The yield of each material was estimated by combining its separate fractions[29].

The materials were identified by m.p. or in doubtful cases by infrared spectra. 3α-Cholestanol (lit. m.p. 181–182°) from the column usually had a m.p. 183–185° but m.p.'s up to 187–189° were frequent. 3β-Cholestanol (lit. m.p. 141–142°) usually had m.p. 143–144° but m.p.'s from 141–143° to 145–147° were observed. 3-Cholestanone (lit. m.p. 128–129°) had m.p.'s ranging from 118–120° to 129–130°. Most were 124–126° or higher.

The following is a typical run: A solution of 3-cholestanone (100 mg.) in tetrahydrofuran (10 ml.) was added in one portion to a stirred solution of lithium borohydride (33 mg.) in tetrahydrofuran (30 ml.) at room temperature. After 4 hr. hydrochloric acid (25 ml., *N*) was added cautiously, and then the mixture was extracted with ether (25 ml.). The aqueous layer was washed with three further lots (each 10 ml.) of ether. The combined ethereal layers were washed with water, aqueous sodium hydrogen carbonate, and again with water, and the solution was dried (Na_2SO_4). The solvent was evaporated and the crude product (102 mg. after drying for some hours at 60° *in vacuo*) was chromatographed on alumina. 3α-Cholestanol (6.6 mg. m.p. 182–185°) was eluted in benzene–ether and the first three ether fractions; 3β-cholestanol (92.4 mg. m.p. 143–144°) was eluted in the 5th–10th ethereal fractions. Yield of α-isomer 6.7%; yield of β-isomer 93.3%; total yield of sterols 98%.

The general procedure was modified slightly for reactions run above room temperature. In these cases the solvent was brought to the desired temperature, the hydride was added, and then as quickly as possible the ketone was introduced. In reactions involving inverse addition the order of the latter two steps was reversed.[22]

When pyridine was used as solvent, the method of work-up of the reaction was changed. After the reaction was complete, aqueous sodium hydroxide (25 ml., *N*) was added cautiously and the stirring of the mixture was continued for 1 hr. Water (25 ml.) was added and the product extracted with ether (75 ml.). The aqueous layer was then extracted with three further lots of ether (15 ml. each). The combined ethereal solutions were washed with water, hydrochloric acid (*N*), and water and were dried (Na_2SO_4). The crude product was obtained on evaporation of the ether.

The results of all these experiments are summarized in Table I.

Control Experiments.—The following standard mixtures of 3-cholestanol epimers were made up and chromatographed on alumina: 70% β- and 30% α- (on chromatography gave 70.7% β-, m.p. 142–143°, and 29.3% α-, m.p. 183–184°); 76% β- and 24% α- (on chromatography gave 74.5% β-, m.p. 143–144°, and 25.5% α-, m.p. 187–188°)[30]; and 90% β- and 10% α- (on chromatography gave 89.8% β-, m.p. 143–144°, and 10.2% α-, m.p. 184–186°).

These results indicate that chromatography on alumina is a satisfactory method for estimating the isomers.

A number of experiments were done to confirm that the cholestanols are not epimerized under the reaction conditions.

A mixture of 3β-cholestanol (20 mg.) and lithium aluminum hydride (10 mg.) in ether (20 ml.) was stirred at room temperature for 2 hr. The mixture was worked up by the general procedure. The yield of product was 20.4 mg., m.p. 142–143°, infrared spectrum identical with starting material.

A mixture of 3α-cholestanol (10 mg.) and lithium aluminum hydride (5 mg.) in ether (20 ml.) was stirred for 2 hr. On work-up the mixture yielded 9.7 mg. of product, m.p. 185–188°, infrared spectrum identical with starting material.

A mixture of 3β-cholestanol (100.4 mg.) and sodium borohydride (52.1 mg.) in isopropyl alcohol was refluxed for 4 hr. The mixture on the usual work-up gave 95.6 mg. crude product which was chromatographed on alumina. Only one fraction (89.6 mg. m.p. 143–145°) could be obtained. There was no trace of the α-epimer. An earlier experiment on a 20-mg. scale had given a product m.p. *ca.* 120° with infrared spectrum identical with starting material.[31]

A mixture of 3α-cholestanol (10 mg.) and sodium borohydride (5 mg.) was refluxed in isopropyl alcohol for 4 hr. The m.p. of the product was 183–186°. Its infrared spectrum was the same as the starting material.

Attempted Estimation of Isomers by Infrared Spectra.—Standard solutions (50 mg. in 5 ml. of CCl_4) of 3α- and 3β-cholestanol were made up. The compositions varied from 6–50% of the α-isomer. The infrared spectra were determined and the peaks at 9.65 μ and 9.32 μ were studied as a basis for analyzing mixtures of the 3-cholestanol epimers. The peak at 9.65 μ appeared to be the more suitable. However, repetition of the spectra (even after the instrument had been serviced) showed small changes in the % transmission at 9.65 μ. As these changes could introduce uncertainties of up to 8% in the estimations, the method was not used.

(29) In one run of the lithium aluminum hydride–ether 0.5 hr. series' the weight of the β-isomer was estimated from the separate weights of the individual fractions.

(30) The poorness of this result is due probably to the fact that the amounts of the isomers were determined by adding the weights of individual fractions instead of the usual procedure of weighing the combined fractions of each isomer.

(31) 3β-Cholestanol has a double m.p., 125° and 141–142°.

Benzo[*b*]thiophene. III.[1] Synthesis of Hydroxylated Diphenylalkanes from Anisyl Derivatives of Benzo[*b*]thiophene

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The desulfurization with Raney nickel W4 of benzo[*b*]thiophene derivatives substituted by an anisyl group gives methoxylated diphenylalkanes which can be demethylated by means of pyridinium chloride. The anisoylation of 2,3-diethylbenzo[*b*]thiophene occurs mainly in the 6-position, secondarily in the 5-position.

After being discovered by Bougault, Cattelain, and Chabrier,[2] the desulfurizing reduction with Raney nickel of cyclic sulfur compounds was applied several times in the benzo[*b*]thiophene series in order to establish structures.[1a,3]

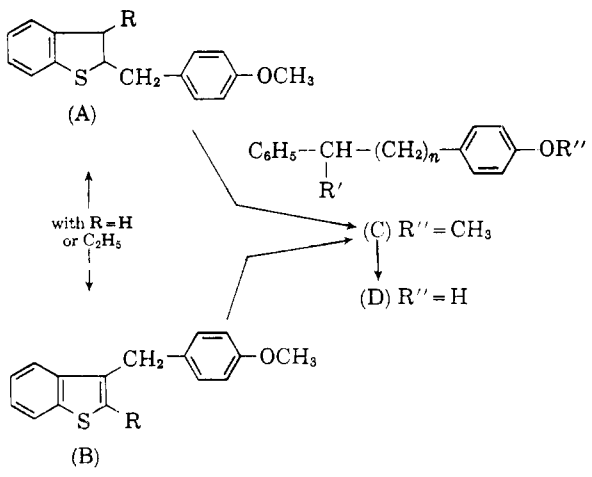
We have been using this procedure as a preparative method for some hydroxylated diphenyl-

(1) Our former publications in this series are (a) Part I: *Bull. soc. chim. France*, 1534 (1961); (b) Part II: *Compt. rend.*, **254**, 2605 (1962).

(2) *Bull. soc. chim. France*, 1699 (1938); 34 (1939); 780 (1940).

alkanes, which would be difficult to prepare, if at all, by other methods. For this purpose, we first synthesized many new 2- or 3-anisyl substituted derivatives of benzo[b]thiophene (chart I, formula A and B); then the sulfur ring was opened and the resulting methoxydiphenylalkanes (formula C) were treated with pyridinium chloride to give the corresponding hydroxylated compounds (formula D).

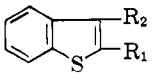
CHART I



Reaction Path A.—The lithium derivative (II) of benzo[b]thiophene (I) on treatment with lithium acetate gave 2-acetylbenzo[b]thiophene (III) according to the procedure indicated by D. A. Shirley, B. H. Gross, and M. J. Danzig.[4] By chlorination with sulfuryl chloride, ketone III was transformed into the corresponding chloracetylated derivative (IV), which was then converted into V by pyridine. The degradation of the latter by sodium hydroxide led to 2-benzo[b]thiophenecarboxylic acid (VI), a known compound.[5] The chloride (VII) of this acid VI was condensed with anisole according to Friedel-Crafts procedure, to yield 2-(4′-methoxybenzoyl)benzo[b]thiophene (VIII). VIII was reduced by the Huang-Minlon method to give 2-(4′-methoxybenzyl)benzo[b]thiophene (X), which was also prepared by action of anisyl chloride on II. The reduction of the ketone VIII led to the corresponding demethylated derivative XI, in addition to the methoxylated compound X.

In order to confirm the reactivity of the 3-position in 2-substituted benzo[b]thiophene, the acetylation of X was undertaken with acetyl chloride in the presence of stannic chloride. Ketone XII was formed in this way and it could be reduced into 2-(4′-methoxybenzyl)-3-ethylbenzo[b]thiophene (XIII).

CHART II



No.	R_1	R_2
I	H—	H—
II	Li—	H—
III	CH_3—CO—	H—
IV	Cl—CH_2—CO—	H—
V	$Cl^-N^+C_2H_5$—CH_2—CO—	H—
VI	CO_2H	H—
VII	Cl—CO—	H—
VIII	4-CH_3O—C_6H_4—CO—	H—
X	4-CH_3O—C_6H_4—CH_2—	H—
XII	4-CH_3O—C_6H_4—CH_2—	CH_3—CO—
XIII	4-CH_3O—C_6H_4—CH_2—	C_2H_5—
XV	H—	4-CH_3O—C_6H_4—CO—
XVI	H—	CO_2H
XVIII	H—	4-CH_3O—C_6H_4—CH_2—
XX	4-CH_3O—C_6H_4—CH_2—	4-CH_3O—C_6H_4—CH_2—
XXI	C_2H_5—	H—
XXII	C_2H_5—	4-CH_3O—C_6H_4—CO—
XXIV	C_2H_5—	4-CH_3O—C_6H_4—CH_2—
XXVI	H—	C_2H_5—
XXVII	4-CH_3O—C_6H_4—CO—	C_2H_5—
XXIX	Li—	C_2H_5—

Some benzo[b]thiophene derivatives were obtained through various reaction paths (Chart II).

Reaction Path B.—3-(4′-Methoxybenzoyl)benzo[b]thiophene (XV) was obtained either as the main product in the direct anisoylation of I, taking

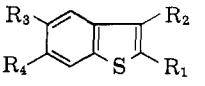
(3) (a) R. Mozingo, D. E. Wolf, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943); (b) F. F. Blicke and D. G. Sheets, *ibid.*, **70**, 3768 (1948); (c) W. Baker, A. S. El-Nawawy, and W. D. Ollis, *J. Chem. Soc.*, 3163 (1952); (d) D. A. Shirley, M. J. Danzig, and F. C. Canter, *J. Am. Chem. Soc.*, **75**, 3278 (1953); (e) B. B. Corson, H. E. Tiefenthal, G. R. Atwood, W. J. Heintzelman, and W. L. Reilly, *J. Org. Chem.*, **21**, 584 (1956); (f) G. M. Badger, N. Kowanko, and W. H. F. Sasse, *J. Chem. Soc.*, 2969 (1960); (g) G. Van Zyl, G. E. Heasley, R. N. Schut, J. W. van Dyke, and R. G. Korteling, *J. Org. Chem.*, **26**, 2916 (1961).

(4) D. A. Shirley, B. H. Gross, and M. J. Danzig, *J. Org. Chem.*, **23**, 1024 (1958).

(5) (a) R. Weissgerber and O. Kruber, *Ber.*, **53**, 1551 (1920); (b) A. Schönberg, E. Petersen, and H. Kaltschmitt, *ibid.*, **66**, 233 (1933); (c) F. F. Blicke and D. G. Sheets, *J. Am. Chem. Soc.*, **71**, 2856 (1949); (d) W. W. Farrar and R. Levine, *ibid.*, **72**, 4433 (1950); (e) D. A. Shirley and M. D. Cameron, *ibid.*, **72**, 2788 (1950); (f) R. Gaertner, *ibid.*, **74**, 4950 (1952).

TABLE I

4-HYDROXYBENZOYL AND 4-HYDROXYBENZYL DERIVATIVES OF BENZO[*b*]THIOPHENE BY DEMETHYLATION



No.	R_1	R_2	R_3	R_4
IX	4-OH—C_6H_4—CO—	H—	H—	H—
XI	4-OH—C_6H_4—CH_2—	H—	H—	H—
XIV	4-OH—C_6H_4—CH_2—	CH_3—CO—	H—	H—
XVII	H—	4-OH—C_6H_4—CO—	H—	H—
XIX	H—	4-OH—C_6H_4—CH_2—	H—	H—
XXIII	C_2H_5—	4-OH—C_6H_4—CO—	H—	H—
XXV	C_2H_5—	4-OH—C_6H_4—CH_2—	H—	H—
XXVIII	4-OH—C_6H_4—CO—	C_2H_5—	H—	H—
XXX	4-OH—C_6H_4—CH_2—	C_2H_5—	H—	H—
XLIV	C_2H_5—	C_2H_5—	H—	4-OH—C_6H_4—CO—
XLV	C_2H_5—	C_2H_5—	4-OH—C_6H_4—CO—	H—
XLVII	C_2H_5—	C_2H_5—	H—	4-OH—C_6H_4—CH_2—

[a] *p*-Nitrobenzoate: yellow microcrystals (from ethanol + a small amount of benzene, m.p.° 148°. Calcd.: C, 68.21; H, 3.87; N, 3.59; S, 8.22. Found: C, 67.63; H, 3.78; N, 3.53; S, 8.00.

stannic chloride as a catalyst, or in the condensation of anisole with the chloride derivative of 3-benzo[*b*]thiophene carboxylic acid (XVI), for which we had previously indicated a new synthesis.[1a] Compound XV, in common with most of 3-ketonic derivatives of benzo[*b*]thiophene[1a] could be reduced neither by hydrazine hydrate and potassium hydroxide nor by zinc and hydrochloric acid. Hence 3-(4′-methoxybenzyl)benzo[*b*]thiophene (XVIII) had to be prepared by anisylation of I with zinc chloride as a catalyst. A by-product in this reaction was 2,3-bis(4′-methoxybenzyl)benzo[*b*]thiophene (XX). It is worth noticing that the acetylation of XVIII was not possible, contrary to what has been reported above for the isomeric anisyl derivative X.

Reaction Path C.—2-Ethylbenzo[*b*]thiophene (XXI), for which we had previously found a convenient preparation,[1a] was submitted to anisoylation in a classical way. The resulting ketone XXII —although stable in an alkaline medium, contrary to the corresponding oxygen compounds in the benzofuran series[6]—could be reduced neither by Clemmensen procedure, nor by the Huang-Minlon one. The latter produced only a demethylation giving the phenolic ketone XXIII. Starting from XXI, 2-ethyl-3-(4′-methoxybenzyl)benzo[*b*]thiophene (XXIV) was obtained through anisyl chloride condensation.

Reaction Path D.—The anisoylation of 3-ethylbenzo[*b*]thiophene (XXVI)[1a] gave ketone XXVII, which was reduced without any difficulty into the 2-anisyl derivative XIII already obtained through reaction series A. Starting again from XXVI, and treating its lithium derivative (XXIX) with anisyl chloride, the same compound XIII was found again.

The anisoyl and anisyl derivatives VIII, X, XII, XV, XVIII, XXII, XXIV, XXVII, and XIII were easily demethylated by pyridinium chloride to give the corresponding compounds: IX, XI, XIV, XVII, XIX, XXIII, XXV, XXVIII and XXX, respectively (Table I).

The desulfurizing ring-opening reductions of anisyl compounds X, XVIII, XIII, XXIV, and XX were performed with Raney nickel W4, giving derivatives indicated in Table II. Among these, the only one already known is XXXI, which had been prepared by another method.[7] On boiling for some time in pyridinium chloride, methoxylated diphenylalkanes XXXI to XXXV gave the phenolic derivatives XXXVI to XL with an average yield of 95%.

In addition to this study of benzo[*b*]thiophene derivatives carrying the anisoyl group on the heterocyclic ring, the possibility of introducing the same ketonic chain into the homocyclic ring was examined, primarily in order to confirm the reactivity of the various positions in this ring and, secondly, with a view to obtaining a new starting material convenient for the ring-opening desulfurization. It had been already shown that the 6-position in 2,3-diethylbenzo[*b*]thiophene (XLI) was the most reactive in Friedel-Crafts reactions with acetyl chloride and succinic anhydride[1a]; it had never been possible, however, to isolate directly the isomeric 5-substituted derivatives.

The condensation of anisoyl chloride on XLI, in the presence of aluminum chloride, gave two isomeric ketones XLII (70%) and XLIII (30%) (Chart III). On one hand, the structure of the main product was established as follows: reduction according to Huang-Minlon's procedure into the anisyl derivative XLVI; under the desulfurizing effect of Raney nickel, this derivative XLVI was transformed into 4-methoxy-4′-(3-hexyl)diphenylmethane (XLVIII) which could be demethylated into IL by means of pyridinium chloride.

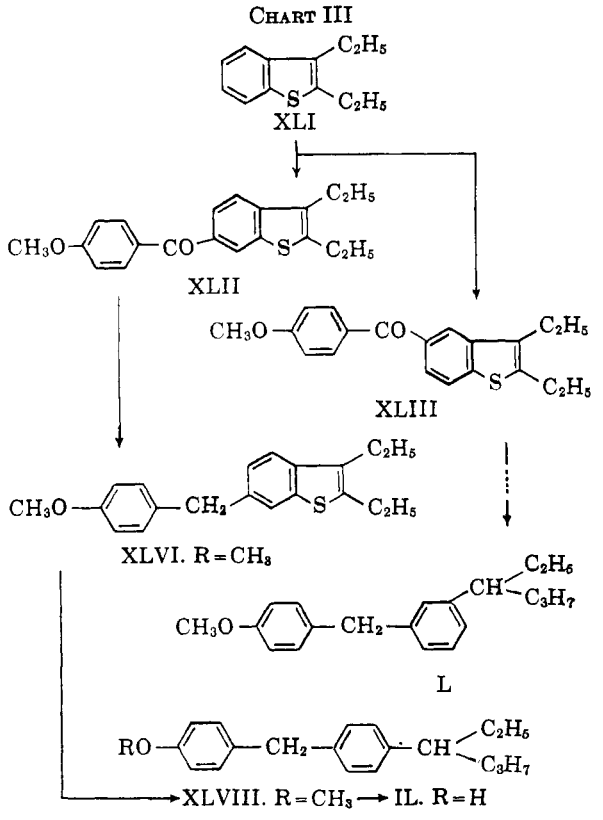
(6) R. Royer and E. Bisagni, *Bull. soc. chim. France*, 395 (1960); E. Bisagni and R. Royer, *Compt. rend.*, **250**, 3339 (1960).

(7) C. S. Rondestvedt, Jr., *J. Am. Chem. Soc.*, **73**, 4509 (1951).

TABLE I (*Continued*)

Yield, %	M.p.°	B.p.° (mm.)	n_D (t°)	Calcd. C	Calcd. H	Calcd. S	Found C	Found H	Found S
90	161			70.86	3.93	12.59	71.16	4.05	12.65
60	147			75.00	5.00	13.33	75.07	3.83	13.05
59	123.5			72.34	4.96	11.34	72.34	5.15	11.55
96	191			70.86	3.93	12.59	71.19	4.22	12.65
75.5	[a]	258 (20)	1.6610 (26)	75.00	5.00	13.33	74.98	4.88	13.21
83		289–290 (17)		72.34	4.96	11.37	72.14	5.19	11.51
84		253 (13)	1.6462 (22)	76.10	5.97	11.94	75.81	6.21	11.91
99	172			72.34	4.96	11.34	72.26	4.87	11.09
64	84			76.11	5.97	11.94	75.94	5.80	11.62
85	174.5			73.54	5.80	10.32	73.27	5.90	10.43
55		302 (18)		73.54	5.80	10.32	73.21	5.61	10.20
95	89			77.02	6.75	10.81	76.88	6.99	10.58

CHART III



The structures of both of the latter derivatives—and then those of the corresponding benzo[b]thiophenes—were determined from the examination of their infrared spectrum, which showed no characteristic bands of *meta*-substitution on the benzene ring, but only those of *para*-substitution (Fig. 1). This spectral proof might not appear as the best and a chemical one might be preferred. Several attempts were made to obtain such a chemical proof —*via* the single-path synthesis of XLVIII, starting either from anisole or 3-hexylbenzene—but all gave unseparable mixtures of isomeric compounds.

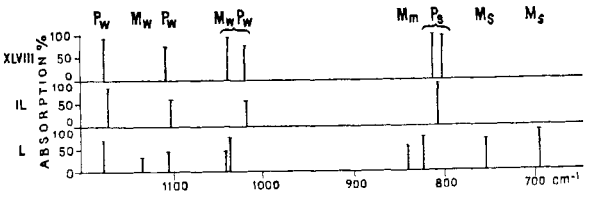


Fig. 1.—Infrared spectra. P, *para;* M, *meta;* m, medium; s, strong; w, weak.

Thus, the degradation of suitable substituted benzo[b]thiophene appears as the most practical route to build 4,4′-disubstituted diphenylmethane of the type XLVIII and IL.

On the other hand, the reduction of XLIII led to a non-isolated anisyl derivative, which underwent the desulfurizing reduction, giving compound L, an isomer of XLVIII. As expected, this new diphenylmethane derivative possesses an infrared spectrum, which shows the specific bands of *meta*-substitution on 3-hexylbenzene, as well as those revealing the *para*-substitution of its anisyl substituent.

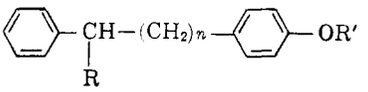
As regards the chemistry of benzo[b]thiophene, it must be noted that these results also demonstrate the fact previously pointed out that the homocyclic part of 2,3-disubstituted benzo[b]thiophenes is able to react with acid chloride under Friedel-Crafts conditions and that the position chiefly attacked on this ring is the one *meta* with respect to the heteroatom. One of us has already reached the same conclusion for the benzofuran series.[8]

Finally, methoxylated compounds XLII, XLIII, and XLVI were transformed by pyridinium chloride into XLIV, XLV, and XLVII (Table I), as was done with the corresponding derivatives substituted on the heterocyclic ring of benzo[b]thiophene.

(8) E. Bisagni and R. Royer, *Bull. soc. chim. France*, 1968 (1960); *ibid.*, 925 (1962).

TABLE II

4-METHOXY- AND 4-HYDROXYDIPHENYLALKANES FROM ANISYL DERIVATIVES OF BENZO[*b*]THIOPHENE



No.	R	*n*	R′	B.p.° (mm.)	n_D (t°) or m.p.°	Yields, %	Calcd. C	Calcd. H	Found C	Found H
XXXI	H—	2	CH_3—	190 (16)	1.5508 (20)	82	84.95	7.96	84.55	7.76
XXXII	CH_3—	1	CH_3—	178–179 (17)	1.5586 (19.5)	82.5	84.95	7.96	85.18	8.13
XXXIII	C_2H_5—	2	CH_3—	193 (14)	1.5458 (19.5)	89	85.03	8.66	84.76	9.01
XXXIV	*n*-C_3H_7—	1	CH_3—	188–190 (14)	1.5492 (20)	89	85.03	8.66	85.35	9.03
XXXV	4-CH_3O—C_6H_4—$(CH_2)_2$—	1	CH_3—	288–289 (24)	1.5847 (21.5)	82	83.23	7.51	83.29	7.13
XXXVI	H	2	H—	200 (13)	1.5708 (19)		84.90	7.54	85.27	7.57
XXXVII	CH_3—	1	H—	193 (14)	63		84.90	7.54	84.85	7.62
XXXVIII	C_2H_5—	2	H—	203 (14)	1.5537 (21.5)		85.00	8.33	85.60	8.02
XXXIX	*n*-C_3H_7—	1	H—	201–202 (15)	81.5		85.00	8.33	85.02	8.53
XL	4-CH_3O—C_6H_4—$(CH_2)_2$—	1	H—	303 (20)	...		83.01	6.91	83.12	6.72

Experimental[9]

Chlorination of III.—A solution of 41 g. of III,[4] 32 g. of sulfuryl chloride in 300 ml. of chloroform was refluxed for 1.5 hr. The solvent was evaporated and the residue was recrystallized from ethanol to give 42 g. (85.5 %) of IV as colorless needles, m.p. 120°.

Anal. Calcd. for $C_{10}H_7OSCl$: C, 57.00; H, 3.32; Cl, 16.86; S, 15.67. Found: C, 56.90; H, 3.15; Cl, 16.30; S, 14.98.

2-Benzo[*b*]thenoylmethylpyridinium Chloride (V).—Thirty-five grams of IV and 35 g. of pyridine were heated together for 2 min. After cooling, the solid product was triturated in acetone and filtered off. Thus, 46 g. (95.5 %) of V was obtained and purified by digestion in boiling acetone giving yellow microcrystals, m.p. 242° (by projection; by progressional heating, decomposition above 195°).

Anal. Calcd. for $C_{15}H_{12}OSNCL$: C, 62.21; H, 4.14; N, 4.83; S, 11.05; Cl, 12.26. Found: C, 61.90; H, 4.16; N, 4.71; S, 11.52; Cl, 12.50.

Degradation of V.—Forty-six grams of V was heated for 1.5 hr. in a solution of 15 g. of sodium hydroxide in 400 ml. of water. The liquor was filtered through glasswool and acidified with hydrochloric acid. This gave 28 g. (79%) of *2-benzo[b]thiophenecarboxylic acid* (VI) which formed colorless microcrystals by recrystallization from ethanol, m.p. 240°. (A m.p. of 240–241.5° was reported in the literature.[5c]).

Acid Chloride VII.—Twenty-eight grams of VI and 25 g. of thionyl chloride in 100 ml. of benzene were refluxed for 2 hr. After elimination of the excess of thionyl chloride, the distillation gave 25.5 g. (82%) of VII: b.p. 176° (17 mm.), m.p. 84–86°. By treatment with aniline in a pyridinic medium, VII was transformed into *2-benzo[b]thenoylanilide* which yielded some bright colorless needles in ethanol, m.p. 184°.

Anal. Calcd. for $C_{15}H_{11}ONS$: C, 71.14; H, 4.34; N, 5.53; S, 12.65. Found: C, 71.47; H, 4.39; N, 5.35; S, 12.80.

2-(4′-Methoxybenzoyl)benzo[*b*]thiophene (VIII).—Eighty grams of aluminum chloride was added, in a short time, to a mixture of 24 g. of VII and 14 g. of anisole in 250 ml. of carbon disulfide. The reaction started quickly and a crystalline complex appeared. The mixture was left for 16 hr. at 15° and heated with dilute hydrochloric acid. Then the usual treatment gave 28 g. (85.5%) of VIII: b.p. 280–281° (17 mm.) green needles, m.p. 128°. VIII developed an orange red color on treatment with H_2SO_4.

Anal. Calcd. for $C_{16}H_{12}O_2S$: C, 71.64; H, 4.47; S, 11.94. Found: C, 71.60; H, 4.22; S, 12.15.

Reduction of VIII.—A mixture of 10.5 g. of VIII and 3.33 g. of hydrazine hydrate in 100 ml. of diethylene glycol was heated for 15 min. After cooling, 3.33 g. of potassium hydroxide was added. The mixture was refluxed for a further 40 min. and poured into water. The aqueous solution was carefully extracted with benzene, then acidified with dilute hydrochloric acid. A small quantity of *2-(4′-hydroxybenzyl)-benzo[b]thiophene* (XI) was obtained (see Table I). The organic layer was treated as usual to yield 5.5 g. (55.5%) of *2-(4′-methoxybenzyl)benzo[b]thiophene* (X); b.p. 242° (17 mm.); colorless leaflets, (from a mixture of benzene and petroleum ether) m.p. 111°.

Anal. Calcd. for $C_{16}H_{14}OS$: C, 75.59; H, 5.51; S, 12.59. Found: C, 75.79; H, 5.56; S, 12.80.

Condensation of Anisyl Chloride on II.—To a cold, well-stirred ethereal solution of 0.3 mole of II (prepared according to D. A. Shirley and M. D. Cameron[10] by action of 0.4 mole of *n*-butyllithium on 0.3 mole of I), 49 g. of *p*-anisyl chloride[11] was added. A vigorous reaction took place, the temperature rising to 35°. The stirring was continued for 2 hr. while the mixture was heated on a water bath with gentle refluxing. Then, after having been left overnight at room temperature, the mixture was cautiously treated with iced water, the water layer extracted three times with ether, and ths solvent evaporated. The distillation under a vacuum of the residue gave 27 g. of X, described above.

Acetylation of X.—A 21.3-g. sample of X, 7.3 g. of acetyl chloride, and 24 g. of stannic chloride in 100 ml. of benzene were treated as usual for 3 hr. at 20°. Distillation at 275–280° (16 mm.) gave 12 g. (49%) of *2-(4′-methoxybenzyl)-3-acetylbenzo[b]thiophene* (XII) whose fractionation led to a viscous green liquid, b.p.: 268–270° (16 mm.), n_D 1.6487 (21.5°) which became crystalline at about 20° and developed a red brown hue on treatment with sulfuric acid.

Anal. Calcd. for $C_{18}H_{16}O_2S$: C, 72.97; H, 5.40; S, 10.81. Found: C, 72.68; H, 5.81; S, 10.72.

Reduction of XII was performed according to the Huang-Minlon procedure with 8 g. of XII, 2 g. of hydrazine hydrate, and 2 g. of potassium hydroxide in 100 ml. of diethylene glycol. XIII is a light yellow liquid, b.p.: 250–252° (16 mm.), n_D 1.6348 (21°). Yield: 4.9 g. (64.5%).

Anal. Calcd. for $C_{18}H_{18}OS$: C, 76.59; H, 6.39; S, 11.34. Found: C, 76.39; H, 6.43; S, 11.65.

Anisoylation of I.—A 40-g. sample of I, 62.5 g. of anisoyl chloride in 300 ml. of benzene was treated with 87 g. of stannic chloride added in 30 min. The duration of reaction was 2.45 hr. at 20°. The aqueous decomposition must be carried out by heating. The distillation between 265° and 275° (13 mm.) gave 54 g. (67%) of a mixture of XV and of the isomeric compound VIII. The percentage of each of them was determined by infrared spectrophotometry, indi-

(9) Melting points are uncorrected; microanalyses were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England.

(10) D. A. Shirley and M. D. Cameron, *J. Am. Chem. Soc.*, **74**, 664 (1952).

(11) R. Quelet and J. Allard, *Bull. soc. chim. France*, [5] **3**, 1794 (1936).

cating about 70% of the former. The rectification gave, as the main fraction [265–267° (13 mm.)]. 36 g. (45%) of almost pure XV, which after several recrystallizations in ethanol yielded colorless microcrystals, m.p. 122.5°.

Anal. Calcd. for $C_{16}H_{12}O_2S$: C, 71.64; H, 4.47; S, 11.94. Found: C, 71.40; H, 4.73; S, 12.15.

The other fraction (18 g.) of the rectification [b.p.: 274 (14 mm.)] remained as a mixture of XV and VIII even after several crystallizations in ethanol.

Single-Path Synthesis of XV.—A mixture of 16 g. of the chloride derivative of X[1a], 10 g. of anisole and 12 g. of aluminum chloride in 170 ml. of carbon disulfide was left for 15 hr. at 15°. The decomposition was performed by means of hot water acidified by hydrochloric acid. The distillation [b.p. 271–272° (16 mm.)] produced 13 g. (62%) of colorless needles, m.p. 122.5°, which developed a gold hue with sulfuric acid.

Anal. Calcd. for $C_{16}H_{12}O_2S$: C, 71.64; H, 4.47; S, 11.94. Found: C, 71.38; H, 4.58; S, 12.25.

Anisylation of I.—Seventy grams of anisyl chloride was added drop by drop for 1.5 hr. to a mixture of 70 g. of I and 15 g. of zinc chloride in 500 ml. of chloroform, which was refluxed and stirred. Heating was continued for 2.5 hr.; then the reaction product was poured into dilute hydrochloric acid, treated as usual, distilled and rectified, giving: 31 g. (44%) of I recovered; b.p. 235–240° (15 mm.), 37 g. (50%) of *3-(4'-methoxybenzyl)benzo[b]thiophene* (XVIII): colorless microcrystals, m.p. 79° from a mixture of 85% petroleum ether and 15% cyclohexane.

Anal. Calcd. for $C_{16}H_{14}OS$: C, 75.59; H, 5.51; S, 12.59. Found: C, 75.57; H, 5.71; S, 12.66.

B.p. 318–325° (15 mm.): 18 g. (16.5%) of *2,3-bis-(4'-methoxybenzyl)benzo[b]thiophene* (XX): a viscous yellow liquid, n_D 1.6452 (23.5°).

Anal. Calcd. for $C_{24}H_{22}O_2S$: C, 77.00; H, 5.88; S, 8.55. Found: C, 76.71; H, 5.71; S, 8.68.

Anisoylation of 2-Ethylbenzo[b]thiophene[1a] (XXI).—After keeping 20 g. of XXI, 23.5 g. of anisoylchloride, 40 g. of stannic chloride in 150 ml. of benzene for 3 hr. at 20°, then treating the mixture according to the usual method, 34 g. (93%) of *2-ethyl-3-(4'-methoxybenzoyl)benzo[b]thiophene* (XXII) was obtained [b.p. 263–265° (16 mm.)]; colorless microcrystals (from ethanol), m.p. 70°, giving an orange-red color in sulfuric acid.

Anal. Calcd. for $C_{18}H_{16}O_2S$: C, 72.97; H, 5.40; S, 10.81. Found: C, 72.94; H, 5.56; S, 10.91.

Anisylation of XXI.—To a boiling mixture of 40 g. of XXI (in excess) and 7 g. of zinc chloride in 250 ml. of chloroform, 30.1 g. of anisyl chloride[11] was added drop by drop for 90 min. Heating was continued for 2.5 hr. The usual treatment gave 35 g. (65%, calculated for the anisyl chloride) of *2-ethyl-3-(4'-methoxybenzyl)benzo[b]thiophene* (XXIV): fluorescent amber liquid, b.p. 240–242° (14 mm.); n_D 1.6257 (21.5°).

Anal. Calcd. for $C_{18}H_{18}OS$: C, 76.59; H, 6.38; S, 11.34. Found: C, 76.60; H, 6.48; S, 11.36.

Picrate Derivative of XXIV.—Orange needles (from ethanol), m.p. 82.5°.

Anal. Calcd. for $C_{24}H_{21}O_8SN_3$: C, 56.37; H, 4.10; N, 8.21; S, 6.26. Found: C, 56.51; H, 4.31; N, 8.40; S, 6.23.

Anisoylation of 3-Ethylbenzo[b]thiophene[1a] (XXVI).—A mixture of 10 g. of XXVI, 11.6 g. of anisoyl chloride, and 18 g. of stannic chloride in 50 ml. of benzene were treated for 3 hr. 10 min. at 20°. There was obtained 16.5 g. (90.5 %) of *2-(4'-methoxybenzoyl)-3-ethylbenzo[b]thiophene* (XXVII): b.p. 271° (14 mm.); colorless cottonous needles, m.p. 94° developing a blood color in sulfuric acid.

Anal. Calcd. for $C_{18}H_{16}O_2S$: C, 72.97; H, 5.40; S, 10.81. Found: C, 72.74; H, 5.57; S, 10.98.

Reduction of XXVII.—Nine grams of XXVII and 2.3 g. of hydrazine hydrate in 80 ml. of diethylene glycol were heated for 15 min. After cooling, 2.3 g. of potassium hydroxide was added and the heating recommenced for 15 min. (a decomposition taking place after this time). The usual treatment, followed by distillation and rectification, gave 3 g. (35%) of *2-(4'-methoxybenzyl)-3-ethylbenzo[b]thiophene* (XIII) formerly obtained from starting from XII.

Synthesis of XIII by Means of the Lithium Derivative of XXVI.—This lithium derivative was made in an ethereal medium with 27 g. of XXVI and an excess of butyllithium, itself prepared from 30.1 g. of *n*-butyl bromide and 3.08 g. of lithium chips. Anisyl chloride (29.9 g.) was added drop by drop, for a short time, into the cold ethereal solution of the lithium derivative. The temperature rose spontaneously. The reaction was completed within 2 hr. of gentle refluxing. After a night at room temperature, the usual treatment was applied. In this way 11 g. (23.5%) of the pure compound XIII were obtained.

Compounds in Table I.—Anisoyl and anisyl derivatives of benzo[b]thiophene were demethylated by gentle refluxing with twice their weight of pyridinium chloride, till the mixture became homogeneous (10 to 60 min., depending on the structures of the products). The hot reaction mixture was poured into dilute hydrochloric acid. In almost all cases, the demethylated compounds crystallized more or less rapidly and were recrystallized directly in benzene or petroleum ether or a mixture of benzene and a small quantity of ethanol. They were purified by distillation in the liquid form.

Compounds in Table II. (a) **Desulfurizing Ring-Opening Reductions**—To a 400 ml. ethanolic suspension of Raney nickel W4 (prepared according to Mozingo,[3a] from 380 g. of Nickel aluminum alloy) was added 0.1 mole of the anisyl derivative to be reduced. The mixture was refluxed for 45 min., cooled to 40°, and filtered through a Buchner funnel; the catalyst, always kept wet, was washed with three 50-ml. portions of ethanol, then destroyed with dilute hydrochloric acid. The filtrate was diluted with 2 l. of water and extracted with ten 30-ml. portions of chloroform. The chloroform solution was evaporated and the residue was submitted to a vacuum distillation.

(b) **Demethylations of methoxylated diphenylalkanes** were performed in the same manner as those of the anisyl and anisoyl derivatives of benzo[b]thiophene.

Anisoylation of 2,3-Diethylbenzo[b]thiophene[1a] (XLI).—To a solution of 20 g. of XLI and 17.8 g. of anisoyl chloride in 250 ml. of carbon disulfide was added in three portions 14.2 g. of aluminum chloride. The reaction mixture was left for 15 hr. at about 15° and treated as usual. The distillation gave, first, 6.8 g. (34%) of recovered XLI; at about 285–310° (18 mm.), 26.3 g. (67%) of a mixture of the isomeric compounds XLII and XLIII. After several recrystallizations from ethanol at low temperature, 18.5 g. of *2,3-diethyl-6-(4'-methoxybenzoyl)benzo[b]-thiophene* (XLII) was obtained as colorless little prisms, m.p. 102.5°, giving a bright red color with sulfuric acid.

Anal. Calcd. for $C_{20}H_{20}O_2S$: C, 74.07; H, 6.17; S, 9.87. Found: C, 74.38; H, 6.03; S, 9.68.

The solvent from the recrystallizations of XLII was evaporated. The residue was distilled then cooled and a small amount of XLII extracted by crystallization. After further distillation and cooling, *2,3-diethyl-5-(4'-methoxybenzoyl)benzo[b]thiophene* (XLIII) almost free of XLII was finally obtained as a very viscous yellow liquid, b.p. 277–279° (17.5 mm); n_D, 1.6467 (22°).

Anal. Calcd. for $C_{20}H_{20}O_2S$: C, 74.07; H, 6.17; S, 9.87. Found, C, 73.68; H, 6.01; S, 10.18.

Reduction of XLII.—Following the usual technique with 14 g. of XLII, 3.26 g. of hydrazine hydrate, and 3.26 g. of potassium hydroxide in 150 ml. of diethylene glycol after heating for 1.25 hr., was obtained 9.8 g. (73%) of *2,3-diethyl-6-(4'-methoxybenzyl)benzo[b]thiophene* (XLVI): a very viscous yellow liquid, b.p. 277° (17 mm.); n_D 1.6178 (22°).

Anal. Calcd. for $C_{20}H_{22}OS$: C, 77.41; H, 7.09; S, 10.32. Found: C, 77.32; H, 7.16; S, 10.15.

4-Methoxy-4'-(3-hexyl)diphenylmethane (XLVIII).—Submitting 7 g. of XLVI to the desulfurizing reduction technique

described above, 6 g. (94%) of XLVIII was obtained. This compound appeared as a colorless liquid, b.p. 224° (18 mm.), n_D, 1.5410 (23°).

Anal. Calcd. for $C_{20}H_{26}O$: C, 85.10; H, 9.21. Found: C, 84.80; H, 9.34.

Demethylation of XLVIII.—A mixture of 6.5 g. of XLVIII and 13 g. of pyridinium chloride was heated for 1.5 hr. then poured into dilute hydrochloric acid and extracted with benzene. The treatment of the organic layer gave 3 g. (48%) of *4-hydroxy-4'-(3-hexyl)diphenylmethane* (IL): amber liquid, b.p. 236° (17 mm.), n_D, 1.5530 (25°).

Anal. Calcd. for $C_{19}H_{24}O$: C, 85.07; H, 8.95. Found: C, 84.50; H, 92.0.

***p*-Nitrobenzoate of IL** was obtained as colorless pearly leaflets, m.p. 52.5°.

Anal. Calcd. for $C_{26}H_{27}O_4N$: C, 74.82; H, 6.47; N, 3.35. Found: C, 74.90; H, 7.00; N, 3.36.

4-Methoxy-3'-(3-hexyl)diphenylmethane (L).—The reduction of 6 g. of XLIII was carried out by heating it for 1.5 hr. with 1.5 g. of hydrazine hydrate, and 1.4 g. of potassium hydroxide in 100 ml. of diethylene glycol. This gave 3.2 g. of a resinous red compound [b.p. 288–295° (25 mm.)] which was directly desulfurized by refluxing for 45 min. in the presence of 65 g. of Raney nickel in 180 ml. of ethanol. Compound L is an amber liquid, b.p. 225° (20 mm.), n_D, 1.5380 (26°).

Anal. Calcd. for $C_{20}H_{26}O$: C, 85.10; H, 9.21. Found: C, 84.72; H, 9.51.

Infrared spectra were recorded on a Perkin Elmer double beam spectrophotometer $n°$ 21, fitted with a sodium chloride prism. The samples examined were placed between two rock-salt plates.

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The Unexpected Fate of an Attempted Steroid Synthesis

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In an attempted synthesis of equilenin, 2-propionyl-6-methoxynaphthalene (I) was converted, *via* the hydroxymethylene derivative II and the isoxazole III, into the cyano ketone IV which, as its sodio derivative, was alkylated with ethyl bromoacetate. The product proved to be a mixture of C- and O-alkylated derivatives. On base-catalyzed condensation with succinate, the former substance (V) failed to give the desired product (VI); hence the synthetic objective could not be realized. The O-alkylation product VII gave a crystalline condensation product which proved to be the furano compound VIII as shown by spectroscopy studies of VIII and its reaction products X, XI, and XII.

Some years ago[1] we planned a total synthesis of the female sex hormone equilenin by an approach which obviated the use of 1,6-disubstituted naphthalene derivatives,[2] employing instead the more accessible 2,6-disubstituted derivative, namely, 2-propionyl-6-methoxynaphthalene (I).[3] Thus it was proposed to convert this ketone by a known sequence of steps,[2b] *via* II and III, into the cyano ketone IV which in turn was to be alkylated with ethyl bromoacetate. Condensation of the resulting keto ester nitrile V with succinic ester was envisaged for the completion of ring D,[2b] to give VI, and finally the acetic acid side chain was to serve for completion of ring C by cyclization into the 1-position in the naphthalene nucleus.

The early steps of the synthesis proceeded as planned, but we first met with difficulty in the reaction of the cyano ketone IV with ethyl bromoacetate, which proceeded to give a mixture of C- and O-alkylated material (V and VII). On treatment of this mixture with succinic ester under conditions for the Stobbe reaction, the only condensation product that could be isolated eventually proved to be derived from the O-alkylated material. The C-alkylated material, unfortunately, gave none of the desired keto ester VI; hence the original objective could not be realized.[4]

In an effort to ascertain the structure of the crystalline condensation product, a number of its reactions were studied which, until recently, we had not been able to interpret to our satisfaction. The present report constitutes an account of our experiments with an interpretation which has now been made possible through the use of infrared and n.m.r. spectroscopy.

The hydroxymethylene derivative of 6-methoxy-2-propionylnaphthalene II, m.p. 152.1–153.7°, was obtained in 92% yield by the treatment of this ethyl ketone with ethyl formate in the presence of sodium methoxide. The crude hydroxymethylene derivative II was treated with hydroxylamine hydrochloride in glacial acetic acid to give in 98% yield the isoxazole III, m.p. 122–123.2°, conversion of which into the alkali-soluble cyano ketone IV was effected by treatment with sodium alkoxide. In this way it was possible to isolate, in 96% yield, α-(6-methoxy-2-naphthoyl)-propionitrile (IV), which has the potential carbon atoms 13, 14, and 17 and also the methyl group at carbon 13 of the equilenin structure.

(1) Richard T. Rapala, Ph.D. thesis, University of Wisconsin, 1949.

(2) *Cf.*(a) W. E. Bachmann, W. Cole, and A. L. Wilds, *J. Am. Chem. Soc.*, **62**, 824 (1940). (b) W. S. Johnson, J. W. Petersen, and C. D. Gutsche, *ibid.*, **67**, 2274 (1945).

(3) R. D. Haworth and G. Sheldrick, *J. Chem. Soc.*, 864 (1934).

(4) Much of the work described below was performed before the "useless" nature of the products was appreciated. While this study is of interest in its own right, it serves to emphasize the not uncommon fate of many well laid synthetic plans.