amount of dark residue was removed by filtration. The solution was diluted and acidified to turbidity, which, after standing in the ice-box all day, changed to a colorless crystalline precipitate, weighing 0.35 g. (80%). The analytical sample was obtained by recrystallization from 40% ethanol to give colorless fine crystals, m.p. 190–192° (shrinking at 185°).

Anal. Calcd. for $C_{16}H_{20}O_7$: C, 59.25; H, 6.10. Found: C, 59.36; H, 6.26.

2,3,4-Trimethoxybenzosuberan-5,6-dicarboxylic Anhydride (XI).—The benzosuberan diacid (IX) (2 g.) was refluxed with 10 ml. of acetic anhydride for two hours. The excess solvent was evaporated under vacuum, leaving a thick oil weighing 1.52 g. (82%), which was recrystallized from acetic acid to give colorless needles, m.p. 176.5–177.5°.

Anal. Calcd. for $C_{16}H_{18}O_6$: C, 62.79; H, 5.93. Found: C, 63.00; H, 6.13.

2,3,4-Trimethoxybenzosuber-5-ene-5-carboxylic Acid (XIII).—A mixture of 3 g. of VII and 40 ml. of 16% sulfuric acid was refluxed with stirring for 5 hours, causing some yellowish solid to separate gradually. After cooling in the ice-box for a few hours, the residue was filtered off and dissolved in dilute sodium hydroxide solution. Since very little insoluble material separated, the solution was acidified. The colorless crystalline precipitate was filtered off and dried; yield 2 g. (91%), m.p. 195–198°. Recrystallization of the crude product from dilute ethanol gave colorless small scales, m.p. 198–200°. In another run, the starting material weighed 5.5 g. and the yield of acid was 3.4 g. (86%).

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.75; H, 6.47. Found: C, 64.82; H, 6.50.

Ethyl 2,3,4-Trimethoxybenzosuber-5-ene-5-carboxylate (XIV).—The acid (XIII) (1 g.) was refluxed with 10 ml. of absolute ethanol and 1 ml. of concd. sulfuric acid for 5 hours. The resulting mixture was diluted with cold water and extracted with ether. The ether solution, after being washed with 5% sodium bicarbonate solution and then water, was evaporated to yield an oil weighing 1.27 g. (77%), which was crystallized from dilute ethanol. After standing in the ice-box for 2 weeks, the oil which first separated on cooling, solidified partially to crystals. Recrystallization in the same manner was repeated twice to give colorless fine crystals, m.p. 44–45°.

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.66; H, 7.19. Found: C, 66.64; H, 7.36.

2,3,4-Trimethoxybenzosuberan-5-carboxylic Acid (XV).—A mixture of 0.5 g. of 2,3,4-trimethoxybenzosuber-5-ene-5-carboxylic acid (XIII) in 10 ml, of acetic acid was hydrogenated over 1 g. of palladium–carbon catalyst at 60° and 40 lb. pressure for 5 hours; stirring without heating was continued for another 4 hours. Filtration of catalyst followed by evaporation of the solvent left a gum weighing 0.45 g. (90%), which was recrystallized from dilute ethanol once to yield colorless fine crystals, m.p. 138–140°.

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.28; H, 7.14. Found: C, 64.38; H, 6.98.

Ethyl γ-(3,4,5-Trimethoxyphenyl)-propylmalonate (XVI).—The keto diester (VII) (4.0 g.) was heated in a distilling flask under vacuum. When the metal-bath temperature reached 130°, the substance simultaneously started to bubble and evolve a gas. The reaction was finished at the end of the 1.5 hr. taken to raise the bath temperature to 150°. The product was then distilled at 187–188° (0.7 mm.) to give 2.3 g. (62%) of a colorless viscous oil.

Anal. Calcd. for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66. Found: C, 61.96; H, 7.86.

Alkaline and Acid Hydrolysis of Ethyl 2,3,4-Trimethoxybenzosuber-5-ene-5,6-dicarboxylate (VIII) (a).—The diester (0.5 g.) was refluxed with 10 ml. of 15% sodium hydroxide for 5 hours. Very little neutral material was removed with ether, and the solution was acidified with dilute hydrochloric acid to yield at first a yellowish turbidity which gradually changed to a light yellow precipitate. This was recrystallized once from ether–pentane to give yellow needles of XII, weighing 0.32 g. (80%), m.p. 119–120°, no depression on admixture with an authentic sample[3] of 2,3,4-trimethoxybenzosuber-5-ene-5,6-dicarboxylic anhydride.

Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 62.89; H, 5.32.

(b).—The diester (1 g.) was refluxed with 15 ml. of 16% sulfuric acid for 15 hours. After cooling, an oil separated; this was taken up with ether and the resulting ether solution was washed with dilute $NaHCO_3$ solution and then with water. Acidification of the $NaHCO_3$ solution yielded nothing. The ether solution was worked up, and almost all of the starting material was recovered unchanged.

Attempted Hydrogenation of the Anhydride (XII).—Hydrogenation of 2,3,4-trimethoxybenzosuber-5-ene-5,6-dicarboxylic anhydride (XII) in acetic acid with palladium-carbon catalyst at 60° and 40 lb. pressure for 10 hours was unsuccessful. No hydrogen was absorbed and all of the starting material was recovered.

BETHESDA, MARYLAND

[CONTRIBUTION FROM THE BEN MAY LABORATORY FOR CANCER RESEARCH, UNIVERSITY OF CHICAGO]

Hormonal Antimetabolites. I. Derivatives of *meso*-2,2′-Dithienylhexane

BY JEAN SICÉ AND MORTON MEDNICK

RECEIVED AUGUST 18, 1952

As a first step toward the eventual procurement of sex hormone antagonists, the thiophene isolog of hexestrol and related analogs of progesterone and desoxycorticosterone have been prepared from dithienylhexane (III), obtained by coupling of thienylhalopropanes. None of these substances showed any estrogenic activity in mice.

To date a few unsuccessful attempts to find direct antagonists to sexual and cortical hormones have been reported. Because of the interest of this Laboratory in hormone-dependent tumors, a different approach to this problem has been undertaken. Estrogens inhibit normal growth but produce cancer in many organs; androgens partially inhibit the effect of estrogens. Estrogens cause regression of certain human cancers of the prostate and breast. Androgens may accelerate the growth of prostatic cancer and depress the activity of some mammary carcinoma.[1] The sex hormones used clinically overstimulate the secondary sex characteristics, thereby producing some objectionable side effects (feminization or masculinization); direct antagonists should provide a therapeutic action free from secondary effects.

The correlation of the chemical structure with the physiological activity of the stilbenic estrogens brings out the essential role of both the hydrocarbon skeleton and the phenolic groups; the purpose of this study is to determine whether an alteration in the electronic distribution of the aromatic nuclei, in this series, can produce an antagonistic analog (antiestrogen or antiandrogen) of these substances.[2] Lacassagne and Buu-Hoï[3] have shown that the

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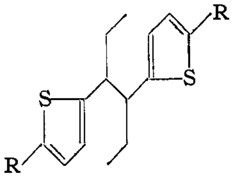
[1] *Cf.* C. Huggins, *Yale J. Biol. Med.*, **19**, 319 (1947); *J. Urology*, **68**, 875 (1952).

[2] *Cf.* D. W. Woolley, "A Study of Antimetabolites," John Wiley and Sons, Inc., New York, N. Y., 1952.

[3] L. Corre, M. de Clercq, Ng. Ph. Buu-Hoï, Ng. Hoán and A. Lacassagne, *Bull. soc. chim. biol.*, **30**, 674 (1948).

estrogenic activity of the synthetic diaryl- and triarylethylenes decreases with the respective rings: phenyl, naphthyl, xenyl, thienyl, furyl, Some unsymmetrical thiophene analogs of stilbestrol have been reported.[4] The synthesis of symmetrical derivatives of *meso*-di-(2-thienyl)-hexane is described in this communication,



III, R = –H
IV, R = $-SO_2NH_2$
V, R = –I
VI, R = $-OCH_3$
VIIa, R = $-COCH_3$,
VIIb, R = $-COCH_2Br$
VIII, R = $-COCH_2OCOCH_3$

The substance (III), which provides a convenient starting material for the synthesis of these compounds, is best obtained by a Wurtz–Fittig coupling of 1-(2-thienyl)-1-halopropanes (II), These halides are satisfactorily prepared by treatment of 1-(2-thienyl)-1-hydroxypropane (I) with anhydrous hydrogen halides; (I) is obtained in good yields either by condensation of 2-thienyllithium[5] with propionaldehyde or of 2-thiophenecarboxaldehyde with ethylmagnesium bromide.

Secondary halides of this type (II) have not as yet received much attention[6]; their ability to couple under the influence of various reagents does not follow that of their benzene analogs, Table I.

The use of an aryllithium-catalyzed coupling[7] of (IIa) provides the most convenient way of obtaining dithienylhexane (III); the chloride (IIb) treated with butyllithium yields only a small amount (1.5%) of (III). A crystalline substance can be isolated in each case from the products of the reaction and is assigned the *meso* configuration by analogy with the synthesis of hexestrol; a liquid which presumably contains some *dl*-dithienylhexane remains in the mother liquors and has not yet been characterized.

TABLE I

YIELDS OBTAINED BY COUPLING OF THIENYLHALOPROPANES AND ANISOLE HYDROHALIDES

Reagent	Halide	Thiophene	Benzene
Mg	Cl	2	0[a]
	Br	7	15[a]
$CoCl_2$ + R-Mg-X	Cl	12	20[b]
	Br	12	30[b]
ArLi	Br	13	10[c]

[a] A. M. Docken and M. A. Spielman, THIS JOURNAL, **62**, 2163 (1940). [b] M. S. Kharasch and M. Kleiman, *ibid.*, **65**, 491 (1943); A. L. Wilds and W. B. McCormack, *J. Org. Chem.*, **14**, 45 (1949). [c] Unpublished data from this Laboratory.

The crystalline substance (III) can be converted to the bis-sulfonamide (IV), halogenated (V) and acetylated (VIIa) by usual methods in good yields. As might be expected, the new substituents enter the 5-position of the nuclei, as shown by infrared spectroscopy (disappearance of the doublet at 830, 860 cm.$^{-1}$).[8]

Our failure to improve the known preparation[9] of methoxythiophene led us to investigate a modification of Ullmann's reaction[10]; the halogen of a halothiophene can indeed be replaced by an alkoxy group, with sodium alkoxides at moderate temperature in the presence of metallic oxides. This procedure furnishes the thiophene isostere (VI) of hexestrol dimethyl ether in good yield from the corresponding dihalide (V). Bromination of the diacetyldithienylhexane (VIIa) gives a dihalide (VIIb) that can be transformed into the corresponding diacetoxy–diacetyl compound (VIII) in fair yield.

The pharmacodynamic properties of these compounds are being investigated in this Laboratory. A preliminary screening[11] has failed to reveal any estrogenic activity at a 0.1 mg. dose level for the compounds tested (III, IV, VI and VIIa).

Experimental

The authors are indebted to Mr. W. Saschek for the microanalyses (unless otherwise specified) and to Mr. N. Phillips for the infrared spectra (Nujol mulls in a Perkin–Elmer spectrophotometer). The melting points were determined in evacuated capillaries and are corrected; boiling points are uncorrected. The alumina for chromatography was neutral and of activity II (Brockmann).

1-(2-Thienyl)-1-propanol (I).—Efficient stirring under an inert atmosphere was maintained throughout the condensations. (A) Forty ml. of thiophene was added over a 5-minute period, with cooling, to 500 ml. of a molar solution of butyllithium in ether, stirred at room temperature for an hour, then cooled to −10°. Propionaldehyde (35 ml.) in absolute ether (70 ml.) was added to the cold mixture, over a 30-minute period; the cold-bath was removed and the suspension left to warm up to room temperature.

(B) With ice-cooling, 0.75 mole of 2-thiophenecarboxaldehyde[12] was added dropwise to 1 mole of ethylmagnesium bromide dissolved in 500 ml. of ether. The mixture was left to warm up to room temperature overnight.

In either case, the mixture was poured onto ice, the solvent layer washed with dilute ammonium hydroxide and dried over potassium carbonate. After two distillations under reduced pressure the product boiled at 89° (7 mm.); yielded 60 and 86%, respectively; $n^{20}\text{D}$ 1.5350, d^{20}_4 1.1054.

Anal. Calcd. for $C_7H_{10}OS$: C, 59.11; H, 7.09; MR_D, 40.89. Found: C, 59.47; H, 7.29; MR_D, 40.05.

The **phenylurethan** crystallized from hexane in colorless needles, m.p. 82–84°.

Anal. Calcd. for $C_{14}H_{15}O_2NS$: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.26; H, 6.17; N,[13] 5.55.

***meso*-3,4-Di-(2-thienyl)-hexane (III).**—A solution of I in four volumes of dry C.P. pentane was saturated with dry hydrogen bromide (or chloride) gas at such a rate that the temperature remained between −5° and −10°. Toward the end of the reaction the solution turned pink. The solvent layer was decanted and evaporated under reduced pressure of dry nitrogen. The residue was dissolved in absolute ether and used immediately for the following step.

Efficient stirring under an inert atmosphere was maintained throughout the condensations.

Organolithium Method (A).—A solution of phenyllithium, prepared from 1.4 g. of lithium and 10 ml. of bromobenzene, in 80 ml. of ether was added in a slow stream to a cold (−30 to −40°) solution of 1-(2-thienyl)-1-bromopropane (IIb),

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[4] Ng. Ph. Buu-Hoï and Ng. Hoán, *J. Org. Chem.*, **17**, 350 (1952); W. R. Biggerstaff and O. L. Stafford, THIS JOURNAL, **74**, 419 (1952).

[5] H. Gilman and D. A. Shirley, *ibid.*, **71**, 1870 (1949); G. B. Bachman and L. V. Heisey, *ibid.*, **70**, 2378 (1948).

[6] *Cf.* W. S. Emerson and T. M. Patrick, *J. Org. Chem.*, **13**, 729 (1948); J. H. Clark, *et al.*, *ibid.*, **14**, 216 (1949).

[7] G. Wittig and H. Witt, *Ber.*, **74**, 1474 (1941).

[8] F. P. Hochgesang in Hartough's "Thiophene and Its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952.

[9] C. D. Hurd and K. L. Kreuz, THIS JOURNAL, **72**, 5543 (1950).

[10] B. B. Dey, *et al.*, *J. Sci. Ind. Research (India)*, **5B**, 25 (1946).

[11] J. S. Evans, R. F. Varney and F. C. Koch, *Endocrinology*, **28**, 747 (1941).

[12] Generously supplied by Monsanto Chemical Co.

[13] Microanalyses performed by Micro-Tech Laboratories, Skokie, Ill.

from 14.22 g. of I, in 150 ml. of ether. The faint yellow mixture was left to warm up for 30 minutes then poured onto 100 g. of ice. The solvent layer was washed with dilute hydrochloric acid, aqueous sodium bicarbonate, dried over sodium sulfate and evaporated. The yellow residue distilled at 97–98° (0.01 mm.) (bath temperature 125–130°); the trap contained impure bromobenzene. The distillate crystallized from ethanol (25 ml.) yielding 1.75 g. of colorless octagons, m.p. 76–77°. **The infrared spectrum** (Fig. 1) is basically that of a 2-alkylthiophene,[8] except for the constant presence throughout this series of a band at 800 cm.$^{-1}$. This curve was determined with a Beckman spectrophotometer in CS_2 and CCl_4 solutions (*c* 10.0); a Nujol mull gave an identical spectrum.

Anal. Calcd. for $C_{14}H_{18}S_2$: C, 67.14; H, 7.25. Found: C, 66.97; H, 7.20.

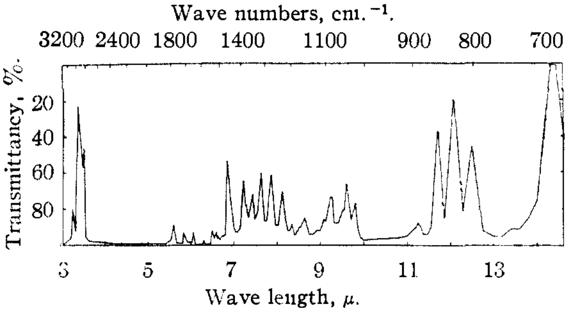

Fig. 1.—Infrared absorption curve of *meso*-di-2-thienylhexane.

(B).—One hundred ml. of a molar solution of butyllithium in ether were added slowly to an ice-cold solution of 1-(2-thienyl)-1-chloropropane (IIa), from 0.1 mole of I, in 150 ml. of ether; the mixture was stirred for 30 minutes and worked up as previously. Distillation of the residue gave two fractions: 9.2 g. of a colorless liquid, b.p. 40–45° (0.01 mm.) (bath temperature 60–85°) and 3.1 g., b.p. 98–108° (0.01 mm.), which gave 0.18 g. of (III). The low boiling fraction turned purple on standing and failed to give any stable homogeneous material after two subsequent distillations from sodium.

Cobalt-Grignard Method.—An ether solution (200 ml.) of ethylmagnesium bromide (from 25 g. of ethyl bromide and 5.75 g. of magnesium) was treated with 1.34 g. of anhydrous cobaltous chloride and the mixture was stirred for 6 to 12 hours. This reagent was then treated with a solution of IIa, from 19.25 g. of I, in 90 ml. of ether, added over a 5-minute period, provoking a vigorous evolution of gas. The black suspension is poured onto ice and hydrochloric acid, and the solvent layer treated the same as above. The black tarry residue of evaporation (15.65 g.) was taken up in hexane and passed over a column (66 g.) of alumina. The eluate (100 ml.) was evaporated leaving a green liquid (14.80 g.) which distilled at 86–96° (0.005 mm.) (bath temperature 120–140°) (10.56 g.). Part of the distillate crystallized from ethanol in colorless octagons (2.20 g.) identical with the product obtained previously. The yield of the reaction was not affected by running the condensation at −30 to −40° or substituting IIb for IIa, although the amount of tars is smaller in the latter case. The mother liquors of the crystallization distilled at 87–92° (0.01 mm.) (6.3 g.).

Magnesium Method.—An ether solution (25 ml.) of IIa from 15.23 g. of (I), was added over a 20-minute period to 9.73 g. of magnesium in 80 ml. of ether; the reaction was started with a few drops of ethyl bromide and the pink mixture stirred overnight and worked up as above. 0.25 g. of III was obtained from 2.4 g. of distillate, b.p. 88–90° (0.005 mm.).

***meso*-3,4-Di-(5-sulfonamido-2-thienyl)-hexane** (IV).—One gram of III is sulfonated and converted to the sulfonamide by following the procedure of Huntress.[14] The reaction product (0.32 g.) is chromatographed on 2.0 g. of alumina in a benzene–acetone mixture (1:1); the eluate crystallized from acetone–benzene to give the bis-sulfonamide in colorless needles (20% yield), m.p. 218–220°. **The infrared spectrum** differs from that of III by the absence of the doublet at 830, 860 cm.$^{-1}$ and the presence of strong bands at 1005, 1161, 1320 to 1344 cm.$^{-1}$ (SO_2NH_2) and of a doublet at 3255, 3355 cm.$^{-1}$ (NH_2).

Anal. Calcd. for $C_{14}H_{20}O_4N_2S_4$: C, 41.15; H, 4.93; N, 6.86. Found: C, 41.59; H, 4.96; N, 6.85.

***meso*-3,4-Di-(5-iodo-2-thienyl)-hexane** (V).—A solution of 0.675 g. of III in 2 ml. of benzene was treated portionwise with 0.97 g. of mercuric oxide and 1.42 g. of iodine at room temperature. The mixture was taken up in ether, washed with sodium thiosulfate, dried and evaporated, leaving 1.24 g. of a beige powder. Colorless crystals (0.90 g.) were obtained after crystallization from methanol and sublimation at 90° under high vacuum, m.p. 139–140°.

Anal. Calcd. for $C_{14}H_{16}I_2S_2$: C, 33.48; H, 3.21; I, 50.54. Found: C, 33.73; H, 3.47; I, 50.34.

***meso*-3,4-Di-(5-methoxy-2-thienyl)-hexane** (VI).—0.825 g. of V was refluxed for 20 hours with 0.13 g. of cupric oxide and 5 ml. of a $^1/_5$ molar solution of sodium methoxide in absolute methanol. Water (20 ml.) was added to the cooled mixture which was then extracted with benzene, dried and evaporated. The residue (0.45 g.) was chromatographed over 10.0 g. of alumina in hexane, the eluate (0.41 g.) crystallized from benzene–hexane in colorless needles; after sublimation at 85° under high vacuum, m.p. 98–100°. **The infrared spectrum** differs from that of III by the presence of only one weak band at 860 cm.$^{-1}$ in the doublet region; and of strong bands at 761, 1152 (C–O–C), 1192 and 1206 cm.$^{-1}$, all of which are present in the spectrum of 2-methyl-5-methoxythiophene.

Anal. Calcd. for $C_{16}H_{22}O_2S_2$: C, 61.89; H, 7.14; S, 20.66. Found[13]: C, 61.85; H, 7.25; S, 20.81.

***meso*-3,4-Di-(5-acetyl-2-thienyl)-hexane** (VIIa).—A solution of 0.5 g. of III in 0.5 ml. of acetic anhydride was treated with one drop of 85% ortho-phosphoric acid,[15] then heated at 110° for 90 minutes. The crystalline material that had separated was filtered, washed with ethanol, crystallized from acetone and sublimed at 125–130° under high vacuum; colorless needles (0.58 g.), m.p. 182–184°. **The infrared spectrum** differs from that of III by the presence of only one weak band at 840 cm.$^{-1}$, the absence of the band at 699 cm.$^{-1}$ and the presence of strong bands at 863, 999, 1280 and 1651 cm.$^{-1}$ ($COCH_3$).[16] **The ultraviolet spectrum** showed the bathochromic and hyperchromic effects characteristic of the 2-thienyl ketones and carboxylic acids[17] substituted into the 5-position; λ_{max}^{EtOH} 267 and 301 mμ with ϵ, respectively, 16,400 and 27,300.

Anal. Calcd. for $C_{18}H_{22}O_2S_2$: C, 64.63; H, 6.63. Found: C, 64.76; H, 6.71.

***meso*-3,4-Di-(5-bromoacetyl-2-thienyl)-hexane** (VIIb).—A 5 *N* solution (0.4 ml.) of bromine in carbon tetrachloride was added dropwise to a solution of 0.167 g. of VIIa in chloroform, through which a steady stream of dry nitrogen was passed. The reaction started at 30–35° and proceeded best at 20°. As soon as the evolution of hydrogen bromide was subsided, the mixture was evaporated to dryness *in vacuo* at 20°, leaving a white powder (0.24 g.) that crystallized from ethanol in colorless needles, m.p. 155–158° (dec.).

Anal. Calcd. for $C_{18}H_{20}O_2Br_2S_2$: Br, 32.47. Found: Br, 32.56.

***meso*-3,4-Di-(5-acetoxyacetyl-2-thienyl)-hexane** (VIII).—The crude bromide (VIIb), from 0.167 g. of (VIIa), m.p. 142–145° (dec.), was taken up in 25 ml. of dry acetone and treated with 2.00 g. of anhydrous potassium acetate. This suspension was shaken at room temperature for 2 hours and gently refluxed for an additional hour. The yellowish solution was filtered and evaporated to dryness *in vacuo*. The yellow residue was taken up in ether, washed with dilute aqueous sodium bicarbonate, water, dried over sodium sulfate and evaporated. The partially crystallized substance was chromatographed on 5.0 g. of alumina. A mixture of hexane–benzene (1:1) eluated 100 mg. of oil; benzene eluated 120 mg. (53%) of colorless needles, m.p. 141–143°. Crystallization from acetone–hexane and ethyl acetate–ether did not change the melting point. **The infrared spec-**

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(14) E. H. Huntress and J. S. Autenrieth, THIS JOURNAL, **63**, 3446 (1941).

(15) H. D. Hartough and A. I. Kosak, *ibid.*, **69**, 3093 (1947).

(16) R. N. Jones, P. Humphries, F. Herling and K. Dobriner, *ibid.*, **74**, 2820 (1952).

(17) H. H. Szmant and A. J. Basso, *ibid.*, **73**, 4521 (1951) and unpublished data (J. S.).

trum differs from that of (III) by the absence of bands at 830 and 699 cm.$^{-1}$, and the presence of strong bands at 911, 1215, 1674 and 1741 cm.$^{-1}$ ($COCH_2OCOCH_3$).[16]

Anal. Calcd. for $C_{22}H_{26}O_6S_2$: C, 58.64; H, 5.82. Found: C, 58.31; H, 6.00.

This investigation was supported by grants from the American Cancer Society, as recommended by the Committee on Growth of the National Research Council, and the Jane Coffin Childs Memorial Fund for Medical Research.

CHICAGO 37, ILLINOIS

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, STANDARD OIL CO. (INDIANA)]

Sulfuric Acid Isomerization of Methylalkanes, Dimethylalkanes and Dimethylcyclohexanes

BY A. K. ROEBUCK AND B. L. EVERING

RECEIVED OCTOBER 27, 1952

Sulfuric acid was investigated as a catalyst for the isomerization of fourteen alkanes and cycloalkanes, and the rate of approach to equilibrium was measured. Increasing the initial acid concentration from 95.5 to 99.8% increased the rate of isomerization as much as 64-fold. Equilibrium compositions determined experimentally agree well with those calculated from heats of combustion, except for the interconversion of 2,3-dimethylpentane and 2,4-dimethylpentane. No significant change in the degree of branching of the hydrocarbon chain was observed, but methyl groups migrated readily. Rearrangements occur only at a tertiary carbon and are of three kinds: a rapid rearrangement of methyl groups with respect to plane, as in geometric isomers; a less-rapid shift of a methyl group along the hydrocarbon chain; and a relatively slow shift of a methyl group around the hydrocarbon ring.

Introduction

Considerable work has been done on the isomerization of various alkanes and naphthenes with sulfuric acid as the catalyst, but little has been reported on isomerization rates. The sulfuric acid isomerization of alkanes has been studied largely in connection with the products that result from alkylation.[1] Gordon and Burwell[2] compared the isomerization rates of several methylalkanes, and showed that sulfuric acid racemizes optically active 3-methylheptane; normal paraffins and those containing quaternary carbons are not isomerized. Certain methylalkanes and dimethylalkanes have been isomerized with little side reaction; the conversions were limited by equilibria.[3] Measurement of the relative rates of isomerization of the isomeric hexanes with aluminum chloride showed the interconversion of 2- and 3-methylpentane to be the most rapid reaction.[4]

No work has been reported on the sulfuric acid isomerization of the dimethylcyclohexanes, although a study with dimethylcyclopentane has recently been reported.[5] Isomerization of dimethylcyclohexanes with aluminum chloride gives largely *cis*-1,3-dimethylcyclohexane, the most stable isomer.[6] The *cis–trans* isomerization of the 1,2- and 1,4-dimethylcyclohexanes was observed by Zelinsky and Margolis,[7] who passed the hydrocarbons over active nickel at 175°. With aluminum chloride,[8] *cis*-1,2-dimethylcyclopentane was converted rapidly to the *cis–trans* equilibrium mixture, which was then converted slowly to methylcyclohexane.

The present paper deals with the quantitative measurement of equilibria and with the effects of sulfuric acid concentration and hydrocarbon structure on the isomerization rates of fourteen hydrocarbons. Sulfuric acid gives rise to a minimum of side reactions and thus permits more accurate measurement of equilibria and isomerization rates.

Experimental

2-Methylpentane, 3-methylpentane, 2,3-dimethylpentane, 2,4-dimethylpentane and 2,3-dimethylhexane were obtained from the Phillips Petroleum Co. and used without further purification. Grignard synthesis followed by dehydration of the alcohol and hydrogenation of the olefin was used to prepare 2-methylhexane, 3-methylhexane and 2,4-dimethylhexane. 3-Methylheptane was prepared from 2-ethylhexanol by dehydration and hydrogenation. The synthesized alkanes were fractionated in a 1-inch Stedman column of 60 theoretical plates, and fractions having the accepted boiling points and refractive indices were retained. Dimethylcyclohexanes were prepared by hydrogenating the individual xylenes and separating the *cis* and *trans* isomers in the Stedman column. In the case of *m*-xylene, which was contaminated with *p*-xylene, only *cis*-1,3-dimethylcyclohexane could be isolated. Physical constants of all fourteen hydrocarbons are compared with the values of Rossini[9] in Table I; the indicated purities were determined by mass-spectrometric analysis of the alkanes and by infrared analysis of the dimethylcyclohexanes. The hydrocarbons were free of olefins, as determined by negative reaction with potassium permanganate, and contained less than 3 p.p.m. of peroxide.[10]

Sulfuric acid of the desired concentration was prepared by mixing commercial 96% acid and fuming sulfuric acid. The actual strength was established with an accuracy of ±0.1% by titration against 0.2 *N* sodium hydroxide.

The isomerization studies were made by vigorously stirring the hydrocarbon with an equal weight of sulfuric acid in a round-bottomed flask equipped with a wire-loop stirrer[11]

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