to chromatographic analysis on activated alumina and was eluted with 2–4 volume % of ethyl acetate in benzene. The *exo* sulfone was eluted first, although the separation was not clean. The recoveries were not good, giving 108 mg. (9.5%) of ***exo*-dehydronorbornyl *p*-tolyl sulfone**, m.p. 70–71° after recrystallization from petroleum ether, and 202 mg. (17.5%) of ***endo*-dehydronorbornyl *p*-tolyl sulfone**, m.p. 80–80.5° after recrystallization from petroleum ether.

Anal. Calcd. for $C_{14}H_{16}O_2S$: C, 67.71; H, 6.50. Found: (*exo*) C, 67.62; H, 6.42; (*endo*) C, 67.44; H, 6.50.

When the *exo*-dehydronorbornyl *p*-tolyl sulfone was subjected to catalytic hydrogenation in ethanol over palladium-on-charcoal catalyst at one atmosphere pressure, one mole of hydrogen was absorbed per mole of olefin to give *exo*-norbornyl *p*-tolyl sulfone (IIb), m.p. 81–82° after three recrystallizations from petroleum ether.

Anal. Calcd. for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.24. Found: C, 67.00; H, 7.34.

A similar experiment with the *endo* unsaturated sulfone gave the *endo* compound IIIb, m.p. 85.3–85.5° after three recrystallizations from petroleum ether.

Anal. Calcd. for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.24. Found: C, 67.00; H, 7.31.

***p*-Tolyl Vinyl Sulfone.**—This sulfone was prepared according to the procedure described by Ford-Moore, Peters and Wakelin[28] for the phenyl analog.

To a solution of 98.6 g. (0.471 mole) of *p*-tolyl β-chloroethyl sulfone[29] in 900 ml. of benzene, 50.6 g. (0.5 mole) of triethylamine was added. The mixture was allowed to stand overnight. It was filtered and 53.9 g. (83%) of triethylammonium chloride was obtained. The filtrate was steam distilled to remove benzene. The residue was crystallized from 95% ethanol and gave a first crop of crystals weighing 33 g., m.p. 66° (reported[30] 65°). Partial evaporation of the mother liquors produced an additional 4.7 g. of crystals. The yield was 44% on the basis of isolated sulfone.

Dehydronorbornyl *p*-Tolyl Sulfones from Cyclopentadiene and *p*-Tolyl Vinyl Sulfone.—Solutions of freshly distilled cyclopentadiene (375 mg., 5.7 mmoles) and *p*-tolyl vinyl sulfone (863 mg., 4.7 mmoles) in 10 ml. of benzene containing a few mg. of 4-*t*-butylcatechol were heated in a furnace at 160 ± 3° for one hour and for 18 hours. At the end of the appropriate time, the tubes were removed, cooled and opened. The solutions were poured onto activated alumina columns and the *endo* and *exo* sulfones were separated fairly well by elution with 2–4% ethyl acetate in benzene. The middle fractions of the eluant often were mixtures of the two isomers and the compositions of these fractions were established with reference to a melting point–composition diagram. The one-hour sample gave 604 mg. (51%) of *endo*-dehydronorbornyl sulfone and 302 mg. (26%) of the *exo* sulfone, while the 18-hour sample gave 36% of the *endo* compound and 33% of the *exo* isomer. Intermediate times of reaction gave intermediate *endo-exo* ratios.

Competition of Norbornylene and Cyclohexene for a Limited Amount of *p*-Thiocresol.—Into a reaction flask cooled in a Dry Ice-bath was added 1.81 g. (19.2 mmole) of norbornylene and 2.00 ml. (1.62 g., 19.2 mmoles) of freshly distilled cyclohexene ($n^{20}D$ 1.4460). When this mixture was cold, 2.45 g. (19.7 mmoles) of *p*-thiocresol was added. The cold-bath was removed and the reaction began as the mixture warmed to room temperature. The flask was shaken several times to aid mixing. The temperature in the reaction flask rose slowly to a maximum of 56°. When the reaction was complete, as evidenced by a decrease in the temperature in the reaction flask, the flask was heated to recover the unreacted olefin; the temperature of the heating-bath was raised finally to 150°. The distillate, which was collected in a receiver immersed in a Dry Ice-bath, weighed 1.202 g. and had a refractive index $n^{20}D$ 1.4471. A plot of refractive index at 20° against mole per cent. norbornylene in cyclohexene from mixtures of known composition indicated the distillate to be approximately 6 mole per cent. in norbornylene. This was substantiated by the preparation of the triazole derivative of norbornylene. The refractive index plot which was linear over the range studied (0–50% norbornylene) gave an extrapolated value of $n^{20}D$ 1.4634 for norbornylene.

Reaction of Phenyl Azide with the Norbornylene–Cyclohexene Distillate.—To the cyclohexene-norbornylene distillate obtained above, $n^{20}D$ 1.4471, was added 508 mg. (4.28 mmoles) of phenyl azide.[31] The mixture was allowed to stand at room temperature overnight. Evaporation to dryness gave 63 mg. (0.53 mmole) of crude 3a,4,5,6,7,7a-hexahydro-1-phenyl-4,7-methanobenzotriazole, which melted at 96–97.5° after one recrystallization from methanol. A mixed m.p. with an authentic sample of the norbornylene phenylazide adduct[32] (m.p. 100–101°) was 97–99.5°.

Another experiment showed that the triazole derivative was formed in 62% yield based on norbornylene under the above conditions. Assuming a 60% yield in the present experiment, about 0.9 mmole of norbornylene was present in the original distillate. The amount of cyclohexene present was therefore 1.1 g. (14 mmoles). The composition of the distillate was thus 6 mole per cent. norbornylene. This result checks the quantitative refractive index experiment.

BOULDER, COLORADO

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(29) H. Gilman and N. J. Beaber, THIS JOURNAL, **47**, 1449 (1925).
(30) French Patent 789,947 (1935); *Chem. Z.*, **107**, I, 1504 (1936).
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[CONTRIBUTION FROM DEFENCE RESEARCH CHEMICAL LABORATORIES]

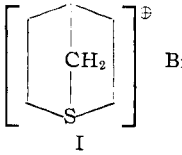
Some Derivatives of Bicyclo[2,2,1]heptane-1-thionium Bromide[1]

BY W. F. COCKBURN AND A. F. MCKAY[1a]

RECEIVED FEBRUARY 12, 1954

7-Hydroxymethylbicyclo(2,2,1)heptane-1-thionium bromide, and 7-ethylbicyclo(2,2,1)heptane-1-thionium chloride, bromide and nitrate were synthesized and tested for biological activity.

As part of a study of the synthesis of bicyclic ring systems, Prelog has described two such molecules in which one of the bridghead atoms is sulfur[2,3] (I and II). In view of the unusual nature of these compounds, it was of interest to attempt to introduce substituents into this type of molecule, preferably close to the sulfur atom. Such an alteration in



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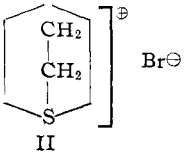

II

structure might be expected to affect the biological properties.

Tetrahydrothiapyran-4-carboxylic acid (III)[2,4]

(1) Issued as DRCL Report No. 147.
(1a) Monsanto Canada Limited, Ville La Salle, Quebec.
(2) V. Prelog and E. Cerkovnikov, *Ann.*, **537**, 214 (1939).
(3) V. Prelog and D. Kohlbach, *Ber.*, **72B**, 672 (1939).
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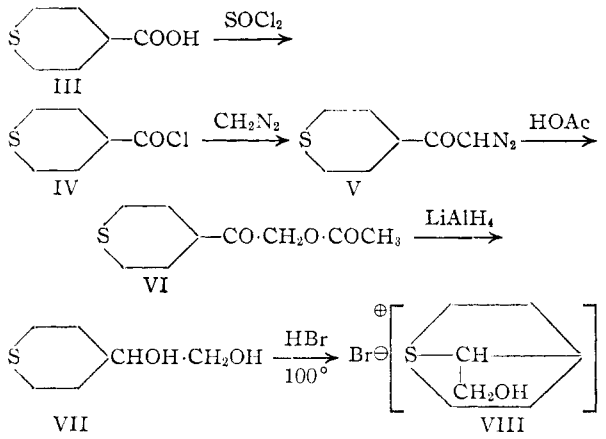
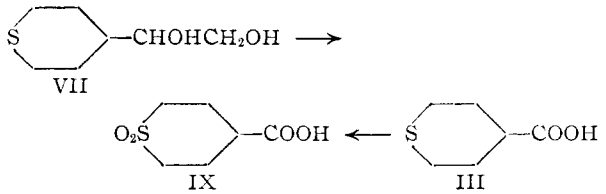
was the starting material for these syntheses. 7-Hydroxymethylbicyclo(2,2,1)heptane - 1 - thionium bromide was prepared by

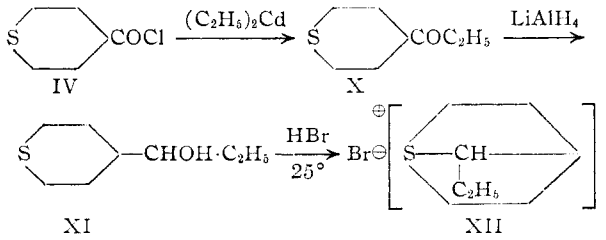


The structure of the glycol VII was verified by analysis, and by the presence of a strong hydroxyl band in its infrared spectrum. For further confirmation, it was oxidized with potassium permanganate to 1,1-dioxytetrahydrothiapyran-4-carboxylic acid (IX), which was also obtained by the oxidation of tetrahydrothiapyran-4-carboxylic acid (III).



The structure of the sulfonium salt VIII is assumed by analogy with the work of Prelog, who found that a five-membered ring formed much more readily than the corresponding six-membered ring. In addition, replacement of the secondary hydroxyl group with bromine, by the hydrobromic acid, would be much more rapid than replacement of the primary hydroxyl. The alternative structure, involving a two-carbon bridge and a secondary hydroxyl group, is not completely excluded, however.

7-Ethylbicyclo(2,2,1)heptane-1-thionium halide was synthesized in the manner



The sulfonium nitrate was formed from the bromide by treatment with aqueous silver nitrate, thus confirming the ionic nature of the bromine atom.

Approximate values of the LD 50 for both these compounds were obtained by intraperitoneal injection of an aqueous solution into white mice, from three to eight mice being used at each dosage level. Survival for 24 hours was taken as evidence of a non-lethal dose. The results of these tests indicated a toxicity for 7-hydroxymethylbicyclo(2,2,1)-heptane-1-thionium bromide (VIII) of about 35 mg./kg., or slightly less than one-tenth the toxicity of the unsubstituted parent compound I.[2] This result is what would be expected with a weakly electron-attracting group such as hydroxymethyl, if the physiological action is due to dissociation at the sulfur atom.[5] The results with the 7-ethyl compounds were less conclusive, however, since no significant increase in toxicity over compound I was observed. This may be due to the weakness of the electron-releasing tendency of the ethyl group. The nitrate was found to be slightly less toxic than either the chloride or the bromide.

Acknowledgments.—The authors are indebted to Dr. C. E. Hubley for the measurement of the infrared spectra reported, and to Dr. M. Chaput for the biological testing. Thanks are also due to Mr. R. L. Benness, for skillful technical assistance.

Experimental[6]

Tetrahydrothiapyran-4-carboxylic Acid.[2,4]—This substance was prepared by a seven-step process from bis-(β-chloroethyl) ether and malonic ester, m.p. 109–112°, overall yield 9%.

Tetrahydrothiapyran-4-carboxylic Acid Chloride.[2]—The above acid was treated with a slight excess of purified thionyl chloride at room temperature. After the initial effervescence had subsided (about 30 minutes) the product was distilled *in vacuo*, b.p. 100–101° (10 mm.), yield 97%. A small sample of the acid chloride, on treatment with concentrated ammonia, yielded the acid amide, m.p. 190.5–191°. Prelog reports a m.p. of 184.5° for this substance.

4-Propionyltetrahydrothiapyran.—Ethylmagnesium bromide was prepared from 2.1 g. (0.086 atom) of magnesium and 10.5 g. (0.096 mole) of ethyl bromide. The ether solution was cooled in ice, and 8.25 g. (0.045 mole) of anhydrous cadmium chloride added with stirring. After 15 minutes, a further 0.5 g. of cadmium chloride was added, making a total of 8.75 g. (0.048 mole). The mixture was stirred for 15 minutes longer, and 9.45 g. (0.057 mole) of tetrahydrothiapyran-4-carboxylic acid chloride in 20 ml. of anhydrous ether added dropwise. The mixture was refluxed for 40 minutes, when a grey spongy mass suddenly separated. Cracked ice was then added cautiously to hydrolyze the complex, and the reaction was worked up in the usual way. The product was an evil-smelling oil, b.p. 115° (9 mm.), $n^{25}D$ 1.5046.

Anal. Calcd. for $C_8H_{14}OS$: C, 60.70; H, 8.91; S, 20.26. Found: C, 60.40; H, 8.98; S, 20.17.

The infrared spectrum was measured as a liquid film, and was found to exhibit a strong peak at 1700 cm.$^{-1}$ due to the carbonyl group; yield 83%.

The 2,4-dinitrophenylhydrazone was prepared, and crystallized from ethanol in golden-orange flakes, m.p. 133–136°.

Anal. Calcd. for $C_{14}H_{18}O_4N_4S$: C, 49.69; H, 5.36; N, 16.56. Found: C, 50.02; H, 5.52; N, 16.96.

1-(Tetrahydrothiapyran-4)-1-propanol.—4-Propionyltetrahydrothiapyran in ten times its own volume of anhydrous ether was added gradually to an ether slurry of lithium aluminum hydride (large excess), and the mixture refluxed with stirring for one hour. The product was worked up in the usual manner, being obtained by vacuum-distillation as a very viscous oil, b.p. 123–124° (8 mm.), $n^{25}D$ 1.5177.

(5) M. A. Stahmann, J. S. Fruton and M. Bergmann, *J. Org. Chem.*, **11**, 704 (1946), have ascribed the physiological action of some sulfonium salts prepared by them, in part at least, to an unstable sulfonium sulfur atom, which dissociates with the formation of an active alkylating agent. Since such a dissociation would leave the bonding electrons with the sulfur atom, any substituent which tends to draw these electrons closer to the α-carbon atom might be expected to inhibit the dissociation, while an electron-releasing group should facilitate it.

(6) All melting points are corrected, unless otherwise stated. Microanalyses are by C. W. Beazley, Skokie, Ill. The molecular weight of 7-ethylbicyclo(2,2,1)heptane-1-thionium bromide was determined by the Huffmann Microanalytical Laboratories of Wheatridge, Col.

Anal. Calcd. for $C_8H_{16}OS$: C, 59.95; H, 10.07; S, 20.01. Found: C, 59.38; H, 10.00; S, 19.93.

The infrared spectrum was measured as a liquid film, and exhibited a band at 3400 cm.$^{-1}$ due to the hydroxyl group, and no peaks in the carbonyl region; yield 94%.

1-(Tetrahydrothiapyran-4)-ethane-1,2-diol.[7-9] **(i) Preparation of the Diazoketone.**—To a solution of 0.1 mole of diazomethane in ether[10] was added 5.43 g. (0.033 mole) of tetrahydrothiapyran-4-carboxylic acid chloride, during the course of 15 minutes. The solution was stirred at room temperature for 35 minutes, and evaporated to dryness under reduced pressure, the temperature being kept below 30°. The residue, weighing 5.75 g., consisted mostly of crystalline diazoketone, although a faint smell of the acid chloride was still detectable.

(ii) Conversion to the Acetoxymethyl Ketone.—Glacial acetic acid (30 ml.) was heated to 60°, and the diazoketone added portionwise over 15 minutes, causing a mild effervescence. The solution was maintained at 60–70° for one hour, after which 0.003 mole of potassium acetate was added to react with any chloroketone present, and the solution refluxed for 30 minutes. After cooling, the reaction was allowed to stand at room temperature for two hours, then poured into 400 ml. of ether and left in the ice-box overnight. The ether was extracted with water (150 ml.) and 10% sodium hydroxide (2 × 150 ml.) to remove acetic acid. The combined aqueous extracts were re-extracted with ether (2 × 50 ml.) and this ether added to the main ether extract. The combined ether solutions were dried with potassium carbonate, and concentrated to 150 ml. In previous runs, it was found that complete removal of the ether caused partial decomposition of the acetoxymethylketone, with the formation of a red tar.

(iii) Reduction to the Glycol.—The ether solution containing the acetoxymethyl ketone was added during the course of 20 minutes with stirring, to a slurry of 3 g. (0.08 mole) of lithium aluminum hydride in 100 ml. of anhydrous ether, and the mixture refluxed for 75 minutes. The excess reagent was decomposed by the cautious addition of sufficient water to form solid lithium aluminate, and the ether solution filtered.

The lithium aluminate was dissolved in 10% sodium hydroxide and the solution extracted overnight with ether, on a liquid–liquid extractor. The combined ether extracts were dried with potassium carbonate, and concentrated to an oil. This oil was found to be difficult to purify. It was worked up by a combination of vacuum-distillation in a Späth bulb (b.p. 130–140° (0.5 mm.)) and crystallization from a few ml. of benzene–petroleum ether, with careful reworking of all mother liquors. Chromatography on alumina was found to be relatively ineffective as a means of purification. The product was obtained as small, colorless, flaky crystals, m.p. 71.5–72°.

Anal. Calcd. for $C_7H_{14}O_2S$: C, 51.82; H, 8.70; S, 19.76. Found: C, 52.05; H, 8.94; S, 19.85.

The infrared spectrum (Nujol mull) showed a peak at 3120 cm.$^{-1}$ due to the hydroxyl groups; total yield of purified glycol was 2.75 g. (50%).

Oxidation of Tetrahydrothiapyran-4-carboxylic Acid.—Aqueous potassium permanganate (1 g./100 ml.) was added from a buret to a stirred aqueous solution of tetrahydrothiapyran-4-carboxylic acid. A permanent pink color was obtained after the addition of a volume corresponding to two atoms of oxygen. The precipitated manganese dioxide was removed by filtration, the filtrate was made slightly alkaline by the addition of sodium hydroxide solution and extracted twice with an equal volume of ether. The aqueous solution was then acidified with dilute sulfuric acid, and extracted overnight with ether on a continuous liquid–liquid extractor. The ether extract was dried with sodium sulfate, the ether removed by distillation, and the semi-crystalline residue dried in a desiccator. The oily part was then removed by washing with a few ml. of ether–ligroin (50% by vol.) and the solid residue recrystallized by dissolving it in a few ml. of acetone, and adding 70–80° petroleum ether till a faint turbidity was produced. The product was a colorless crystalline solid which melted at 195–196°, with hazing at 190°, when inserted in the melting point block at 175°. When heated from room temperature, the m.p. was 192–193°.

Anal. Calcd. for $C_6H_{10}O_4S$: C, 40.43; H, 5.66; S, 17.99. Found: C, 40.87; H, 5.60; S, 17.46.

Oxidation of 1-(Tetrahydrothiapyran-4)-ethane-1,2-diol.—This compound was oxidized according to the above procedure, and found to consume approximately five atoms of oxygen. Treatment with charcoal was found to be necessary in order to obtain colorless material. The m.p. of the product was 191–194°. This was raised to 194–196° by admixture with 1,1-dioxytetrahydrothiapyran-4-carboxylic acid (m.p. 195–196°) obtained by the oxidation of tetrahydrothiapyran-4-carboxylic acid.

7-Hydroxymethylbicyclo(2,2,1)heptane-1-thionium Bromide.—A solution containing 0.3 g. of 1-(tetrahydrothiapyran-4)-ethane-1,2-diol in 5 ml. of 40% hydrobromic acid was heated in a sealed tube at 100° for 24 hours. The brown liquid so obtained was extracted with benzene (3 × 10 ml.) and with ether (3 × 10 ml.) to remove excess glycol, but neither extract was found to contain an appreciable amount of material. The aqueous solution was evaporated under reduced pressure at 50°, and the residue dried overnight in a vacuum desiccator. The semi-solid mass was dissolved in 10 ml. of ethanol, boiled with charcoal and filtered. The ethanol solution was concentrated to 3 ml. and the product precipitated by the dropwise addition of acetone, giving 0.2 g. of needles, m.p. 206–210° (sealed tube). Two further recrystallizations from 5 ml. of alcohol–acetone (50% by vol.) raised the m.p. to 218°, if the sample were inserted in the bath at 200° with rapid heating. The m.p. was difficult to reproduce, however, and depended on the rate of heating, and temperature of insertion. This compound was very hygroscopic; yield of material of m.p. 206–210° was 50%.

Anal. Calcd. for $C_7H_{13}BrOS$: C, 37.34; H, 5.82; S, 14.24. Found: C, 37.84; H, 6.06; S, 14.31.

7-Ethylbicyclo(2,2,1)heptane-1-thionium Halides.—A solution containing 2 g. of 1-(tetrahydrothiapyran-4)-1-propanol in 40 ml. of 40% hydrobromic acid was left at room temperature for eight days. The reaction mixture was extracted with benzene (25 ml.) and the aqueous solution concentrated under reduced pressure, below 50°, to a viscous oil. After drying several days in a vacuum desiccator, this residue was dissolved in 2 ml. of hot ethanol, ether was added to turbidity (3 ml.) and the mixture allowed to crystallize slowly. Two crops of long needles were obtained, m.p. 189–190° (sealed tube), yield 42%. This m.p. depended on the rate of heating and temperature of insertion in the bath. The product was hygroscopic, and was handled in a dry-box.

Anal. Calcd. for $C_8H_{15}BrS$: C, 43.04; H, 6.77; S, 14.36; Br, 35.81. Found: C, 42.87; H, 6.94; S, 14.47; Br, 36.15.

The molecular weight of the bromide was determined by the ebullioscopic method as 128, water being employed as the solvent. Since the molecule consists of two ions, this corresponds to an actual value of 256, as compared with the calculated value of 223. This slightly high figure may be due to the hygroscopic nature of the compound.

The chloride was obtained by a similar procedure employing concentrated hydrochloric acid. The product was more hygroscopic than the bromide; colorless platelets, m.p. 161–162° (sealed tube), yield 20%.

Anal. Calcd. for $C_8H_{15}ClS$: C, 53.75; H, 8.46. Found: C, 53.04; H, 8.86.

The nitrate was obtained from the bromide by treatment with aqueous silver nitrate. The product was extremely hygroscopic, and was obtained as fine needles, m.p. 136–137° (sealed tube).

Anal. Calcd. for $C_8H_{15}NO_3S$: C, 46.80; H, 7.36; S, 15.63. Found: C, 47.05; H, 7.17; S, 15.94.

OTTAWA, ONTARIO, CANADA

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