with ether, the combined ethereal extract was dried over magnesium sulfate, and then treated with a seven-fold molar excess of methyl iodide. After the mixture had stood at room temperature for several hours it was filtered and the filtrate was evaporated to dryness to leave an oil that was crystallized from methanol and recrystallized from benzene. The material melted at 244.5–245°, analyzed for furonitrile, and probably was **furonitrile trimer**.

Anal. Calcd. for C_5H_3NO: C, 64.51; H, 3.25; N, 15.05. Found: C, 64.30; H, 3.36; N, 15.27.

Methyl N-Methyl-2-thiofurimidate Methiodide. Method A.—To a solution of methyl N-methyl-2-thiofurimidate hydriodide (2.0 g., 7 mmoles) in a minimal quantity of water there was added a solution of sodium carbonate (0.83 g., 8 mmoles) also in a minimal quantity of water. The resultant alkaline solution was extracted four times with ether, the combined ethereal extract was dried over magnesium sulfate, and then evaporated to dryness. The residual **methyl N-methyl-2-thiofurimidate** was dissolved in 10 cc. of acetone, there was then added to this solution 2.5 cc. (48 mmoles) of methyl iodide, and the mixture was allowed to stand five days at room temperature. The crystalline product removed by filtration weighed 1.3 g. and an additional 0.1 g. was obtained by the addition of ether to the filtrate. The two crops were combined and recrystallized from acetone to obtain the pure product. On standing for two weeks the melting point of the material dropped and its melting range broadened.

Method B.—To a solution of N,N-dimethyl-2-thiofuramide (4.2 g., 0.027 mole) in 25 cc. of acetone was added methyl iodide (15.4 g., 0.108 mole). An exothermic quaternization occurred and after five minutes the reaction mixture was nearly solid. It was then refluxed 15 minutes on a steam-bath, chilled and filtered. The crude product, which weighed 7.6 g. and melted at 117–120°, was recrystallized to give 3.7 g. of pure product.

3,5-Di-(2-furyl)-1,2,4-thiadiazole.—To a solution of 2-thiofuramide (2.0 g., 0.0157 mole) in 20 cc. of absolute ethanol there was added a solution of iodine (8.2 g., 0.0324 mole) in 80 cc. of absolute ethanol. After three hours at room temperature some sulfur had precipitated and after three days at room temperature the sulfur was removed by filtration. The filtrate required 415 cc. of 0.1 *N* sodium thiosulfate to effect decolorization (0.69 molar equivalent of iodine consumed per mole of thioamide), during which the product was precipitated. The crude product weighed 1.3 g., melted at 104–105.5°, and after recrystallization weighed 1.1 g.

3,5-Di-(4-pyridyl)-1,2,4-thiadiazole.—To a solution of thioisonicotinamide (2.0 g., 0.0145 mole) in 50 cc. of warm absolute ethanol there was added a solution of iodine (11.0 g., 0.0435 mole) in 110 cc. of absolute ethanol. The reaction was slightly exothermic and maintained itself just under reflux temperature for about an hour. The mixture then was allowed to stand at room temperature overnight, during which time a large mass of dark needles had deposited. The mixture was refluxed 45 minutes, during which the needles dissolved, and the remaining insoluble sulfur was (difficultly) removed by filtration. The filtrate was chilled in an ice-bath and the precipitated dark needles (4.7 g.) were removed by filtration and washed with cold ethanol. The filtrate from which the dark needles had been removed also, coincidentally, required 415 cc. of 0.1 *N* sodium thiosulfate for decolorization (1.52 molar equivalents of iodine consumed per mole of thioamide). The dark crystals were suspended in 30 cc. of water, the mixture was made alkaline with 2 cc. of 4 *N* sodium hydroxide, and then treated with an excess of solid sodium thiosulfate to effect decolorization. The mixture was warmed gently to hasten the reduction of the iodine and then chilled to precipitate 1.5 g. of product. Recrystallization of the product from methanol or benzene did not raise its melting point.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CONNECTICUT]

Friedel–Crafts Isopropylation of Methyl 2-Thienyl Ketone[1a]

BY EARL C. SPAETH AND CHRISTINE B. GERMAIN[1b]

RECEIVED MAY 14, 1954

The Friedel–Crafts monoisopropylation of methyl 2-thienyl ketone has been studied to determine the product compositions. Regardless of catalyst or reaction conditions, the major product of this reaction is 4-isopropyl-2-thienyl methyl ketone. Small amounts of 5-isopropyl-2-thienyl methyl ketone also are formed. The 3-isopropyl isomer was not detected in any reaction product.

Few reports have appeared on the alkylation of a thiophene compound containing an electron-withdrawing substituent in an α-position. The directive effect of such a substituent on an incoming alkyl group would be of interest.[2,3] The only study of isomer composition in such alkylations is on the alkylation of ethyl 2-thiophenecarboxylate with *t*-butyl chloride and aluminum chloride.[4] A mixture of isomeric esters was produced which, when saponified, gave a mixture of *t*-butyl-2-thiophenecarboxylic acids containing approximately 60% of the 5-*t*-butyl isomer.

The monoisopropylation of methyl 2-thienyl ketone was chosen for study. The product of this reaction should contain only 5-isopropyl-2-thienyl methyl ketone (I), 4-isopropyl-2-thienyl methyl ketone (II) and 3-isopropyl-2-thienyl methyl ketone (III). In order to detect and estimate the amount of each of these in an alkylation reaction mixture, authentic samples were necessary.

5-Isopropyl-2-thienyl Methyl Ketone (I).—This substance was prepared by acetylation of 2-isopropylthiophene with acetyl chloride and aluminum chloride.[5] It is likely that this reaction produces only I. Hartough[6] has reported that an analogous compound, 2-methylthiophene, undergoes less than 1%, if any, of β-substitution during a similar acetylation reaction. 2-Isopropylthiophene was prepared from methyl 2-thienyl ketone by reaction with methylmagnesium iodide, dehydration of the resulting tertiary alcohol, and catalytic hydrogenation of the isopropenyl group. Inasmuch as

(1) (a) Abstracted in part from the 1953 Ph.D. thesis of Christine B. Germain. Presented in part before the Organic Division, American Chemical Society, Chicago, Ill., Sept., 1953. (b) Research Corporation Fellow, 1952–1953.

(2) W. G. Appleby, A. F. Sartor, S. H. Lee, Jr., and S. W. Kapranos, THIS JOURNAL, **70**, 1552 (1948); W. M. Kutz and B. B. Corson, *ibid.*, **68**, 1477 (1946); **71**, 1503 (1949); H. Pines, B. Kvetinskas and J. A. Vesely, *ibid.*, **72**, 1568 (1950).

(3) W. Steinkopf and T. Höpner, *Ann.*, **501**, 184 (1933).

(4) N. Messina and E. V. Brown, Abstracts of Papers, XII International Congress of Pure and Applied Chemistry, Organic Chemistry Division, Sept., 1951, p. 425; N. Messina, Ph.D. Dissertation, Fordham University, 1951, p. 50.

(5) H. Scheibler and M. Schmidt, *Ber.*, **54**, 147 (1921).

(6) H. D. Hartough, "Thiophene and Its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952, p. 145.

the methyl 2-thienyl ketone was prepared by acetylation of thiophene, a reaction which produces less than 1% of the 3-isomer,[6] the sample of 2-isopropylthiophene used probably contained less than 1% of 3-isopropylthiophene.

4-Isopropyl-2-thienyl Methyl Ketone (II) and 3-Isopropyl-2-thienyl Methyl Ketone (III).—A mixture of substances was prepared by acetylation of 3-isopropylthiophene with acetyl chloride and aluminum chloride.[5] Distillation separated this mixture into two distinct fractions, each having the composition of an isopropylthienyl methyl ketone. These were presumed to be II and III. It is unlikely that an appreciable amount of 4-isopropyl-3-thienyl methyl ketone is formed during this acetylation reaction. The 3-isopropylthiophene was prepared by ring closure from the disodium salt of isopropylsuccinic acid and phosphorus heptasulfide. Contamination by 2-isopropylthiophene therefore is unlikely.

Structure Elucidations.—Assignment of structures to the two acetylation products from 3-isopropylthiophene was possible by oxidation of each to the corresponding isopropyl-2-thiophenecarboxylic acid with sodium hypochlorite,[7] followed by hydrogenolysis of each acid with Raney nickel alloy and sodium hydroxide solution.[8] Thus II would be converted to γ-isopropylvaleric acid and III to β-isopropylvaleric acid. The aliphatic acids were isolated as the *p*-bromophenacyl esters which were compared with an authentic sample of the *p*-bromophenacyl ester of γ-isopropylvaleric acid. The mixed melting points indicate that the low-boiling component from the acetylation of 3-isopropylthiophene is III while the high-boiling component from this reaction is II.

Confirmation of these structural assignments is possible by a comparison of the ultraviolet absorption spectra[9] of I, II and III with those reported for the corresponding three isomeric methyl-2-thienyl methyl ketones.[10] Maxima are as follows: 5-isopropyl, 293–296 and 264–265 mμ; 5-methyl, 294 and 263–264 mμ; 4-isopropyl, 295–297 and 262 mμ; 4-methyl, 295–297 and 261 mμ; 3-isopropyl, 274–275 mμ; 3-methyl, 273–274 mμ.

Experimental[11]

3-Isopropyl-2-thienyl Methyl Ketone (III) and 4-Isopropyl-2-thienyl Methyl Ketone (II).—A 43-g. sample of a monoacetylation product of 3-isopropylthiophene[6] was distilled through an efficient column.[12] Two distinct fractions were obtained. The first of these (14.9 g., 31% based on 3-isopropylthiophene) distilled up to 53° (0.2 mm.). After a 1.8-g. intermediate fraction, the second fraction (23.1 g., 48% based on 3-isopropylthiophene) distilled sharply at 65° (0.2 mm.). Each of these two main fractions was redistilled twice through the same column, center cuts being taken during each distillation.

The lower boiling compound was shown subsequently to be **3-isopropyl-2-thienyl methyl ketone** (III), b.p. 58° (0.6 mm.), $n^{20}D$ 1.5422.

A semicarbazone of 3-isopropyl-2-thienyl methyl ketone was prepared, m.p. 183–185.5°.

Anal. Calcd. for $C_{10}H_{15}ON_3S$: C, 53.31; H, 6.71. Found: C, 53.46; H, 6.74.

The higher boiling compound was shown subsequently to be **4-isopropyl-2-thienyl methyl ketone** (II), b.p. 73° (0.5 mm.), $n^{20}D$ 1.5422.

A semicarbazone of 4-isopropyl-2-thienyl methyl ketone was prepared, m.p. 210.5–211.5°.

Anal. Calcd. for $C_{10}H_{15}ON_3S$: C, 53.31; H, 6.71. Found: C, 53.51; H, 6.60.

A semicarbazone of 5-isopropyl-2-thienyl methyl ketone[5,13] was prepared, m.p. 208–209°.

Anal. Calcd. for $C_{10}H_{15}ON_3S$: C, 53.31; H, 6.71. Found: C, 53.60; H, 6.64.

Synthesis and Hydrogenolysis of 3- and 4-Isopropyl-2-thiophenecarboxylic Acids.—The ketones were oxidized[7] in 80–90% yield to the corresponding isopropyl-2-thiophenecarboxylic acids. The acids were purified by recrystallization with aqueous ethanol, followed by vacuum sublimation.

4-Isopropyl-2-thiophenecarboxylic acid, m.p. 92–93°. *Anal.* Calcd. for $C_8H_{10}O_2S$: C, 56.44; H, 5.92. Found: C, 56.52; H, 5.83.

***p*-Bromophenacyl ester of 4-isopropyl-2-thiophenecarboxylic acid,** m.p. 80.5–81.5°. *Anal.* Calcd. for $C_{16}H_{15}O_3BrS$: C, 52.32; H, 4.12. Found: C, 52.14; H, 4.26.

3-Isopropyl-2-thiophenecarboxylic acid, m.p. 110–111.5°. *Anal.* Calcd. for $C_8H_{10}O_2S$: C, 56.44; H, 5.92. Found: C, 56.64; H, 5.73.

***p*-Bromophenacyl ester of 3-isopropyl-2-thiophenecarboxylic acid,** m.p. 88–89°. *Anal.* Calcd. for $C_{16}H_{15}O_3BrS$: C, 52.32; H, 4.12. Found: C, 52.17; H, 4.30.

A mixture of Raney nickel alloy and aqueous sodium hydroxide was allowed to react[8] with each isopropyl-2-thiophenecarboxylic acid. The resulting aliphatic acids were isolated by ether extraction of the acidified hydrogenolysis reaction mixture and removal of the ether at reduced pressure. The crude acids were transformed to the *p*-bromophenacyl esters. That from 4-isopropyl-2-thiophenecarboxylic acid (from the higher boiling monoacetylation product) melted at 55–56° and did not depress the m.p. of an authentic sample of the *p*-bromophenacyl ester of γ-isopropylvaleric acid.[14] That from 3-isopropyl-2-thiophenecarboxylic acid (from the lower boiling monoacetylation product) melted at 32.5–33.5°.

Anal. Calcd. for $C_{16}H_{21}O_3Br$: C, 56.31; H, 6.20. Found: C, 56.48; H, 6.34.

Alkylation Procedures. Method A.—The catalyst and 400 ml. of dry carbon disulfide were combined and cooled to −10°. A mixture of methyl 2-thienyl ketone and isopropyl chloride, both freshly distilled, was added dropwise with stirring during one-half hour. The reaction mixture was allowed to warm to room temperature or was heated to the reflux temperature. After stirring for the specified time, the reaction mixture was poured onto ice with vigorous stirring. The aqueous layer was separated and extracted with ether. The non-aqueous layer was washed once with water, twice with 10% sodium carbonate, and once with a saturated sodium chloride solution. The non-aqueous layer and ether washings were combined and dried with anhydrous sodium sulfate. Distillation produced a fraction boiling over a range of 70–130° at 5–10 mm. This distillate was analyzed as described below. High boiling residues always remained after distillation of isopropylation reaction mixtures. Attempts to distil these residues resulted in their decomposition.

Method B.—The catalyst and 400 ml. of dry carbon disulfide were combined, and freshly distilled methyl 2-thienyl ketone was added dropwise with stirring at room tempera-

(7) H. D. Hartough and L. G. Conley, THIS JOURNAL, **69**, 3096 (1947).

(8) D. Papa, E. Schwenk, and B. Whitman, *J. Org. Chem.*, **7**, 587 (1942); D. Papa, E. Schwenk and H. F. Ginsberg, *ibid.*, **14**, 723 (1949).

(9) (a) Spectra were determined with a Beckman model DU spectrophotometer using 1-cm. silica cells and 5.9×10^{-5} *M* solutions in 95% ethanol. (b) The complete spectral curves are contained in the Ph.D. thesis of C. B. G., University of Connecticut, 1953.

(10) H. H. Szmant and A. J. Basso, THIS JOURNAL, **73**, 4521 (1951).

(11) Melting points were taken with calibrated, completely immersed, short-range thermometers. Boiling points are uncorrected. Microanalyses were performed by Clark Microanalytical Laboratory, Urbana, Ill., or The Laboratory of Microchemistry, Teaneck, N. J. Each analytical value for carbon or hydrogen is the average of the values from two analyses.

(12) A Wheeler, all-glass, vacuum, semi-micro fractionating column with a modified Sargent hollow-tube design, model number GV-130-2 of the Precision Distillation Apparatus Co.

(13) B.p. 72° (0.4 mm.) was observed.

(14) N. Levin, D. Papa and E. Schwenk, THIS JOURNAL, **69**, 1830 (1947).

ture during one-half hour. Stirring at room temperature was continued for one to two hours. Dry propylene then was introduced below the liquid surface either at 25° or at the reflux temperature of the reaction mixture. After stirring for the specified time, the reaction mixture was poured onto ice. The product was isolated as in method A.

Method C.—This procedure using hydrogen fluoride and stainless steel equipment was similar to that described by Calcott.[15] Liquid hydrogen fluoride was stirred at 0° while methyl 2-thienyl ketone was added dropwise during five minutes. Propylene then was introduced below the liquid surface with stirring during three hours at 0°. The excess hydrogen fluoride then was allowed to evaporate at room temperature. After 24 hours, the reaction mixture was poured onto ice and neutralized with solid sodium carbonate. About four volumes each of water and ether were added and the product was isolated as in method A.

Analytical Procedure. Fractional Distillation.—Each mixture of isopropyl-2-thienyl methyl ketones and unreacted methyl 2-thienyl ketone, isolated as described in the alkylation procedures, was subjected to a careful fractional distillation.[12] Four fractions usually were taken and a typical distillation at 0.5 mm. gave the following data (°C., ml.): 45.0, 3.0; 46.0–73.5, 1.2; 73.5–75.0, 5.0; 74.0–75.0, 11.0. The first fraction was unreacted methyl 2-thienyl ketone. The second fraction contained this substance and some of the mixture of isopropyl-2-thienyl methyl ketones. The yields of the monoisopropylation product were based on the combined weights of the third and fourth fractions. The conversions of methyl 2-thienyl ketone to this product were based on these yields and the weight of the first fraction.

Infrared Absorption Analysis.—The instrument was a Beckman IR-2 spectrophotometer with a sodium chloride prism. Points of strong absorption[9b] unique to each isopropyl-2-thienyl methyl ketone were: I, 810 cm.$^{-1}$; II, 850 cm.$^{-1}$; III, 975 cm.$^{-1}$. Any III formed during an isopropylation could be expected to be present in the second distillation fraction. The absorption of each such fraction was measured at 975 cm.$^{-1}$ after suitable dilution with carbon disulfide. These measurements never indicated the presence of III in a reaction mixture. Methyl 2-thienyl ketone containing 5% of III gave measurable absorption at 975 cm.$^{-1}$. This corresponds to less than 1% of III in a reaction mixture.

The absorption of the fourth distillation fraction was measured at 810 and 850 cm.$^{-1}$ after suitable dilution with carbon disulfide. The weight percentages of I and II were calculated independently of each other with the aid of calibration curves.[16]

In order to further verify the conclusion that the reaction products contain mainly II, a semicarbazone was prepared using a sample of the product from the first experiment in Table I. After one recrystallization with a recovery of 73%, this semicarbazone had a m.p. 209–210.5°. It gave no depression when mixed with an equal amount of the semicarbazone of the authentic sample of II but gave a m.p. 200–204.5° when mixed with approximately 5% of the semicarbazone of the authentic sample of I.

Results

Tables I and II summarize some of the results of the isopropylation of methyl 2-thienyl ketone. In spite of the wide variation in reaction conditions, the isopropyl group always displayed a marked tendency to enter the 4-position of the thiophene ring. The normal directive influence of the sulfur atom apparently is not important in this reaction.

There is a point of interest concerning the last experiment of Table II. Weinmayr observed that isopropylation of 2-thiophenecarboxylic acid with isopropyl ether and hydrogen fluoride gives a 30% yield of an acid with a melting point of 81° and the composition of a monoisopropylthiophenecarboxylic acid.[17] The melting points of 3-, 4- and 5-isopropyl-2-thiophenecarboxylic acids are 110–111.5°, 92–93° and 81°,[18] respectively. Apparently Weinmayr obtained the 5-isopropyl isomer. Isopropylation of methyl 2-thienyl ketone with propylene and hydrogen fluoride has produced mainly II. The reasons for this difference are not apparent at present.

Numerous attempts were made to isopropylate methyl 2-thienyl ketone with isopropyl chloride or

TABLE I

ISOPROPYLATION OF METHYL 2-THIENYL KETONE WITH ISOPROPYL CHLORIDE AND ALUMINUM CHLORIDE

Variation[a]	Yield, %	Conversion, %	Position substd., % 4-	5-
None except catalyst[b]	43	53	92	4
None except catalyst[c]	51	63	87	11
Reacn. mixture refluxed[b]	50	64	95	3
Reacn. time 48 hours[b]	37	58	99	1
Reacn. time 12 hours[c]	52	63	88	11
No solvent[c]	42	61	86	15
0.25 mole isopropyl chloride[b]	48	51	78	19
0.1 mole isopropyl chloride[c]	64[d]	..	97	3
0.21 mole aluminum chloride[c,e]	9	31	97	1

[a] Except as noted: all reactions by method A, 0.4 mole of aluminum chloride, 0.2 mole of isopropyl chloride, 0.2 mole of methyl 2-thienyl ketone, 24-hour reaction time, −10 to 25° reaction temperature. Catalysts: [b] Eimer and Amend granular, reagent grade, anhydrous aluminum chloride; [c] J. T. Baker granular, anhydrous aluminum chloride. [d] Yield based on 0.1 mole of isopropyl chloride. [e] When 0.19 mole of aluminum chloride was used in an otherwise identical run, no isopropylation product was obtained.

TABLE II

ISOPROPYLATION OF METHYL 2-THIENYL KETONE WITH VARIOUS CATALYSTS AND ALKYLATING AGENTS

Method[a]	Catalyst	Alkylating agent, mole	Yield, %	Conversion, %	Position Substd., % 4-	5-
B[b]	$AlCl_3$[c]	Propylene,[d] 0.4	13[e]	34	95	5
A[f]	$AlBr_3$[g]	*i*-PrCl, 0.2	62	73	82	18
B[h]	$AlBr_3$[g]	Propylene, 0.2	51[e]	64	89	9
A[f]	$FeCl_3$[i]	*i*-PrCl, 0.2	20[j]	35	92	9
C[k]	HF[l]	Propylene, 0.8	3	9	83	13

[a] Except as noted: 0.4 mole of catalyst, 0.2 mole of methyl 2-thienyl ketone, 24-hour reaction time, carbon disulfide as solvent. [b] Propylene was introduced at the reflux temperature during 3.5 hours. The reaction then was stopped. No monoalkylation product was formed by an otherwise identical experiment in which 0.2 mole of propylene was introduced at 25° during five hours. [c] Catalyst *c* of Table I. [d] Matheson C.P. grade, 99.0% purity. [e] The product was yellow-orange in color even after distillation. All other products described in Tables I and II were colorless after distillation. [f] Reaction temperature −10 to 25°. [g] Eimer and Amend reagent grade, anhydrous aluminum bromide. [h] Propylene was introduced during 1.25 hours at about 25° and the reaction was allowed to continue for 24 hours at 25°. [i] Eimer and Amend C.P. sublimed, anhydrous ferric chloride. [j] In this experiment, a larger amount of amorphous high-boiling residue remained after distillation than in any other experiment described in Tables I and II. [k] Carbon disulfide was omitted; used 0.4 mole of methyl 2-thienyl ketone. Similar experiments with isopropyl chloride or isopropyl alcohol in place of propylene produced no monoisopropylation products. The recovery of methyl 2-thienyl ketone was 50–75%. A similar recovery was observed when the alkylating agent was omitted. [l] 200 ml. of Matheson anhydrous liquid hydrogen fluoride served as both catalyst and solvent.

(15) W. S. Calcott, J. M. Tinker and V. Weinmayr, THIS JOURNAL, **61**, 1010 (1939).

(16) N. Wright, *Ind. Eng. Chem., Anal. Ed.*, **13**, 6 (1941).

(17) V. Weinmayr, THIS JOURNAL, **72**, 918 (1950).

(18) N. Messina and E. V. Brown, *ibid.*, **74**, 922 (1952). This acid was prepared also by a similar method during the course of the present work. M.p. 80–80.5° was observed.

propylene in the presence of catalysts other than those mentioned in Table II. These catalysts were zinc chloride, antimony trichloride, titanium tetrachloride, tin tetrachloride, zirconium tetrachloride, boron trifluoride etherate, 75% sulfuric acid, 85% phosphoric acid and 92% phosphoric acid. Reaction conditions were similar to those reported for successful alkylations of thiophene or benzene, or were similar to methods A and B of the present paper. In each experiment, either the starting product was largely recovered or the reaction mixture was a tar.

It is possible that *only one* of the two observed monoisopropylation products, I and II, is a primary alkylation product and that the observed mixtures are due to partial isomerization of this one isomer under the reaction conditions of isopropylation. Several experiments were carried out to test this possibility. In one, pure I was substituted for the usual mixture of isopropyl chloride and methyl 2-thienyl ketone in a reaction with aluminum chloride otherwise identical with the second experiment of Table I. The recovery of isopropyl-2-thienyl methyl ketone was 65% and no II could be detected in this recovered substance by infrared analysis. In another experiment, a portion of the reaction product from the second experiment of Table I was mixed with 0.02 times an equimolar amount of isopropyl chloride and was allowed to react with twice an equimolar amount of aluminum chloride otherwise exactly as for the previous experiment. The recovery of the starting product was 56% and its composition was 8% I and 92% II. The differences between this composition and that of the starting product (Table I) probably are not significant. In a third experiment, a portion of the reaction product from the second experiment of Table I was mixed with an equimolar amount of methyl 2-thienyl ketone and four times an equimolar amount of aluminum chloride and was allowed to react otherwise exactly as for the previous experiment. The recovery of methyl 2-thienyl ketone was 80%, the recovery of isopropyl-2-thienyl methyl ketone was 67%, and the composition of the latter was 10% I and 91% II. These three experiments seem to indicate that intra- or intermolecular migration of the isopropyl group of a primary monoisopropylation product is not important in determining the composition of an alkylation product.

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

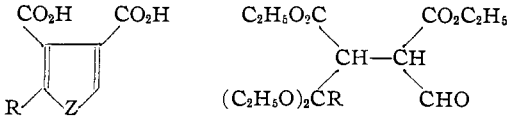
2,3-Furan, Pyrrole and Thiophenedicarboxylic Acids

BY REUBEN G. JONES

RECEIVED JANUARY 31, 1955

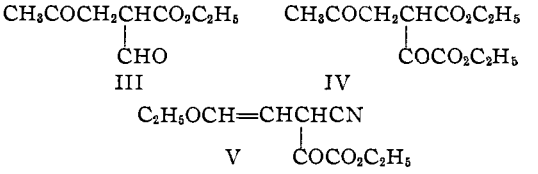
Ethyl 2-formyl-4-ketovalerate, ethyl-2-ethoxalyl-4-ketovalerate and ethyl 2-ethoxalyl-4-ethoxy-3-butenonitrile have been prepared and characterized. From these intermediates the following acids and some of their esters and other derivatives have been prepared: 5-methyl-3-furancarboxylic acid, 5-methyl-2,3-furandicarboxylic acid, 2,3-furandicarboxylic acid, 5-methyl-3-pyrrolecarboxylic acid, 5-methyl-2,3-pyrroledicarboxylic acid, 5-methyl-2,3-thiophenedicarboxylic acid and 2,3-thiophenedicarboxylic acid.

In connection with one of the projects in this Laboratory a number of 2,3- and 3,4-dicarboxylic acids of furan, pyrrole and thiophene were desired. Although several of the dicarboxylic acids of this group are known, the methods of preparation are generally difficult and unsatisfactory. Recently a convenient synthesis of the 3,4-dicarboxylic acids like I was described involving as intermediates the potential 1,4-dicarbonyl esters II.[1]



I Z = O, NH, S; R = H, CH_3 II

A similar approach now has been investigated for the synthesis of 2,3-dicarboxylic acids of furan, pyrrole and thiophene. This paper reports the preparation of ethyl 2-formyl-4-ketovalerate (III), ethyl 2-ethoxalyl-4-ketovalerate (IV) and ethyl 2-ethoxalyl-4-ethoxy-3-butenonitrile (V) and the cyclizations of these intermediates to form furan, thiophene and pyrrole derivatives.



When the readily available levulinic acid esters like VI are formylated under Claisen conditions intractable mixtures are obtained. Formylation apparently takes place at each of the three reactive centers. Oxalation of ethyl levulinate also gives a mixture of products, but in this case about a 30% yield of diethyl α,γ-diketopimelate (the product resulting from condensation at the δ-position of VI) can be isolated.[2] In order to direct formylation and oxalation exclusively to the α-position of VI it would be necessary to neutralize the reactive β- and δ-centers. This has been done by converting VI to

(1) E. C. Kornfeld and R. G. Jones, *J. Org. Chem.*, **19**, 1671 (1954).

(2) W. Wislicenus, *Ber.*, **21**, 2583 (188).