

208. Syntheses in the Thiopyran Series. Part I. Tetrahydro-derivatives.

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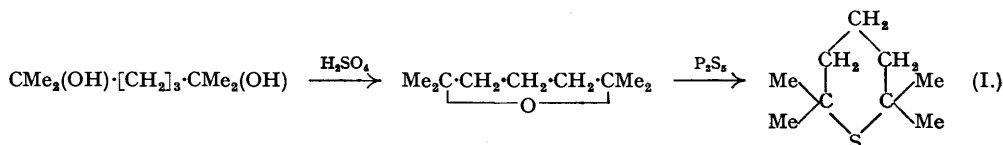
Reaction of a 1:5-dibromo-compound with sodium sulphide is not applicable to the synthesis of those members of the tetrahydrothiopyran series which contain tertiary carbon atoms in the 2- and the 6-position. In such cases it is possible to achieve the synthesis by cyclisation of the appropriate 2:6-diol to give the corresponding tetrahydropyran, followed by reaction of the latter with phosphorus pentasulphide. By this method 2:2:6:6-tetramethyl- and 2:2:6-trimethyl-6-ethyl-tetrahydrothiopyran have been prepared.

RECORDED investigation of compounds of the tetrahydrothiopyran series has been limited to two of the simplest members, pentamethylene sulphide and 1-methylpentamethylene sulphide, which have been readily obtained by reaction of the appropriate dihalide with sodium sulphide (Clarke, *J.*, 1912, 101, 1805; v. Braun, *Chem. Zentr.*, 1909, II, 1994; Grischkewitsch-Trochimowski, *Chem. Zentr.*, 1923, I, 1503). A few of the corresponding saturated thiopyrones have been prepared either by addition of hydrogen sulphide to a keto-diene or by cyclisation of a suitable aliphatic sulphide (Arndt and co-workers, *Ber.*, 1925, 58, 1633; 1930, 63, 313, 2393; Bennett and Scora, *J.*, 1927, 194), but otherwise no work has been recorded on this class of compound.

Although pentamethylene bromide reacts fairly readily with sodium sulphide, the yields of tetrahydrothiopyran are less than those reported to be obtainable with the chloride. This is in accord with the work of Bost and Conn (*Oil and Gas J.*, 1933, 32, No. 3, 17), who obtained only 30% of 2-methyltetrahydrothiopyran from 1:5-dibromohexane. In the present work it was desired to prepare tetra-substituted 2:6-derivatives, and to this end 2:6-dibromo-2:6-dimethylheptane was synthesised from ethyl glutarate:



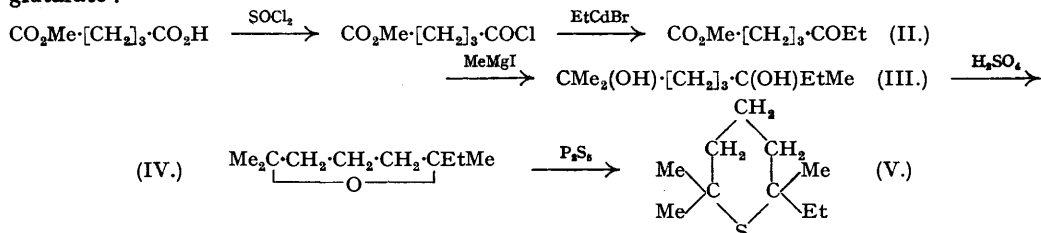
On trial, however, the lability of the bromine attached to the tertiary carbon atoms proved to be such that reaction of the bromide with sodium sulphide in alcoholic solution resulted only in the replacement of Br by OEt, and the corresponding reaction without a solvent resulted in loss of hydrogen bromide with formation of monobromodimethylheptenes and geraniolene (C_9H_{16}). This failure necessitated recourse to the less attractive method presented by conversion of a suitable pyran into the sulphur analogue. 2:6-Dimethylheptane-2:6-diol had already been observed to cyclise when it was heated in the presence of mineral acid, so giving 2:2:6:6-tetramethyltetrahydropyran* (Bruylants, *Rec. Trav. chim.*, 1910, 29, 130). This pyran was found to give a small yield of the desired 2:2:6:6-tetramethyltetrahydrothiopyran (I) when it was heated with phosphorus pentasulphide. The reaction, however, was complex, giving accompanying (resinous) products, which were not investigated.



Synthesis of unsymmetrical members of the thiopyran series presented greater difficulty, but since the essential oxide-sulphide conversion must remain the same in view of the presence of tertiary groupings, the only concern was the building up of the required carbon

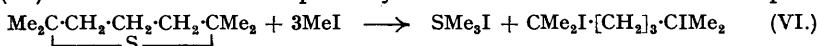
* It is to be noted that no isomerisation involving shift of the $\cdot\text{OH}$ groups, such as has been observed by Franke and Gomolka (*Monatsh.*, 1929, 56, 331) in the case of $\alpha\omega$ -diols, $\text{CH}_2(\text{OH})\cdot[\text{CH}_2]_n\cdot\text{CH}_2\cdot\text{OH}$, is possible in this dehydration, owing to the tertiary nature of the hydroxylated carbon atom: if water is eliminated with the formation of a double bond, the Markownikow rule will ensure that any re-addition of water will give the original alcohol $[\cdot\text{CH}_2\cdot\text{C}(\text{OH})\text{Me}_2 \xrightarrow{-\text{H}_2\text{O}} \cdot\text{CH}:\text{CMe}_2 \xrightarrow{+\text{H}_2\text{O}} \cdot\text{CH}_2\cdot\text{C}(\text{OH})\text{Me}_2]$. In consequence only six-membered rings can arise. The six-membered nature of the subsequent thiopyran rings has been confirmed by the identity of their infra-red spectra with those of necessarily six-membered cyclic sulphides derived from hydrogen sulphide addition to di-isoprenes (Sutherland and Sheppard, in the press; Naylor, in the press).

framework. This was accomplished by the following steps, starting from methyl hydrogen glutarate :



Clutterbuck and Raper (*Biochem. J.*, 1925, 19, 393) report the preparation of methyl δ -ketoheptanoate (II) by reaction of ethylzinc iodide with the half-ester half-acid chloride of glutaric acid, but do not record yield. In the present work the zinc alkyl was replaced by ethylcadmium bromide, which reacted with the acid chloride group while leaving the ester group untouched, and a satisfactory yield (58%) of the δ -keto-ester (II) was isolated. By reaction with 3 mols. of methylmagnesium iodide (II) was converted into 2 : 6-dimethyloctane-2 : 6-diol (III), which condensed in the presence of warm dilute acid to 2 : 2 : 6-trimethyl-6-ethyl-tetrahydropyran (IV). The final stage was treatment of (IV) with phosphorus pentasulphide to yield 2 : 2 : 6-trimethyl-6-ethyltetrahydrothiopyran (V).

The tetrahydrothiopyrans are quite stable towards acids and alkalis, but oxidise slowly in air. They unite with methyl iodide in the cold, but the resulting methiodides often separate as oils, which are difficult to crystallise. The rings of the sulphides (I) and (V) open when the compounds are heated with methyl iodide, the sulphur being removed as trimethylsulphonium iodide. This behaviour is in contrast to the stability of cyclic sulphides, containing primary α -carbon atoms, and is interesting in comparison with the formation of trimethylsulphonium iodide by the action of methyl iodide at 15° on compounds containing the diallylic sulphide grouping, $\cdot\text{CH}_2\text{CH}\cdot\text{CH}_2\cdot\text{S}\cdot\text{CH}_2\cdot\text{CH}\cdot\text{CH}_2\cdot$ (Selker and Kemp, *Ind. Eng. Chem.*, 1944, 36, 17). The di-iodide (VI) was not isolated and is probably too unstable to be obtained in the pure state.



EXPERIMENTAL.

(Microanalyses were carried out by Dr. W. T. Chambers, Miss H. Rhodes, and Miss E. Farquhar.)

Pentamethylene Sulphide.—Pentamethylene bromide was prepared from piperidine by the method described in *Organic Syntheses*, Coll. Vol. I, pp. 93, 419. A solution of the bromide (40 g.) and anhydrous sodium sulphide (50 g.) in ethanol (250 ml.) was refluxed for 3 hours. After addition of excess of water the product was extracted with ether and twice distilled. Pentamethylene sulphide (6 g., 34%) was obtained as a liquid, b. p. 140°/756 mm., n_D^{20} 1.5055 (Found : C, 59.0; H, 10.0; S, 31.3. Calc. for $\text{C}_5\text{H}_{10}\text{S}$: C, 58.9; H, 9.8; S, 31.4%).

Synthesis of 2 : 2 : 6-Tetramethyltetrahydrothiopyran (I).—(a) *Action of sodium sulphide on 2 : 6-dibromo-2 : 6-dimethylheptane.* Magnesium (4.5 g.) under ether was dissolved in a solution of methyl iodide (270 g.) in ether (350 ml.), and to the cooled solution of methylmagnesium iodide was introduced with stirring ethyl glutarate (64 g.) in ether (75 ml.). When the reaction moderated, the solution was refluxed for 1 hour, left overnight, and then poured slowly into aqueous ammonium chloride (200 g. in 700 ml.) containing crushed ice (2000 g.). 2 : 6-Dimethylheptane-2 : 6-diol was extracted with ether both before and after concentration of the aqueous solution, and was obtained from this extract as the monohydrate (30 g.) which was distilled at 85°/1 mm. to give the anhydrous alcohol (21 g.), m. p. 76°. Dry hydrogen bromide was bubbled through an ethereal solution of the alcohol at 0°; after neutralisation of excess acid with sodium hydrogen carbonate, 2 : 6-dibromo-2 : 6-dimethylheptane crystallised out in white needles, m. p. 34° (Found : C, 38.1; H, 6.4. Calc. for $\text{C}_9\text{H}_{18}\text{Br}_2$: C, 37.8; H, 6.3%). The dibromide lost hydrogen bromide very readily, even at room temperature, under reduced pressure. A solution of sodium sulphide (20 g.) and the dibromide (5 g.) in ethanol (50 ml.) was refluxed for 2½ hours, then diluted with water and ether extracted. The extract contained geraniolene (b. p. 40°/13 mm.) and impure 2 : 6-diethoxy-2 : 6-dimethylheptane (b. p. 70°/13 mm.; n_D^{20} 1.4452), but no sulphur-containing compounds. By heating together the dibromide (5 g.) and dry powdered sodium sulphide (25 g.) for 5 hours at 100–110° was obtained a mixture of geraniolene (b. p. 38°/12 mm.), impure bromo-2 : 6-dimethylheptane (b. p. ca. 50°/1 mm.; n_D^{20} 1.4748), and unchanged dibromide (b. p. 72°/1 mm.; m. p. 24°).

(b) *Action of phosphorus pentasulphide on 2 : 2 : 6-tetramethyltetrahydropyran.* 2 : 6-Dimethylheptane-2 : 6-diol (15 g.), prepared as above, was shaken with 2N-sulphuric acid at 100° for 3 hours; the product contained unchanged diol, geraniolene, and 2 : 2 : 6-tetramethyltetrahydropyran, b. p. 48°/1 mm. The last (7 g.) was sealed with phosphorus pentasulphide (24 g.) in a nitrogen-filled Carius tube, and heated for 6 hours at 110–120°. The product was extracted with aqueous alkali, dried over potassium carbonate, and distilled. After redistillation 2 : 2 : 6-tetramethyltetrahydrothiopyran (I) (2 g.) was obtained as a colourless liquid, b. p. 66°/12 mm., n_D^{20} 1.4763 (Found : C, 68.3; H, 11.6; S, 20.1. $\text{C}_{10}\text{H}_{20}\text{S}$ requires C, 68.4; H, 11.4; S, 20.2%). On standing for 1–3 days at 0° with twice its

own volume of methyl iodide, the product yielded white crystals of a *methiodide*, which recrystallised from ethanol-petrol (b. p. 60–80°) on cooling below –20°; m. p. 130° (decomposition occurred from 130° to 150°) (Found: I, 40.8. $C_{11}H_{23}IS$ requires I, 40.5%). Reaction with excess of methyl iodide for 16 hours at 100° gave crystals, which after being washed with a little methanol and recrystallised from ethanol (absolute) yielded needles of trimethylsulphonium iodide, decomp. ca. 200° (Found: I, 61.8; S, 15.5. Calc. for C_9H_9IS : I, 62.2; S, 15.7%).

Synthesis of 2:2:6-Trimethyl-6-ethyltetrahydrothiopyran (V).—Glutaric anhydride. Glutaric acid (290 g.) and acetic anhydride (400 ml.) were heated under reflux for 2 hours; the acetic acid was then distilled off, and the heating continued with a further 300 ml. of acetic anhydride. After removal of the acetic acid and anhydride, glutaric anhydride (235 g., 96%) was distilled over at 150°/10 mm. [Despite the claims of Krafft and Noerdlinger (*Ber.*, 1889, 22, 817) that glutaric acid is wholly dehydrated by refluxing alone for 2–3 hours, it was not found possible to complete the conversion into the anhydride by this method.]

Methyl hydrogen glutarate (see Clutterbuck and Raper, *loc. cit.*). Glutaric anhydride (235 g.) and methanol (132 g., 2 mols.) were refluxed for 1 hour, and the product, after removal of methanol, was distilled at 10 mm. The distillate consisted of methyl glutarate, methyl hydrogen glutarate, and some glutaric acid. The first and the last fraction were combined with glutaric acid extracted from the residue, and were reconverted into glutaric anhydride (*via* the acid) and re-esterified with methanol. The overall yield of methyl hydrogen glutarate was 240 g. (80%), b. p. 147–151°/10 mm., n_D^{20} 1.4372.

Glutaric acid half ester half chloride. A mixture of the acid ester (240 g.) and thionyl chloride (720 g.) was warmed until gas evolution started, and then very gently for one hour and refluxed for a further hour. After removal of excess thionyl chloride, the product (258 g., 97%) distilled at 98°/10 mm.

Methyl δ -Ketoheptoate (II).—An ethereal solution of ethylmagnesium bromide was prepared from magnesium (42 g.) and ethyl bromide (188 g.). Powdered cadmium chloride (288 g.), rendered completely anhydrous by being heated for 1 hour on a sand-bath and allowed to cool in a desiccator over phosphoric oxide, was slowly added with stirring to the Grignard solution cooled in ice. When the solution set nearly solid it was necessary to add more ether and shake vigorously during the addition of the remaining chloride. The ice-bath was then removed, and the mixture stirred for 30 minutes. Absence of excess of Grignard reagent was ensured by testing with Michler's ketone.

To the solution of ethylcadmium bromide (10% excess reckoned on cadmium chloride) at 0° was slowly added with vigorous stirring the half ester half chloride (258 g.) in ether (300 ml.). When the mixture set solid more ether was introduced, and the addition was continued with constant shaking. After refluxing for 1 hour on the steam-bath, the mixture was diluted with ice, and then dilute sulphuric acid was added until the precipitate just dissolved. The ether layer was separated and was shaken successively with dilute aqueous ammonia, dilute sulphuric acid, dilute aqueous sodium hydrogen carbonate, and water. After drying over magnesium sulphate and removal of ether, the product was distilled at 104–110°/10 mm. Refractionation gave 144 g. (58%) of methyl δ -ketoheptoate, b. p. 108°/10 mm., n_D^{20} 1.4296. On standing for several days with semicarbazide hydrochloride and potassium acetate in aqueous alcohol, the ester yielded a *semicarbazone*, which recrystallised from 95% alcohol to give colourless plates, m. p. 113° (Found: C, 50.2; H, 7.9; N, 19.6. $C_9H_{11}O_3N_3$ requires C, 50.2; H, 7.9; N, 19.6%).

2:6-Dimethyloctane-2:6-diol (III).—An ethereal solution of methylmagnesium iodide (3.25 mol.), prepared from magnesium (40.5 g.) and methyl iodide (236 g.), was stirred at 0° during the gradual introduction of methyl δ -ketoheptoate (70 g.) in ether (100 ml.). When addition was complete, the solution was refluxed for 4 hours and then allowed to stand over the week-end. The product was decomposed with a solution of ammonium chloride (105 g.) in water (1500 ml.) at 0°, and the ether layer was separated. The aqueous layer was evaporated down to ca. 1200 ml., and constantly extracted with ether for 40 hours. After drying, and removal of ether, the 2:6-dimethyloctane-2:6-diol from the combined extracts was distilled at 87–90°/0.1 mm. The diol (60 g., 78%) was a colourless viscous liquid, n_D^{20} 1.4563, which at 0° slowly crystallised to give an oily white solid, m. p. 25–37°, and slowly sublimed at 20°/10⁻⁵ mm. to white crystals, m. p. 47–49.5° (Found: C, 68.1; H, 12.2. $C_{10}H_{22}O_2$ requires C, 69.0; H, 12.6%).

2:2:6-Trimethyl-6-ethyltetrahydroropyran (IV).—2:6-Dimethyloctane-2:6-diol (28 g.) was vigorously stirred for 30 minutes at 100° with 2N-sulphuric acid (250 ml.). The residual oil was combined with an ether extract of the aqueous layer, and dried over potassium carbonate. After removal of ether the product (12 g., 48%) distilled over at 65–74°/0.1 mm.; dimethyloctadiene was obtained in the lower-boiling fractions (ca. 34°/1 mm.). Refractionation of the product gave 2:2:6-trimethyl-6-ethyltetrahydroropyran, a mobile, colourless, sweet-smelling liquid, b. p. 89°/10 mm., n_D^{20} 1.4508 (Found: C, 76.7; H, 12.8. $C_{10}H_{20}O$ requires C, 76.9; H, 12.8%).

2:2:6-Trimethyl-6-ethyltetrahydrothiopyran (V).—An intimate mixture of 2:2:6-trimethyltetrahydroropyran (12 g.) and phosphorus pentasulphide (35 g.) was heated for 5 hours at 100° in a Carius tube sealed under nitrogen. The solid oily residue was extracted thoroughly with ether, then decomposed by water, and the aqueous solution extracted with ether. The ethereal extract was shaken 3 times with 10% aqueous sodium hydroxide and subsequently dried over magnesium sulphate. After removal of ether, the product (3.5 g., 26%) distilled over at 40°/0.2 mm. After 2 further fractional distillations 2:2:6-trimethyl-6-ethyltetrahydrothiopyran was obtained as a mobile, colourless liquid with a characteristic odour, b. p. 87°/13 mm., n_D^{20} 1.4849 (Found: C, 69.6; H, 11.7; S, 18.6. $C_{10}H_{20}S$ requires C, 69.8; H, 11.6; S, 18.6%). When this was kept with methyl iodide at 0°, the methiodide slowly separated as a red oil, but reaction at 100° (20 hours' reaction in a tube sealed under nitrogen) gave trimethylsulphonium iodide (Found: C, 15.7; I, 61.9. Calc. for C_9H_9IS : C, 15.7; I, 62.2%).

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