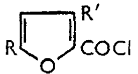
507. *Furans. Part III.*[1] *The Synthesis of 2-Isovalerylfurans from Furoylacetic Esters.*

By P. A. Finan and G. A. Fothergill.

Furoyl chloride and its 3- and 5-methyl derivative have been converted into the ethyl furoylacetates and thence into the 2-isovalerylfurans. Diethyl α-furoyl-α-isopropylmalonate was prepared but could not be converted into 2-isovalerylfuran.

In Part I [2] of this series we described the preparation of furyl ketones by the condensation of furfuraldehyde and 5-methylfurfuraldehyde with Grignard reagents, followed by oxidation of the alcohols produced. This approach was unsuccessful, however, for the synthesis of 3-methylfuryl ketones, owing to the failure of 3-methylfurfuraldehyde to condense with Grignard reagents. We subsequently synthesised [1,2] some 3-methylfuryl ketones by the Friedel–Crafts reaction. We now report a convenient preparation of ethyl 3-methylfuroylacetate (III; R = H, R′ = Me), and its conversion into 2-isovaleryl-3-methylfuran, elsholtzia ketone (V; R = H, R′ = Me), thus providing a new synthetic approach to 3-methylfuryl ketones.



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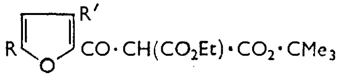

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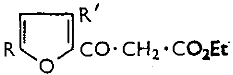

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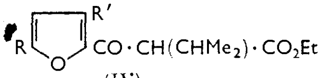

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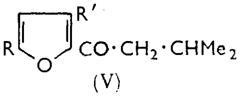

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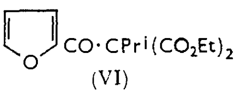

(VI)

First, furoyl chloride was condensed with ethyl t-butyl malonate,[3] and the resulting ethyl t-butyl α-2-furoylmalonate (II; R = R′ = H) was treated with toluene-*p*-sulphonic acid, giving ethyl furoylacetate (III; R = R′ = H). Several methods were tried for the conversion of the latter into the ester (IV; R = R′ = H). Treatment of the sodium derivative in ethanol with isopropyl bromide gave ethyl α-furoyl-β-methylbutyrate (IV; R = R′ = H) in 47% yield; use of either benzene–dimethylformamide [4] or ethanol–dimethylformamide [5] as solvent gave poorer yields; better yields were obtained by treatment of the sodium derivative with isopropyl iodide in xylene or ethanol. The alkylated keto-ester (IV; R = R′ = H), on treatment with dilute acid, gave 2-isovalerylfuran (V; R = R′ = H), identical (physical constants, light-absorption data, crystalline derivatives) with the compound prepared previously [1] by the Friedel–Crafts reaction.

5-Methylfuroyl chloride (I; R = Me, R′ = H) was condensed with the ethoxymagnesium derivative of ethyl t-butyl malonate, giving the ester (II; R = Me, R′ = H), which was converted into ethyl 5-methylfuroylacetate (III; R = Me, R′ = H). The sodium derivative of the latter in ethanol was treated with isopropyl iodide, giving the ester (IV; R = Me, R′ = H), which with dilute acid gave 2-isovaleryl-5-methylfuran (V; R = Me, R′ = H).

In a similar reaction sequence, ethyl 3-methylfuroylacetate (III; R = H, R′ = Me) was prepared in good yield from 3-methylfuroyl chloride. This preparation appears to be superior to that (condensation of ethyl 3-methylfuroate with ethyl acetate in the presence of sodium) reported by Asahina *et al.*[6] Treatment of the sodium derivative of

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[1] Part II, preceding paper.

[2] Finan and Fothergill, *J.*, 1962, 2262.

[3] Breslow, Baumgarten, and Hauser, *J. Amer. Chem. Soc.*, 1944, **66**, 1286.

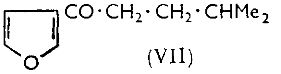
[4] Stork and Burgstahler, *J. Amer. Chem. Soc.*, 1951, **73**, 3544.

[5] Tschudy and Collins, *J. Org. Chem.*, 1959, **24**, 556.

[6] Asahina, Murayama, Shibata, Kariyone, Kuwada, and Asano, *Acta Phytochim. Japan*, 1924, **2**, 1.

the keto-ester in ethanol with isopropyl iodide gave compound (IV; R = H, R′ = Me), which with dilute acid gave 2-isovaleryl-3-methylfuran (V; R = H, R′ = Me), identical with the naturally occurring elsholtzia ketone.[7]

An attempt was then made to modify the above approach to furyl ketones so that the furan intermediates might be introduced at a later stage. Furoyl chloride was condensed with the ethoxymagnesium derivative of diethyl α-isopropylmalonate, giving diethyl α-furoyl-α-isopropylmalonate (VI). The latter was recovered unchanged, however, after prolonged treatment with dilute acid. Treatment of the ester (VI) with alkali gave furoic acid. These results are in accord with the observations of some other workers. Bowman[8] has reported that diethyl α-acyl-α-alkylmalonates could not be cleaved to ketones, and Hauser and his collaborators[9] have found that, whereas diethyl α-*p*-nitrobenzoylmalonate on treatment with acid gave 4-nitroacetophenone, diethyl α-n-butyl-α-*p*-nitrobenzoylmalonate under similar conditions failed to give the 4-nitrophenone. Johnson and Offenhauer[10] found similarly that, while diethyl α-(4-*p*-acetoxyphenylcyclohexyl)malonate gave 4-*p*-acetoxycyclohexyl methyl ketone in high yield, diethyl α-(4-*p*-acetoxyphenylcyclohexyl)-α-propylmalonate could not be converted into the corresponding pentyl ketone. By contrast, however, Arata and Achiwa[11] reported a synthesis of perilla ketone (VII) by treatment of the ester (VIII) with dilute acid.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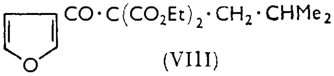
(VIII)

EXPERIMENTAL

General procedures were as stated in the preceding paper.

Ethyl furoylacetate had $\lambda_{max.}$ (in hexane) 277 and 300 mμ (ε 10,600 and 10,900, respectively), $\nu_{max.}$ 3100 and 1570 (furan), 1735 (C=O of ester), and 1675 cm.$^{-1}$ (C=O of chelated β-keto-ester), and gave a 2,4-*dinitrophenylhydrazone*, deep red needles (from ethanol), m. p. 139° (Found: C, 49·7; H, 4·0; N, 15·2. $C_{15}H_{14}N_4O_7$ requires C, 49·7; H, 3·9; N, 15·5%), $\lambda_{max.}$ (in $CHCl_3$) 386 mμ (ε 28,200).

Ethyl α-Furoyl-β-methylbutyrate (IV; R = R′ = H).—(*a*) Ethyl furoylacetate (6 g., 0·03 mole) was added with stirring to sodium ethoxide (from sodium, 0·75 g., 0·03 g.-atom) in ethanol (40 ml.). After 0·5 hr. isopropyl iodide (8 g., 0·05 mole) was added and the mixture was heated under reflux until neutral to litmus (7 hr.). Most of the ethanol was evaporated under reduced pressure, and the residue was poured into water. Extraction with ether and working-up in the usual way gave *ethyl α-furoyl-β-methylbutyrate* (5·1 g., 68%), b. p. 99°/0·6 mm., n_D^{25} 1·4960 (Found: C, 64·0; H, 7·0. $C_{12}H_{16}O_4$ requires C, 64·3; H, 7·1%), $\nu_{max.}$ 3100 and 1560 (furan), 1735 (C=O of ester), and 1675 cm.$^{-1}$ (C=O of ketone).

When isopropyl bromide was used, with a reflux period of 24 hr., a lower yield (47%) of the alkylated keto-ester was obtained.

(*b*) Ethyl furoylacetate (0·03 mole) was added to sodium ethoxide (0·03 mole) in ethanol (30 ml.). The mixture was stirred for 0·5 hr. and then isopropyl bromide (6 g., 0·05 mole) in dimethylformamide (5 ml.) was added. The mixture was heated under reflux for 24 hr. Working-up as described in (*a*) gave the alkylated keto-ester (1·2 g., 16%).

(*c*) Ethyl furoylacetate (0·03 mole) was added to sodium ethoxide (0·03 mole) in ethanol (30 ml.). The mixture was heated under reflux for 0·5 hr. and then evaporated under anhydrous conditions. To the residue in benzene–dimethylformamide (1 : 1 v/v; 50 ml.), isopropyl bromide (0·05 mole) was added and the mixture was heated under reflux for 36 hr. After cooling, water was added and the mixture was extracted with ether. Working-up in the usual way gave the alkylated keto-ester (1·7 g., 23%).

[7] Naves and Ochsner, *Helv. Chim. Acta*, 1960, 406.

[8] Bowman, *J.*, 1950, 322.

[9] Walker and Hauser, *J. Amer. Chem. Soc.*, 1946, **68**, 1386; Puterbaugh, Swaner, and Hauser, *ibid.*, 1952, **74**, 3438.

[10] Johnson and Offenhauer, *J. Amer. Chem. Soc.*, 1945, **67**, 1045.

[11] Arata and Achiwa, *Kanazawa Daigaku Yakugakubu Kenkyu Nempo*, 1958, **8**, 29 (*Chem. Abs.*, 1959, **53**, 5228).

(*d*) The sodium derivative of ethyl furoylacetate (0·03 mole) and isopropyl iodide (0·05 mole) in xylene (40 ml.) were heated under reflux for 24 hr. Working-up in the usual way gave the alkylated keto-ester (3·7 g., 50%).

2-*Isovalerylfuran* (V; R = R′ = H).—Ethyl α-furoyl-α-methylbutyrate (4 g.) was heated in a mixture of 2N-sulphuric acid (50 ml.) and acetic acid (12 ml.) under reflux until evolution of carbon dioxide had ceased (1 hr.). The mixture was cooled and extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate and water and dried. Evaporation gave an oil which was chromatographed on alumina. Elution with light petroleum gave 2-isovalerylfuran (0·95 g., 37% based on unrecovered keto-ester), b. p. 92°/15 mm., n_D^{25} 1·4891, identical (ultraviolet and infrared spectra; 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 128°; semicarbazone, m. p. and mixed m. p. 170°) with the compound[1] obtained by the Friedel–Crafts reaction. Elution with ether gave unchanged keto-ester (0·5 g.).

Ethyl 5-*Methylfuroylacetate* (III; R = Me, R′ = H).—5-Methylfuroyl chloride (14·5 g., 0·1 mole) in ether (25 ml.) was added to the ethoxymagnesium derivative of ethyl t-butyl malonate (0·1 mole). The mixture was heated under reflux, with stirring, for 16 hr. Working-up in the usual way gave crude ethyl t-butyl α-5-methylfuroylmalonate which was heated with toluene-*p*-sulphonic acid (1 g.) in benzene until gas evolution had ceased (2 hr.). *Ethyl* 5-*methylfuroylacetate* (13·3 g., 68%) was obtained as a pale yellow oil, b. p. 150°/20 mm., n_D^{25} 1·5085 (Found: C, 61·1; H, 6·1. $C_{10}H_{12}O_4$ requires C, 61·5; H, 6·15%), $\nu_{max.}$ 3080, 1580, and 1508 (furan), 1735 (C=O of ester), and 1665 cm.$^{-1}$ (C=O of chelated ketone). This gave a 2,4-*dinitrophenylhydrazone*, pale orange needles (from ethanol), m. p. 192° (Found: C, 50·9; H, 4·2; N, 15·3. $C_{16}H_{16}N_4O_7$ requires C, 50·9; H, 4·3; N, 15·0%), $\lambda_{max.}$ (in $CHCl_3$) 393 mμ (ε 29,300).

Ethyl β-*Methyl*-α-5-*methylfuroylbutyrate* (IV; R = Me, R′ = H).—Ethyl 5-methylfuroylacetate (6·3 g., 0·03 mole) was added to sodium ethoxide (0·03 mole) in ethanol at 0°. The mixture was stirred at 0° for 0·5 hr. and then isopropyl iodide (0·05 mole) was added. The mixture was heated under reflux, with stirring, for 12 hr. *Ethyl* β-*methyl*-α-5-*methylfuroylbutyrate* (6·1 g., 78%) was obtained as a pale yellow oil, b. p. 107—109°/0·5 mm., n_D^{25} 1·5026 (Found: C, 64·6; H, 7·5. $C_{13}H_{18}O_4$ requires C, 65·6; H, 7·6%), $\nu_{max.}$ 3100, 1590, and 1520 (furan), 1745 (C=O of ester) and 1675 (C=O of ketone).

2-*Isovaleryl*-5-*methylfuran* (V; R = Me, R′ = H).—Ethyl β-methyl-α-5-methylfuroylbutyrate (6 g.) in 2N-sulphuric acid (100 ml.) and acetic acid (12 ml.) was heated under reflux until evolution of carbon dioxide had ceased. Extraction with ether followed by working-up in the usual way gave 2-isovaleryl-5-methylfuran (1·0 g., 25%), b. p. 99°/15 mm., n_D^{25} 1·4967, identical (ultraviolet and infrared spectra; 2,4-dinitrophenylhydrazones, orange needles, and brown needles, m. p.s and mixed m. p.s 142° and 173°, respectively; semicarbazone, m. p. and mixed m. p. 162°) with the compound[1] prepared by the Friedel–Crafts reaction.

Ethyl 3-*Methylfuroylacetate* (III; R = H, R′ = Me).—3-Methylfuroyl chloride (14·5 g., 0·1 mole) was condensed with the ethoxymagnesium derivative of ethyl t-butyl malonate (0·1 mole) in the usual way. The resulting crude ethyl t-butyl α-3-methylfuroylmalonate was heated under reflux with toluene-*p*-sulphonic acid (1 g.) in benzene (30 ml.) until gas evolution had ceased (2 hr.). Working-up gave ethyl 3-methylfuroylacetate, b. p. 149—150°/25 mm., n_D^{25} 1·5010 (lit.,[6] b. p. 145—150°/15 mm., n_D^{19} 1·5004), $\nu_{max.}$ 3100 and 1580 (furan), 1740 (C=O of ester), and 1670 cm.$^{-1}$ (C=O of chelated ketone). This gave a 2,4-*dinitrophenylhydrazone*, orange needles (from ethanol), m. p. 128° (Found: C, 51·2; H, 4·3; N, 15·2. $C_{16}H_{16}N_4O_7$ requires C, 50·9; H, 4·3; N, 15·0%), $\lambda_{max.}$ (in $CHCl_3$) 395 mμ (ε 26,100).

Ethyl β-*Methyl*-α-3-*methylfuroylbutyrate* (IV; R = H, R′ = Me).—Ethyl 3-methylfuroylacetate (6·3 g., 0·03 mole) was added to sodium ethoxide (0·03 mole) in ethanol (30 ml.) at 0°. A white precipitate was formed. The mixture was stirred at 0° for 0·5 hr., and then isopropyl iodide (0·05 mole) was added. The resulting clear solution was heated under reflux, with stirring, for 12 hr. Working-up gave *ethyl* β-*methyl*-α-3-*methylfuroylbutyrate* (6·1 g., 78%), b. p. 109—110°/1·5 mm., n_D^{25} 1·4909 (Found: C, 64·7; H, 7·2. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%), $\nu_{max.}$ 3100 and 1580 (furan), 1735 (C=O of ester), and 1665 cm.$^{-1}$ (C=O of ketone).

2-*Isovaleryl*-3-*methylfuran* (V; R = H, R′ = Me).—Ethyl β-methyl-α-3-methylfuroylbutyrate (3·8 g.) in 2N-sulphuric acid (60 ml.) and acetic acid (10 ml.) was heated under reflux until revolution of carbon dioxide had ceased. Extraction with ether and working-up in the usual way gave a dark oil which was chromatographed on alumina. Elution with light petroleum gave 2-isovaleryl-3-methylfuran (1·0 g., 50% based on unrecovered keto-ester), b. p. 86—87°/10 mm., n_D^{25} 1·4842 (lit.,[7] b. p. 59·5—60°/2·2 mm., n_D^{20} 1·4868), identical[1,7] (ultraviolet and infrared spectra; 2,4-dinitrophenylhydrazones, orange needles, and red needles, m. p. and mixed m. p.s 126° and 189—190°, respectively; semicarbazone, m. p. and mixed m. p. 170°) with the naturally occurring elsholtzia ketone.

Diethyl α-Furoyl-α-isopropylmalonate (VI).—To magnesium turnings (2·5 g., 0·10 g.-atom) in ethanol (2·5 ml.) containing a drop of carbon tetrachloride, a portion (3 ml.) of a mixture of diethyl α-isopropylmalonate (20 g., 0·1 mole) and ethanol (8 ml.) was added with stirring. When the reaction had subsided the rest of the mixture was added dropwise at such a rate as to maintain gentle reflux. Ether (30 ml.) was then added and the mixture was heated under reflux, with stirring, until all the magnesium had reacted. The solvent was evaporated under anhydrous conditions, the residue was taken up in ether and filtered. Furoyl chloride (13 g., 0·1 mol.) in ether (60 ml.) was added dropwise to the filtrate under anhydrous conditions, a solid being precipitated. The mixture was heated under reflux for 0·75 hr., cooled, treated with water, and then with dilute sulphuric acid. Extraction with ether, followed by the usual working-up, gave a colourless oil, b. p. 130°/0·02 mm., which solidified. Recrystallisation from light petroleum gave *diethyl α-furoyl-α-isopropylmalonate* (20·6 g., 70%), plates, m. p. 48° (Found: C, 60·7; H, 6·7. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8%), $\lambda_{max.}$ (in hexane) 268 mμ (ε 22,600), $\nu_{max.}$ (in Nujol) 3120 and 1575 (furan), 1760 and 1725 (C=O of non-enolisable β-diester), and 1695 cm.$^{-1}$ (C=O of ketone).

Attempted Decarboxylation of Diethyl α-Furoyl-α-isopropylmalonate.—(*a*) The keto-ester (5 g.) was heated in 2N-sulphuric acid (70 ml.) and acetic acid (50 ml.) for 3 days. Working-up in the usual way gave unchanged keto-ester (3·8 g., 76%), m. p. and mixed m. p. 48°.

(*b*) The keto-ester (5 g.) was heated in ethanolic 2N-potassium hydroxide (100 ml.) for 5 hr. The mixture was cooled, acidified with dilute hydrochloric acid, and extracted with ether. Removal of solvent left an oil which was taken up in aqueous sodium hydrogen carbonate. Acidification gave furoic acid (1·7 g., 90%), m. p. and mixed m. p. 133°.

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