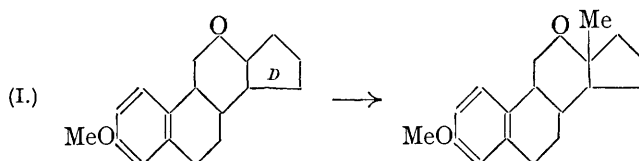


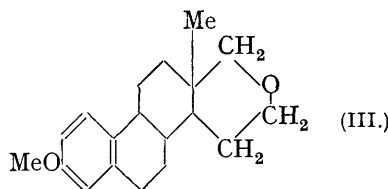
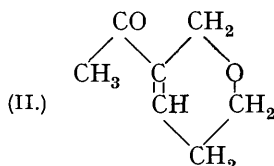
77. *Experiments on the Synthesis of Substances related to the Sterols.*  
 Part XXXIV. *Some Thiopyranophenanthrene Derivatives.*

By (Miss) N. A. MCGINNIS and SIR ROBERT ROBINSON.

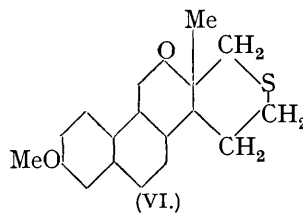
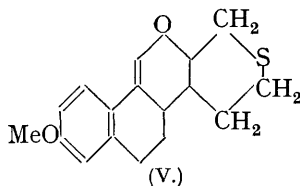
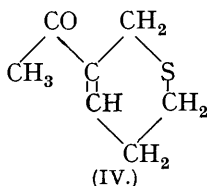
Peak and Robinson (Part XVIII, J., 1937, 1581) showed that 2-ketododecahydrochrysenes and 3-keto-7-methoxyoctahydrocyclopentenophenanthrene (I) can be methylated in the angle-position vicinal to the carbonyl group.



An extension of this method is much to be desired, because of the small number of stages in the synthesis, but this demands the retention of a point of attack in ring *D* or the devising of some equivalent of this ring which can subsequently be transformed. The ketone (I) is obtained from 1-acetylcyclopentene and if this could be replaced by 3-acetyl- $\Delta^3$ -dihydropyran (II) the object in view might be achieved by synthesis of (III), subsequent opening of the pyran ring, oxidation to a dicarboxylic acid, and finally homologation and cyclisation (cf. Litvan and Robinson, J., 1938, 1997, for the last two steps) to  $\alpha$ -oestrone methyl ether.



No method for the synthesis of (II) has yet been devised and some preliminary work on this topic is mentioned in the experimental section. Meanwhile, however, 3-acetyl- $\Delta^3$ -dihydrothiopyran (IV) has been obtained and condensed with 6-methoxy- $\alpha$ -tetralone in the presence of sodamide to 3-keto-7-methoxy-1:2:3:9:10:11:5':6'-octahydrothiopyrano(4':3':1:2)phenanthrene (V).



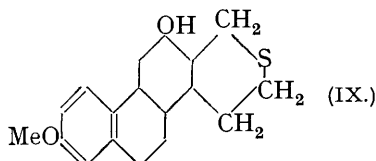
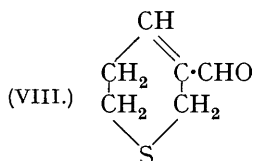
This substance has been oxidised to a *sulphone*, reduced to a saturated *sec.-alcohol*, and the latter oxidised to a saturated *ketone* and then *C*-methylated. The product by analogy with the work of Peak and Robinson (*loc. cit.*) should be (VI).

Unfortunately the work had to be abandoned at this stage, but it serves as a model that encourages perseverance in the attempt to prepare (II) or some equivalent.

WOHL and EMMERICH (*Ber.*, 1900, **33**, 2762) have prepared  $\beta$ -hydroxypropionacetal, but the yield is very unsatisfactory and many attempts to improve it have failed. Therefore the projected etherification with methyl  $\beta$ -chloroethyl ketone and subsequent ring closure could not be attempted. Various methods starting with trimethylene glycol, trimethylene bromide, and 1 : 3-dibromobutane broke down for one reason or another.

The most direct synthesis of 3-acetyl- $\Delta^3$ -dihydrothiopyran (IV) would be by the dehydration (and cyclisation) of  $\beta$ -aldehydeethyl  $\gamma$ -ketobutyl sulphide, but the reaction of a mixture of methyl  $\beta$ -chloroethyl ketone and  $\beta$ -chloropropionacetal with potassium sulphide gave no mixed sulphide but only bis- $\gamma$ -ketobutyl sulphide ( $\text{CH}_3\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2$ )<sub>2</sub>S (VII). The *semicarbazone* obtained from this specimen corresponded to the derivative of 3-acetyl-4-methyl- $\Delta^3$ -dihydrothiopyran produced by cyclic dehydration. Even the condensation of methyl  $\beta$ -chloroethyl ketone with  $\gamma\gamma$ -diethoxypropanethiol in alcoholic potassium ethoxide gave (VII), as shown by the analysis of a *bis*-2 : 4-dinitrophenylhydrazone.

A much more indirect method was therefore necessary. *Bis*- $\gamma\gamma$ -diethoxypropyl sulphide underwent hydrolysis and cyclo-dehydration on boiling with *N*-sulphuric acid with production of  $\Delta^3$ -dihydrothiopyran-3-aldehyde (VIII). This was converted into 3-( $\alpha$ -hydroxyethyl)- $\Delta^3$ -dihydrothiopyran by reaction with methylmagnesium iodide and this *sec.*-alcohol was oxidised to (IV) by an application of Oppenauer's method (*Rec. Trav. chim.*, 1937, **56**, 137).



Condensation with 6-methoxy- $\alpha$ -tetralone gave the ketone (V), of which two stereoisomerides were obtained; the isomeride-a, produced in much the larger relative amount, was demethylated to the corresponding *phenol* and oxidised to a *sulphone*. Attempts to reduce the unsaturated ketone group of this sulphide were unsuccessful, largely as a result of its sparing solubility, and the sulphide (V) itself was not amenable to catalytic reduction. It was, however, reduced to the saturated alcohol (IX) by means of sodium and *isoamyl* alcohol and (IX) was oxidised by the Oppenauer method as modified by Butenandt and Peters (*Ber.*, 1938, **71**, 2688) to a saturated *ketone*.

Following the procedure of Peak and Robinson (*loc. cit.*) the resulting *ketone* was C-methylated and though we have no fresh proof of the course of the reaction to offer, the argument from analogy that the product is (VI) is a strong one.

#### EXPERIMENTAL.

*Attempted Preparation of  $\beta$ -Hydroxypropionacetal.*— $\beta$ -Chloropropionacetal was treated with (1) fused sodium acetate in acetic acid, and refluxed for 3 hours; (2) potassium acetate and a little potassium iodide in alcohol, and refluxed for 3 hours; (3) potassium acetate in alcohol, and refluxed; (4) silver oxide in methyl alcohol, and refluxed for 13 hours; (5) calcium carbonate in water, and refluxed for 16 hours; (6) litharge in water, and refluxed for 4 hours; (7) sodium iodide in acetone, and shaken in the cold; (8) sodium iodide in alcohol, and refluxed for 5 hours; (9) magnesium oxide in water, and refluxed for 2 hours. In no case was the desired substance or a useful intermediate produced. Decomposition with the formation of acraldehydediethylacetal occurred in some cases.

By the method of Wohl and Emmerich (*loc. cit.*), but heating at 100° instead of 115°, there were obtained from 50 g. of  $\beta$ -chloropropionacetal, 3 g. of the alcohol, b. p. 90—93°/14 mm. Wohl and Emmerich (*loc. cit.*) give b. p. 98°/20 mm.

*Attempted Preparation of  $\gamma$ -Hydroxypropyl  $\gamma$ -Ketobutyl Ether and Other Intermediates.*—Trimethylene glycol (80 g.) was treated with potassium (8.6 g.) and methyl  $\beta$ -chloroethyl ketone (21.3 g.); a fraction (4.5 g.), b. p. 125—130°/10 mm., was isolated. It gave a 2 : 4-dinitrophenylhydrazone which, crystallised from pyridine, had m. p. 218—221° (Found : N, 24.7%) and has not been identified. The attempted preparations of bis- $\gamma$ -hydroxypropyl ether and the corresponding dichloride also failed. Trimethylene glycol (150 g.) was refluxed (1) under diminished pressure with *d*-camphorsulphonic acid (6 g.); (2) under diminished pressure with

*p*-toluenesulphonic acid (4 g.); (3) (53.2 g.) with dry sodium ethoxide (27.2 g.) for 2 hours, the mixture cooled, *p*-toluenesulphonyl chloride (38 g.) added slowly, and the whole heated to 170°. No product could be isolated in any case. Trimethylene chlorohydrin, heated with concentrated sulphuric acid, gave 1 : 3-dichloropropane. When it was heated with aluminium sulphate or with *p*-toluenesulphonic acid, no ether was produced.

*Bis-γ-hydroxypropyl Sulphide*.—The sulphide was prepared by the method of Bennett and Hock (J., 1925, 127, 2673). It formed a phenylurethane which crystallised from benzene in needles, m. p. 122—123°, and further crystallisation did not raise the m. p. (Found : C, 62.1; H, 6.2; N, 7.3. Calc. for C<sub>20</sub>H<sub>24</sub>O<sub>4</sub>N<sub>2</sub>S : C, 61.9; H, 6.2; N, 7.2%). Bennett and Hock (*loc. cit.*) give m. p. 146—148°.

The *diacetate* was obtained as follows : A mixture of bis-*γ*-hydroxypropyl sulphide (85 g.), acetic anhydride (350 g.), and fused sodium acetate (20 g.) was heated on a steam-bath for 3 hours. Water was then added, the mixture neutralised with sodium bicarbonate, and the liquid filtered. The product was isolated by means of ether and distilled as a clear yellow oil (105 g.), b. p. 129—234°/0.6 mm. (Found : C, 50.8; H, 7.6. C<sub>10</sub>H<sub>18</sub>O<sub>4</sub>S requires C, 51.2; H, 7.7%).

*Bis-γ-acetoxypropylsulphone*.—A solution of the sulphide (12 g.) in acetone (20 c.c.) was added to one of potassium permanganate (11 g.) in acetone (1.5 l.), and the mixture shaken in the cold for 2 days. The excess of permanganate was destroyed with a few drops of hydrogen peroxide, the solution filtered and dried, and the solvent evaporated; the residue, a pale yellow solid (12.4 g.), was crystallised from benzene-light petroleum (b. p. 80—100°); it had m. p. 53—55° (Found : C, 45.1; H, 6.8. C<sub>10</sub>H<sub>18</sub>O<sub>6</sub>S requires C, 45.1; H, 6.8%).

A solution of sodium hydroxide (4.1 g.) in water (5 c.c.) was added to the acetylated sulphone (12.4 g.) dissolved in alcohol. The mixture was refluxed for 4 hours, acidified with hydrochloric acid, and evaporated almost to dryness, and the residue taken up in acetone. After filtration, the acetone solution was dried, and the solvent removed; the residue distilled as a colourless, viscous oil, b. p. 140—142°/0.5 mm. (Found : C, 47.1; H, 8.5%). A phenylurethane, which crystallised from alcohol in needles, m. p. 123—125° (Found : C, 61.5, 61.7; H, 5.7, 5.8%), was obtained from the material. This would appear to be the above-mentioned derivative of bis-*γ*-hydroxypropyl sulphide (C<sub>8</sub>H<sub>14</sub>O<sub>2</sub>S requires C, 48.0; H, 9.3%) and it is clear that the sulphone has been largely reduced to the sulphide under the influence of the hot aqueous alcoholic alkali.

*Methyl β-Chloroethyl Ketone*.—The following modification of the method of Blaise and Maire (*Bull. Soc. chim.*, 1908, 3, 270; cf. Kenner and Statham, *Ber.*, 1936, 69, 16; E.P. 282,412) was employed. Powdered aluminium chloride (468 g.) was added with stirring to acetyl chloride (450 g.), cooled in ice and salt; dry ethylene was then passed into the mixture and the temperature was maintained at about 0°. About 67 l. of ethylene were absorbed. The product was poured on ice and extracted with chloroform, the extract dried, the solvent evaporated, and the product distilled, b. p. 50°/15 mm. (200 g.).

*Bis-γ-ketobutyl Sulphide*.—The substance was obtained incidentally in experiments made with a different object. (a) A solution of potassium hydroxide (16.1 g.) in alcohol (280 c.c.) was saturated with hydrogen sulphide during 4—5 hours. β-Chloropropionacetal (48 g.) in an equal volume of alcohol was added dropwise, and the mixture refluxed until the odour of hydrogen sulphide had disappeared. The potassium chloride was removed and more potassium hydroxide (16.1 g.) was added with stirring until all had dissolved. The mixture was then cooled in ice and salt and methyl β-chloroethyl ketone (30 g.) in alcohol (25 c.c.) was slowly added with stirring. The mixture was then refluxed for 2 hours, cooled, and filtered. The alcohol was removed under reduced pressure, water was added, and the oil which separated was collected by means of ether. The residual light brown oil had b. p. 108—114°/1—2 mm. (Found : C, 56.7; H, 8.1; S, 18.0. C<sub>8</sub>H<sub>14</sub>O<sub>2</sub>S requires C, 55.2; H, 8.1; S, 18.4%). The product formed a *semi-carbazone* which crystallised from alcohol in pale yellow needles, m. p. 227—228° (Found : C, 50.2; H, 6.5. C<sub>9</sub>H<sub>15</sub>ON<sub>3</sub>S requires C, 50.7; H, 7.0%). This is therefore the semicarbazone of an anhydro-derivative.

(b) *γγ*-Diethoxypropanethiol (8.2 g.), made by following Meyer's process for ethylene mercaptan (*Ber.*, 1886, 19, 3263), was slowly added to a solution of potassium (2 g.) in alcohol (25 c.c.). The solution was cooled in a freezing mixture and methyl β-chloroethyl ketone (3.5 g.) in alcohol (5 c.c.) was added dropwise. The mixture was kept at room temperature for 12 hours, and the product isolated in the known manner. The fraction, b. p. > 130°/1 mm., formed a *bis-2 : 4-dinitrophenylhydrazone* which crystallised from pyridine in orange prisms, m. p. 150—152° (Found : C, 45.2; H, 4.0; N, 21.9. C<sub>20</sub>H<sub>22</sub>O<sub>8</sub>N<sub>8</sub>S requires C, 44.9; H, 4.1; N, 21.0%).

*Bis- $\gamma$ -diethoxypropyl Sulphide*.—A solution of  $\beta$ -chloropropionacetal (54 g.) in alcohol (100 c.c.) was mixed with a saturated aqueous solution of potassium sulphide (66 g.) and enough alcohol to give a clear solution. The mixture was heated in an autoclave at 130° for 12 hours, and the *product* isolated as a clear yellow oil (34 g.), b. p. 130—132°/0.27 mm. (Found: C, 57.4; H, 10.3.  $C_{14}H_{30}O_4S$  requires C, 57.1; H, 10.2%).

$\Delta^3$ -*Dihydrothiopyran-3-aldehyde* (VIII).—The above acetal (98.6 g.) was refluxed with *n*-sulphuric acid (150 c.c.) for 20 minutes and the mixture was then steam-distilled. A yellow oil (35.7 g.) was isolated from the distillate by means of ether, b. p. 115—118°/12—15 mm. (Found: C, 56.6; H, 6.1.  $C_8H_{12}OS$  requires C, 56.3; H, 6.3%). The *aldehyde* formed a semicarbazone, which crystallised from acetic acid in colourless prisms, m. p. 226—228°, and a 2:4-dinitrophenylhydrazone, which crystallised from pyridine in elongated, bright orange prisms, m. p. 247—248° (Found: C, 46.9; H, 4.0; N, 18.3.  $C_{12}H_{12}O_4N_4S$  requires C, 46.8; H, 3.9; N, 18.2%).

3- $\alpha$ -*Hydroxyethyl- $\Delta^3$ -dihydrothiopyran*.—Dihydrothiopyranaldehyde (28.4 g.) in a large volume of dry ether (300 c.c.) was gradually added with vigorous stirring to an ethereal solution of methylmagnesium iodide (6.3 g. of magnesium) cooled in a freezing mixture. The stirring was continued for 6 hours at room temperature; the mixture was then decomposed with ice and ammonium chloride (50 g.). The ethereal layer was separated, and the aqueous solution saturated with salt and extracted with ether. The residue (after drying and removal of the solvent) had b. p. 95—115°/4—5 mm. As the product was found to contain unchanged aldehyde, it was treated with semicarbazide, the semicarbazone collected, and the filtrate again worked up with ether and the oil distilled, b. p. 119—120°/4—5 mm. (18.5 g.) (Found: C, 58.1; H, 8.2.  $C_7H_{12}OS$  requires C, 58.3; H, 8.3%). The *alcohol* gave a positive iodoform reaction. The unchanged aldehyde was recovered from the semicarbazone by treatment with *n*-sulphuric acid and steam-distillation.

3-*Acetyl- $\Delta^3$ -dihydrothiopyran* (IV).—The *sec.*-alcohol was oxidised by the method of Oppenauer (*loc. cit.*). Hydroxyethyl-dihydrothiopyran (14 g.) in dry acetone (600 c.c.) was added to a solution of aluminium *tert.*-butoxide (48 g.) in dry benzene (800 c.c.) and heated at 60—65° for 10 hours. The mixture was acidified with dilute sulphuric acid, the benzene layer separated, and the aqueous layer extracted with ether. The benzene and ethereal solutions were washed with water, dried, and distilled, yielding a yellow oil (10.5 g.), b. p. 95—103°/1—3 mm. The product gave the iodoform reaction and formed a *semicarbazone* which crystallised from aqueous acetic acid in long prisms, m. p. 227—228° (Found: C, 48.6; H, 6.6; N, 21.1.  $C_8H_{13}ON_3S$  requires C, 48.2; H, 6.5; N, 21.1%).

3-*Keto-7-methoxy-1:2:3:9:10:11:5':6'-octahydrothiopyrano(4':3':1:2)phenanthrene-a* (V).—A mixture of powdered sodamide (3.0 g.), 6-methoxy- $\alpha$ -tetralone (13.2 g.), and dry ether (330 c.c.) was refluxed for 8 hours with stirring in a current of dry nitrogen. The mixture was cooled in a freezing mixture, and acetyldihydrothiopyran (10.5 g.) in dry ether (40 c.c.) slowly added with stirring. After 1—2 hours the cooling bath was removed, and agitation continued for 12 hours. The mixture was acidified with dilute hydrochloric acid and the crystalline material was collected, washed with water, alcohol and ether, and dried (14.0 g.). It crystallised from butyl alcohol in long, fine needles, m. p. 234—236° (Found: C, 71.9; H, 6.7; S, 10.8.  $C_{18}H_{20}O_2S$  requires C, 72.0; H, 6.7; S, 10.7%). The *ketone* is sparingly soluble in alcohol and ethyl acetate, more readily soluble in acetic acid. The 2:4-dinitrophenylhydrazone formed dark red prisms, m. p. 268° (decomp.). A gummy residue obtained by evaporating the mother-liquors may contain isomerides. On keeping, the ethereal solution from which this main product-a had been separated deposited a white solid. This crystallised from alcohol in flocks of needles, m. p. 190—194° (Found: C, 72.0; H, 6.6.  $C_{18}H_{20}O_2S$  requires C, 72.0; H, 6.7%). The *substance* contains sulphur and yields a 2:4-dinitrophenylhydrazone, orange-red needles, m. p. 250° (decomp.). It is doubtless a stereoisomeride (-b) of (V). It is much more readily soluble in ethyl and butyl alcohols and in acetic acid than the higher-melting isomeride-a. There is some indication that there may be a third still more readily soluble and lower-melting isomeride in the mother-liquors.

3-*Keto-7-hydroxy-1:2:3:9:10:11:5':6'-octahydrothiopyrano(4':3':1:2)phenanthrene*.—The methoxy-compound (2.2 g.) along with acetic acid (50 c.c.) and hydriodic acid (20 c.c., *d* 1.7) was heated (oil-bath at 130—140°) for 10 minutes; after cooling, the contents were poured into water. The liquid was decolorised by sulphur dioxide, and the reddish product collected and dried. The crude material (1.9 g.) was dissolved in hot 2% caustic soda, the solution filtered, and the filtrate acidified with hydrochloric acid. The solid crystallised from butyl alcohol in clusters of fine, very pale yellow needles which decomposed above 240° (Found:

C, 71.4; H, 6.1.  $C_{17}H_{18}O_2S$  requires C, 71.3; H, 6.3%). No coloration was developed with alcoholic ferric chloride solution.

*3-Keto-7-methoxy-1 : 2 : 3 : 9 : 10 : 11 : 5' : 6'-octahydrothiopyrano(4' : 3' : 1 : 2)phenanthrene Dioxide.*—The oxidation of the thiopyran (V) to the sulphone was accomplished by the method of Hinsberg (*Ber.*, 1910, 43, 289). Perhydrol (6 c.c. of 30%) was added to a solution of ketomethoxyoctahydrothiopyranophenanthrene-a in acetic acid (600 c.c.). After keeping at room temperature for 2 days crystals were deposited in almost theoretical yield. The sulphone crystallised from acetic acid in rhombic plates, m. p. 279—281° (Found: C, 64.8; H, 6.2.  $C_{18}H_{20}O_4S$  requires C, 65.1; H, 6.0%). The substance gave a 2 : 4-dinitrophenylhydrazone; it was very sparingly soluble in most organic solvents but dissolved to some extent in boiling acetic and formic acids, and in hot cyclohexanol.

*3-Hydroxy-7-methoxy-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12 : 5' : 6'-decahydrothiopyrano(4' : 3' : 1 : 2)phenanthrene (IX).*—Ketomethoxyoctahydrothiopyranophenanthrene-a (7.5 g.) was dissolved in boiling dry isoamyl alcohol (400 c.c.), and sodium (10.5 g.) added; the mixture was refluxed for 12 hours, cooled, and then steam-distilled. The residue was acidified with hydrochloric acid, and the product collected and dried. The crude material was triturated with cold acetic acid and crystallised from this solvent, being obtained in long prisms, m. p. 179—181° (Found: C, 70.9; H, 7.7.  $C_{18}H_{24}O_2S$  requires C, 71.1; H, 7.9%). The substance showed no ketonic reactions.

*3-Keto-7-methoxy-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12 : 5' : 6'-decahydrothiopyrano(4' : 3' : 1 : 2)phenanthrene.*—The last-described saturated alcohol (6.0 g.) in dry acetone (300 c.c.) was added to a solution of aluminium *tert.*-butoxide (18.0 g.) in dry benzene (550 c.c.), and the mixture refluxed for 24 hours. After neutralisation with dilute sulphuric acid the product was extracted with benzene, the extract dried, and the solvent removed. When the brittle residual mass was treated with alcohol, a small amount of crystalline material was obtained. The product was ketonic, but the m. p. and mixed m. p. with the starting material indicated that it was probably a mixture of the unchanged alcohol and the desired ketone. Further recrystallisation from alcohol did not effect a separation. The product was dissolved in cold pyridine, and semicarbazide hydrochloride added. A small amount of crystalline material was deposited on keeping, which crystallised from alcohol in clusters of needles, m. p. 239—241° (decomp.) (Found: C, 62.6; H, 6.5; N, 12.2.  $C_{18}H_{23}O_2N_3S$  requires C, 62.6; H, 6.7; N, 12.2%). The semicarbazone was obtained in poor yield and better results were obtained by adopting the modification of Butenandt and Peters (*loc. cit.*). A solution of aluminium isopropoxide (4.5 g.) in dry toluene (210 c.c.) was added to one of hydroxymethoxydecahydrothiopyranophenanthrene (2.8 g.) in cyclohexanone (40 c.c.). The mixture was refluxed (oil-bath) for 10 hours, cooled, neutralised with dilute sulphuric acid, and steam-distilled. The residue was extracted with benzene, the extract dried, and the benzene evaporated, leaving a reddish-brown, viscous oil which partly crystallised. The crystals (1.4 g.) were collected and recrystallised from alcohol, from which long, fine, matted needles, m. p. 192—193°, were obtained (Found: C, 71.3; H, 7.2.  $C_{18}H_{22}O_2S$  requires C, 71.5; H, 7.3%). The substance formed a 2 : 4-dinitrophenylhydrazone.

*3-Keto-7-methoxy-2-methyl-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12 : 5' : 6'-octahydrothiopyrano(4' : 3' : 1 : 2)-phenanthrene (VI).*—Methyl iodide (5 c.c.) was added to the ketomethoxydecahydrothiopyranophenanthrene (1.0 g.) dissolved in a solution of potassium (0.8 g.) in *tert.*-butyl alcohol (30 g.) and the resultant pale yellow solution was refluxed for 3 hours. Ice was added and the solid which separated was collected, dissolved in a large excess of alcohol, and slowly run through an alumina column. On concentration of the solution a white solid separated and this crystallised from alcohol in irregular plates, m. p. 156—157° (Found: C, 72.2; H, 7.6.  $C_{19}H_{24}O_2S$  requires C, 72.2; H, 7.6%). The substance gave a 2 : 4-dinitrophenylhydrazone.

At this stage the work had to be abandoned and we were unable to follow up the investigation in several desirable directions.