434. *Studies with Furans. Part I. The Synthesis of Furans having a β-Methylcrotonoyl Side-chain.*

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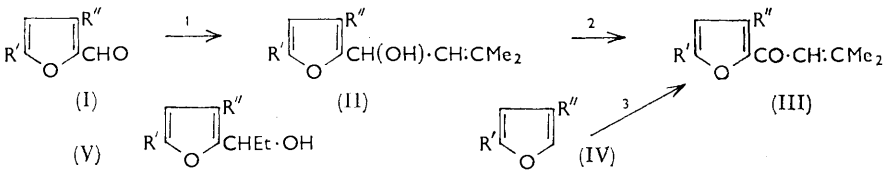
Furfuraldehyde and 5-methylfurfuraldehyde were condensed with 2-methylpropenylmagnesium bromide to give the alcohols (II; R′ = H or Me, R″ = H), which were oxidised to the β-methylcrotonoylfurans (III; R′ = H or Me, R″ = H). A similar series of reactions failed with 3-methylfurfuraldehyde. Naginata ketone, 3-methyl-2-β-methylcrotonoylfuran (III; R′ = H, R″ = Me), was, however, synthesised from 3-methylfuran by a Friedel–Crafts reaction.

Most of the naturally occurring furans are terpenoid.[1] The C_{10} compounds known can be classified under (I) compounds which have a C_6 side-chain attached to a furan ring

[1] For a review, see Levisalles, *Perfumery Essent. Oil Record*, 1958, **49**, 504, 627.

(*e.g.*, perillene, perilla ketone,[2] the clausenans,[3] batatic acid,[4] ipomeanin [5]), and (2) compounds which have a C_5 side-chain attached to a methyl-substituted furan (elsholtzia ketone,[6] naginata ketone; [7] menthofuran [8] can also be considered as a compound of this class). This paper describes the synthesis of compounds of class (2) where the side-chain is β-methylcrotonoyl, as is present in naginata ketone [7] (III; R′ = H, R″ = Me), a component of the essential oil from *Elsholtzia oldhami* Hemsl.

Model experiments were carried out on 2-furoic acid and its derivatives. Lithium furoate was treated with 2-methylpropenyl bromide in ether in the presence of lithium, following the method used by Braude and Coles [9] to prepare αβ-unsaturated ketones. No pure ketonic product could be isolated. Treatment of 2-furoyl chloride with 2-methylpropenyl-lithium in ether or in tetrahydrofuran failed to give a pure product. As in the known [10] ketone synthesis, 2-furamide was treated with an excess of 2-methylpropenylmagnesium bromide in tetrahydrofuran; no ketonic product was isolated but a small



1, $Me_2C{:}CH{\cdot}MgBr$. 2, MnO_2. 3, $Me_2C{:}CH{\cdot}COCl$.

yield of 1-2′-furyl-3-methylbut-2-en-1-ol (II; R′ = R″ = H) was obtained. Use of less vigorous conditions gave a reduced yield of the alcohol and much unchanged furamide. Treatment of 2-furoyl chloride with 2-methylpropenylmagnesium bromide in tetrahydrofuran at room temperature (normal addition) and at −60° (inverse addition) failed to give any useful product in reasonable yield. From the latter experiment in which aqueous ammonium acetate was used in working up, a 45% yield of 2-furamide and a small amount of the alcohol (II; R′ = R″ = H) were obtained. The 2-furamide arose from reaction of unchanged 2-furoyl chloride with ammonium acetate (an observation which led us to investigate the action of ammonium acetate on other acid chlorides [11]).

It was then decided to approach the synthesis of β-methylcrotonoylfurans by way of the furan aldehydes. Furfuraldehyde was condensed with 2-methylpropenylmagnesium bromide in tetrahydrofuran, giving the previous alcohol (II; R′ = R″ = H) and this was oxidised with activated manganese dioxide [12] at room temperature to 2-β-methylcrotonoylfuran (III; R′ = R″ = H). Similarly 5-methylfurfuraldehyde (I; R′ = Me, R″ = H) gave the 5-methylfuryl analogue (II; R′ = Me, R″ = H) which was oxidised to 5-methyl-2-β-methylcrotonoylfuran (III; R′ = Me, R″ = H). The latter, which is an isomer of naginata ketone, was obtained crystalline. Numerous attempts were made to condense 3-methylfurfuraldehyde [6b] (I; R′ = H, R″ = Me) with 2-methylpropenylmagnesium bromide but a reasonable yield of a homogeneous compound could not be obtained. In most of the experiments a large amount of the aldehyde was recovered. Attempts were

[2] Goto, *J. Pharm. Soc. Japan*, 1937, **57**, 77; Sebe, *J. Chem. Soc. Japan*, 1943, **64**, 1130.
[3] Rao, *J. Sci. Ind. Res.* (*India*), 1948, **7**, No. 1B, 11.
[4] Kubota and Naya, *Chem. and Ind.*, 1954, 1427.
[5] Kubota, Matsura, and Ichikawa, *Chem. and Ind.*, 1954, 902.
[6] (*a*) Asahina and Murayama, *Arch. Pharm.*, 1914, **252**, 435; *J. Pharm. Soc. Japan*, 1951, **398**, 361; Asahina, Murayama, Shibata, Kariyone, Kuwada, and Asano, *Acta Phytochim. Japan*, 1924–1926, **2**, 1; (*b*) Reichstein, Zschokke, and Georg, *Helv. Chim. Acta*, 1931, **14**, 1277.
[7] (*a*) Fujita and Ueda, *Chem. and Ind.*, 1960, 236; (*b*) Naves and Ochsner, *Helv. Chim. Acta*, 1960, **43**, 406, 568.
[8] Charabot and Herbert, *Bull. Soc. chim. France*, 1904, **31**, 405; Carles, *Parfumerie Moderne*, 1929, **22**, 615; Treibs, *Ber.*, 1937, **70**, 85.
[9] Braude and Coles, *J.*, 1950, 2012.
[10] Beis, *Compt. rend.*, 1903, **137**, 575.
[11] Finan and Fothergill, unpublished work.
[12] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.

made to condense this aldehyde with ethylmagnesium bromide but none of the expected alcohol (V; R′ = H, R″ = Me) was obtained although furfuraldehyde is known [13] to undergo a similar condensation and in our hands 5-methylfurfuraldehyde gave the isomeric alcohol (V; R′ = Me, R″ = H) in high (76%) yield.

The synthesis of naginata ketone by elaboration of 3-methylfurfuraldehyde being thus foiled, direct introduction of the β-methylcrotonoyl side-chain into the furan nucleus was studied. Extensive reports [14] on the acylation of furan, 2-methylfuran, and 2,5-dimethylfuran by acid anhydrides and acid chlorides were available. Accordingly furan was treated with β-methylcrotonoyl chloride in the presence of boron trifluoride in ether at 0°, giving a fair yield of 2-β-methylcrotonoylfuran (III; R′ = R″ = H), identical with the product obtained from furfuraldehyde. Anhydrous zinc chloride was also successful as a condensing agent in this reaction. Friedel–Crafts reaction of 2-methylfuran with β-methylcrotonoyl chloride gave 5-methyl-2-β-methylcrotonoylfuran (III; R′ = Me, R″ = H) identical with the product obtained from 5-methylfurfuraldehyde. Treatment of 3-methylfuran [15] (IV; R′ = H, R″ = Me) with β-methylcrotonoyl chloride under similar conditions gave 3-methyl-2-β-methylcrotonoylfuran (III; R′ = H, R″ = Me) whose physical constants and light absorption data were in excellent agreement with those of naginata ketone.[7] The synthetic material gave a 4-phenylsemicarbazone identical with a specimen prepared from the natural product. Treatment of the synthetic ketone with 2,4-dinitrophenylhydrazine gave a crystalline derivative, m. p. 151°, identical with that obtained by us from a specimen of the natural product under similar conditions. Naves and Ochsner [7b] succeeded in separating the latter 2,4-dinitrophenylhydrazone into two isomers, m. p. 164° and 177° respectively. We were unable to achieve this but in the case of 2-β-methylcrotonoylfuran (III; R′ = R″ = H) we did obtain two 2,4-dinitrophenylhydrazones; 5-methyl-2-β-methylcrotonoylfuran (III; R′ = Me, R″ = H), however, gave only one derivative. Work on the exact nature of these isomeric derivatives is in progress.

The above synthesis of naginata ketone is a further example of exclusive electrophilic attack on the 2-position of 3-methylfuran. The isolation by Reichstein [6b] of 3-methylfurfuraldehyde only from the Gattermann reaction on 3-methylfuran, and the production [16] of 3-methyl-2-nitrofuran as the only isomer on nitration of 3-methylfuran are other examples of this specificity.

Experimental

Operations involving the use of Grignard reagents or alkenyl-lithiums were carried out under nitrogen. Ether extracts were dried over anhydrous sodium sulphate. Liquid products were distilled under nitrogen. The light petroleum used had b. p. 40—60°.

Lithium 2-Furoate.—An aqueous solution of 2-furoic acid was warmed on the steam-bath with an excess of lithium carbonate. When evolution of carbon dioxide had ceased the mixture was cooled, filtered, and evaporated under reduced pressure and the residue was recrystallised from ethanol, giving *lithium 2-furoate* as needles, m. p. 304—305° (Found: C, 50·6; H, 2·9. $C_5H_3LiO_3$ requires C, 50·9; H, 2·55%).

Furamide from Furoyl Chloride.—2-Methylpropenylmagnesium bromide (0·1 mol.) in tetrahydrofuran was passed slowly into 2-furoyl chloride (0·1 mol.) in tetrahydrofuran at −60°. The mixture was stirred at −40° for 1 hr. and then treated with saturated aqueous ammonium acetate. Working up in the usual way gave an oily mixture together with furamide (6 g., 50%), m. p. and mixed m. p. 142°.

1-2′-*Furyl*-3-*methylbut*-2-*en*-1-*ol* (II; R′ = R″ = H).—Furfuraldehyde (24 g., 0·25 mol.) in

[13] Pawlinoff and Wagner, *Ber.*, 1884, **17**, 1967; Peters and Fischer, *J. Amer. Chem. Soc.*, 1930, **52**, 2079.

[14] See Dunlop and Peters, " The Furans," Reinhold Publ. Corp., New York, 1953, p. 421, and references therein.

[15] Cornforth, *J.*, 1958, 1310.

[16] Rinkes, *Rec. Trav. chim.*, 1930, **49**, 1118; Gilman and Burtner, *J. Amer. Chem. Soc.*, 1933, **55**, 2903; Witte and Lind, U.S.P. 2,502,114/1950.

tetrahydrofuran (100 ml.) was added slowly to 2-methylpropenylmagnesium bromide (0·25 mol.) in tetrahydrofuran (250 ml.) at 0°. The mixture was heated under reflux for 1 hr., cooled, and treated with water. Working up in the usual way gave the *alcohol* as a pale yellow oil (23 g., 60%), b. p. 69°/0·1 mm., n_D^{25} 1·4997 (Found: C, 70·9; H, 8·1. $C_9H_{12}O_2$ requires C, 71·1; H, 7·9%), $\nu_{max.}$ 3320, 1670 (C=C), 1600, and 1500 cm.$^{-1}$ (furan ring). The ultraviolet spectrum showed only end-absorption.

2-β-*Methylcrotonoylfuran* (III; R′ = R″ = H).—(a) *By oxidation of the above alcohol.* The alcohol (4 g.) was shaken with activated [12] manganese dioxide (40 g.) in light petroleum (200 ml.) at room temperature for 6 hr. The mixture was filtered and evaporated to a brown oil. Distillation gave 2-β-*methylcrotonoylfuran* (1·9 g., 50%), a pale yellow oil, b. p. 47—48°/0·04 mm., n_D^{25} 1·5440 (Found: C, 71·7; H, 6·9. $C_9H_{10}O_2$ requires C, 72·0; H, 6·6%), $\lambda_{max.}$ (in hexane) 286 and 294 mμ (ε 16,000 and 16,300, respectively), $\nu_{max.}$ 1664 (C=O), 1625 (C=C), and 1570 cm.$^{-1}$ (furan ring). The ketone, on treatment with 2,4-dinitrophenylhydrazine in ethanol containing sulphuric acid, gave a mixture of 2,4-dinitrophenylhydrazones which on fractional crystallisation from ethyl acetate–methanol gave *derivative* (1), orange needles, m. p. 180° (Found: C, 54·2; H, 4·3; N, 16·7. $C_{15}H_{14}N_4O_5$ requires C, 54·5; H, 4·25; N, 16·9%), $\lambda_{max.}$ (in chloroform) 396 mμ (ε 26,700), and *derivative* (2), red needles, m. p. 161° (Found: C, 54·3; H, 3·9; N, 17·2%), $\lambda_{max.}$ (in chloroform) 399 mμ (ε 25,100).

(b) *By Friedel–Crafts reaction.* (i) Boron trifluoride in ether (45% w/w; 2 ml.) was added to furan (5·6 g.) and β-methylcrotonyl chloride (9·6 g.) at 0°. The mixture was shaken and then left at room temperature for 1 hr. Water was added and the dark mixture was extracted with ether. The extract was washed with water and aqueous sodium hydrogen carbonate, dried, and concentrated to a brown oil. This was chromatographed on activated neutralised alumina (light petroleum as eluant), giving a pale yellow oil which was distilled, to give 2-β-methylcrotonoylfuran (4·9 g., 40%), b. p. 61°/0·7 mm., n_D^{25} 1·5462. The light-absorption properties were identical with those of the product described above; treatment with 2,4-dinitrophenylhydrazine as described gave two derivatives which were identical (m. p. and mixed m. p., light absorption) with those obtained as above. (ii) Anhydrous zinc chloride (0·1 g.) was added to furan (1·4 g.) and β-methylcrotonoyl chloride (2·4 g.). The mixture was warmed on the steam-bath for 1 hr. The dark blue mixture was cooled and extracted with ether. Working up as described above gave 2-β-methylcrotonoylfuran (1·25 g., 40%).

3-*Methyl*-1-(5-*methyl*-2-*furyl*)*but*-2-*en*-1-*ol* (II; R′ = Me, R″ = H).—(*a*) 5-Methylfurfuraldehyde (b. p. 86—87°/20 mm., n_D^{25} 1·5250; 0·15 mol.) was added to 2-methylpropenylmagnesium bromide (0·15 mol.) in tetrahydrofuran at 0°. The mixture was stirred overnight at room temperature and then treated with aqueous ammonium chloride. Working up in the usual way gave 3-*methyl*-1-(5-*methyl*-2-*furyl*)*but*-2-*en*-1-*ol* as a pale yellow oil (55%), b. p. 61°/0·01 mm., n_D^{25} 1·5101 (Found: C, 71·8; H, 8·5. $C_{10}H_{14}O_2$ requires C, 72·2; H, 8·45%), $\nu_{max.}$ 3350, 1664 (C=C), 1570 and 1520 cm.$^{-1}$ (furan ring).

(*b*) 5-Methylfurfuraldehyde (5·5 g., 0·05 mol.) was added to 2-methylpropenyl-lithium (0·07 mol.) in ether. The mixture was stirred overnight at room temperature and then aqueous ammonium acetate was added. Working up in the usual way gave the alcohol (0·8 g., 8·5%), b. p. 64°/0·02 mm., n_D^{25} 1·5070, whose infrared spectrum was identical with that of the product obtained as above.

5-*Methyl*-2-β-*methylcrotonoylfuran* (III; R′ = Me, R″ = H).—(a) *By oxidation of the preceding alcohol.* The alcohol (6 g.) was oxidised with activated [12] manganese dioxide (60 g.) in light petroleum (120 ml.) at room temperature for 36 hr. 5-*Methyl*-2-β-*methylcrotonoylfuran* (3·2 g., 54%) was obtained as a pale yellow oil, b. p. 74°/0·2 mm., which solidified to pale yellow needles, m. p. 48° (Found: C, 73·6; H, 7·8. $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·3%), $\lambda_{max.}$ (in hexane) 298 mμ (broad, ε 16,100), $\nu_{max.}$ 1660 (C=O), 1620 (C=C), 1510 cm.$^{-1}$ (furan ring). On treatment with 2,4-dinitrophenylhydrazine in ethanol containing sulphuric acid it gave a 2,4-*dinitrophenylhydrazone*, red needles (from ethyl acetate–methanol), m. p. 143° (Found: C, 55·5; H, 4·8; N, 16·1. $C_{16}H_{16}N_4O_5$ requires C, 55·8; H, 4·7; N, 16·3%), $\lambda_{max.}$ (in chloroform) 397 mμ (ε 29,700).

(b) *By Friedel–Crafts reaction.* A mixture of 2-methylfuran (1·5 g.) and β-methylcrotonoyl chloride (2·4 g.) was treated with boron trifluoride in ether (45% w/w; 0·5 ml.) for 1 hr. at room temperature. Working up in the usual way gave 5-methyl-2-β-methylcrotonoylfuran (1·4 g., 46%), b. p. 82°/0·5 mm., m. p. and mixed m. p. 48° (2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 143°).

1-(5-*Methyl*-2-*furyl*)*propan*-1-*ol* (V; R′ = Me, R″ = H).—5-Methylfurfuraldehyde (0·1 mol.) was added to ethylmagnesium bromide (0·1 mol.) in tetrahydrofuran. The mixture was heated under reflux for 1 hr., cooled, and treated with water. Working up in the usual way gave the *alcohol* (76%), b. p. 49—50°/0·3 mm., n_D^{25} 1·4789 (Found: C, 68·5; H, 8·7. $C_8H_{12}O_2$ requires C, 68·6; H, 8·6%), $\lambda_{max.}$ (in hexane) 222 mμ (ε 8600), $\nu_{max.}$ 3340, 1565 and 1516 (furan ring), 1022 cm.$^{-1}$ (αβ-unsaturated secondary alcohol).

The alcohol (3 g.) in dry pyridine (15 ml.) was treated with acetic anhydride (10 ml.) at room temperature overnight. This led to the *acetate* (2·7 g., 63%), b. p. 109—110°/20 mm., n_D^{25} 1·4667 (Found: C, 66·2; H, 7·6. $C_{10}H_{14}O_3$ requires C, 66·0; H, 7·7%), $\nu_{max.}$ 1735 (acetate C=O), 1560 and 1530 cm.$^{-1}$ (furan ring). The ultraviolet spectrum showed only end-absorption.

3-*Methyl*-2-β-*methylcrotonoylfuran* (III; R′ = H, R″ = Me).—A mixture of 3-methylfuran [15] (1 g.) and β-methylcrotonoyl chloride (1·6 g.) was treated with a few drops of boron trifluoride in ether (45% w/w) and left aside for 1 hr. The mixture was worked up as described for the Friedel–Crafts reactions above. 3-Methyl-2-β-methylcrotonoylfuran, naginata ketone (0·8 g., 40%), was obtained as a pale yellow oil, b. p. 52°/0·2 mm., n_D^{25} 1·5397, $\lambda_{max.}$ (in hexane) 286 and 294 mμ (ε 14,800 and 16,000, respectively) [lit.,[7b] b. p. 80—81°/3 mm., n_D^{25} 1·5350, $\lambda_{max.}$ (in iso-octane) 282·5 and 291 mμ (ε 14,700 and 15,800, respectively)] (Found: C, 72·9; H, 7·2. $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·3%). The infrared spectrum was identical with that of the naturally occurring ketone. The ketone with 4-phenylsemicarbazide in ethanol gave a derivative, m. p. 117° undepressed on admixture with a specimen prepared from the natural product (supplied by Dr. Naves). Treatment of the ketone with 2,4-dinitrophenylhydrazine in ethanol containing sulphuric acid gave a 2,4-dinitrophenylhydrazone, red needles (from ethyl acetate–methanol), m. p. 151° (Found: C, 55·0; H, 4·5; N, 16·3. Calc. for $C_{16}H_{16}N_4O_5$: C, 55·8; H, 4·7; N, 16·3%), $\lambda_{max.}$ (in chloroform) 406 mμ (ε 30,200), undepressed on admixture with a 2,4-dinitrophenylhydrazone prepared by us from a specimen of the natural product.

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