; R_2 = Cl; R_3 = R_4 = H
c, R_1 = C_6H_5; R_2 = CF_3; R_3 = R_4 = H
d, R_1 = 2-pyridyl; R_2 = Br; R_3 = R_4 = H
e, R_1 = CH_3; R_2 = R_3 = OCH_3; R_4 = H
f, R_1 = 2-pyridyl; R_2 = R_4 = Br; R_3 = H

hydrolysis of the intermediates II or III, respectively, with alkali. The amino ketones I were known with the exception of If, which was obtained by bromination of 2-(2-amino-5-bromobenzoyl)pyridine[5] (Id). The structure of the dibromo ketone was not determined but it was assumed by analogy[6] that the second bromine entered position 3.



Id If

(5) R. I. Fryer, R. A. Schmidt, and L. H. Sternbach, *J. Pharm. Sci.*, **53**, 264 (1964).

(6) L. H. Sternbach, E. Reeder, O. Keller, and W. Metlesics, *J. Org. Chem.*, **26**, 4488 (1961).

With the exception of IIe and IIf, the "ethyl xanthates" II were not isolated in pure form, while the thiocyanates III were obtained as crystalline products. The *o*-mercapto ketones IV were used without prior purification for the condensation with 2-bromoethylamine. In one instance, the disulfide VIIe was isolated as by-product.

The 2,3-dihydro-1,4-benzothiazepines V could be converted by acid hydrolysis into VI which recyclized readily to V, when heated in pyridine. Oxidation of V with hydrogen peroxide in acetic acid yielded the "sulfone-epoxide" XIV[7] which, upon heating in xylene, rearranged in quantitative yield to the isomeric N-oxide XV. This reaction parallels the behavior of oxaziridines as described in the literature.[8] The ultraviolet absorption spectra of the two isomeric compounds XIV and XV were characteristically different. XIV showed no absorption above 250 mμ in isopropyl alcohol while XV had three maxima at 219 mμ (ε 28,000), 254–255 (12,420), and 317–320 (8500) due to the nitrone grouping. The N-oxide oxygen was readily removed by treatment of XV with phosphorus trichloride to yield the sulfone XIIb.

When XVb was refluxed with acetic anhydride, the sulfone XIXb was obtained, probably *via* the acetoxy derivative XXb, which, under the conditions of the reaction, loses 1 mole of acetic acid with subsequent formation of the 2,3 double bond.[9]

Reduction of XIXb with $LiAlH_4$ under mild conditions gave the dihydro compound XIIb which, in turn, yielded the tetrahydro compound XIb by catalytic hydrogenation. The 2,3-dihydro-1,4-benzothiazepine V could be reduced with $NaBH_4$ or with $LiAlH_4$ (energetic conditions) to the tetrahydro derivative X. Both V and X were oxidized with sodium periodate to the corresponding sulfoxides XVII and IX, respectively.[10] Acid hydrolysis of XVIIb yielded XVIb which recyclized in boiling pyridine to XVIIb. Oxidation of Xe with hydrogen peroxide in acetic acid afforded the sulfone XIe. The sulfoxide XVII reacted with thionyl chloride to yield the 2-chloro derivative XVIII[11] which could also be obtained by treatment of V with sulfuryl chloride.

The tetrahydro-1,4-benzothiazepine X could be alkylated in position 4. Refluxing with diethylaminoethyl chloride in chlorobenzene yielded XIII, which crystallized as the hydrochloride on cooling.

Experimental

All melting points are corrected. The infrared and ultraviolet absorption spectra and the n.m.r. spectra of starting materials and reaction products were compared whenever necessary in order to establish structural changes. The infrared spectra were determined in 1–5% chloroform solutions using a Perkin-Elmer Model 21 spectrophotometer, the ultraviolet absorption spectra in isopropyl alcohol and in 0.1 *N* hydrochloric acid, and the n.m.r.

(7) For compounds IX to XX, see Scheme II.

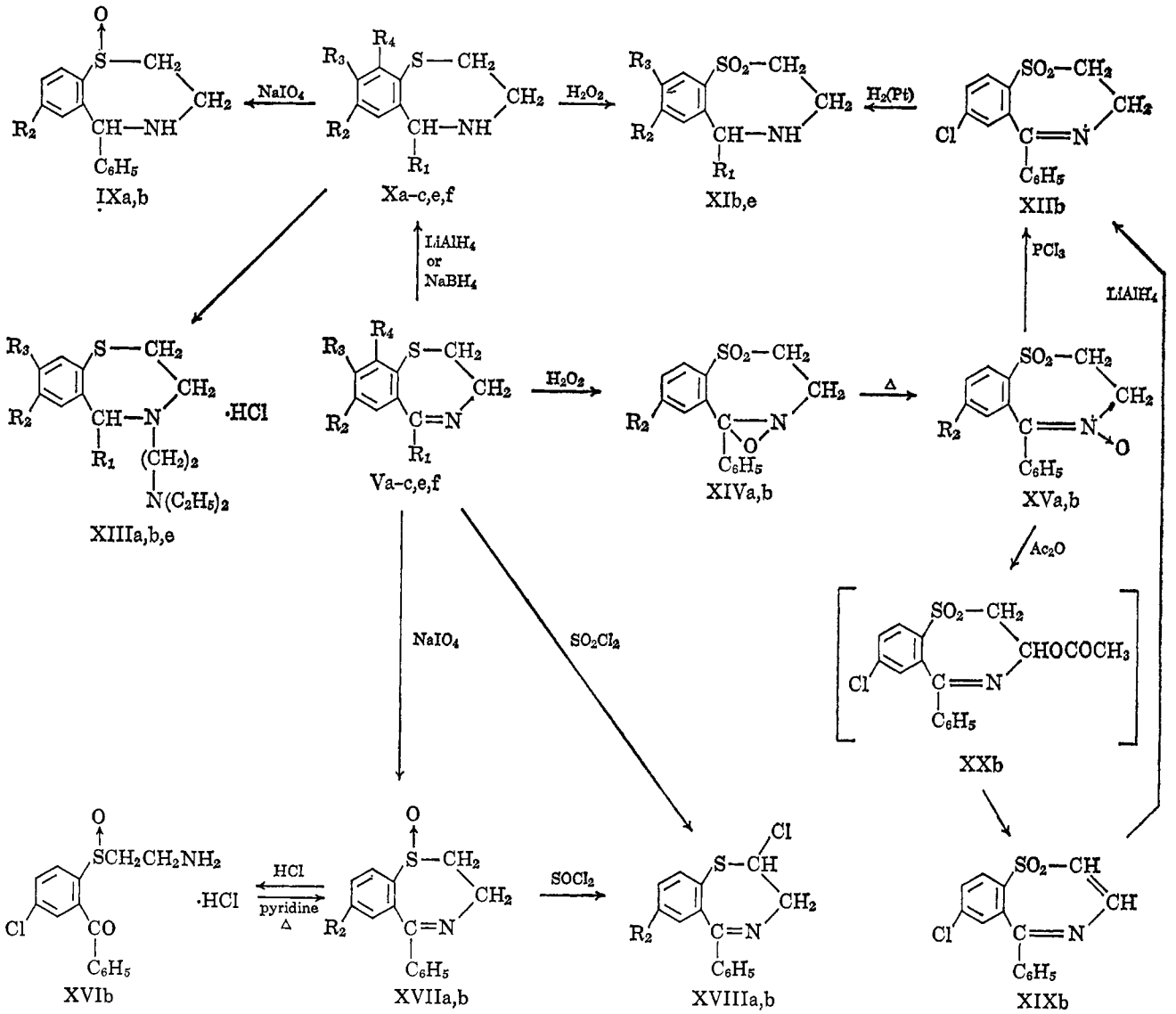
(8) W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 5739 (1957); see also W. Metlesics, G. Silverman, and L. H. Sternbach, *J. Org. Chem.*, **28**, 2459 (1963).

(9) An analogous rearrangement of a sulfoxide with simultaneous formation of a double bond was reported by L. Horner and P. Kaiser [*Ann.*, **626**, 19 (1959)]. See also W. E. Parham and M. D. Bhavsar, *J. Org. Chem.*, **28**, 2686 (1963).

(10) N. J. Leonard and C. R. Johnson [*J. Org. Chem.*, **27**, 282 (1962)] described this method for the oxidation of thioethers.

(11) Similar cases were reported by F. G. Bordwell and B. M. Pitt [*J. Am. Chem. Soc.*, **77**, 572 (1955)].

SCHEME II[a]



[a] For meaning of a, b, c, e, and f, see Scheme I.

spectra using a Varian A-60 spectrometer. The spectra were in every case in good agreement with the assigned structures.

2-Amino-3,5-dibromophenyl 2-Pyridyl Ketone (If).[12]—A solution of bromine (1.55 g., 0.01 mole) in 30 ml. of glacial acetic acid was added dropwise at 15–17° (ice bath) to a stirred solution of 2.8 g. (0.01 mole) of 2-amino-5-bromophenyl 2-pyridyl ketone (Id)[5] in 50 ml. of glacial acetic acid. After stirring for 2 hr. at room temperature, the red crystalline hydrobromide was collected by filtration, washed with glacial acetic acid, and dried under reduced pressure. The base was liberated by decomposition with 25 ml. of water. The crystals were collected by filtration, and dried under reduced pressure at 50°; yield, 2.8 g. (78%). After recrystallization from ethanol, the bright yellow needles melted at 133–135°.

Anal. Calcd. for $C_{12}H_8Br_2N_2O$: C, 40.48; H, 2.27. Found: C, 40.81; H, 2.54.

2,3-Dihydro-5-phenyl-1,4-benzothiazepine (Va). Method A.—To 450 ml. of concentrated sulfuric acid, cooled to 10°, was added slowly with stirring 69 g. (1 mole) of sodium nitrite. The mixture was heated to 80° until a clear solution was obtained. After cooling to 30°, 197 g. (1 mole) of 2-aminobenzophenone (Ia) was added in portions, keeping the temperature between 30 and 40°. After stirring for 1 hr., the solution was poured slowly into 3 l. of ice–water. To the filtered solution was added with stirring a solution of 200 g. of sodium fluoroborate in 800 ml. of water. The precipitated diazonium fluoroborate was separated by filtration, washed with a minimum of water, and added within 10 min. to a vigorously stirred solution of 246 g. (1.5 moles) of recrystallized potassium ethyl xanthate[13] in 1.5 l. of water heated to 75°. After the addition was completed, the mixture was stirred for 5 min., cooled, and extracted with ether. The ether extract was dried over sodium sulfate, filtered, and evaporated to dryness under reduced pressure. The crude oily residue, ethyl xanthic acid 2-benzoylphenyl ester (IIa), was added to a solution of 240 g. of potassium hydroxide in 1200 ml. of 50% aqueous ethanol, and the reaction mixture was stirred and refluxed for 15 min., while 35 g. of zinc dust was introduced in portions. Water (1 l.) was then added, the mixture was filtered over a filter aid, and the filtrate, after cooling, was added to a solution of 205 g. (1 mole) of 2-bromoethylamine hydrobromide in 350 ml. of water. After stirring for 15 min. at room temperature, the reaction mixture was extracted with methylene chloride. The organic layer was separated, dried over sodium sulfate, filtered, acidified with methanolic hydrochloric acid, and evaporated to dryness under reduced pressure. The residue was dissolved in 1 l. of pyridine. The solution was refluxed for 1 hr. and concentrated under reduced pressure, and the residue was dissolved in a mixture of methylene chloride and water. The organic layer was separated, dried, and evaporated to dryness under reduced pressure. The oily residue was dissolved in ether and filtered over 500 g. of Woelm alumina (grade I), and the filter bed was washed with ether.

(12) This compound was first obtained by Dr. G. Chase to whom we are grateful for a large supply of the material.

(13) Technical material recrystallized from a fivefold amount of boiling ethanol. The yield was considerably lower when crude material was used.

The filtrate was evaporated to dryness under reduced pressure, and the residue was crystallized from ether–petroleum ether (b.p. 30–60°). 2,3-Dihydro-5-phenyl-1,4-benzothiazepine (Va) was obtained as colorless prisms melting at 62–64°; yield, 98 g. (41%). Recrystallization from ether–petroleum ether raised the melting point to 64–65°.

Anal. Calcd. for $C_{15}H_{13}NS$: C, 75.27; H, 5.47. Found: C, 75.54; H, 5.67.

Va Hydrochloride.—A solution of the base in an excess of methanolic hydrogen chloride was concentrated under reduced pressure. The residue, crystallized from a mixture of methylene chloride and ether, formed yellow prisms which melted at 201–202°.

Anal. Calcd. for $C_{15}H_{13}NS\cdot HCl$: C, 65.32; H, 5.12. Found: C, 65.40; H, 5.31.

Method B.—2-Aminobenzophenone (Ia, 197 g., 1 mole) was diazotized and the diazonium compound was isolated as the fluoroborate as described in method A. The diazonium salt was added to a suspension of copper thiocyanate (obtained by combining a solution of 250 g. of copper sulfate in 1 l. of hot water with a solution of 223 g. of potassium thiocyanate in 500 ml. of water, and filtering the precipitated copper thiocyanate) in 1 l. of water containing 100 g. of potassium thiocyanate. The mixture was stirred overnight; the precipitate was isolated by filtration, washed with water, and extracted with 1 l. of boiling ether. The ether extract was dried over sodium sulfate, filtered, and added to 2 l. of petroleum ether. The mixture, after decantation from an insoluble oil, deposited crystals on chilling which were isolated by filtration (28 g.). Concentration of the filtrate yielded an oily product which, upon crystallization from ethanol, afforded an additional crop of crystals (15.4 g.); total yield, 43.4 g. (18%). After recrystallization from ether–petroleum ether and then from dilute ethanol, 2-thiocyanatobenzophenone (IIIa) was obtained in the form of pale yellow crystals melting at 82–82.5°.

Anal. Calcd. for $C_{14}H_9NOS$: C, 70.27; H, 3.79. Found: C, 70.07; H, 4.07.

IIIa (78 g., 0.33 mole) was dissolved in 800 ml. of ethanol, 200 ml. of 40% sodium hydroxide and 60 g. of sodium hydrosulfite were added, and the mixture was refluxed for 30 min. A solution of 68 g. (0.33 mole) of 2-bromoethylamine hydrobromide in 150 ml. of water was then added, the mixture was stirred for 15 min. at room temperature and worked up as described under method A; yield, 25 g. (32%). After recrystallization from ether–petroleum ether, the colorless prisms of Va melted at 64–65°. The mixture melting point with Va obtained by method A showed no depression.

2-(2-Aminoethylmercapto)benzophenone (VIa). Hydrochloride.—A solution of 5.5 g. (0.02 mole) of Va in 60 ml. of 3 *N* hydrochloric acid was refluxed for 20 hr. The solution was evaporated to dryness under reduced pressure, and the residue was recrystallized from isopropyl alcohol–ether. VIa was obtained as colorless prisms melting at 152–153°; yield, 5.5 g. (81%).

Anal. Calcd. for $C_{15}H_{15}NOS\cdot HCl$: C, 61.32; H, 5.49. Found: C, 61.14; H, 5.37.

7-Chloro-2,3-dihydro-5-phenyl-1,4-benzothiazepine (Vb) and Its Hydrochloride. Method A.—2-Amino-5-chlorobenzophenone (Ib,[14] 232 g., 1 mole) was converted *via* the ethyl xanthic ester IIb to 5-chloro-2-mercaptobenzophenone (IVb) which was condensed with 2-bromoethylamine to yield Vb as described for the synthesis of Va. 7-Chloro-2,3-dihydro-5-phenyl-1,4-benzothiazepine (Vb) was isolated as the hydrochloride in the form of yellow prisms melting at 233–234° dec.; yield, 123 g. (39%).

Anal. Calcd. for $C_{15}H_{12}ClNS\cdot HCl$: C, 58.07; H, 4.22. Found: C, 58.08; H, 4.69.

Free Base.—The hydrochloride was treated with sodium hydroxide and the base was extracted with ether. It crystallized from ether as colorless prisms melting at 79–80°.

Anal. Calcd. for $C_{15}H_{12}ClNS$: C, 65.80; H, 4.42. Found: C, 65.99; H, 4.58.

Method B.—The thiazepine Vb was also prepared *via* the thiocyanato ketone IIIb as described for Va. 2-Amino-5-chlorobenzophenone (Ib, 116 g., 0.5 mole) yielded 78 g. (57%) of 5-chloro-2-thiocyanatobenzophenone (IIIb), which, after recrystallization from ethanol, melted at 98–99°.

Anal. Calcd. for $C_{14}H_8ClNOS$: C, 61.43; H, 2.95; S, 11.71. Found: C, 61.94; H, 3.20; S, 11.42.

(14) F. D. Chattaway, *J. Chem. Soc.*, **85**, 340 (1904).

Conversion of IIIb to the mercapto ketone IVb, followed by condensation of the latter with 2-bromoethylamine, yielded 33 g. (21%) of Vb.

5-Chloro-2-(2-aminoethylmercapto)benzophenone (VIb). Hydrochloride.—A solution of 1.9 g. of Vb in 20 ml. of 3 *N* hydrochloric acid was heated on the steam bath for 1 hr., diluted with ice–water, made alkaline, and extracted with methylene chloride. The organic layer was separated, dried, and evaporated to dryness under reduced pressure. The residue was dissolved in methanol and the solution was acidified with methanolic hydrogen chloride. Excess ether was added, and the crystalline product was isolated by filtration; yield, 1.1 g. (55%). After recrystallization from ethanol–ether VIb was obtained as pale yellow needles melting at 168–169°.

Anal. Calcd. for $C_{15}H_{14}ClNOS\cdot HCl$: C, 54.87; H, 4.60. Found: C, 55.19; H, 4.64.

2,3-Dihydro-5-phenyl-7-trifluoromethyl-1,4-benzothiazepine (Vc) and Its Hydrochloride.—Method A described for the preparation of Va was used. 2-Amino-5-trifluoromethylbenzophenone (Ic,[4] 26.5 g., 0.1 mole) yielded 7.5 g. (22%) of Vc as the hydrochloride which formed yellow prisms from isopropyl alcohol, m.p. 231–232°.

Anal. Calcd. for $C_{16}H_{12}F_3NS\cdot HCl$: C, 55.90; H, 3.81. Found: C, 55.91; H, 3.89.

The free base was prepared in the usual manner. It was obtained, after recrystallization from petroleum ether, as colorless prisms melting at 90–91°.

Anal. Calcd. for $C_{16}H_{12}F_3NS$: C, 62.53; H, 3.94. Found: C, 62.38; H, 3.97.

5-Trifluoromethyl-2-(2-aminoethylmercapto)benzophenone (VIc). Hydrochloride.—To a solution of 2.2 g. of 2-mercaptoethylamine hydrochloride in 125 ml. of pyridine was added 1 g. of sodium hydride (53% dispersion in mineral oil), 5.6 g. of 2-chloro-5-trifluoromethylbenzophenone (VIII)[4] was then added, and the reaction mixture was heated for 3 hr. on the steam bath and evaporated to dryness under reduced pressure. The residue was treated with dilute hydrochloric acid and ether, and the precipitated solid product was isolated by filtration; yield, 0.7 g. After recrystallization from isopropyl alcohol, VIc was obtained as colorless needles melting at 178–179°.

Anal. Calcd. for $C_{16}H_{14}F_3NOS\cdot HCl$: C, 53.11; H, 4.18. Found: C, 53.27; H, 4.55.

7-Bromo-2,3-dihydro-5-(2-pyridyl)-1,4-benzothiazepine (Vd) and Its Hydrochloride.—To a solution of 16 g. of copper sulfate in 65 ml. of hot water was added a solution of 14.5 g. of potassium thiocyanate in 35 ml. of water. The precipitated copper thiocyanate was collected by filtration, washed with water, and suspended in 65 ml. of water containing 25 g. of potassium thiocyanate. To the stirred suspension was added dropwise the cold diazonium chloride solution[15] prepared from 14 g. (0.05 mole) of 2-amino-5-bromophenyl 2-pyridyl ketone (Id).[5] During the addition, the temperature of the reaction mixture was maintained at 70–75°. After the addition was completed, 8 g. of sodium bicarbonate was added, the mixture was cooled, and the precipitate was collected by filtration, washed with water, and dried under reduced pressure at 50°. The dry solids were extracted repeatedly with hot ethanol, and the combined extracts, on cooling, deposited 6.3 g. (39%) of crystals. After recrystallization from ethanol, 3-bromo-6-thiocyanatophenyl 2-pyridyl ketone (IIId) was obtained as off-white needles, melting at 159–161°.

Anal. Calcd. for $C_{13}H_7BrN_2OS$: C, 48.87; H, 2.21; S, 10.04. Found: C, 48.95; H, 2.32; S, 10.04.

Treatment of IIId (6.3 g.) with alkali, followed by condensation with 2-bromoethylamine as described for the synthesis of Va (method B), afforded 1.9 g. (27%) of 7-bromo-2,3-dihydro-5-(2-pyridyl)-1,4-benzothiazepine (Vd) hydrochloride. After recrystallization from ethanol–ether, the yellow prisms melted at 205–210° dec.

Anal. Calcd. for $C_{14}H_{11}BrN_2S\cdot HCl$: C, 47.27; H, 3.70; S, 9.01. Found: C, 47.16; H, 3.69; S, 9.35.

The free base was prepared in the usual manner, giving white crystals from isopropyl alcohol, m.p. 166–168°.

Anal. Calcd. for $C_{14}H_{11}BrN_2S$: C, 52.67; H, 3.47. Found: C, 52.37; H, 3.44.

2,3-Dihydro-7,8-dimethoxy-5-methyl-1,4-benzothiazepine (Ve) and Its Hydrochloride. Method A.—To a cooled solution of 7.5 g. (0.03 mole) of 6′-amino-3′,4′-dimethoxyacetophenone

(15) For details, see the following experiment: Ve (method A).

(Ie)[16] in 75 ml. of 1 *N* hydrochloric acid was added dropwise a solution of 2.9 g. (0.042 mole) of sodium nitrite in 10 ml. of water, while the temperature was maintained at 0–5°. After the addition was completed, the solution was stirred for 1 hr. in the cooling bath and then added in small portions to a stirred solution of 8 g. of recrystallized potassium ethyl xanthate[13] in 10 ml. of water. During the addition the temperature was kept at 70–75°. After about three-fourths of the diazonium chloride solution had been added, 1 g. of sodium carbonate was added to the xanthate solution to keep the reaction mixture alkaline. After the addition was completed, the mixture was heated at 75° for 30 min., cooled, and extracted with ether. The ether extract was washed with 5% sodium hydroxide solution and water, dried over sodium sulfate, filtered, and taken to dryness under reduced pressure. The residue crystallized when triturated with a small amount of ether. The crystals (3.5 g., 30%) were collected by filtration and recrystallized from aqueous ethanol. Ethylxanthic acid 2-acetyl-4,5-dimethoxyphenyl ester (IIe) was obtained as pale yellow needles melting at 94–95°.

Anal. Calcd. for $C_{13}H_{16}O_4S_2$: C, 51.98; H, 5.37; S, 21.35. Found: C, 51.47; H, 5.44; S, 21.17.

Treatment of IIe (7 g.) with alkali followed by condensation with 2-bromoethylamine as described for the synthesis of Va (method A) yielded 1.2 g. (19%) of the hydrochloride of Va. After recrystallization from ethanol–ether the light yellow crystals melted at 200–201° dec.

Anal. Calcd. for $C_{12}H_{15}NO_2S \cdot HCl$: C, 52.64; H, 5.89; S, 11.71. Found: C, 52.71; H, 6.12; S, 11.83.

Method B.—6′-Amino-3′,4′-dimethoxyacetophenone (Ie, 30 g., 0.12 mole) was converted to 3′,4′-dimethoxy-6′-thiocyanatoacetophenone (IIIe) using the procedure described for the preparation of IIId. The 27 g. (74%) of crude IIIe which was obtained gave, after recrystallization from acetonitrile–water, light tan needles melting at 144–146°.

Anal. Calcd. for $C_{11}H_{11}NO_3S$: C, 55.68; H, 4.67; S, 13.51. Found: C, 55.83; H, 4.68; S, 13.62.

Treatment of IIIe (18 g.) with alkali, followed by condensation with 2-bromoethylamine as described for the synthesis of Va (method B) afforded 9.1 g. (44%) of Ve.

The free base was prepared in the usual manner, giving white prisms from heptane, m.p. 101–103°.

Anal. Calcd. for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37. Found: C, 60.88; H, 6.55.

2′,2″-Dithiobis(4′,5′-dimethoxyacetophenone) (VIIe).—This compound was obtained in low yield during the synthesis of Ve by either method A or B. It was separated from the crude Ve by treating the mixture with ethanol, in which VIIe was insoluble. The crystals were collected by filtration and recrystallized from acetonitrile, m.p. 187–189°.

Anal. Calcd. for $C_{20}H_{22}O_6S_2$: C, 56.85; H, 5.25; N, 15.18. Found: C, 56.82; H, 5.03; N, 15.48.

6′-(2-Aminoethylmercapto)-3′,4′-dimethoxyacetophenone (VIe). Hydrochloride.—A solution of 1 g. of Ve in 20 ml. of 3 *N* hydrochloric acid was refluxed for 18 hr. The hot solution was treated with activated carbon, filtered, and chilled. The crystals were isolated by filtration and recrystallized from ethanol; yield, 0.2 g.; m.p. 177–178°. From the aqueous filtrate 0.5 g. of the starting material (Ve) was recovered.

Anal. Calcd. for $C_{12}H_{17}NO_3S \cdot HCl$: C, 49.39; H, 6.22. Found: C, 49.32; H, 6.39.

7,9-Dibromo-5-(2-pyridyl)-2,3-dihydro-1,4-benzothiazepine (Vf).—2-Amino-3,5-dibromophenyl 2-pyridyl ketone (If, 35.6 g., 0.1 mole) was suspended in 200 ml. of 3 *N* hydrochloric acid and diazotized with a solution of 8.2 g. of sodium nitrite in 20 ml. of water. The diazonium chloride solution thus obtained was added at room temperature to a suspension of copper thiocyanate prepared from 30 g. of copper sulfate and 12.4 g. of potassium thiocyanate, as described for the synthesis of Vd. The mixture was stirred at room temperature for 20 hr. The precipitate was collected by filtration and extracted with hot ethanol. On chilling, 24.4 g. (61%) of crystals was obtained which, after recrystallization, gave 3,5-dibromo-2-thiocyanatophenyl 2-pyridyl ketone IIIf in the form of white needles melting at 113–114°.

Anal. Calcd. for $C_{13}H_{16}Br_2N_2OS$: C, 39.22; H, 1.52. Found: C, 39.29; H, 1.81.

Treatment of IIIf (6 g.) with alkali, followed by condensation with 2-bromoethylamine as described for the synthesis of Va (method B) afforded 1.6 g. (27%) of Vf, which, after recrystallization from isopropyl alcohol, melted at 154–155°.

Anal. Calcd. for $C_{14}H_{10}Br_2N_2S$: C, 42.23; H, 2.53. Found: C, 42.52; H, 2.73.

Compound Vf was also synthesized from If *via* the ethylxanthic ester IIf by the procedure used for the synthesis of Ve (method A). Ethyl xanthic acid 4,6-dibromo-2-picolinoylphenyl ester (IIf) was obtained as yellow needles after recrystallization from ethanol, m.p. 161–162°.

Anal. Calcd. for $C_{15}H_{11}Br_2NO_2S_2$: C, 39.06; H, 2.41. Found: C, 39.41; H, 2.39.

Treatment of IIf with alkali followed by condensation with 2-bromoethylamine yielded Vf, melting at 154–155°. The mixture melting point with a sample of Vf obtained from If *via* IIIf (method B) showed no depression.

5-Phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepine (Xa).—A solution of 23.9 g. (0.1 mole) of Va in 200 ml. of dry tetrahydrofuran was added slowly at room temperature to a stirred suspension of 8 g. (0.2 mole) of lithium aluminum hydride in 600 ml. of tetrahydrofuran. The reaction mixture was refluxed for 2 hr., cooled, and decomposed by the careful addition of 1 l. of wet ether. After filtration over a Hyflo bed, the solution was dried and evaporated to dryness under reduced pressure. The residue was treated with ether and gave 17.5 g. (73%) of crystalline Xa. After recrystallization from ether, colorless needles melting at 89–90° were obtained.

Anal. Calcd. for $C_{15}H_{15}NS$: C, 74.65; H, 6.26. Found: C, 74.56; H, 5.99.

7-Chloro-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine (Xb). Hydrochloride.—The thiazepine Vb (34 g., 0.125 mole) was reduced with lithium aluminum hydride in tetrahydrofuran using the procedure described for Xa. The crude end product was dissolved in ethanol, methanolic hydrogen chloride and excess ether were added, and the crystalline product was isolated by filtration; yield, 34 g. (88%). After recrystallization from ethanol–ether, Xb was obtained as light yellow needles melting at 267–268°.

Anal. Calcd. for $C_{15}H_{14}ClNS \cdot HCl$: C, 57.69; H, 4.84. Found: C, 57.73; H, 4.66.

2,3,4,5-Tetrahydro-5-phenyl-7-trifluoromethyl-1,4-benzothiazepine Hydrochloride (Xc).—Compound Vc (12.2 g., 0.04 mole) was reduced by the procedure used for the synthesis of Xb, and yielded 12 g. (86%) of Xc. After recrystallization from isopropyl alcohol, colorless prisms melting at 255–257° were obtained.

Anal. Calcd. for $C_{16}H_{14}F_3NS \cdot HCl$: C, 55.25; H, 4.35. Found: C, 55.50; H, 4.41.

7,8-Dimethoxy-5-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine (Xe) and Its Hydrochloride.—To a solution of 11.8 g. (0.043 mole) of Ve in 200 ml. of water was added 44 ml. of 1 *N* sodium hydroxide and 100 ml. of ethanol. To this solution was added a solution of 9.5 g. of sodium borohydride in 75 ml. of water, and the mixture was allowed to stand at room temperature for 18 hr. After acidification and dilution with 500 ml. of water, the solution was made alkaline again and extracted with methylene chloride. The extract was dried over magnesium sulfate, filtered, acidified with dry hydrochloric acid, and evaporated to dryness under reduced pressure. The crystalline residue (9.2 g., 83.5%), after recrystallization from ethanol–ether, gave the hydrochloride in the form of colorless prisms melting at 261–263° dec.

Anal. Calcd. for $C_{12}H_{17}NO_2S \cdot HCl$: C, 52.26; H, 6.58; S, 11.62. Found: C, 52.19; H, 6.90; S, 11.41.

The free base Xe was prepared in the usual manner, giving white crystals from aqueous methanol, m.p. 57–59°.

Anal. Calcd. for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16. Found: C, 60.16; H, 7.24.

7,9-Dibromo-5-(2-pyridyl)-2,3,4,5-tetrahydro-1,4-benzothiazepine (Xf).—To a solution of 3 g. of Vf in 300 ml. of methanol was added a solution of 9 g. of sodium borohydride in 30 ml. of water in three equal portions within 8 hr. The reaction mixture was allowed to stand at room temperature for 5 days. The solution was acidified with concentrated hydrochloric acid, made alkaline, treated with activated charcoal, and evaporated to dryness under reduced pressure. Water and chloroform were added to the residue and the organic layer was separated, dried, and taken to dryness. The residue was treated with ether and the crystals were collected by filtration; yield, 1.9 g. (64%). After recrystallization from isopropyl alcohol, Xf melted at 146–148°.

(16) J. C. E. Simpson, *J. Chem. Soc.*, 94, (1946).

Anal. Calcd. for $C_{14}H_{12}Br_2N_2S$: C, 42.02; H, 3.02. Found: C, 42.25; H, 3.21.

2,3,4,5-Tetrahydro-5-phenyl-1,4-benzothiazepine 1-Oxide (IXa).—To a stirred and cooled solution of 74.8 g. (0.02 mole) of Xa in 100 ml. of methanol was added a solution of 4.2 g. (0.02 mole) of sodium periodate in 40 ml. of water. The mixture was stirred for 4 hr. at room temperature and the precipitated sodium iodate was then removed by filtration. The filtrate was concentrated to a small volume under reduced pressure and extracted with methylene chloride. The organic layer was separated, dried, and evaporated to dryness under reduced pressure. Addition of ether to the residue induced crystallization; yield, 2.8 g. (55%). After recrystallization from methylene chloride–ether, IXa was obtained as colorless needles melting at 147–148°.

Anal. Calcd. for $C_{15}H_{15}NOS$: C, 70.01; H, 5.88. Found: C, 70.09; H, 5.85.

7-Chloro-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1-Oxide (IXb). Hydrochloride.—Xb (4 g. of the free base)[17] was oxidized in methanol solution with sodium periodate by the procedure described for the synthesis of IXa. The crude reaction product was dissolved in methanol and acidified with methanolic hydrogen chloride. Excess ether was added and the crystalline product (2 g., 42%) was isolated by filtration. Recrystallization from methanol–ether yielded the hydrochloride as colorless prisms melting at 230–231°.

Anal. Calcd. for $C_{15}H_{14}ClNOS \cdot HCl$: C, 54.88; H, 4.61. Found: C, 54.81; H, 4.85.

7,8-Dimethoxy-5-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1,1-Dioxide (XIe) and Its Hydrochloride.—The hydrochloride of Xe (2.7 g.) was dissolved in 25 ml. of glacial acetic acid, 4.4 g. of 30% hydrogen peroxide was added, and the mixture was allowed to stand at room temperature for 10 days. After removal of the solvent under reduced pressure, the residue was treated with hot methylene chloride, and the insoluble crystalline hydrochloride of XIe was collected by filtration; yield, 2.2 g. (73%). Recrystallization from methanol–ether gave XIe as colorless prisms melting at 252–254° dec.

Anal. Calcd. for $C_{12}H_{17}NO_4S \cdot HCl$: C, 46.82; H, 5.89; S, 10.42. Found: C, 46.81; H, 6.16; S, 10.35.

The free base, obtained in the usual manner, was crystallized from benzene and contained 0.5 mole of the solvent, m.p. 151–153°.

Anal. Calcd. for $C_{12}H_{17}NO_4S \cdot 0.5C_6H_6$: C, 58.04; H, 6.50; N, 4.51; S, 10.33. Found: C, 58.03; H, 6.66; N, 4.30; S, 10.22.

After drying at 110° for 24 hr. under reduced pressure, the base was obtained free of solvent, m.p. 151–153°.

Anal. Calcd. for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.32. Found: C, 53.33; H, 6.49.

4-(2-Diethylaminoethyl)-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine Hydrochloride (XIIIa).—To a stirred solution of 9.5 g. (0.04 mole) of Xa in 50 ml. of chlorobenzene was added a solution of 13.6 g. (0.1 mole) of β-diethylaminoethyl chloride (liberated from the commercially available hydrochloride) in 75 ml. of chlorobenzene, and the mixture was refluxed for 18 hr. On cooling, a crystalline product was obtained which was collected by filtration and dried; yield, 12.5 g. (85%). After recrystallization from methylene chloride–ether, XIIIa was obtained as colorless needles melting at 193–194°.

Anal. Calcd. for $C_{21}H_{28}N_2S \cdot HCl$: C, 66.90; H, 7.75. Found: C, 66.90; H, 7.60.

7-Chloro-4-(2-diethylaminoethyl)-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine Hydrochloride (XIIIb).—The hydrochloride of Xb (31 g., 0.1 mole) was converted into the base in the usual manner. The oily base was dissolved in 75 ml. of chlorobenzene and to this solution was added a solution of 45 g. of β-diethylaminoethyl chloride in 100 ml. of chlorobenzene. Following the procedure described for the synthesis of XIIIa, a crystalline product (35 g., 85%) was isolated. After recrystallization from acetone, XIIIb was obtained as colorless needles melting at 195–196°.

Anal. Calcd. for $C_{21}H_{27}ClN_2S \cdot HCl$: C, 61.30; H, 6.86; Cl, 17.24. Found: C, 61.53; H, 6.94; Cl, 17.20.

4-(2-Diethylaminoethyl)-7,8-dimethoxy-5-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine Hydrochloride (XIIIe).—To a solution of 49 g. (0.02 mole) of Xe in 70 ml. of chlorobenzene was added 6.8 g. (0.05 mole) of β-diethylaminoethyl chloride, and the mixture was refluxed for 18 hr. On cooling, a crystalline product (4.8 g., 63%) separated which, after recrystallization from ethanol–ether, formed colorless needles melting at 172–174°.

Anal. Calcd. for $C_{18}H_{30}N_2O_2S \cdot HCl$: C, 57.65; H, 8.33; S, 8.55. Found: C, 57.44; H, 8.49; S, 8.61.

4,5-Epoxy-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-Dioxide (XIVa).—To a solution of 12 g. (0.05 mole) of Va in 130 ml. of acetic acid was added 20 ml. of 30% hydrogen peroxide. The mixture was left at room temperature for 17 days and diluted with water. The precipitated product (5 g.), collected by filtration, formed colorless prisms melting at 169–170° after recrystallization from methylene chloride–ether.

Anal. Calcd. for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56. Found: C, 62.65; H, 4.84.

7-Chloro-4,5-epoxy-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-Dioxide (XIVb).—To a solution of 43.2 g. (0.158 mole) of Vb in 400 ml. of glacial acetic acid was added 70 ml. of 30% hydrogen peroxide. After standing for 2 weeks at room temperature, the crystalline precipitate was collected by filtration (27 g.). Dilution of the filtrate with water yielded an additional 2 g. of product; total yield, 29 g. (57%). Recrystallization from methylene chloride gave XIVb as colorless prisms, m.p. 265–266°. However, when introduced into a melting point apparatus at 200° it melted at 205°, resolidified, and melted then at 265–266°.[18]

Anal. Calcd. for $C_{15}H_{12}ClNO_3S$: C, 55.99; H, 3.76. Found: C, 55.66; H, 3.88.

2,3-Dihydro-5-phenyl-1,4-benzothiazepine 1,1,4-Trioxide (XVa).—A solution of 2 g. of XIVa in 60 ml. of xylene was refluxed for 30 min. On cooling, 1.8 g. (90%) of crystals was obtained and isolated by filtration. Recrystallization from methylene chloride–ether gave XVa as colorless needles melting at 238–239°.

Anal. Calcd. for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56. Found: C, 62.62; H, 4.68.

7-Chloro-2,3-dihydro-5-phenyl-1,4-benzothiazepine 1,1,4-Trioxide (XVb).—Five grams of XIVb was refluxed in 100 ml. of xylene for 10 min. On cooling, 4.5 g. (90%) of crystals was obtained. Recrystallization from methylene chloride gave XVb as colorless needles melting at 265–266°.

Anal. Calcd. for $C_{15}H_{12}ClNO_3S$: C, 55.99; H, 3.76. Found: C, 56.24; H, 3.97.

7-Chloro-5-phenyl-1,4-benzothiazepine 1,1-Dioxide (XIXb).—Compound XVb (19.2 g., 0.06 mole) was suspended in 200 ml. of acetic anhydride and the mixture was refluxed with stirring for 5 hr. After removal of the solvent under reduced pressure, the residue was treated with benzene and the crystals were collected by filtration (10 g., 55%). Recrystallization from methylene chloride–ether gave XIXb in the form of yellow prisms melting at 207–208°.

Anal. Calcd. for $C_{15}H_{10}ClNO_2S$: C, 59.31; H, 3.32; N, 4.61. Found: C, 59.37; H, 3.52; N, 4.95.

7-Chloro-2,3-dihydro-5-phenyl-1,4-benzothiazepine 1,1-Dioxide (XIIb). Method A.—To a stirred suspension of 7.3 g. (0.022 mole) of XVb in 300 ml. of chloroform was added 9 ml. (0.1 mole) of phosphorus trichloride, and the mixture was refluxed for 1 hr. Ice and excess 50% potassium hydroxide were added, and stirring was continued until complete solution was achieved. The organic layer was separated, dried, and evaporated to dryness under reduced pressure. The residue crystallized upon addition of acetone; yield, 5.1 g. (73%). After recrystallization from acetone, XIIb was obtained as colorless prisms melting at 164–165°.

Anal. Calcd. for $C_{15}H_{12}ClNO_2S$: C, 58.92; H, 3.96. Found: C, 58.77; H, 4.19.

Method B.—To a suspension of 0.8 g. (0.021 mole) of lithium aluminum hydride in 90 ml. of dry tetrahydrofuran was added 1.5 g. (0.005 mole) of XIXb. The mixture was stirred at room temperature for 30 min. and then cooled in an ice bath, and the excess lithium aluminum hydride was destroyed by the gradual addition of wet ether. After filtration over a Hyflo bed, the solution was dried and evaporated to dryness under reduced pressure. The residue was dissolved in ethanol containing hydrogen chloride and excess ether was added. The hydrochloride of XIIb was isolated by filtration (0.4 g.) and converted to the base

(17) Obtained from the hydrochloride Xb in the usual manner as an oil and used without purification.

(18) Identical with the melting point of XVb. The epoxide XIVb, when heated, is converted to the N-oxide XVb.

in the usual manner. It was identified by melting point, mixture melting point, and infrared spectrum with XIIb, obtained by method A.

7-Chloro-2,3,4,5-tetrahydro-5-phenyl-1,4-benzothiazepine 1,1-Dioxide (XIb).—A solution of 21.3 g. (0.07 mole) of XIIb in 20 ml. of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure in the presence of 1.8 g. of platinum oxide. After the absorption of 1.2 l. of hydrogen (21 hr.), the catalyst was removed by filtration, and the solution was evaporated to dryness under reduced pressure. The residue was dissolved in methylene chloride; the solution was washed with dilute alkali and concentrated to a volume of about 50 ml. The concentrate was passed over a column of 200 g. of Woelm aluminum (grade I), and the column was eluted with methylene chloride. The residue obtained from the first 250 ml. of eluate, after evaporation to dryness under reduced pressure, was treated with ether and yielded 7.9 g. (36%) of crystals. Recrystallization from ether gave XIb as colorless plates melting at 159–160.5°.

Anal. Calcd. for $C_{15}H_{14}ClNO_2S$: C, 58.53; H, 4.58. Found: C, 58.86; H, 4.56.

2,3-Dihydro-5-phenyl-1,4-benzothiazepine 1-Oxide (XVIIa).—To a stirred and cooled solution of 4.7 g. (0.02 mole) of Va in 100 ml. of methanol was added a solution of 4.2 g. (0.02 mole) of sodium periodate in 40 ml. of water. The mixture was stirred for 1 hr. at 30° and for 4 hr. at room temperature. The precipitated sodium iodate was removed by filtration, and the filtrate was concentrated to a small volume. The concentrate was extracted with methylene chloride; the organic layer was separated, dried, and evaporated to dryness under reduced pressure. The residue was treated with ether and yielded 3.5 g. (70%) of XVIIa, which, after recrystallization from ether, gave colorless prisms melting at 158–160°.

Anal. Calcd. for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13. Found: C, 70.31; H, 5.00.

7-Chloro-2,3-dihydro-5-phenyl-1,4-benzothiazepine 1-Oxide (XVIIb). Hydrochloride.—Compound Vb (5.4 g., 0.02 mole) was dissolved in 200 ml. of methanol and oxidized with a solution of 4.5 g. (0.021 mole) of sodium periodate in 42 ml. of water by the procedure described for the synthesis of XVIIa. The reaction product was isolated as the hydrochloride (4.4 g., 67%). After recrystallization from methanol–ether, the hydrochloride of XVIIb was obtained as light yellow prisms melting at 206–207°.

Anal. Calcd. for $C_{15}H_{12}ClNOS \cdot HCl$: C, 55.52; H, 4.02. Found: C, 55.54; H, 4.34.

7-Chloro-2-(2-aminoethylsulfinyl)benzophenone Hydrochloride (XVIb).—A solution of 5.8 g. (0.02 mole) of XVIIb in 600 ml. of 3 *N* hydrochloric acid was heated on the steam bath for 4 hr., and the mixture was evaporated to dryness under reduced pressure. The residue, when treated with a mixture of ethanol and isopropyl alcohol, yielded 6.3 g. (92%) of crystals. After recrystallization from methanol–ether, XVIb was obtained as light yellow needles melting at 152–153°.

Anal. Calcd. for $C_{15}H_{14}ClNO_2S \cdot HCl$: C, 52.33; H, 4.39. Found: C, 52.32; H, 4.05.

2-Chloro-2,3-dihydro-5-phenyl-1,4-benzothiazepine (XVIIIa).—To a refluxing stirred solution of 4.7 g. (0.02 mole) of Va in 100 ml. of methylene chloride was added within 20 min. a solution of 1.6 ml. (0.021 mole) of sulfuryl chloride in 25 ml. of methylene chloride, and the mixture was refluxed for 1 hr. longer. The precipitated crystals were collected by filtration and dissolved in a mixture of methylene chloride and ice-cold dilute potassium hydroxide. The organic layer was separated, dried, and evaporated to dryness under reduced pressure, and the residue was treated with ether–petroleum ether to give 2.9 g. (54%) of crystals. After recrystallization from ether–petroleum ether, XVIIIa was obtained as colorless prisms melting at 93–94°.

Anal. Calcd. for $C_{15}H_{12}ClNS$: C, 65.80; H, 4.42. Found: C, 66.04; H, 4.40.

2,7-Dichloro-2,3-dihydro-5-phenyl-1,4-benzothiazepine (XVIIIb).—Compound XVIIb (18.5 g., 0.065 mole) was added in portions to 65 ml. of thionyl chloride. When the reaction had subsided, the solution was poured on ice, made alkaline with 50% potassium hydroxide, and extracted with methylene chloride. The organic layer was separated, dried, and evaporated to dryness under reduced pressure; the residue, on treatment with ether–petroleum ether, yielded 12 g. (60%) of crystals. After recrystallization from ether, XVIIIb was obtained as colorless prisms melting at 126–127°.

Anal. Calcd. for $C_{15}H_{11}Cl_2NS$: C, 58.45; H, 3.60. Found: C, 58.29; H, 3.32.

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Vilsmeier Formylation of 4-Dimethylaminostilbene

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Vilsmeier formylation of 4-dimethylaminostilbene using the complex prepared from phosphorus oxychloride and dimethylformamide gave 4-dimethylamino-α-phenylcinnamaldehyde (**2**) and 4-dimethylamino-3-formyl-α-phenylcinnamaldehyde (**3**). Formylation on the vinylene carbon atom, which results in the formation of **2** from 4-dimethylaminostilbene, also occurred with 4-dimethylamino-4′-nitrostilbene, giving rise to 4-dimethylamino-α-(4-nitrophenyl)cinnamaldehyde (**5**), but did not occur with 2,4-dimethoxystilbene. The latter gave the aromatic aldehyde 4,6-dimethoxy-3-stilbenecarboxaldehyde (**8**). The structure of the formylation products was established by chemical evidence, infrared, n.m.r. and mass spectrometry.

In connection with other work, it was desirable to develop a synthesis of the hitherto undescribed 4′-dimethylamino-4-stilbenecarboxaldehyde (**1**). The facile formylation of reactive aromatic and heterocyclic rings with the Vilsmeier complex[1] suggested the formylation of 4-dimethylaminostilbene as a possible synthetic route to **1**.

Results and Discussion

Formylation of 4-dimethylaminostilbene with the complex prepared from phosphorus oxychloride and dimethylformamide gave 4-dimethylamino-α-phenylcinnamaldehyde (**2**) and the diformyl derivative, 4-dimethylamino-3-formyl-α-phenylcinnamaldehyde (**3**). The use of 1 equiv. of complex led to the isolation of **2** in 33% yield; some dialdehyde **3** was formed and some starting material remained. The dialdehyde **3** was obtained in greatest yield (60%) by employing a large excess (4 equiv.) of complex and a long reaction time.

Structure **2**, 4-dimethylamino-α-phenylcinnamaldehyde, rather than **1** for the monoaldehyde, was suggested by examination of the infrared and n.m.r. spectra and was confirmed by chemical evidence. The infrared spectrum which failed to show the *trans* CH=CH

(1) For a recent review of the Vilsmeier reaction, see M.-R. DeMaheas, *Bull. soc. chim. France*, **112**, 1989 (1962).