C^{14} and sodium acetate-2-C^{14}. Samples of the labeled esters were brominated at 25° in carbon tetrachloride with sufficient bromine to give 10, 40 and essentially 100% reaction. In the cases of partial reaction, the unreacted methyl cinnamate was vacuum-distilled from the dibromo ester and the residue was recrystallized from methanol to give methyl dibromocinnamate having a melting point of 119°. For the 100% reaction purification was by recrystallization only. Product samples were oxidized using Van Slyke solution and assayed using the vibrating reed electrometer.

Diels–Alder Reaction[10] of β-Nitrostyrene-α-C^{14} and 2,3-Dimethylbutadiene.—The choice of this Diels–Alder reaction for isotope fractionation study was based partially on the fact that it gives relatively high yields at 80 to 100° of a crystalline, easily purified adduct. The β-nitrostyrene-α-C^{14} was synthesized[11] from benzaldehyde-α-C^{14} and nitromethane. To obtain the labeled adduct from complete reaction of the labeled dienophile, 30 mmoles of 2,3-dimethylbutadiene, 20 mmoles of β-nitrostyrene-α-C^{14} and 20 ml. of dry toluene were heated to reflux temperature overnight. Excess diene and toluene were distilled off *in vacuo* and the adduct, m.p. 91.5–92.5°, was obtained by recrystallization from aqueous ethanol and vacuum sublimation. To obtain the labeled adduct representing 30% reaction of the dienophile the same procedure was repeated using 50 mmoles of β-nitrostyrene-α-C^{14} and 15 mmoles of 2,3-dimethylbutadiene. The adduct was separated from unreacted dienophile (after distilling the solvent) by fractional extraction of the concentrate with 95% ethanol. The product thus separated was further purified to m.p. 91–92° by recrystallization from aqueous ethanol and vacuum sublimation. The purified products from 100% reaction and 30% reaction were burned[5] using Van Slyke solution and assayed[5] using the vibrating reed electrometer.

Test for Reversibility of the Diels–Alder Reaction.—Since certain Diels–Alder reactions are considered to be reversible, it was of interest to demonstrate that even at 130° (30 to 50° above the temperature at which the Diels–Alder reaction was run in this case) there was no appreciable rate of exchange between the adduct and uncombined dienophile. This demonstration was effected by heating β-nitrostyrene-α-C^{14} with an equimolar amount of unlabeled adduct as a melt for 24 hours at 130°. The adduct was isolated and after careful purification, showed only background activity. The possibility was thus eliminated that a rate isotope effect actually existed in this Diels–Alder reaction studied but was masked by rapid exchange between the adduct and unreacted dienophile.

IV. Examination of Carbon-14 Dioxide Absorption in Alkaline Media for Isotope Fractionation.—In experiments to determine whether isotope fractionation occurs in carbon-14 dioxide absorption, the gas was passed through (a) dilute sodium hydroxide and (b) benzylamine[12] in dibenzyl ether in such fashion as to give 80% absorption of the gas in each case. The extent of reaction was determined by the pressure and volume in the manometric system used. In each case the specific activity of the original gas was compared with the specific activity of the unabsorbed gas after reaction. Specific activity measurements were performed, always at the same temperature and pressure, in a 10-ml. stainless steel ion chamber[4] which was sealed into the manometric system. The sample data of Table IV indicate no isotope fractionations for these reactions.

TABLE IV

DATA INDICATING NO ISOTOPE FRACTIONATION IN CARBON-14 DIOXIDE ABSORPTION

Absorbent	Original sp. act. $C^{14}O_2$ (as millivolts)	Absorption of $C^{14}O_2$, %	Sp. act. of unabsorbed $C^{14}O_2$ (as millivolts)
200 ml. of C.P. dibenzyl ether and 1.7 ml. of C.P. benzylamine	986	80	987
200 ml. of 0.1 *N* aqueous sodium hydroxide	980	80	980

(10) C. F. H. Allen, A. Bell and J. W. Gates, *J. Org. Chem.*, **8**, 373 (1943).

(11) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 2nd Ed., 1947, p. 413.

(12) A. B. Wright and M. B. Moore, THIS JOURNAL, **70**, 3865 (1948).

OAK RIDGE, TENN

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

Preparation and Reactions of 2-Methoxythiophene

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2-Methoxythiophene was obtained by a copper-catalyzed Williamson synthesis. The ether function was found to overcome appreciably the directive influence of the hetero-atom in orienting some attack by electrophilic reagents on the 3-position; radical reagents reacted only with the 5-position. The readily available 5-methoxy-2-thienyllithium is a convenient material for the introduction of the 5-alkoxy-2-thienyl group into a molecule. A modification of the aldehyde synthesis of Bouveault is described.

2-Thienol and its methyl ether have recently been characterized; 3-thienol and its ethers have not yet been isolated. These two series of substances are important for the study of directive influences on nuclear substitutions of thiophene. Moreover, they would render available compounds of potential biological interest[1] containing an isostere of the phenyl ether group. But the free hydroxy substances exhibit an hemimercaptenol–thiolactone tautomerism or a keto–enol prototropy[2,3] and are unstable. A more satisfactory[2] preparation of 2-methoxythiophene and a study of its behavior in characteristic reactions are presented in this communication.

(1) *Cf.* J. Sicé and M. Mednick, THIS JOURNAL, **75**, 1628 (1953).

(2) C. D. Hurd and K. L. Kreuz, *ibid.*, **72**, 5543 (1950).

(3) P. Friedlaender and St. Kielbasinski, *Ber.*, **45**, 3389 (1912).

Iodothiophene reacted readily, bromothiophene slowly, chlorothiophene did not react with sodium alkoxides. The addition of minute quantities of sodium iodide accelerated the reaction of bromothiophene, but did not affect that of chlorothiophene. Cupric oxide[4] was more satisfactory as catalyst than cuprous oxide or copper. The concentration and the ratio of halide to sodium alkoxide and cupric oxide, and the quality of the latter, influenced the rate of the reaction. The yields were good and the products easily purified.

The strongly *ortho-para* orienting alkoxy group on carbon atom-2 increased the directive influence of the sulfur atom to the 5-position, but competed with it to induce some attack by electrophilic reagents (mercuration, nitration, acylation, in de-

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

creasing order) on the 3-position. This latter influence however did not affect substitutions by radical reagents (metalation, N-bromosuccinimide). If the carbon atom-5 was blocked, the 3-position could be metalated as the ortho position of an alkyl phenyl ether.[5] Attempts to sulfonate, chloromethylate or formylate (I) were unsuccessful, this compound and its derivatives being labile to strong acids.

Methoxythiophene (I) was found to react immediately with phenyllithium to give quantitatively 5-methoxy-2-thienyllithium (II), which yielded by carbonation 5-methoxy-2-thenoic acid (III). Hydrogenolysis of this acid (III) with Raney nickel[6] furnished, in good yield, 5-methoxyvaleric acid—which gives an easy preparation of this compound. A Wurtz–Fittig synthesis between II and alkyl halides or sulfates gave the corresponding 5-methoxy-2-alkenylthiophenes, the unsaturated sides chains of which are sensitive to cupric oxide. 5-Methoxy-2-methylthiophene reacted slowly with butyllithium and yielded by carbonation 2-methoxy-5-methyl-3-thenoic acid.

5-Methoxy-2-thenaldehyde (IV) was prepared in good yield through a Bouveault synthesis.[7] The original procedure has been shown to give rise to two side reactions[8] that lower the yield; substitution[9] of N-methylformanilide for dialkylformamides is not quite satisfactory. Good results were obtained by adding the organometallic reagent to dimethylformamide in slight excess. The secondary products of the reaction (dimethylamine and unreacted dimethylformamide) are water soluble, which simplified the isolation of the aldehyde. The methoxythenaldehyde (IV) condensed with 2-thenaldehyde, but the only crystalline material (12% yield) isolated from the reaction was identified as 5-methoxy-2,2′-thenil. Attempts to degrade[10] the latter substance or 2,2′-thenil showed the perfect stability of both compounds to periodic acid. It has been reported[11] that some sulfides do not behave normally with periodates.

5-Methoxy-2-thenyl alcohols were obtained from the aldehyde IV or the organometallic II by the usual procedures; they were unstable and the secondary alcohols decomposed on distillation. These substances were extremely sensitive to acidic reagents and therefore attempts to prepare any of their usual derivatives resulted in the formation of resins.

A monobromo compound was obtained in good yield by treatment of I with N-bromosuccinimide[12]; it was identified as 5-methoxy-2-bromothiophene through its conversion to the carboxylic acid III.

The acylation of 2-methoxythiophene with stannic chloride and acetyl chloride at low temperature, gave a mixture of two isomers. One compound (15% yield) was identified on the basis of its ultraviolet absorption as 5-methoxy-2-acetothienone. The second substance (1% yield) was assigned the structure of 2-methoxy-3-acetothienone by analogy with the results obtained by nitration of I. All attempts to acylate I with acetic anhydride, using orthophosphoric acid as a catalyst[13] resulted in the resinification of the starting material.

The nitration of methoxythiophene (I), by the acetyl nitrate method, gave again two substances. One of these compounds (24% yield) was identical with the known[14] 2-methoxy-3-nitrothiophene. Its isomer (36% yield) was assigned the 5-methoxy-2-nitrothiophene structure by analogy with the results obtained by acylation.

The ultraviolet spectral absorption of the 5-methoxythenoic acids prepared during the course of this work have been compared with those of the corresponding methylthenoic acids. These substances show two bands which have been called[15] P_1 and P_2 (Table I).

TABLE I

Compound	λ_1	ϵ_1	λ_2	ϵ_2	λ_1/λ_2	ϵ_2/ϵ_1
5-Methyl-2-	2730	8900	2480	6500	1.10	0.70
5-Methoxy-2-	2870	8700	2430	3500	1.18	0.40
2-Methyl-5-methoxy-3-[a]	2750	2600	2340	6300	1.18	2.40
2-Methoxy-5-methyl-3-	2790	3800	2380	4800	1.17	1.30
2,5-Dimethyl-3-	2750	1600	2450	7600	1.12	4.90

[a] S. Mitra, N. K. Chakrabarty and S. K. Mitra, *J. Chem. Soc.*, 1116 (1939).

The similar behavior, except for the hypochromic shift of the P_1 bands, of the 5-methyl(methoxy)-2-thenoic acids and the meta-substituted benzoic acids[16] was unexpected.

Experimental

The author is indebted to Mr. W. Saschek for the microanalyses (unless otherwise specified), to N. Phillips and N. S. Ham for the infrared spectra (Perkin–Elmer spectrophotometer, model 12 C, Nujol mulls for solids). The ultraviolet spectra were determined in a Beckman quartz spectrophotometer. The melting points were determined in evacuated capillaries and corrected; the boiling points were not corrected. The alumina for chromatography was neutral, of activity II (Brockmann). All the organometallic reactions were kept under an inert atmosphere.

2-Methoxythiophene (I).—2-Iodothiophene[17] (59 g.) and pulverized cupric oxide (11.2 g.) were added to a solution of sodium methoxide (from 19.7 g. Na) in absolute methyl alcohol (225 g.). The mixture was stirred and gently refluxed for 30 hours. The cooled suspension was then filtered, poured in two volumes of cold water and extracted with ether. The solvent layer was washed with water, dried and evaporated. Distillation of the residue from sodium gave 25.75 g. (80%), of a colorless liquid; b.p. 74–75° (50 mm.), $n^{25}D$ 1.5261, d^{25}_4 1.120, $\lambda_{max}^{pentane}$ 2410 Å (ϵ 4,300). The infrared spectrum showed a band in the C–O–C region (1153 cm.$^{-1}$) and is remarkable by the absence of the doublet

(5) H. Gilman and R. L. Bebb, THIS JOURNAL, **61**, 109 (1939); G. Wittig, U. Pockels and H. Droege, *Ber.*, **71**, 1903 (1938).

(6) F. F. Blicke and D. G. Sheets, THIS JOURNAL, **70**, 3768 (1948).

(7) L. Bouveault, *Bull. soc. chim.*, [3] **31**, 1322 (1904).

(8) N. Maxim and R. Mavrodineanu, *ibid.*, [5] **2**, 591 (1935); **3**, 1084 (1936).

(9) G. Barger and A. P. T. Easson, *J. Chem. Soc.*, 2100 (1938); G. Wittig, *Angew. Chem.*, **53**, 243 (1940).

(10) P. W. Clutterbuck and F. Reuter, *J. Chem. Soc.*, 1467 (1938).

(11) W. A. Bonner and R. A. Driskо, THIS JOURNAL, **73**, 3099 (1951).

(12) Ng. Ph. Buu-Hoi, *Ann.*, **556**, 1 (1944).

(13) H. D. Hartough and A. I. Kosak, THIS JOURNAL, **69**, 3093 (1947).

(14) C. D. Hurd and K. L. Kreuz, *ibid.*, **74**, 2965 (1952).

(15) For *first primary* and *second primary*—*cf.* L. Doub and J. M. Vandenbelt, *ibid.*, **69**, 2714 (1947); **71**, 2414 (1949). The wave lengths and molar absorbancy indices reported in this table are those of the band-envelopes obtained by analysis of the experimental curves.

(16) C. M. Moser and A. I. Kohlenberg, *J. Chem. Soc.*, 804 (1951).

(17) H. Y. Lew and C. R. Noller, *Org. Syntheses*, **30**, 53 (1950).

(820, 850 cm.$^{-1}$) which occurs[18] in thiophenes monosubstituted in the 2-position, except 2-acetylthiophene.

A similar result was obtained by substituting 2-bromothiophene[19] (45.7 g.) and sodium iodide (215 mg.) for iodothiophene. The mixture was then refluxed for 90 hours and treated as above.

2-Methoxy-3,5-thienylbis-mercuric Chloride.—A solution of 0.1 ml. of I in 1.0 ml. of ethanol was shaken for 20 hours with 8.5 g. of a saturated aqueous solution of mercuric chloride and 1.7 g. of a 33% aqueous solution of sodium acetate. The heavy white precipitate was filtered off, washed with water and air dried (0.47 g.). Two crystallizations from dimethylformamide–ethanol yielded 0.38 g. (65%) of colorless needles, m.p. 268–270° (dec.).

Anal. Calcd. for $C_5H_4OSCl_2Hg_2$: S, 5.49. Found[20]: S, 5.18.

The mother liquors from the crystallizations contained a substance that crystallized from ethanol in colorless needles, m.p. 139–141° (dec.). It possibly was **2-methoxy-5-thienylmercuric chloride** but the analytical values were not satisfactory.

Anal. Calcd. for $C_5H_5OSClHg$: C, 17.20; H, 1.44; S, 9.18. Found[20]: C, 16.27; H, 1.27; S, 8.34, 8.23.

2-Ethoxythiophene.—This compound was obtained by substituting a solution of sodium ethoxide in absolute ethanol for the sodium methoxide in methanol; b.p. 56° (13 mm.), $n^{27}D$ 1.5116, d^{27}_4 1.075.

Anal. Calcd. for C_6H_8OS: C, 56.21; H, 6.29; [R]D, 36.39. Found: C, 56.30; H, 6.43; [R]D, 35.77.

5-Methoxy-2-thienyllithium (II) and 5-Methoxy-2-thenoic Acid (III).—Methoxythiophene (3.0 g.) was added with stirring to a solution of phenyllithium prepared from 0.35 g. of lithium and 2.6 ml. of bromobenzene in 20 ml. of ether. The mixture turned yellow-green in 20 minutes. After 40 more minutes, the contents of the flask were poured onto a slurry of Dry Ice in ether and the mixture was worked up as usual. Crystallization from benzene and sublimation at 75° under high vacuum gave colorless needles (2.45 g., 61%), m.p. 162–163° (dec.), $\lambda^{H_2O}_{max}$ 2430 and 2870 Å. (ϵ, respectively, 3,500 and 8,700).

Anal. Calcd. for $C_6H_6O_3S$: C, 45.56; H, 3.82. Found: C, 45.72; H, 4.00.

5-Methoxy-2-methylthiophene.—To an ice cold solution of methoxythienyllithium (II), prepared from 10 ml. of I, in 100 ml. of ether, was added dropwise, in 15 minutes, a solution of dimethyl sulfate (12 ml.) in 20 ml. of ether. The mixture was stirred at room temperature for 20 hours, then poured onto ice and extracted with ether. The ether phase was washed repeatedly with dilute aqueous ammonium hydroxide, dried and evaporated. Distillation of the residue from sodium gave 5.16 g. (40%) of a colorless liquid, b.p. 51–52° (10 mm.), $n^{18}D$ 1.5216, d^{18}_4 1.097, $\lambda^{pentane}_{max}$ 2490 Å. (ϵ 5,000).

Anal. Calcd. for C_6H_8OS: C, 56.21; H, 6.29; [R]D 36.39. Found: C, 56.48; H, 6.79; [R]D 35.61.

5-Methoxy-2-methylthienylmercuric Chloride.—This derivative was prepared as previously described. The dried, raw precipitate (0.48 g.) was extracted with hot ethanol and the soluble portion was recrystallized from the same solvent yielding 0.135 g. (43%) of colorless needles, m.p. 170–173°.

Anal. Calcd. for $C_6H_7OSClHg$: C, 19.84; H, 1.94. Found[20]: C, 19.89; H, 2.31.

5-Methoxy-2-methyl-3,4-thienylbis-mercuric Chloride.—The ethanol-insoluble portion of the preceding preparation was crystallized from dimethylformamide–ethanol and gave colorless needles, m.p. 276–277° (dec.).

Anal. Calcd. for $C_6H_6OSCl_2Hg_2$: S, 5.36. Found[20]: S, 5.61.

5-Methoxy-2-allylthiophene.—To a methoxythienyllithium (II), prepared from 6.0 ml. of I, in 50 ml. of ether, was added 4.25 ml. of allyl chloride. The mixture was stirred overnight, then refluxed for 3 hours. When cooled, the contents of the flask were poured onto ice and the solvent layer worked up as usual. Two distillations under nitrogen gave 7.0 g. of a colorless, fragrant liquid; b.p. 93° (17 mm.), $n^{27}D$ 1.5231, d^{27}_4 1.052. This substance was quite stable when stored under nitrogen but resinified rapidly when exposed to the air.

Anal. Calcd. for $C_8H_{10}OS$: C, 62.30; H, 6.54; [R]D 45.16. Found: C, 62.59; H, 7.00; [R]D 44.80.

2-Methoxy-5-methyl-3-thenoic Acid.—Methoxymethylthiophene (3.0 g.) was stirred with a solution of butyllithium (prepared from 0.36 g. of Li and 2.7 ml. of butyl chloride in 50 ml. of ether) for 24 hours, then refluxed for 45 minutes, and then carbonated and worked up as usual. Crystallization from benzene and sublimation at 80° under high vacuum gave colorless needles (2.0 g., 50%), m.p. 147–148°, $\lambda^{H_2O}_{max}$ 2380 (inflexion) and 2790 Å. (ϵ, respectively, 5,200 and 3,800).

Anal. Calcd. for $C_7H_8O_3S$: C, 48.82; H, 4.68. Found: C, 48.60; H, 4.81.

5-Methoxy-2-thenaldehyde (IV).—A solution of methoxythienyllithium (II), prepared from 10 ml. of I, in 125 ml. of ether, was added in a slow stream to an ice-cold solution of dimethylformamide[21] (8 ml., 1.1 moles) in ether (75 ml.), with efficient stirring. The yellow suspension was left at room temperature overnight, then poured onto ice. The ether layer was washed with water, dried (Na_2SO_4), evaporated and the residue distilled. The distillate (9.27 g., 67%), b.p. 79–81° (0.9 mm.) crystallized from ether–hexane at −20° in colorless needles, m.p. 24–26°. A sample for analysis was redistilled (75° under 0.6 mm.), which did not alter the melting point.

Anal. Calcd. for $C_6H_6O_2S$: C, 50.68; H, 4.25. Found: C, 50.52; H, 4.45.

Its ***p*-nitrophenylhydrazone** crystallized from ethanol in red needles, m.p. 171–172°.

Anal. Calcd. for $C_{12}H_{11}O_3N_3S$: C, 51.97; H, 4.00; N, 15.15. Found: C, 52.02; H, 4.25; N, 15.42.

5-Methoxy-2,2′-thenil.—A solution of equal weights (1.42 g.) of IV and of 2-thenaldehyde in 7.5 ml. of ethanol was refluxed for 90 minutes with a solution of 0.3 g. of potassium cyanide in 4.5 ml. of water. The cooled mixture was then diluted with water and extracted with benzene. Evaporation of the solvent, after washing and drying, left a red oil (2.70 g.), which was chromatographed over 60.0 g. of alumina. The fractions (0.52 g.) eluted with hexane–benzene (1:1) and benzene crystallized from ethanol and gave yellow needles (0.31 g.), m.p. 63–64°; repeated crystallizations from hexane failed to yield a colorless material (0.15 g.) but raised the m.p. to 65–66°. The infrared spectrum did not show any absorption in the OH region (3368 cm.$^{-1}$ for benzoin), and showed a surprisingly weak band at 1150 cm.$^{-1}$ (C–O–C).

Anal. Calcd. for $C_{11}H_8O_3S_2$: C, 52.36; H, 3.20; S, 25.42. Found: C, 52.35; H, 3.38; S, 25.27.[20]

5-Methoxy-2-thenyl Alcohol.—A solution of 4.37 g. of the aldehyde IV in 6 ml. of tetrahydrofuran was added gradually with cooling to a solution of sodium borohydride[22] (0.44 g., 1.4 eq.) in 3 ml. of water. The mixture was then stirred for 2 hours, poured into 10 ml. of 2 *N* sodium hydroxide and extracted with ether. The solvent layer was washed with dilute ammonium hydroxide, dried and evaporated. The colorless residue distilled at 84° (0.7 mm.); yield 75%; $n^{30}D$ 1.5493, d^{30}_4 1.210. Difficulties were encountered in the combustion of this substance.

Anal. Calcd. for $C_6H_8O_2S$: C, 49.98; H, 5.59; [R]D 37.91. Found: C, 49.51; H, 5.51; [R]D 37.92.

A similar reduction of 2-thenaldehyde gave an 85% yield of 2-thenyl alcohol.

5-Methoxy-2-bromothiophene.—Ten grams of N-bromosuccinimide was added in one portion to 10 ml. (1.8 moles) of methoxythiophene (I) dissolved in dry carbon tetrachloride (20 ml.). The flask was vigorously swirled in ice-water as soon as the strongly exothermic reaction had begun. The mixture was gently refluxed for 10 minutes, after the reaction appeared to be complete, and then worked up as usual; 5.18 g. of methoxythiophene was recovered. Two distillations under nitrogen gave a faintly yellow liquid, b.p. 92–93° (19 mm.), yield 62%; $n^{26}D$ 1.5689, d^{26}_4 1.623.

(18) F. P. Hochgesang in Hartough's "Thiophene and its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952.

(19) Michigan Chemical Corporation, Saint Louis, Michigan.

(20) Microanalyses performed by Micro-Tech Laboratories, Skokie, Ill.

(21) Generously supplied by the Grasselli Chemicals Department of E. I. du Pont de Nemours & Company, Wilmington, Del.

(22) *Cf.* E. C. Hermann and A. Kreuchunas, THIS JOURNAL, **74**, 5168 (1952).

Anal. Calcd. for C_5H_5OBrS: Br, 41.39; [R]D 39.53. Found:[20] Br, 42.03; [R]D 38.96.

This compound was then converted to 5-methoxy-2-thenoic acid (III) by stirring overnight 3.60 g. of the halide with 0.90 g. of magnesium and 1 ml. of ethyl bromide. The cloudy mixture was then poured onto a slurry of Dry Ice and ether and the reaction products worked up as usual. There was obtained 0.60 g. (20%) of white needles, m.p. 161–162° (dec.), which did not depress the melting point of authentic III. No other material could be isolated from the mother liquors.

Acylation of 2-Methoxythiophene. A. 5-Methoxy-2-acetothienone.—A solution of 2.0 g. of I in 5 ml. of dry carbon disulfide, cooled to −20°, was added in 3 portions over a 10-minute period to a solution of acetyl chloride (1.2 ml.) and stannic chloride (2.0 ml.) in carbon disulfide (15 ml.) maintained at −20°, and then kept at that temperature for 5 additional minutes. The purple, heterogeneous mixture was then poured on ice (10 g.) and hydrochloric acid (1.0 ml.). The solvent layer was rapidly decanted, washed with water and saturated aqueous sodium bicarbonate. It was dried over sodium carbonate and evaporated, leaving a yellow oil (1.73 g.). The oil was chromatographed over 35.0 g. of alumina. Mixtures of hexane and benzene (9:1 and 4:1) eluted 0.76 g. of material which distilled at 60° (0.001 mm.). The distillate (0.42 g.) crystallized in yellow needles which became colorless and melted at 34–35° after recrystallization from hexane; λ_{max}^{EtOH} 2560 and 3140 Å. (ϵ, respectively, 4,100 and 14,200).

Anal. Calcd. for $C_7H_8O_2S$: C, 53.83; H, 5.16. Found: C, 53.67; H, 5.31.

Its ***p*-nitrophenylhydrazone** crystallized from dilute alcohol in scarlet needles, m.p. 198–199°.

Anal. Calcd. for $C_{13}H_{13}ON_3S$: C, 53.59; H, 4.50. Found: C, 53.54; H, 4.81.

B. **2-Methoxy-3-acetothienone.**—The column of alumina was then washed with benzene–hexane (1:1) and benzene, which eluted 0.155 g. of crystalline material. Two crystallizations from hexane and a sublimation at 85° under high vacuum gave 35 mg. of colorless crystals, m.p. 127–128°; λ_{max}^{EtOH} 2420 and 3030 Å. (ϵ, respectively, 16,300 and 10,200).

Anal. Calcd. for $C_7H_8O_2S$: C, 53.83; H, 5.16. Found: C, 54.07; H, 5.27.

Nitration of 2-Methoxythiophene.—A solution of 0.3 ml. of nitric acid (*d*, 1.50) in 2.0 ml. of acetic anhydride, cooled to −20°, was added in the course of one hour to a solution of 0.5 ml. of I in 3.0 ml. of acetic anhydride, kept at −20°. The purple mixture was then poured onto 20 g. of ice mixed with 8 g. of 50% aqueous sodium hydroxide and extracted with 5 ml. of benzene. Fifty ml. of hexane was then added to the dried organic layer, which precipitated out a certain amount of tar. The solvent was decanted and evaporated. The partially crystalline residue was crystallized from hexane, then sublimed at 80° under high vacuum to give 0.150 g. of colorless needles, m.p. 99–101°. The melting point was not depressed[23] on admixture with authentic **2-methoxy-3-nitrothiophene.**

The mother liquors from the preceding crystallizations were evaporated to dryness and the residue (0.40 g.) distilled in high vacuum (bath temperature 75°). The distillate (0.32 g.) was then chromatographed on 10.2 g. of alumina. The hexane eluate gave, after concentration, recrystallization from the same solvent and sublimation at 55° under high vacuum, 0.25 g. of yellow needles, m.p. 61–63°, which were assumed to be **5-methoxy-2-nitrothiophene.**

Anal. Calcd. for $C_5H_5O_3NS$: C, 37.73; H, 3.17. Found: C, 37.81; H, 3.43.

The column of alumina was then washed with benzene, which eluted some material that was crystallized from hexane; m.p. and m.m.p. with previous material 99–101°, yield 20 mg.

An attempt to prepare 2,4-dinitro-5-methoxythiophene from the mononitro compound with mixed nitric–sulfuric (1:2) acids in chloroform, at −20°, resulted in a 25% recovery of the starting material and tars.

5-Methoxyvaleric Acid.—Methoxythenoic acid (III) (0.80 g.) and sodium bicarbonate (0.42 g.) in water (50 ml.) were shaken at room temperature with 18.0 g. of Raney nickel (Adkins W-7) for 5 hours, then heated at 75° for 30 minutes. The catalyst was separated from the cooled mixture by centrifugation and washed with 0.1 *N* sodium hydroxide. The collected solutions were then concentrated under reduced pressure to 10 ml. and extracted with ether. Evaporation of the dried ether solution left a sirupy residue (0.55 g., 82%). The ***p*-bromophenacyl ester** prepared from 0.25 g. of this material crystallized from dilute ethanol in glistening leaflets (0.23 g., 80%), m.p. 39–41°.

Anal. Calcd. for $C_{14}H_{17}O_4Br$: C, 51.08; H, 5.21; Br, 24.28. Found[20]: C, 51.15; H, 5.43; Br, 24.11.

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(23) Determination kindly performed by Dr. K. L. Kreuz.

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[CONTRIBUTION FROM THE SAMUEL C. HOOKER LABORATORY OF THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

Studies in Organic Sulfur Compounds. V.[1] Synthesis of 21-Thiolacetates of Adrenal Cortical Hormones

BY CARL DJERASSI AND A. L. NUSSBAUM[2]

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In order to make available for biological experiments cortical hormone analogs in which the 21-hydroxyl function is replaced by sulfur, the 21-thiolacetate analogs of desoxycorticosterone, Reichstein's substance S and cortisone as well as those of a number of intermediates and model compounds were prepared. The methods of preparation involved either decomposition of the appropriate diazoketone with thioacetic acid or treatment of the steroidal 21-hydroxy-20-ketone with tosyl chloride followed by sodium iodide interchange and reaction with potassium thiolacetate. A characteristic infrared band near 8.8 μ appears to be due to the C–S stretching vibration in thiolacetates.

The biochemical role played by SH-containing substances has been realized for some time,[3] but recent work,[4] particularly with coenzyme A, has indicated that thiolesters also fulfill a very important function in biochemical processes. While the biochemical mechanism by which the steroidal cortical hormones act in the body is not yet understood, it appeared of interest to synthesize certain hormone analogs in which the hydroxyl group of the essential 20-keto-21-hydroxy function is replaced by sulfur and to determine the effect of this structural change upon biological activity. That variations at the C-21 position of the cortical hormones

(1) For earlier papers see: (a) *J. Org. Chem.*, **13**, 848 (1948); (b) THIS JOURNAL, **73**, 1528 (1951); (c) *ibid.*, **73**, 4961 (1951); (d) *J. Org. Chem.*, **17**, 1413 (1952).

(2) U. S. Public Health Service Predoctorate Fellow at Wayne University, 1952–1953.

(3) E. S. Guzman-Barron, *Adv. Enzym.*, **11**, 201 (1951).

(4) L. H. Noda, S. A. Kuby and H. A. Lardy, THIS JOURNAL, **75**, 913 (1953), give most of the leading references.