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SYNTHESIS OF HETEROCYCLIC STEROIDS—III*

AN UNSUCCESSFUL ATTEMPT AT THE SYNTHESIS OF B-NOR-6-THIAEQUILENIN THROUGH 3-CYANO-7-METHOXY-4-OXO-1,2,3,4-TETRAHYDRODIBENZOTHIOPHENE

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Abstract—The synthesis of 3-cyano-7-methoxy-3-methyl-4-oxo-1,2,3,4-tetrahydrodibenzothiophene is described. The latter could not be converted to B-nor-6-thiaequilenin, the thioster of equilenin since it failed to undergo Stobbe Condensation with diethyl succinate.

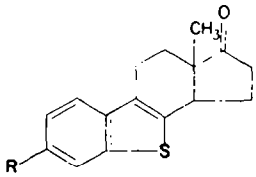
WORK is in progress on the *total* synthesis of heterocyclic steroids wherein the hetero atom forms a part of the cyclopenta-(a)-phenanthrene unit, and where the essential structural features associated with the steroidal molecules, such as the angular methyl group, the oxygen functions and the particular stereochemical pattern have been retained in the relevant positions. The steroidal alkaloids are representatives of the heterocyclic steroids, but in these cases the hetero element is not a part of the C_{17} steroidal skeleton.

The phenolic estrogenic steroids were chosen as starting materials owing to their carcinogenic activity and aromaticity which reduces the number of possible stereoisomers. The phenanthrene-bridge position in the steroids was replaced by the hetero atom by substituting the B-ring by the thiophene, furan and pyrrole rings.

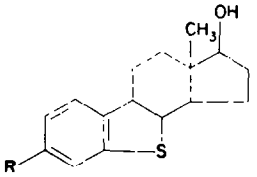
Among the sulphur containing compounds, thiapyrano steroids[1] of ambiguous structure and the total synthesis of the thiopheno analogues of 3-desoxyequilenin (I)[2,3,5] and 3-desoxyisoestradiol (II)[4] have been reported. The present paper records an unsuccessful attempt to synthesize B-nor-6-thiaequilenin (Ia). In parts IV and V of this series, the work on furano and pyrrolo steroids will be described, although preliminary reports on the synthesis of furano-steroids[6] and aza-steroids[7] have already been published.

* Part II, Reference 4.

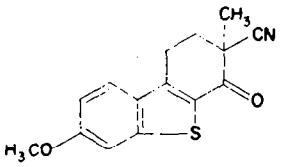
[1] I. N. Nazarov, I. A. Gurvich and A. I. Kuznetsova, *Chem. Abstr.* **47**, 7520 (1953); **49**, 2456 (1955).
[2] R. B. Mitra and B. D. Tilak, *J. Sci. Ind. Res. India* **14B**, 132 (1955).
[3] R. B. Mitra and B. D. Tilak, *J. Sci. Ind. Res. India* **15B**, 497 (1956).
[4] R. B. Mitra and B. D. Tilak, *J. Sci. Ind. Res. India* **15B**, 573 (1956).
[5] R. J. Collins and E. V. Brown, *J. Amer. Chem. Soc.* **79**, 1103 (1957). Collins and Brown have wrongly concluded that "the paper by R. B. Mitra and B. D. Tilak reaches the same conclusions as our work, except that the 154·5° melting reduction product is reported to be the thiophene analogue of 3-desoxyequilenin". We, did not report the compound m.p. 154·5°, which Collins and Brown obtained in the hydrogenation of dehydrothiaequilenin, but obtained I in two isomeric forms m.p. 90–92° and m.p. 146–148°. The two compounds gave almost identical U.V. spectra which were very similar to that of 1,2,3,4-tetrahydrodibenzothiophene, and differed markedly from the spectrum of dehydrothiaequilenin, m.p. 172·5–174°. Compound, m.p. 154·5° obtained by Collins and Brown gave a U.V. spectrum similar to that of dehydrothiaequilenin, and they concluded that the two were polymorphic forms of the same compound. Since the compound m.p. 146–148° gave a spectrum identical with I m.p. 90–92°, and very different from dehydrothiaequilenin, the compound cannot be an impure sample of that m.p. 154·5°, a conclusion which Collins and Brown's comments appear to suggest.
[6] G. V. Bhide, N. L. Tikotkar and B. D. Tilak, *Chem. & Ind.* 1319 (1957).
[7] G. V. Bhide, N. R. Pai, N. L. Tikotkar and B. D. Tilak, *Tetrahedron* **4**, 420 (1958).



I, R = H
I a, R = OH

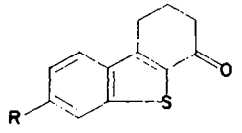


II, R = H
II a R = OH

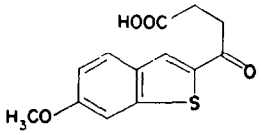


III

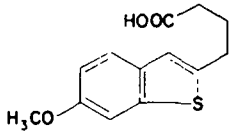
In the synthesis of the equilenin thioster (Ia) the synthesis of 7-methoxy-4-oxo-1,2,3,4-tetrahydrodibenzothiophene (IV) by succinoylation of 6-methoxythionaphthene was first attempted in view of the synthesis[8] of V from thionaphthene. As in the preparation of 6-methoxythionaphthene by cyclization of ω-dimethoxyethyl *m*-methoxyphenyl sulphide[8] a 4-substituted derivative could also be formed, it was necessary to establish the homogeneity and identity of 6-methoxythionaphthene prepared. Demethylation of the latter gave the known 6-hydroxythionaphthene[9] and no 4-hydroxythionaphthene.[10] Unlike the orientation in thionaphthene, where electrophilic substitution usually gives a mixture of 3- and 2-substituted derivatives with the former predominating, Friedel–Crafts' interaction of 6-methoxythionaphthene and β-carbomethoxypropionyl chloride gave a mixture of compounds which contained (proved later), the undesired methyl β-(6-methoxy-2-thionaphthenoyl)-propionate (VI) as the major constituent. The formation of the latter is due to the strong mesomeric effect of the methoxy group leading to higher reactivity at the 2-position. β-Methoxynaphthalene, an isoster of 6-methoxythianaphthene, also behaves similarly in Friedel–Crafts' substitutions.[11]



IV, R = OCH_3
V, R = H



VI



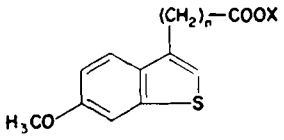
VII

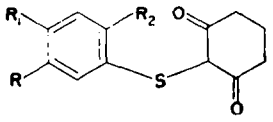
Martin–Clemmensen reduction of VI gave γ-(6-methoxy-2-thionaphthenyl)-butyric acid (VII), but from the Wolff–Kishner–Huang-Minlon reduction no pure compound could be isolated. That the succinoylation of 6-methoxythionaphthene had proceeded in the thiophene part, was proved by Raney nickel desulphurization of VI and oxidation of the resulting sulphur-free product giving *p*-anisic acid. The non-identity of VII with authentic γ-(6-methoxy-3-thionaphthenyl)-butyric acid (VIIIc described later), further showed that the succinoyl group was oriented in the 2-position as shown in VI.

The next approach to IV, was through cyclization of IXa although during the synthesis of V, unsuccessful attempts were made to cyclize IXb it was hoped that due to the strong mesomeric effect of the *para*-methoxy group, cyclization of IXa might succeed. Halogenation of *m*-methoxythiophenol led to a chlorinated derivative of

[8] A. V. Sunthanker and B. D. Tilak, *Proc. Indian Acad. Sci.* **33A**, 35 (1951).
[9] C. Hanzch and B. Schmidhalter *J. Org. Chem.* **20**, 1056 (1955).
[10] L. F. Fieser and R. G. Kennelly, *J. Amer. Chem. Soc.* **57**, 1611 (1935).
[11] P. Hill, W. F. Short and A. Higginbottom, *J. Chem. Soc.* 319 (1936).

m-methoxy-benzenesulphenyl chloride. Interaction of the latter and the sodio derivative of cyclohexane-1,3-dione gave a very small yield of an impure product which analysed for $C_{13}H_{12}O_3SCl_2$ and may be represented by IXc. Attempts to



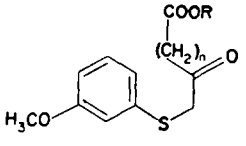


prepare the sulphenyl bromide gave similar results.

VIIIa; n = 3, X = C_2H_5 IXa; R = OCH_3, $R_1 = R_2 = H$
VIIIb; n = 2, X = H IXb; R, R_1, R_2 = H
VIIIc; n = 3, X = H IXc; R = OCH_3, $R_1 = R_2 = Cl$

Finally IV was synthesized as follows: Condensation of *m*-methoxythiophenol with ethyl 6-chloro-5-oxo-caproate (Xa) in pyridine gave ethyl 6-(*m*-methoxyphenyl-mercapto)-5-oxo-caproate (XIa). Cyclization of the latter with polyphosphoric acid gave ethyl γ-(6-methoxy-3-thionaphthenyl)-butyrate (VIIIa) which after saponification to VIIIc may by cyclized to IV.

The chloroketoester Xa was prepared by reacting γ-carboethoxybutyrl chloride[12] with diazomethane to give XIIa and passing hydrogen chloride through the ethereal solution of the diazoketone. The diazoketone synthesis and subsequent treatment with halogen acid[13] and condensation with the mercaptan[14] were carried out according to well-established procedures. Compound Xa is unstable and failed to give accurate analyses. Raney nickel desulphurization of VIIIc and oxidation of the product gave *p*-anisic acid, furnishing proof that the side chain in XIa had cyclized in the *para*-position to the methoxy group. The non-identity of VIIIc and VII obtained earlier showed that succinoylation in 6-methoxythionaphthene had occurred in the 2-position.



X—XCH_2—CO—$(CH_2)_n$—COOR
Xa; X = Cl, n = 3, R = C_2H_5
Xb; X = Cl, n = 2, R = CH_3

XIa; n = 3, R = C_2H_5
XIb; n = 2, R = CH_3

XII—N_2CH—CO—$(CH_2)_n$—COOR
XIIa; n = 3, R = C_2H_5
XIIb; n = 2, R = CH_3

Since glutaric acid required for the synthesis of XIIa is difficultly accessible and expensive, attempts were made to employ succinic acid instead extending the side

[12] W. E. Bachmann, S. Kushner and A. C. Stevenson, *J. Amer. Chem. Soc.* **64**, 974 (1942).
[13] J. Walker, *J. Chem. Soc.* 1304 (1940).
[14] J. E. Banfield, W. Davies, N. W. Gamble and S. Middleton, *J. Chem. Soc.* 4795 (1956).

chain by an Arndt–Eistert homologation. Thus β-carbomethoxy-propionyl chloride[15] was treated with diazomethane to give XIIb, which with hydrogen chloride gave Xb. Condensation of Xb with *m*-methoxythiophenol gave XIb, which was cyclized and the product saponified to give β-(6-methoxy-3-thionaphthenyl)-propionic acid (VIIIb). The yield in the Arndt–Eistert homologation of VIIIb to VIIIc was, however, poor (about 10%) and this route to VIIIc was, therefore, rejected.

Before applying Johnson's equilenin synthesis[16] (successfully employed earlier for the synthesis of the 3-desoxythioster (I) of equilenin[2,3] the Stobbe condensation of IV with diethyl succinate was studied and the desired β-carbethoxy-β-(1,2-dihydro-7-

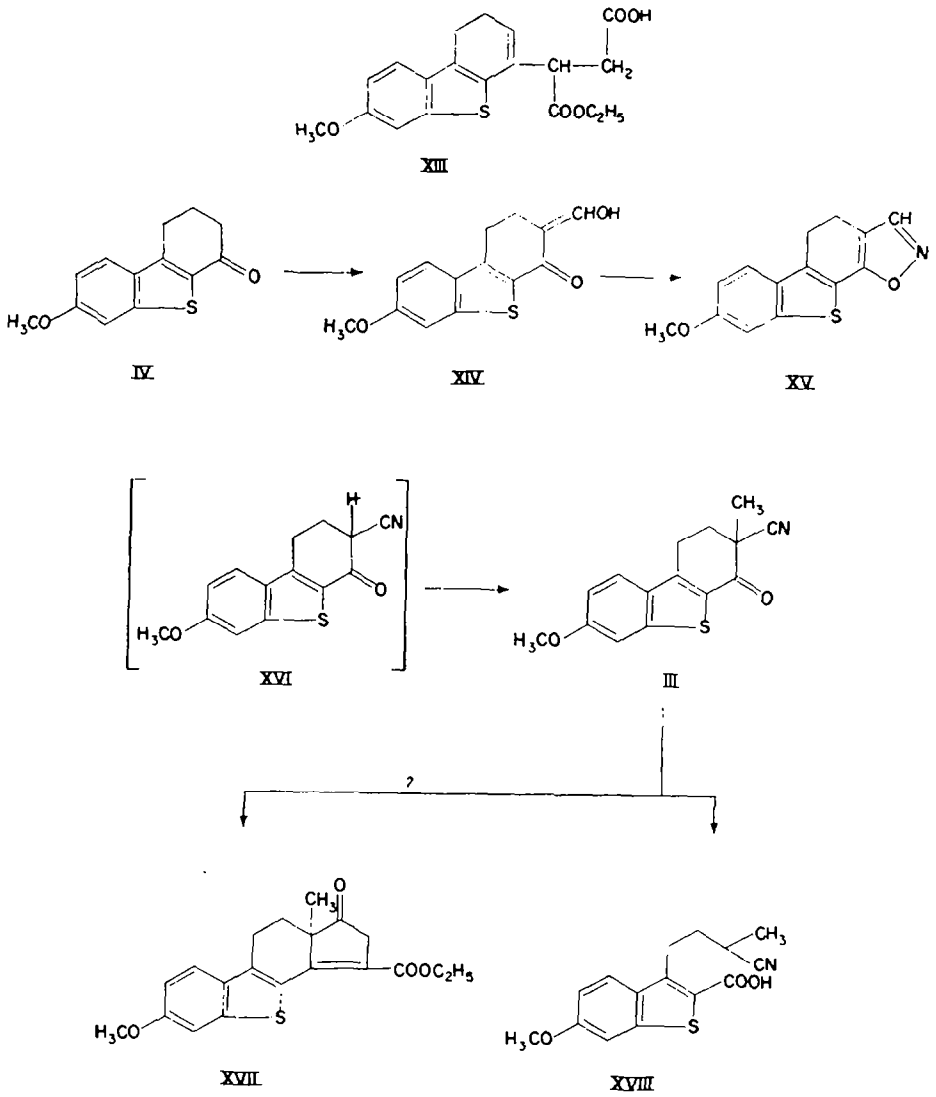


Chart I

[15] J. Cason, *Organic Synthesis* Col. Vol. III, p. 169. John Wiley, New York (1955).
[16] W. S. Johnson, J. W. Petersen and C. D. Gutsche, *J. Amer. Chem. Soc.* **69**, 2942 (1947).

methoxydibenzothiophene-4-yl)-propionic acid (XIII) obtained, though in poor yield (24%).

Compound IV was then converted to 3-cyano-7-methoxy-3-methyl-4-oxo-1,2,3,4-tetrahydrodibenzothiophene (III) as shown in the Chart I. It is not necessary to isolate 3-cyano-7-methoxy-4-oxo-1,2,3,4-tetrahydrodibenzothiophene (XVI) formed during the conversion of XV to III, although the product was isolated for characterization.

All attempts at conversion of III to XVII by Stobbe condensation with diethyl or dimethyl succinate under a variety of conditions were unsuccessful. Under the mild conditions as in the desoxy series,[2,3] the methyl-ketonitrile was recovered unchanged, whereas under more drastic conditions (eg. condensation at 70°), the alicyclic ring was cleaved with the formation of 3-(3′-cyanobutyl)-2-carboxy-6-methoxy-thionaphthene (XVIII). A similar ring-scission has been noticed by Johnson[16]. The synthesis of the equilenin thioster (Ia) though III has, therefore, to be abandoned and the synthesis from IV by the Bachmann route[17] is under way.

EXPERIMENTAL

6-Methoxythionaphthene. A modification of the method followed earlier[8] results in improved yields.

A solution of ω-dimethoxyethyl *m*-methoxyphenyl sulphide[8] (1 g) in dry chlorobenzene (15 ml) was added to a mixture of phosphorus pentoxide (3 g) and syrupy phosphoric acid (11·5 g), and the mixture heated under reflux for 3½ hr. On cooling the chlorobenzene layer was decanted and the residue extracted thrice with 10 ml of benzene, and the latter washed with 2% aqueous sodium hydroxide, then with water and dried. After removal of the solvent the 6-methoxythionaphthene (0·61 g; 85% yield) was distilled b.p. 145–155° (bath) at 15 mm. The crude product gave a *picrate*, m.p. 102–103° (reported[8] m.p. 105–106°).

In runs with larger amounts of the sulphides, the yields were slightly lower (75–80%).

Demethylation of 6-methoxythianaphthene. Demethylation of crude 6-methoxythionaphthene (0·6 g), with pyridine hydrochloride (4 g) was carried out according to the method used earlier.[8] The crude hydroxythionaphthene was obtained as a brown oil (0·3 g; 55% yield). Distillation gave a pale yellow oil (0·26 g), b.p. 180–185° (bath)/13 mm which crystallized into long needles, 100–102°. Purification from a mixture of benzene and pet ether gave *6-hydroxythionaphthene* as colourless needles, m.p. 102–103° (lit[8] 102–102·5°). (Found: C, 63·8; H, 4·4; C_8H_6OS requires: C, 64·0; H, 4·0%). No 4-hydroxythionaphthene could be traced in the above reaction.

Methyl β-(6-methoxy-2-thionaphthenoyl)-propionate (VI). A solution of freshly distilled anhydrous stannic chloride (1·7 ml) in dry thiophene-free benzene (10 ml) was gradually added at 0–5° during 40 min to a stirred mixture of 6-methoxythionaphthene (1·85 g), β-carbomethoxypropionyl chloride[15] (1·7 g), and dry thiophene-free benzene (10 ml). The temp maintained at 0–5° for another 30 min and then allowed to 30° during 1 hr. The reaction mixture was stirred further for 1½ hr at room temp and then poured into a mixture of crushed ice and dil HCl. The orange-coloured benzene layer (washed with 2% aqueous NaOH, and water) left a residue which on crystallization from ether gave VI as small needles (1·12 g; 36% yield), m.p. 92–95°. Two recrystallizations from isopropyl ether gave VI as fine colourless needles, m.p. 96–97·5°. (Found: C, 60·5; H, 5·2; S, 11·2. $C_{14}H_{14}O_4S$ requires: C, 60·4; H, 5·0; S, 11·5%).

Raney nickel desulphurization of VI *and oxidation of the desulphurized product.* A mixture of VI (0·2 g), Raney nickel (2·5 g) and ethanol (30 ml) was refluxed under stirring for 6½ hr. After removal of nickel by filtration, alcohol was removed and the oily residue (negative sulphur test) heated with 5% aqueous HNO_3 (10 ml) in a sealed tube at 150–180° for 12 hr. On cooling, *p*-anisic acid, m.p. 185°, separated.

γ-(6-Methoxy-2-thionaphthenyl)-butyric acid (VII). A mixture of mossy zinc (1 g), mercuric chloride (0·1 g), conc HCl (0·1 ml), and water (1·5 ml) was shaken for 5 min; the supernatant

[17] W. E. Bachmann, Wayne Cole and D. C. Wilds, *J. Amer. Chem. Soc.* **62**, 814 (1940).

solution decanted off, and the other reagents were added in the following order: Water (1 ml), conc HCl (1·75 ml), toluene (1·5 ml) and VI (0·5 g). The mixture was refluxed briskly for 36 hr, HCl (3 ml) portions being added at 6 hr intervals. The product, a dark yellow oil, was saponified by refluxing with baryta (0·5 g) in 80% aqueous ethanol (20 ml) for 1½ hr. After removal of ethanol under reduced pressure, the residue was acidified with HCl and ether-extracted. The ether solution was shaken with aqueous sodium bicarbonate solution. Acidification of the alkaline extract gave VII as a dark resinous solid. On distillation the latter gave a white crystalline solid (0·155 g), b.p. 150–160°/0·07 mm (yield, 35%) which crystallized from aqueous methanol in white flakes, m.p. 77°. (Found: C, 62·3; H, 5·3; S, 13·2. $C_{13}H_{14}O_3S$ requires: C, 62·4; H, 5·6; S, 12·8%).

2-(m-*Methoxy-dichlorophenylmercapto*)-*cyclohexane*-1,3-*dione* (IXc). The calculated amount of dry chlorine was slowly bubbled through a stirred solution of *m*-methoxythiophenol (2 g) in chloroform (30 ml) at 0° for 1 hr. After 30 min the solvent was removed and the residual oil dissolved in dry benzene (25 ml) and a mixture of cyclohexane-1,3-dione (1·6 g) and sodium methoxide (prepared from 0·33 g of sodium) added. The mixture was refluxed for 4 hr, filtered, solvents distilled off and the dark oily residue triturated with ether. After leaving in the refrigerator for several days, yellowish-white crystals separated (0·28 g, m.p. 150–155°). Repeated crystallizations from dil ethanol afforded white needles, m.p. 157°. (Found: C, 50·3; H, 3·9; Cl, 23·1. $C_{13}H_{12}O_3Cl_2S$ requires: C, 48·9; H, 3·8; Cl, 22·3%).

Repeated crystallizations failed to give a purer product.

Ethyl 6-*chloro*-5-*oxocaproate* (Xa). A solution of γ-carbethoxybutyryl chloride[12] (10·9 g) in dry ether (20 ml) was added slowly under vigorous agitation to an ethereal diazomethane solution prepared from nitrosomethyl urea (20 g) at 0–5°. After keeping for 2 hr in cold, most of the ether was removed under reduced pressure at 20–25°. Dry hydrogen chloride gas was then passed through the cooled ethereal solution of the diazoketone for 15 min. Removal of ether gave Xa as a yellow oil (10 g), b.p. 88–94°/0·5 mm (yield 84%). The compound being unstable was immediately condensed with *m*-methoxythiophenol.

Ethyl 6-(m-*methoxyphenylmercapto*)-5-*oxocaproate* (XIa). Compound Xa (11 g) was gradually added under cooling to a solution of *m*-methoxythiophenol (6 g) in pyridine (30 ml). After keeping overnight, the mixture was diluted with 1:1 aqueous HCl and extracted with ether. The ether extract gave an oil which on fractional distillation gave a pale-yellow viscous oil (7·4 g, yield 60%), b.p. 155–160°/0·0025 mm. (Found: C, 60·3; H, 6·3; S, 11·3. $C_{15}H_{20}O_4S$ requires: C, 60·8; H, 6·8; S, 10·8%).

Ethyl γ-(6-*methoxy*-3-*thionaphthenyl*)-*butyrate* (VIIIa). To polyphosphoric acid, obtained from phosphorous pentoxide (12 g) and phosphoric acid (6 ml), was added a solution of XIa (4 g) in benzene (50 ml). The mixture was heated under reflux for 3 hr. The benzene layer was decanted off and the tarry residue extracted twice with boiling benzene. Removal of benzene and distillation gave VIIIa as a pale-yellow oil (3·2 g; yield 83%), b.p. 135–140° (bath)/0·007 mm. (Found: C, 64·4; H, 6·5; S, 11·8. $C_{15}H_{18}O_3S$ requires: C, 64·8; H, 6·5; S, 11·5%).

γ-(6-*Methoxy*-3-*thionaphthenyl*)-*butyric acid* (VIIIc). Compound VIIIa (1·3 g) was hydrolysed by refluxing with baryta (2 g) in 80% ethanol (25 ml) for 1½ hr. After removal of ethanol under reduced pressure, the residue was acidified with HCl and the mixture left overnight. The white crystalline solid which separated was filtered, washed and dried (1·2 g; yield quantitative). Repeated crystallizations from benzene afforded VIIIc as white needles, m.p. 160°. (Found: C, 62·7; H, 5·7; S, 13·2. $C_{13}H_{14}O_3S$ requires: C, 62·4; H, 5·6; S, 12·8%).

Raney nickel desulphurization of VIIIc and oxidation of the desulphurized product (as described earlier for the degradation of compound VI) gave *p*-anisic acid.

7-*Methoxy*-4-*oxo*-1,2,3,4-*tetrahydrodibenzothiophene* (IV). A solution of once-crystallized VIIIc (1 g) m.p. 154–156° in glacial acetic acid (10 ml) and acetic anhydride (20 ml) was treated with a freshly prepared 2% solution of fused zinc chloride in acetic acid (10 ml). The mixture was heated under reflux in a nitrogen atmosphere for 4 hr. The solution cooled and diluted with water yielded VI (0·9 g, yield 96%) which crystallized from ethanol, as white flakes, m.p. 155°. (Found: C, 67·2; H, 4·8; S, 14·3. $C_{13}H_{12}O_2S$ requires: C, 67·2; H, 5·2; S, 13·8%).

The 2,4-*dinitrophenylhydrazone* crystallized from chloroform in bright red plates, m.p. 278°. (Found: N, 13·5. $C_{19}H_{16}O_6N_4S$ requires: N, 13·6%).

Methyl 5-*chloro*-4-*oxo*-*valerate* (Xb). β-Carbomethoxypropionyl chloride[15] (16 g) was converted to methyl 5-chloro-4-oxo-valerate (Xb) as for the preparation of compound Xa. The compound

Xb, (16·4 g yield 93%), b.p. 90–95° (bath)/2 mm being unstable was used immediately without further purification. (Found: C, 44·2; H, 5·5; Cl, 18·8. $C_6H_9O_3Cl$ requires: C, 43·8; H, 5·5; Cl, 21·6%).

Methyl 5-(m-*methoxyphenylmercapto*)-4-*oxovalerate* (XIb). To a solution of *m*-methoxythiophenol (12·5 g) in pyridine (30 ml) was slowly added Xb (16 g) under cooling. The mixture was stirred vigorously for 10 min, then heated on waterbath for 15 min. The product XIb distilled as a yellow oil (9·5 g, yield 40%), b.p. 140–145° (bath/0·027 mm). (Found: C, 58·1; H, 5·8; S, 12·3. $C_{13}H_{16}O_4S$ requires: C, 58·2; H, 6·0; S, 11·9%).

β-(6-Methoxy-3-thionaphthenyl)-propionic acid (VIIIb). Compound XIb, (9·5 g) was cyclized by treatment with a mixture of phosphorous pentoxide (30 g), phosphoric acid (15 ml) and chlorobenzene (100 ml) at boiling point for 3 hr. The cyclization product was then saponified by refluxing with baryta (9 g) in 80% aqueous ethanol (100 ml) for 1½ hr. The acid (VIIIb) was isolated by extraction with ether and purified by dissolution in aqueous sodium bicarbonate. The acid (4·5 g, yield 54% from XIb) crystallized from ethanol in white needles, m.p. 141°. (Found: C, 60·8; H, 5·6; S, 14·0. $C_{12}H_{12}O_3S$ requires: C, 61·0; H, 5·1; S, 13·6%).

Homologation of (VIIIb) *to γ-(6-methoxy-3-thionaphthenyl)-butyric acid* (VIIIc). The acid VIIIb (1 g) was converted to the acid chloride with thionyl chloride (1·5 ml) in dry benzene (5 ml) at room temp for 30 min and then heating under reflux at 40° for 15 min. After removal of solvent and thionyl chloride, the acid chloride was re-dissolved in dry benzene (20 ml) and the solution slowly added under vigorous agitation and ice-cooling (0–5°) to an ethereal diazomethane solution prepared from nitrosomethyl urea (3 g). The diazoketone obtained was dissolved in dioxan (10 ml) and the solution added dropwise with stirring to a mixture of silver oxide (0·2 g), anhydrous sodium carbonate (0·5 g), sodium thiosulphate (0·3 g), and water (20 ml) at 50–60°. Stirring was continued for 1 hr and the temp raised to 90–100°. The solution was cooled, diluted with water, acidified with dil HNO_3 and extracted with ether. The acid VIIIc (0·12 g) was isolated from the ether extract by means of sodium bicarbonate. Crystallization of the crude acid from benzene afforded white needles, m.p. 160°, undepressed on admixture with VIIIc prepared earlier starting from glutaric acid.

β-Carbethoxy-β-(1,2-dihydro-7-methoxydibenzothiophen-4-yl)-propionic acid (XIII). To a cooled solution of potassium (0·13 g) in dry t-butanol (10 ml) was added diethyl succinate (1·3 ml) followed by the ketone IV (0·5 g). After evacuation of air the mixture was covered with nitrogen and shaken mechanically at room temp (27–29°) for 4 hr during which a faint yellowish-orange colouration developed. The mixture was then heated for 5 min on a water bath at 40–45° with shaking. Acidification of the cooled reaction mixture gave a brown coloured oil. Butanol was removed under reduced pressure and the semi-solid residue taken up in ether and extracted with aqueous sodium bicarbonate. The ether extract contained unchanged starting ketone IV (0·21 g). The bicarbonate extract, on acidification, gave yellowish-white flakes of XIII (0·19 g, yield 24%), m.p. 84–86°. Three recrystallizations from ethanol gave nearly colourless needles, m.p. 87–87·5°. (Found: C, 61·5; H, 6·0; S, 9·0. $C_{19}H_{20}O_5S$ requires: C, 63·3; H, 5·6; S, 8·9%. Eq. wt. Found: 353; Calc. 360). For want of material, the product could not be purified further.

3-*Hydroxymethylene-7-methoxy-4-oxo-1,2,3,4-tetrahydrodibenzothiophene* (XIV). A solution of ethyl formate (2 ml) in dry thiophene-free benzene (10 ml) was added to freshly prepared sodium methoxide [from sodium (0·5 g) and absolute methanol (10 ml), evaporation of methanol and drying the methoxide under reduced pressure at 200°]. After evacuation of air, the flask containing the mixture was filled with nitrogen. The mixture was cooled and a solution of the ketone IV (1 g) in dry benzene (30 ml) was added. The flask was again filled with nitrogen as above, stoppered, and shaken mechanically for 5 hr at room temp. The mixture was treated with water, and the benzene layer washed with water and then with aqueous sodium hydroxide. The combined aqueous portions, on acidification, gave the hydroxymethylene derivative (XIV) as a pale yellow solid (1·11 g; yield 99%). Repeated crystallizations from ethanol gave pale yellow needles, m.p. 128°. (Found: C, 64·6; H, 4·8; S, 12·5. $C_{14}H_{12}O_3S$ requires: C, 64·6; H, 4·6; S, 12·3%).

7-*Methoxy-9,10-dihydrodibenzothiopheno-(3,4-d)-isoxazole* (XV). A mixture of the crude hydroxymethylene ketone (XIV) (1·11 g, m.p. 112–115°), hydroxylamine hydrochloride (0·7 g) and glacial acetic acid (25 ml) was refluxed at 160–170° (oil bath). After heating for 20 min boiling water (25 ml) was added to the hot mixture causing crystallization. After 2 hr in the refrigerator, the crystalline product was filtered, washed and dried. The product was dissolved in ether–benzene and the solution washed twice with 2% aqueous NaOH and then with water. Removal of solvents gave a

brownish-white crystalline residue (0·78 g; yield 70%, m.p. 147–149°). Crystallization from benzene gave the isoxazole (XV) as light brown plates, m.p. 150°. (Found: C, 65·2; H, 4·2; N, 5·2. $C_{14}H_{17}O_3NS$ requires: C, 65·4; H, 4·3; N, 5·5%).

3-Cyano-7-methoxy-4-oxo-1,2,3,4-tetrahydrodibenzothiophene (XVI). The crude isoxazole XV (0·28 g, m.p. 138–140°) was added to a solution of potassium (0·17 g) in t-butanol (6 ml). The yellow potassium derivative of the β-ketonitrile separated out. The mixture was heated under reflux for 1 hr, cooled and diluted with water. The mixture was extracted with ether and the aqueous solution set aside. The ethereal layer was washed once with 10% aqueous NaOH. The combined alkaline extracts on careful acidification in cold gave dark-brown needles of the cyanoketone (XVI, 0·16 g, m.p. 173–175°). Several recrystallizations from ethanol gave fine light brown needles, m.p. 180°. (Found: C, 65·6; H, 4·4; N, 5·2. $C_{14}H_{11}O_3NS$ requires: C, 65·4; H, 4·3; N, 5·5%).

3-Cyano-7-methoxy-3-methyl-4-oxo-1,2,3,4-tetrahydrodibenzothiophene (III). Potassium (0·4 g) was dissolved in dry t-butanol (15 ml) and XV (0·86 g) was added with separation of a yellow precipitate. The mixture was refluxed with stirring for 1½ hr (water bath temp 90–100°) and the bath temp then reduced to 75–80°, and methyl iodide (5 ml) added dropwise during 30 min. Heating under reflux with stirring was continued for 2 hr. After removal of butanol (reduced pressure) the pale yellow residue was extracted with ether–benzene and the extract washed (water and 10% aqueous NaOH). The product from ethanol gave nearly colourless plates of the methyl cyanoketone III (0·7 g, yield 78%), m.p. 154° after further crystallizations. (Found: C, 66·5; H, 4·6; N, 5·3; S, 11·8; OMe, 11·4. $C_{15}H_{13}O_2NS$ requires: C, 66·4; H, 4·8; N, 5·2; S, 11·8; OMe, 11·4%).

Stobbe reaction on (III)

A. *Mild conditions*. To a cooled solution of potassium (0·12 g) in t-butanol (10 ml), diethyl succinate (1·5 ml) was added followed by the ketonitrile (III, 0·2 g). After evacuating air, the flask was filled with nitrogen, stoppered and shaken mechanically for 6 hr at room temp. The reaction mixture was acidified with dil HCl, butanol removed (reduced pressure) leaving a yellowish residue from which the unchanged ketone (III, 0·13 g, m.p. 153–154°) was recovered.

Similar results were obtained when dimethyl succinate, potassium methoxide, sodium hydride, sodium methoxide, sodium t-butoxide, etc. were employed and the reaction carried out at room temperature.

B. *Vigorous conditions*. To a solution of potassium (0·15 g) dissolved in dry t-butanol (10 ml), was added under nitrogen atmosphere diethyl succinate (1·2 ml), followed by a warm solution of III (0·26 g) in t-butanol (25 ml). The colour of the reaction mixture changed immediately to lemon yellow. After shaking mechanically for 5 hr under nitrogen atmosphere, the colour deepened to reddish-brown. The flask was then heated on a water-bath at 70° for 30 min and the product worked up as usual. The alkali washings on acidification yielded a pale yellow solid which was purified by extraction of its ethereal solution with aqueous sodium bicarbonate. The bicarbonate solution on acidification afforded yellowish white crystals (0·2 g) of 3-(3′-cyanobutyl)-2-carboxy-6-methoxythionaphthene (XVIII), m.p. 162–164°, m.p. 165° after crystallization from ethanol (Found: C, 62·3; H, 5·2; S, 11·3. $C_{15}H_{15}O_3NS$ requires: C, 62·3; H, 5·2; S, 11·1%).

Other experiments carried out at the boil using dimethyl succinate, sodium hydride, sodium t-butoxide, etc. and employing a large volume of t-butanol to dissolve the sparingly soluble ketone (III) also gave XVIII as the major product.

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