[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF SWARTHMORE COLLEGE]

Thiapyran Derivatives. III. The Preparation, Properties and Reactions of Δ^2-Dihydrothiapyran 1,1-Dioxide

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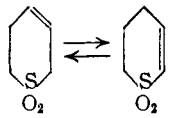
The synthesis of Δ^2-dihydrothiapyran 1,1-dioxide by an indirect route involving the Dieckmann cyclization of ethyl γ-(carbethoxymethylmercapto)-butyrate is described. Rearrangement of the α,β-unsaturated sulfone to its β,γ-unsaturated isomer, Δ^3-dihydrothiapyran 1,1-dioxide, is observed to occur when Δ^2-dihydrothiapyran 1,1-dioxide is treated with triethylamine or dilute alkali. Addition of bromine to the α,β-unsaturated sulfone proceeds less readily than with the β,γ-unsaturated isomer, and addition of hydrogen bromide and hydrogen iodide leads to the 3-halogeno adducts. A number of new tetrahydrothiapyran derivatives which were prepared and characterized in the course of this work are described.

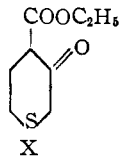
In the preceding paper in this series,[1] the preparation of Δ^3-dihydrothiapyran 1,1-dioxide (I) was described and evidence was presented for the tautomeric mobility of the —CH=CH—CH_2—SO_2— system in this compound. Since, however, all attempts to prepare the Δ^2-isomer (II) by the base-catalyzed isomerization of I were unsuccessful, the



I II

question arose as to the relative stability of the Δ^2-isomer, and it was suggested that the position of equilibrium in this prototropic system may lie so far to the left as to preclude the formation of isolable amounts of II in this way. The synthesis of Δ^2-dihydrothiapyran 1,1-dioxide by an indirect route was undertaken to provide further data on the chemistry of this pair of unsaturated heterocyclic sulfones, and the results are described in the present communication.

The sequence of reactions employed for the preparation of Δ^2-dihydrothiapyran 1,1-dioxide is outlined in Fig. 1. Ethyl γ-chlorobutyrate was condensed in ethanol with the sodium salt of ethyl thioglycolate to give ethyl γ-(carbethoxymethylmercapto)-butyrate (III), which was characterized by hydrolysis to the corresponding diacid (IV). The Dieckmann cyclization of the diester (III) might be expected to lead to either 2-carbethoxytetrahydrothiapyran-3-one (V) or the 4-carbethoxy isomer (X), depending upon



X

the mode of ring closure. The assignment of the 2-carbethoxy structure (V) to the product obtained in the present investigation is based on the observations of Woodward and Eastman[2] on the mode of cyclization in the next lower homologous series. These investigators have reported that the Dieckmann cyclization of methyl β-(carbomethoxymethylmercapto)-propionate in ether at room temperature yields principally 2-carbomethoxy-3-oxotetrahydrothiophene, while in hot toluene the major product is the 4-carbomethoxy isomer. Since the cyclization of III was carried out in ether at 0°, it seems reasonable to assume that the resultant β-ketoester, which was obtained in 82% yield, consisted principally, if not entirely, of the 2-carbethoxy isomer. Either of the two possible isomeric products would, of course, yield the same β-ketosulfide in the next step of the synthesis.

Decarbethoxylation of the β-ketoester (III) was readily accomplished by refluxing with dilute sulfuric acid until the oil phase no longer gave a coloration with ferric chloride (*ca.* six hours). The β-ketosulfide (VI) was reduced to the β-hydroxysulfide (VII) in good yield by the Meerwein–Ponndorf method, and the hydroxyl group was then replaced

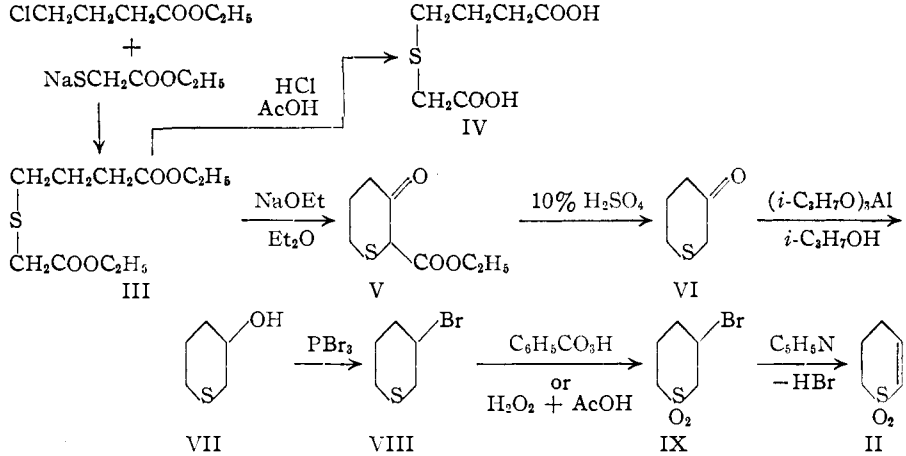


Fig. 1.

with bromine by treatment of VII with phosphorus tribromide. Oxidation of the resultant β-bromosulfide (VIII) to the corresponding sulfone (IX) was brought about most successfully with perbenzoic acid in chloroform (72% yield), although fair yields (45–50%) were also obtained by the somewhat simpler hydrogen peroxide–acetic acid procedure. In contrast to the less reactive isomeric bromosulfone previously assigned[1] the γ-bromo structure, β-bromotetrahydrothiapyran 1,1-dioxide (IX) dissolved readily in cold aqueous alkali with the liberation of bromide ion.

(1) E. A. Fehnel and P. A. Lackey, THIS JOURNAL, **73**, 2473 (1951).

(2) R. B. Woodward and R. H. Eastman, *ibid.*, **68**, 2229 (1946).

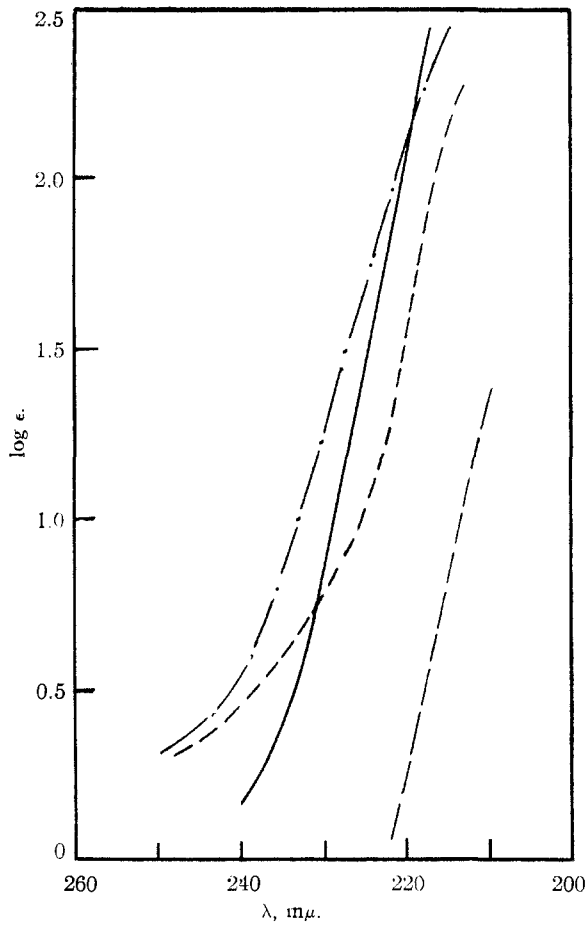
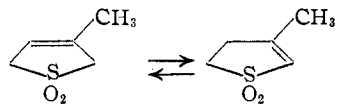


Fig. 2.—Absorption spectra: Δ^2-dihydrothiapyran 1,1-dioxide (II), ——; α-butadiene sulfone, -----; vinyl ethyl sulfone, —·—·—; Δ^3-dihydrothiapyran 1,1-dioxide (I), — — —.

Dehydrobromination of IX with boiling pyridine afforded crude Δ^2-dihydrothiapyran 1,1-dioxide (II) in the form of a viscous oil which resisted all attempts at crystallization and which was purified by conversion to the 2,3-dibromide and subsequent debromination of the recrystallized dibromide with zinc dust. The desired unsaturated sulfone was obtained after vacuum distillation as a colorless crystalline solid, m.p. 44–46°, which exhibited an ultraviolet absorption spectrum similar to those of other α,β-unsaturated sulfones (Fig. 2).

Unlike the Δ^3-isomer, which forms the dibromide rapidly and exothermically when treated with bromine in acetic acid or chloroform, Δ^2-dihydrothiapyran 1,1-dioxide reacts relatively slowly under the same conditions. A similar reluctance to add bromine has been encountered among other α,β-unsaturated sulfones[3] and is presumably due to the diminished nucleophilic activity of the ethylenic system brought about by the adjacent electrophilic sulfonyl group. Once formed, however, the 2,3-dibromide is less readily debrominated with zinc dust than the 3,4-dibromide, and under conditions which afforded an almost quantitative yield of the Δ^3-unsaturated sulfone (I) from the 3,4-dibromide about one-third of the 2,3-dibromide was recovered unchanged. On boiling with 48% hydrobromic acid, Δ^2-dihydrothiapyran 1,1-dioxide (II) yielded an adduct which was identified as 3-bromotetrahydrothiapyran 1,1-dioxide by comparison with the bromosulfone IX of known structure used in the synthesis of II. Treatment of II with 47% hydriodic acid yielded an iodosulfone which may be inferred, on the basis of the results with hydrobromic acid and of the non-identity of the adduct with the known 4-iodo isomer, to be 3-iodotetrahydrothiapyran 1,1-dioxide.

The behavior of Δ^2-dihydrothiapyran 1,1-dioxide (II) in basic media is of interest in connection with the problem of tautomerism in unsaturated sulfones. Studies of the action of bases on several butadiene sulfones and allyl benzyl sulfones have provided evidence for the tendency of the double bond to shift into conjugation with the sulfonyl group. Thus, at equilibrium in aqueous potassium hydroxide the isoprene sulfone system has been shown to consist of approximately 9% of the β-sulfone XI and 91% of the α-sulfone XII,[4] and allyl



XI XII

benzyl sulfone has been transformed into propenyl benzyl sulfone in 50% yield by heating with various tertiary amines.[3a] On the other hand, Backer and de Jong have recently reported that crotyl benzyl sulfone fails to rearrange under conditions which bring about the isomerization of allyl benzyl sulfone and its α- and β-methyl-substituted derivatives.[5] These observations have led the latter investigators to conclude that possibilities for hyperconjugation have a determinative influence on the relative stabilities of certain pairs of Δ^2- and Δ^3-unsaturated sulfone isomers. The same hypothesis appears to be applicable to the pair of unsaturated six-membered heterocyclic sulfones with which we are concerned in the present communication.

As was previously reported,[1] we have been unable to bring about the rearrangement of Δ^3-dihydrothiapyran dioxide (I) into the Δ^2-isomer (II) by any of the usual methods. However, the reverse change, involving the shift of an α,β-double bond to the β,γ-position, has now been found to occur readily in moderately basic media. When a solution of Δ^2-dihydrothiapyran dioxide in dilute aqueous sodium hydroxide was allowed to stand for 24 hours, 67% of the theoretical amount of Δ^3-dihydrothiapyran dioxide was isolated by chloroform extraction and none of the starting material was recovered.[6] Prolonged heating of the Δ^2-isomer (II) with triethylamine also gave the Δ^3-isomer (I) as the only identifiable product, though in poorer

(3) (a) H. J. Backer and G. J. de Jong, *Rec. trav. chim.*, **67**, 884 (1948); (b) J. Böeseken and E. de Roy van Zuydewijn, *Proc. Acad. Sci. Amsterdam*, **39**, 31 (1935) [*C. A.*, **30**, 3403 (1936)].

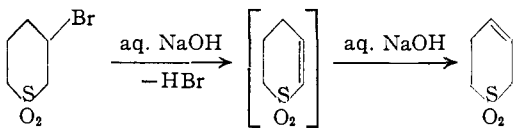
(4) J. Böeseken and E. de Roy van Zuydewijn, *Proc. Acad. Sci. Amsterdam*, **40**, 23 (1937) [*C. A.*, **31**, 4953 (1937)]; E. de Roy van Zuydewijn, *Rec. trav. chim.*, **56**, 1047 (1937).

(5) H. J. Backer and G. J. de Jong, *ibid.*, **70**, 377 (1951).

(6) It is very probable that most, if not all, of the material unaccounted for was present in the aqueous solution as tetrahydrothiapyran-3-ol 1,1-dioxide, formed by the base-catalyzed addition of water to the α,β-unsaturated sulfone. *Cf.* H. J. Backer and J. Strating, *ibid.*, **54**, 618 (1935); E. de Roy van Zuydewijn, ref. in footnote 4.

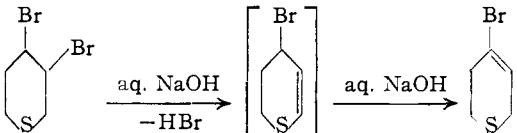
yield (45%) and accompanied by considerable tarry material. After treatment of II with boiling pyridine, only the unchanged Δ^2-isomer (isolated and identified as the dibromide) could be detected in the dark-colored oily product, in agreement with the reported[7] failure of this reagent to bring about the isomerization of either allyl benzyl sulfone or propenyl benzyl sulfone.

In view of these results, it is to be expected that while pyridine might be employed successfully as a dehydrobrominating agent in the synthesis of Δ^2-dihydrothiapyran dioxide (II) from 3-bromotetrahydrothiapyran dioxide (IX), the action of aqueous alkali on IX shoud lead to Δ^3-dihydrothiapyran dioxide (I). This expectation was verified experi-



IX II I

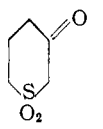
mentally, a 92% yield of the Δ^3-isomer (I) being obtained after treatment of the 3-bromosulfone (IX) with cold dilute aqueous sodium hydroxide for 24 hours. This observation may be offered in further support of the Δ^3-structure XV tentatively assigned to the unsaturated bromosulfone which we had previously obtained by the action of aqueous alkali on 3,4-dibromotetrahydrothiapyran 1,1-dioxide (XIII).[1] In the course of the present in-



XIII XIV XV

vestigation, several attempts were made to isolate the Δ^2-unsaturated bromosulfone XIV postulated as an intermediate in the above reaction by dehydrobrominating XIII with the calculated amount of pyridine or triethylamine in benzene solution. Although pyridine failed to give the desired results, an apparently homogeneous substance (m.p. 83–84°) was isolated in several experiments with triethylamine which gave analytical values close to those calculated for 4-bromo-Δ^2-dihydrothiapyran 1,1-dioxide (XIV) and which underwent the expected rearrangement on treatment with aqueous alkali, providing the Δ^3-isomer XV in good yield.

In addition to the compounds described above in connection with the synthesis of Δ^2-dihydrothiapyran dioxide, several other new tetrahydrothiapyran derivatives were prepared and characterized. Oxidation of tetrahydrothiapyran-3-one (VI) with hydrogen peroxide in acetic acid yielded tetrahydrothiapyran-3-one 1,1-dioxide (XVI), which may be regarded as a monosulfonyl analog of 1,3-cyclohexanedione. Like the simple acyclic β-ketosulfones and β-diketones, this cyclic β-ketosulfone (XVI) dissolves in aqueous sodium hydroxide with the formation of a sodium salt but fails to react with aqueous sodium bicarbonate. This behavior is in striking contrast to the marked intensification of acid strength observed when the β-dicarbonyl system is incorporated into a six-membered ring, as in 1,3-cyclohexanedione, which is almost as strong an acid as acetic acid and which liberates carbon dioxide from aqueous sodium bicarbonate.[8] The failure of steric factors introduced by ring formation to influence similarly the acid strengths of β-ketosulfones and β-diketones seems to support the contention of Arndt and his school[9] that the mechanism underlying the effects of the sulfonyl group on adjacent groups differs both qualitatively and quantitatively from that operating in the carbonyl group. Studies are now under way in this Laboratory which should shed further light on the extent to which the sulfone function is, or is not, capable of participating in various reactions characteristic of the carbonyl group, particularly those in which keto–enol equilibria are involved.



XVI

Hydrogenation of the β-ketosulfone XVI over Raney nickel gave tetrahydrothiapyran-3-ol 1,1-dioxide, which was characterized by conversion to the corresponding β-acetoxysulfone on treatment with acetyl chloride. The methyl ether of tetrahydrothiapyran-3-ol 1,1-dioxide, obtained by the action of dimethyl sulfate on the β-hydroxysulfone in weakly alkaline solution, proved to be identical with the methoxysulfone previously prepared[1] by the addition of methanol to Δ^3-dihydrothiapyran 1,1-dioxide, thus confirming the earlier assignment of the β-methoxy structure to this compound.

Acknowledgment.—The author is happy to acknowlege the support of a portion of this work by a Frederick Gardner Cottrell grant from the Research Corporation.

Experimental[10]

Ethyl γ-Chlorobutyrate.[11]—A solution of 103.5 g. of γ-chlorobutyronitrile in 250 ml. of absolute ethanol was cooled to 0° and saturated with dry hydrogen chloride. After standing for several hours at room temperature, the solution was refluxed for 2 hours, filtered, and concentrated to half its original volume by distillation under a 30-cm. Vigreux column. The residual oil was diluted with several times its volume of water, the lower oil layer was separated, and the upper aqueous layer was extracted several times with ether. The combined oil layer and ether extracts were washed with sodium bicarbonate solution and dried over anhydrous magnesium sulfate. After removal of the ether, the residue was distilled under diminished pressure through a short Vigreux column to give 124.7 g. (86%) of colorless oil, b.p. 81–84° at 20 mm.

Ethyl γ-(Carbethoxymethylmercapto)-butyrate (III).—One hundred and twenty grams (1.0 mole) of ethyl thioglycolate was added to a freshly prepared solution of one mole of sodium ethoxide in 400 ml. of absolute ethanol maintained at 0° under a nitrogen atmosphere. Ethyl γ-chlorobutyrate (144.5 g., 1.0 mole) was run into the cold, me-

(7) E. Rothstein, *J. Chem. Soc.*, 684 (1934).

(8) G. Schwarzenbach and K. Lutz [*Helv. Chim. Acta*, **23**, 1162 (1940)] give the following values for pK_a at 25°: 1,3-cyclohexanedione, 5.26; acetylacetone, 8.94; acetic acid, 4.76. See also R. v. Schilling and D. Vorländer, *Ann.*, **308**, 184 (1899).

(9) F. Arndt and B. Eistert, *Ber.*, **74**, 423 (1941); H. J. Backer, *Bull. soc. chim.*, [5] **17**, 729 (1950).

(10) Microanalyses were performed by the Clark Microanalytical Laboratory, Urbana, Illinois.

(11) *Cf.* L. Henry, *Bull. soc. chim.*, [2] **45**, 341 (1886).

chanically stirred solution over a 5-minute period, and the mixture was allowed to stand in the ice-bath for another 15 minutes, then at room temperature for 30 minutes, and finally was refluxed for one hour. After the precipitate of sodium chloride had been filtered off and most of the solvent removed by distillation, the residue was diluted with water and the layers separated. The lower oil layer was combined with the ether extracts of the aqueous layer, washed once with water, and dried over anhydrous magnesium sulfate. The ether was removed and the residue distilled under reduced pressure to give 200.0 g. (85%) of colorless oil, b.p. 139–142° at 4 mm.

Anal. Calcd. for $C_{10}H_{18}O_4S$: C, 51.26; H, 7.74. Found: C, 51.36; H, 7.73.

Hydrolysis of 5.0 g. of the diester III was accomplished by refluxing with a mixture of 50 ml. of glacial acetic acid and 2.5 ml. of concd. hydrochloric acid for 15 hours. On vacuum evaporation of the resultant solution, the oily residue gradually crystallized to a waxy solid which melted at 65–70°; yield 3.8 g. (100%). Recrystallization from benzene gave pure γ-(**carboxymethylmercapto**)-**butyric acid** (IV) as colorless crystals, m.p. 74–75°.

Anal. Calcd. for $C_6H_{10}O_4S$: C, 40.44; H, 5.66; neut. equiv., 89.1. Found: C, 40.64; H, 5.55; neut. equiv., 89.8.

2-Carbethoxytetrahydrothiapyran-3-one (V).—A suspension of 1.5 moles of alcohol-free sodium ethoxide (freshly prepared from 34.5 g. of sodium) in 750 ml. of dry ether was cooled in an ice-bath, while 175.0 g. (0.75 mole) of ethyl γ-(carbethoxymethylmercapto)-butyrate (III) was added dropwise to the mechanically stirred suspension over a 30-minute period. The mixture became extremely pasty during the latter half of the addition and stirring was discontinued when addition of the ester was complete. The mixture was allowed to stand in the ice-bath for another hour, after which it was decomposed with a mixture of 95 ml. of glacial acetic acid and 600 ml. of ice and water. The aqueous layer was separated and extracted with ether until the extracts no longer gave a blue coloration with ferric chloride in alcohol, and the extracts were added to the original ether layer. The ether solution was washed with aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate and distilled. The β-ketoester was obtained as a colorless oil, b.p. 117–120° at 4 mm., which gave a deep blue color with ferric chloride solution; yield 115.5 g. (82%).

Anal. Calcd. for $C_8H_{12}O_3S$: C, 51.05; H, 6.43. Found: C, 51.11; H, 6.29.

Tetrahydrothiapyran-3-one (VI).—A mixture of 90.0 g. of 2-carbethoxytetrahydrothiapyran-3-one (V) and 650 ml. of 10% sulfuric acid was refluxed for 6 hours, after which it was cooled and the layers were separated. The aqueous layer was extracted several times with ether and the extracts were added to the original oil layer. The ether solution was washed with sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and distilled through a short Vigreux column to give 41.0 g. (74%) of colorless oil, b.p. 77–80° at 5 mm. Redistillation of a portion of this material provided an analytical sample boiling at 101–102° at 18 mm.

Anal. Calcd. for C_5H_8OS: C, 51.68; H, 6.94. Found: C, 51.75; H, 6.78.

The **semicarbazone** of VI was prepared in the usual way[12] and was obtained in the form of colorless leaflets, m.p. 165–166°, after recrystallization from ethanol.

Anal. Calcd. for $C_6H_{11}N_3OS$: C, 41.60; H, 6.40. Found: C, 41.65; H, 6.37.

Tetrahydrothiapyran-3-one 1,1-Dioxide (XVI).—A solution of 11.6 g. (0.10 mole) of tetrahydrothiapyran-3-one (VI) in a mixture of 50 ml. of glacial acetic acid and 50 ml. of acetic anhydride was cooled in an ice-bath, and 25.0 ml. (0.22 mole) of 30% hydrogen peroxide was added in small portions while the temperature of the mixture was maintained at 10–15°. The mixture was allowed to stand in the ice-bath for another 8 hours and was then set aside at room temperature for 7 days, after which a pinch of manganese dioxide was added to catalyze the decomposition of excess hydrogen peroxide and the solvent was removed under reduced pressure at room temperature. The crystalline residue was recrystallized directly from ethanol to give 8.7 g. of colorless needles, m.p. 136–139°. An additional 1.9 g. of product of comparable purity was recovered from the mother liquor and was added to the first crop of crystals to give a total yield of 10.6 g. (72%) of the crude sulfone. Recrystallization from ethanol raised the melting point to 140–140.5°. This product is slightly soluble in water and aqueous sodium bicarbonate (no effervescence) but readily soluble in dilute aqueous sodium hydroxide; it gives no coloration with aqueous or alcoholic ferric chloride.

Anal. Calcd. for $C_5H_8O_3S$: C, 40.52; H, 5.44. Found: C, 40.49; H, 5.38.

The **semicarbazone** of XVI, prepared in the usual way,[12] melted at 206–207° with decomposition after recrystallization from water.

Anal. Calcd. for $C_6H_{11}O_3N_3S$: C, 35.12; H, 5.40. Found: C, 35.16; H, 5.21.

Tetrahydrothiapyran-3-ol 1,1-Dioxide.—A solution of 7.40 g. of tetrahydrothiapyran-3-one 1,1-dioxide (XVI) in 100 ml. of water was hydrogenated over 0.6 g. of Raney nickel at 100° and 100 atmospheres for 30 minutes. After removal of the suspended catalyst, the solution was evaporated to dryness on the steam-bath and the dark-colored waxy residue was extracted repeatedly with boiling benzene until no further solid separated from the extracts on cooling. The crystalline product thus obtained melted at 93–95°; yield 6.5 g. (87%). Recrystallization from a mixture of ethanol and ligroin (65–75°) afforded colorless crystals melting at 94–95°.

Anal. Calcd. for $C_5H_{10}O_3S$: C, 39.98; H, 6.71. Found: C, 40.34; H, 6.89.

Treatment of 1.00 g. of this product with 1.3 g. of dimethyl sulfate according to the procedure previously employed with the 4-hydroxy isomer[1] afforded 0.53 g. of colorless crystals which melted at 65–66° after recrystallization from benzene–petroleum ether and failed to depress the m.p. of 3-methoxytetrahydrothiapyran 1,1-dioxide (m.p. 66–66.5°).[1]

3-Acetoxytetrahydrothiapyran 1,1-Dioxide.—A mixture of 1.00 g. of tetrahydrothiapyran-3-ol 1,1-dioxide and 1.5 ml. of acetyl chloride was heated on the steam-bath under reflux for 5 minutes and was then evaporated to dryness. A quantitative yield (1.28 g.) of the crude acetate, m.p. 128–130°, was thus obtained and was recrystallized from benzene to give 1.15 g. (89%) of colorless crystals, m.p. 130–131°.

Anal. Calcd. for $C_7H_{12}O_4S$: C, 43.74; H, 6.30. Found: C, 44.04; H, 6.25.

Tetrahydrothiapyran-3-ol (VII).—A mixture of 47.7 g. (0.41 mole) of tetrahydrothiapyran-3-one (VI), 235 g. (1.15 moles) of aluminum isopropoxide, and 900 ml. of isopropyl alcohol was refluxed under a 30-cm. Vigreux column in such a way as to maintain a distillation rate of *ca.* 150 ml. per hour. After 3 hours the dinitrophenylhydrazine test[13] for acetone in the distillate became negative, and the reaction mixture was then concentrated further by distillation under reduced pressure. The residue was decomposed with a mixture of 410 ml. of concd. hydrochloric acid and 1 l. of ice and water, and the product was extracted from the aqueous solution with ether. The ether solution was dried over anhydrous magnesium sulfate and distilled to give 39.5 g. (81%) of a colorless viscous oil, b.p. 114–118° at 24 mm. A portion of this material was redistilled to provide an analytical sample, b.p. 76–78° at 2 mm., m.p. 13–15°.

Anal. Calcd. for $C_5H_{10}OS$: C, 50.80; H, 8.53. Found: C, 50.53; H, 8.14.

3-Bromotetrahydrothiapyran (VIII).—Thirty-five grams (0.13 mole) of freshly distilled phosphorus tribromide was added dropwise over a 2-hour period to 39.2 g. (0.33 mole) of tetrahydrothiapyran-3-ol (VII) while the mixture was stirred vigorously and cooled to 10–15° by means of an ice-bath. After the addition was complete, the viscous mixture was warmed to 70° and allowed to cool to room temperature. Dilution with 150 ml. of water produced two layers, which were separated and the upper aqueous layer was extracted several times with ether. The combined oil layer and ether extracts were washed with aqueous sodium bicarbonate and

(12) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 170.

(13) A. L. Wilds, "Organic Reactions," Vol. 2, edited by R. Adams, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 200.

dried over anhydrous magnesium sulfate. After removal of the ether, the residual oil was distilled under diminished pressure to yield 44.3 g. (74%) of colorless oil, b.p. 105–110° at 28 mm. On redistillation most of this material boiled at 68–69° at 4 mm.

Anal. Calcd for C_5H_9SBr: C, 33.16; H, 5.01. Found: C, 33.31; H, 4.96.

3-Bromotetrahydrothiapyran 1,1-Dioxide (IX). (a) Perbenzoic Acid Method.—A solution of *ca.* 38 g. (0.28 mole) of perbenzoic acid in 500 ml. of chloroform was prepared from 79 g. of benzoyl peroxide according to the directions given by Braun.[14] This was added in small portions to a solution of 21.7 g. (0.12 mole) of 3-bromotetrahydrothiapyran (VIII) in 100 ml. of chloroform, while cooling in an ice-bath to keep the temperature at 30–35°. The mixture was then set aside at room temperature for 3 hours, after which it was heated slowly to boiling and allowed to cool. The chloroform solution was freed of acid by washing with 250 ml. of 10% aqueous sodium bicarbonate, and the solvent was removed by distillation on the steam-bath. The semi-crystalline residue was taken up in hot benzene and recrystallized by the addition of petroleum ether to give 18.3 g. (72%) of pale yellow crystals which melted at 88–90°. Recrystallization from benzene–petroleum ether raised the melting point to 90–91°. This product failed to react with alcoholic silver nitrate even on heating but dissolved readily in dilute aqueous sodium hydroxide with the liberation of bromide ion, which could then be detected with silver nitrate in the usual way.

Anal. Calcd. for $C_5H_9BrO_2S$: C, 28.18; H, 4.26. Found: C, 28.23; H, 4.02.

(b) Hydrogen Peroxide Method.—To a solution of 9.05 g. (0.05 mole) of 3-bromotetrahydrothiapyran (VIII) in 50 ml. of glacial acetic acid, 12 ml. (0.11 mole) of 30% hydrogen peroxide was added in small portions while cooling under the tap to keep the temperature at 40–50°. After the exothermic reaction had subsided, the mixture was heated cautiously to boiling and refluxed gently for 5 minutes. The solvent was then removed under reduced pressure at room temperature, leaving a colorless oil which was diluted with water and induced to crystallize by cooling and scratching. The colorless crystalline solid thus obtained melted at 84–87° and showed no m.p. depression on admixture with the product described in the preceding paragraph; yield 5.22 g. (49%).

Dehydrobromination of IX. (a) With Aqueous Sodium Hydroxide.—A suspension of 2.13 g. of 3-bromotetrahydrothiapyran 1,1-dioxide (IX) in 20 ml. of 5% aqueous sodium hydroxide was allowed to stand at room temperature with occasional agitation over a period of 24 hours. The solid gradually dissolved, giving a clear yellow solution from which there was isolated by chloroform extraction 1.21 g. (92%) of colorless crystals, m.p. 67–69°, after recrystallization from cyclohexane. The melting point of this material was not depressed on admixture with authentic Δ^3-dihydrothiapyran 1,1-dioxide prepared as previously described.[1]

(b) With Pyridine.—A solution of 33.4 g. of 3-bromotetrahydrothiapyran 1,1-dioxide (IX) in 100 ml. of anhydrous pyridine was refluxed for 30 minutes, and was then cooled, poured into an ice-cold mixture of 500 ml. of water and 110 ml. of concd. hydrochloric acid, and extracted with chloroform. The combined chloroform extracts were dried over anhydrous magnesium sulfate and the solvent was removed by evaporation under reduced pressure. The residual oil was distilled *in vacuo* to give 16.9 g. (82%) of crude Δ^2-dihydrothiapyran 1,1-dioxide (II) as a semi-crystalline sirup, b.p. 157–161° at 6 mm.

2,3-Dibromotetrahydrothiapyran 1,1-Dioxide.—The crude Δ^2-dihydrothiapyran 1,1-dioxide (II) (16.5 g., 0.125 mole) described in the preceding paragraph was dissolved in 75 ml. of chloroform, 20.8 g. (0.130 mole) of bromine was added, and the solution was set aside at room temperature. A moderate exothermic reaction occurred and crystals began to appear after about 30 minutes. After 3 hours the crystalline precipitate was collected, washed with chloroform, and dried to yield 18.1 g. of colorless needles, m.p. 173–175°. Another 4.8 g. of material of comparable purity was obtained by working up the chloroform filtrate and was added to the original product: total yield 22.9 g. (63%). After recrystallization from acetic acid, the dibromide melted at 175–176° and depressed the melting point of the isomeric 3,4-dibromide (m.p. 178–179°)[1] to *ca.* 140–160°.

Anal. Calcd. for $C_5H_8Br_2O_2S$: C, 20.57; H, 2.76. Found: C, 20.69; H, 2.82.

Δ^2-Dihydrothiapyran 1,1-Dioxide (II).—The 2,3-dibromide (23.9 g., 0.082 mole) was debrominated with zinc dust (10.5 g., 0.16 g. atom) in 500 ml. of 90% ethanol by the method previously described for the preparation of the Δ^3-isomer (I).[1] On dilution of the concentrated alcoholic solution of crude product with water, 8.8 g. of unreacted dibromide (m.p. 172–174°) precipitated and was removed from the solution by filtration. The aqueous filtrate was extracted repeatedly with small portions of chloroform, and the combined extracts were dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure left 5.9 g. (86%, based on unrecovered dibromide) of a pale yellow viscous oil, which resisted all efforts to induce crystallization. Vacuum distillation of this material yielded, as a middle fraction, 3.6 g. of colorless viscous oil, b.p. 190–192° at 25 mm., which slowly crystallized in the form of long needles, m.p. 44–46° after drying on a porous plate. On admixture with a small amount of Δ^3-dihydrothiapyran 1,1-dioxide (I), liquefaction occurred at room temperature.

Anal. Calcd. for $C_5H_8O_2S$: C, 45.42; H, 6.10. Found: C, 45.60; H, 5.95.

Rearrangement of Δ^2-Dihydrothiapyran 1,1-Dioxide (II) to Δ^3-Dihydrothiapyran 1,1-Dioxide (I).—When a solution of 0.18 g. of II in 2 ml. of 5% aqueous sodium hydroxide was allowed to stand at room temperature for 24 hours[15] and was then extracted with chloroform, there was obtained by evaporation of the combined extracts 0.12 g. (67%) of a colorless solid, m.p. 65–69°, which showed no depression of the melting point when mixed with Δ^3-dihydrothiapyran 1,1-dioxide (m.p. 71–72°).[1] Treatment of a solution of 0.10 g. of this product in 0.50 ml. of chloroform with 0.14 g. of bromine resulted in a vigorous exothermic reaction followed by the precipitation of 0.20 g. (90%) of the 3,4-dibromide, m.p. 172–175°; the melting point of this material was depressed on admixture with the 2,3-dibromide described above but not with the 3,4-dibromide described in the preceding paper in this series.[1]

Addition of Hydrogen Halides to Δ^2-Dihydrothiapyran 1,1-Dioxide. (a) Hydrogen Iodide.—A solution of 1.00 g. of the unsaturated sulfone[16] II in 5 ml. of 47% hydriodic acid was refluxed for one hour and was then concentrated to a viscous oil by evaporation on the steam-bath. The semi-crystalline paste which was obtained on cooling was diluted with water and the precipitate was collected, washed with water, and dried; yield 0.99 g. (50%); 83–86°. Recrystallization from water afforded colorless crystals of **3-iodotetrahydrothiapyran 1,1-dioxide** which melted at 85–86°.

Anal. Calcd. for $C_5H_9IO_2S$: C, 23.09; H, 3.49. Found: C, 23.24; H, 3.57.

(b) Hydrogen Bromide.—One gram of the unsaturated sulfone[16] II was refluxed with 5 ml. of 48% hydrobromic acid and worked up as in the preceding paragraph. The product (0.37 g.) melted at 88–90° after recrystallization from water and showed no m.p. depression when mixed with the 3-bromotetrahydrothiapyran 1,1-dioxide (IX) prepared by oxidation of the corresponding sulfide.

4-Bromo-Δ^2-dihydrothiapyran 1,1-Dioxide (XIV) (?).—A mixture of 4.67 g. (0.016 mole) of 3,4-dibromotetrahydrothiapyran 1,1-dioxide, 1.62 g. (0.016 mole) of triethylamine and 120 ml. of dry benzene was refluxed for 20 minutes and was then cooled and filtered, and the filtrate was washed twice with small portions of water. After drying over anhydrous magnesium sulfate, the solvent was removed by distillation on the steam-bath and the residue was recrystallized directly from water to give 2.49 g. (74%) of colorless crystals, m.p. 79–81°. Repeated recrystallizations from benzene–petroleum ether raised the m.p. to 83–84°, and a final recrystallization from cyclohexane failed to raise it further.

(14) G. Braun, "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 431.

(15) The selection of this period of time was determined by convenience and should not be taken to represent the minimum time required to reach equilibrium.

(16) These experiments were carried out with the crude Δ^2-dihydrothiapyran 1,1-dioxide obtained by dehydrobromination of the 3-bromosulfone (IX).

Anal. Calcd. for $C_5H_7BrO_2S$: C, 28.45; H, 3.34; Br, 37.86; S, 15.19. Found: C, 27.72, 27.86; H, 3.45, 3.36; Br, 37.68; S, 14.41.

When a suspension of 0.68 g. of this product in 6 ml. of 5% aqueous sodium hydroxide was allowed to stand at room temperature for one hour with occasional agitation, the crystalline solid obtained on filtration (0.52 g., 76%) melted at 144–145° after recrystallization from water and failed to depress the m.p. of the compound previously described[1] as 4-bromo-$\Delta^{3(or2)}$-dihydrothiapyran 1,1-dioxide.

Ultraviolet Absorption Spectra.—The spectra were determined with a Beckman quartz spectrophotometer, model DU, using an approximately constant spectral band width of 1–2 mμ down to wave lengths in the neighborhood of 220 mμ. Readings at shorter wave lengths were obtained by using the 0.1 switch position and balancing the galvanometer for 100% transmission with the solvent in position before the phototube. Absolute ethanol was used as the solvent. Spectra of other thiapyran derivatives prepared in the present investigation will be described in a forthcoming communication on the ultraviolet absorption spectra of heterocyclic sulfur compounds.

SWARTHMORE, PA. RECEIVED SEPTEMBER 18, 1951

[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE]

Nucleophilic Displacement in the Benzene Series[1]

BY ERNST BERLINER AND LOUISE C. MONACK

The rate constants of the reaction of 4-substituted 2-nitrobromobenzenes with piperidine have been determined. The reaction follows a Hammett relationship with a rho value of 4.95. Differences in rates are mainly determined by differences in activation energies.

Most studies of nucleophilic displacement on aromatic halides have dealt with the effect of three factors: the displaced halogen,[2] the nucleophilic reagent,[3] and the substituent. Of these, the effect of substituents has been investigated least. The activating effect of the nitro group and other electron attracting substituents has been qualitatively observed for many years,[4] and relative activating powers of different groups have also been studied quantitatively.[5] Much less information is available on the effect of electron repelling or deactivating substituents,[6] and very little work is reported in which a series including both activating and deactivating groups has been investigated.[7,8] This is understandable; for reasons which have often been discussed[9] nucleophilic displacement on aryl halides, as on vinyl halides, is a very difficult reaction, which proceeds hardly at measurable rates at room temperature, whereas activated displacements, particularly nitro-activated, are fairly rapid, even at room temperature. Chlorobenzene reacts less than 1% with piperidine in 48 hours at 165°,[10] and aryl halides containing electron repelling groups react slower still. Differences of reactivity under the very drastic conditions necessary to affect any reaction at all become difficult to assess. De Crauw, who studied a series of chlorobenzenes containing both activating and deactivating groups, reports that the amino, hydroxy, methoxy and sulfhydryl compounds were completely inert to sodium methoxide at 180° and eight hours,[8] and almost no difference was found between chlorobenzene and *p*-chloroaniline toward piperidine in boiling benzene.[11] In addition, there is reason to believe that nucleophilic displacement with and without activating groups may proceed by different mechanisms, which in itself makes a comparison meaningless.[10,12]

To overcome these difficulties, and in order to evaluate the effect of both activating and deactivating groups on a nucleophilic displacement reaction under identical conditions, fourteen compounds of the type I were studied with piperidine as reactant and solvent. The ortho-nitro group was introduced in order to activate the bromine, and its effect on the rate constants was assumed to be a constant factor.[13] All differences in rate are then due

(1) Taken from a dissertation submitted by Miss L. C. Monack to the Graduate School of Bryn Mawr College in partial fulfillment of the requirements for the Ph.D. degree.

(2) For instance: R. Löwenherz, *Z. physik. Chem.*, **29**, 401 (1899); H. Franzen and E. Bockhacker, *Ber.*, **53**, 1174 (1920); A. Rheinlander, *J. Chem. Soc.*, **123**, 3099 (1923); B. V. Tronov and E. A. Krueger, *J. Russ. Phys. Chem. Soc.*, **58**, 1270 (1926) [*C. A.*, **21**, 3887 (1927)]; F. W. Bergstrom, R. E. Wright, C. Chandler and W. A. Gilkey, *J. Org. Chem.*, **1**, 170 (1936).

(3) For instance: W. Borsche, *Ann.*, **386**, 351 (1912); *Ber.*, **56**, 1488 (1923); W. Borsche and D. Rantscheff, *Ann.*, **379**, 152 (1911); W. Borsche and H. Bahr, *ibid.*, **402**, 81 (1914); K. W. Rosenmund and E. Struck, *Ber.*, **52**, 1749 (1919); R. J. W. Le Fevre and E. E. Turner, *J. Chem. Soc.*, 1113 (1927); H. J. Van Opstall, *Rec. trav. chim.*, **52**, 901 (1933); A. Singh and D. H. Peacock, *J. Chem. Phys.*, **40**, 669 (1936); O. L. Brady and F. R. Cropper, *J. Chem. Soc.*, 507 (1950).

(4) Pisani, *Ann.*, **92**, 326 (1854); E. Lellmann, *Ber.*, **20**, 680 (1887); M. Schoepf, *ibid.*, **22**, 3281 (1889); **23**, 3440 (1890); **24**, 3771 (1891); P. Fischer, *ibid.*, **24**, 3785 (1891); W. Borsche and I. Exss, *ibid.*, **56**, 2353 (1923); J. Kenner, *J. Chem. Soc.*, **105**, 2717 (1914).

(5) A. F. Holleman and F. E. van Haeften, *Rec. trav. chim.*, **40**, 67 (1921), and many preceding papers of Holleman and his students; Th. J. F. Mattaar, *ibid.*, **41**, 103 (1922); H. Ph. Baudet, *ibid.*, **43**, 707 (1924); A. Brewin and E. E. Turner, *J. Chem. Soc.*, 332 (1928); W. Davies and E. S. Wood, *ibid.*, 1122 (1928); R. B. Sandin and M. Liskear, THIS JOURNAL, **57**, 1304 (1935); W. C. Spitzer and G. W. Wheland, *ibid.*, **62**, 2995 (1940); J. F. Bunnett and A. Levitt, *ibid.*, **70**, 2778 (1948).

(6) H. F. J. Lorang, *Rec. trav. chim.*, **46**, 891 (1927); H. Lindemann and A. Pabst, *Ann.*, **462**, 24 (1928); E. A. Krueger and M. S. Bednova, *J. Gen. Chem.* (*U. S. S. R.*), **3**, 67 (1923) [*C. A.*, **28**, 1593 (1934)]; N. Cambell, W. Anderson and J. Gilmore, *J. Chem. Soc.*, 446 (1940).

(7) G. M. Kraay, *Rec. trav. chim.*, **49**, 1082 (1930); L. M. F. van de Lande, *ibid.*, **51**, 98 (1932).

(8) Th. de Crauw, *ibid.*, **50**, 753 (1931).

(9) E. D. Hughes, *Trans. Faraday Soc.*, **37**, 627 (1941); J. W. Baker, *ibid.*, **37**, 635 (1941); E. D. Hughes and C. K. Ingold *J. chim. phys.*, **45**, 241 (1948); G. W. Wheland, "The Theory of Resonance and its Application to Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 272.

(10) E. Berliner, M. J. Quinn and P. J. Edgerton, THIS JOURNAL, **72**, 5305 (1950).

(11) G. M. Badger, J. W. Cook and W. P. Vidal, *J. Chem. Soc.*, 1109 (1947).

(12) See also J. F. Bunnett, Abstracts of Papers, Meeting of the American Chemical Society, Chicago, Ill., September, 1950, p. 98N.

(13) A similar system, containing various activating groups, was recently studied by J. F. Bunnett, F. M. Draper, P. R. Ryason, P. Noble, R. Zahler and R. G. Tonkyn, abstracts of papers presented to the Meeting of the American Chemical Society, Boston, Mass., April, 1951, p. 47M.