Tetrahedron, 1959, Vol. 7, pp. 236 to 240. Pergamon Press Ltd. Printed in Northern Ireland

TERPENOIDS—VI

A NOVEL UNAMBIGUOUS SYNTHESIS OF DL-AR-TURMERONE[1]

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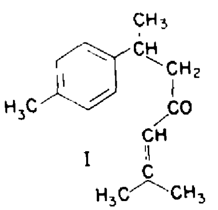
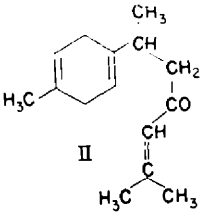
(*Received* 27 *February* 1959)

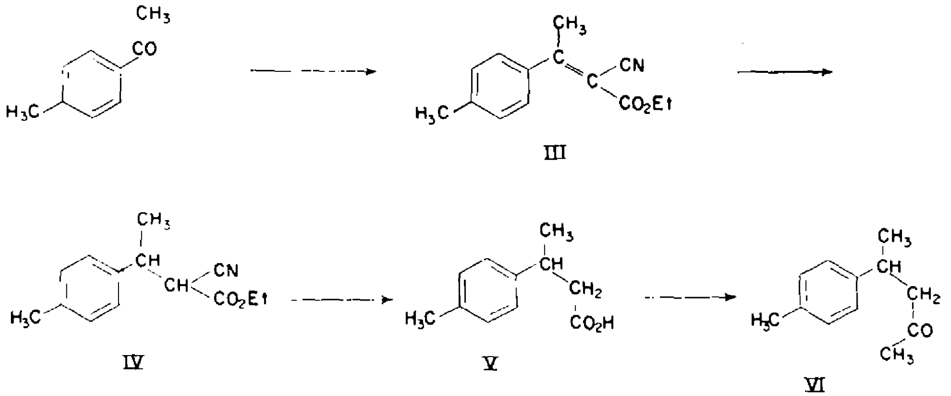
Abstract—A new synthesis of DL-ar-turmerone starting from DL-curcumone is described.

The aromatic ketone DL-ar-turmerone (I) occurs with turmerone (II) a monocyclic sesquiterpene ketone, as chief component of the essential oil from the rhizomes of *Curcuma longa* Linn.


I


II

THE structure of I was determined by Rupe and co-workers,[3,4] and confirmed by a number of syntheses.[3,5,6] We now record a new synthesis of DL-ar-turmerone by a direct and simpler sequence of reactions, involving the intermediate formation of the 3-hydroxy-1-keto-(1-dioxolane)-alkane system which serves as a precursor of the final $\alpha\beta$-unsaturated ketone.[7,8] The starting material, curcumone (VI), was obtained as follows:



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[2] H. Rupe, G. Clar, A. Pfau, and P. Plattner, *Helv. Chim. Acta* 17, 372 (1934).
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[4] H. Rupe and F. Wieder-Kehr, *Helv. Chim. Acta* 7, 654 (1924).
[5] J. Colonge and J. Chambion, *C.R. Acad. Sci., Paris* 222, 557 (1946).
[6] S. M. Mukherji, *J. Ind. Chem. Soc.* 24, 341 (1947).
[7] S. M. Mukherji, R. P. Gandhi and O. P. Vig, *J. Ind. Chem. Soc.* 33, 853 (1956).
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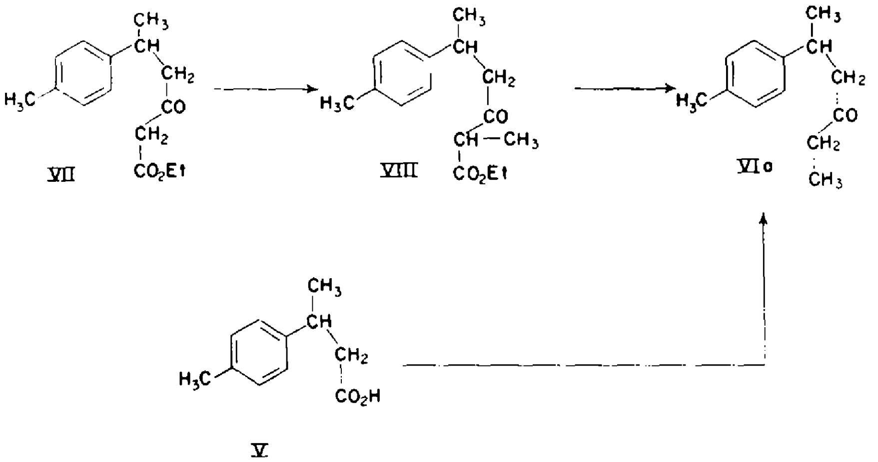
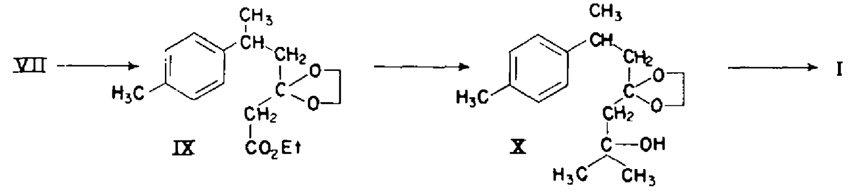
Ethyl β-methyl-β-(*p*-tolyl)-α-cyanoacrylate (III) was obtained by Cope–Knoevenagel condensation of *p*-methyl acetophenone and ethyl cyanoacetate.[9,10] The ester (III) was reduced catalytically in almost quantitative yield to ethyl α-cyano-β-methyl-β-(*p*-tolyl)-propionate (IV) which on hydrolysis gave β-(*p*-tolyl)-butyric acid (V). The acid chloride from V was treated with cadmium dimethyl reagent in benzene and refluxed,[11] yielding β-methyl-β-(*p*-tolyl)-ethylmethyl ketone (Curcumone VI), which was characterized as its semicarbazone derivative.[4] A better and consistent yield (88 %) (based on acid chloride) of the ketone (VI) was, however, obtained by using the method of Walker and Hauser.[12] VI was carbethoxylated with sodium hydride in large excess of diethylcarbonate[13] to ethyl β-keto-δ-methyl-δ-(*p*-tolyl)-valerate (VII). The position of the ethoxycarbonyl group in VII is assumed by analogy,[14] as well as mixed melting point of the 2:4-dinitrophenylhydrazone derivates of 5-methyl-5-(*p*-tolyl)-pentane-3-one (VIa) derived in two ways as indicated in the following scheme:



VII was ketalized with ethylene glycol to obtain ethyl β-keto-(β-dioxolane)-δ-methyl-δ-(*p*-tolyl)-valerate (IX):



IX reacted with methyl magnesium iodide giving the carbinol (X). The ketal-alcohol (X) was then subjected to acid hydrolysis and subsequently distilled in the presence of trace of iodine to obtain DL-ar-turmerone (I). The unsaturated ketone gave a semicarbazone.

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EXPERIMENTAL*

*Ethyl α-cyano-β-methyl-β-(*p*-tolyl)-acrylate* (III)

(a) A mixture of *p*-methyl-acetophenone (134 g), ethyl cyanoacetate (113 g), ammonium acetate (15·5 g), acetic acid (48 g) and anhydrous benzene (300 ml) was refluxed under a Dean and Stark apparatus for 15–20 hr. The contents were cooled, water added and the organic substance extracted in ether–benzene. The vacuum distillation of the product gave 140 g (61 %) of a viscous oil, b.p. 160–170°/10 mm (Found: C, 73·1; H, 6·75. $C_{14}H_{15}O_2N$ requires: C, 73·34; H, 6·59 %).

(b) A mixture of *p*-methylacetophenone (67 g), ethyl cyanoacetate (113 g), ammonium acetate (6 g), acetic acid (48 g), and benzene was refluxed under a water separator until no more water came over. Ammonium acetate (2 g) was added and the contents refluxed for 3–4 hr. Refluxing was again interrupted several times till a total of 16 g of the ammonium acetate had been added. Heating was continued for several hours after the last addition of the catalyst. As in (a) 80 g (70 %) of III was obtained.

*Ethyl α-cyano-β-methyl-β-(*p*-tolyl)-propionate* (IV)

(a) The alkylidene ester (III, 50 g) was reduced in alcohol (98 %, 200 ml) and acetic acid (2–3 ml) with Pd-charcoal (5 %, 5 g). Hydrogen gas (5400 ml) was absorbed, yielding the reduction product (45 g, 90 %), b.p. 160–162°/10 mm (Found: C, 72·70; H, 7·41. $C_{14}H_{17}O_2N$ requires: C, 72·45; H, 7·30 %).

(b) The hydrogenation proceeded more rapidly when Pd-strontium carbonate (10 %) was employed as catalyst in ethanol.

*β-Methyl-β-(*p*-tolyl)-propionic acid* (V)

IV (100 g) was refluxed with conc HCl (600 ml) for about 50 hr. After cooling the crude material (58 g, 76 %) m.p. 87–88° was purified through its sodium salt.

The analytical sample obtained after crystallization from ethanol, m.p. 90·5°, lit.[4] m.p. 91°. (Found: C, 73·8; H, 7·68. $C_{11}H_{14}O_2$ requires: C, 74·13; H, 7·92 %).

*β-Methyl-β-(*p*-tolyl)-propionyl chloride*

The acid (V, 50 g), diluted with anhydrous benzene (100 ml), and thionyl chloride (70 g) were heated (water bath) for about 2 hr. After removal of benzene and excess thionyl chloride, the acid chloride was distilled at 120°/5 mm yield, 50 g (90·6 %).

*β-Methyl-β-(*p*-tolyl)-ethylmethyl ketone* (VI)

(a) To the well-cooled Grignard reagent (prepared from 13·2 g Mg, 78 g methyl iodide and 300 ml dry ether) was added, with stirring, anhydrous cadmium chloride (46·5 g), and the mixture refluxed for 3–4 hr. Ether was replaced by anhydrous benzene (400 ml). The acid chloride (44 g) was added slowly refluxing the benzene for an additional 1½ hr. The contents were decomposed with dil ice-cold H_2SO_4 and ether extracted, washed free of acid, dried. The ketone (VI) 29·5 g, 75 % was obtained as a light oil, b.p. 130°/12 mm. The semicarbazone after crystallization from dil alcohol, melted at 145°, lit.[4] m.p. 146°. (Found: N, 17·5. $C_{13}H_{19}ON_3$ Calc. for N, 18·01 %).

(b) Ethoxymagnesium malonate was prepared from magnesium metal (2·68 g), absolute ethanol (13 ml), anhydrous ether (50 ml) and diethyl malonate (17·6 g) according to the procedure of Walker and Hauser.[12] The acid chloride (19·7 g) was added during stirring and the contents refluxed for an additional ½ hr. After cooling, the reaction mixture was decomposed with dil H_2SO_4 and the acyl malonic ester derivative ether extracted and the solvent evaporated. The residue was refluxed with a mixture of glacial acetic acid (30 ml), water (20 ml) and conc H_2SO_4 (5 ml) for 5 hr. KOH (20 %) was added till alkaline and the product extracted with ether, which on distillation yielded 15·5 g (88 %) of the ketone (VI), b.p. 130°/12 mm.

The semicarbazone m.p. and mixed m.p. with the sample obtained in (a), 144–145°.

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[*] Melting and boiling points are uncorrected. Microanalyses by Drs. Weiler and Strauss, Oxford.

*Ethyl β-keto-δ-methyl-δ-(*p*-tolyl)-valerate* (VII)

VI (16·3 g) was added with stirring to a refluxing mixture of sodium hydride (4·8 g), anhydrous ether (500 ml) and diethyl carbonate (23·6 g). After the addition the contents were stirred and refluxed for another 2 hr and the mixture decomposed with cold dilute acetic acid and extracted with ether. The ethereal solution was washed once with water, then with 5% sodium bicarbonate solution until free of acid, and finally with water and dried. After the removal of ether, the residual heavy oil was distilled under reduced pressure. The fraction distilling at 190–193°/10 mm was collected; yield, 9·6 g (42%).

The β-keto-ester gave a violet-red coloration with alcoholic ferric chloride solution. (Found: C, 72·20; H, 7·85. $C_{15}H_{20}O_3$ requires: C, 72·55; H, 8·12%).

*Ethyl β-keto-αδ-dimethyl-δ-(*p*-tolyl)-valerate* VIII)

VII (5 g) was added to a cooled solution of potassium metal (1 g), in dry t-butyl alcohol (50 ml) and the mixture left for 4–6 hr until the solution became strongly coloured (orange). Thereafter, it was heated on the water-bath for ½ hr and again cooled. Methyl iodide (4 g) was introduced and the mixture refluxed for 3–4 hr and the t-butyl alcohol was distilled. Water was added to dissolve potassium iodide and the organic material ether extracted. From the dried ethereal solution (4 g, 75%) of the oily methyl-keto-ester (VIII) distilling at 170–175°/4 mm was obtained. (Found: C, 72·8; H, 8·5. $C_{16}H_{22}O_3$ requires: C, 73·25; H, 8·45%).

*5-Methyl-5-(*p*-tolyl)-pentan-3-one(homo-curcumone)* (VIa)

(a) *The reaction of curcumic acid chloride with cadmium diethyl.* Cadmium diethyl reagent was prepared from ethyl bromide (13·1 g), magnesium turnings (3 g), anhydrous cadmium chloride (11 g) in dry ether (50 ml). Ether was replaced by benzene (75 ml) and to the refluxing mixture, with stirring, curcumic acid chloride (12 g) in anhydrous benzene (25 ml) was added during 15 min and stirring and refluxing continued for another 20 min. Homocurcumone (9 g, 77·5%) b.p. 125°/5–6 mm, was obtained as a colourless oil. (Found: C, 82·42; H, 9·63. $C_{13}H_{18}O$ requires: C, 82·06; H, 9·54%).

The 2:4-dinitrophenylhydrazone of VIa was deposited as yellow needles which after two crystallizations from ethyl acetate-methanol mixture melted at 113–114°. (Found: N, 15·7. $C_{19}H_{22}O_4N_4$ requires: N, 15·2%).

(b) *The hydrolysis of* (VIII). The keto-ester (VIII, 3 g) was refluxed with a mixture of conc H_2SO_4 (2 ml), acetic acid (8 ml) and water (5 ml) for 5–6 hr. After cooling, sufficient potassium hydroxide solution (20%) was added until alkaline. The ethereal solution of the oily product was washed free of alkali, dried and the solvent evaporated leaving the ketone (VIa) b.p. 125°/5–6 mm.

The 2:4-dinitrophenylhydrazone, m.p. 113° was undepressed on admixture with the sample of 2:4-dinitrophenylhydrazone obtained as in (a).

*Ethyl (β-keto-β-dioxolane)-δ-methyl-δ-(*p*-tolyl)-valerate* (IX)

The keto-ester (VII, 10 g), ethylene glycol (4 g), *p*-toluene-sulphonic acid (0·1 g) and anhydrous benzene (100 ml) were refluxed (oil-bath at 120°) under a constant water separator for 6 hr. After cooling, sodium ethoxide in alcohol and water was added, and the organic material extracted with ether. This yielded (9·28 g, 88%) of IX as a colourless viscous oil, b.p. 218–220°/12 mm (Found: C, 69·5; H, 8·3. $C_{17}H_{24}O_4$ requires: C, 68·83; 8·27%).

*(β-Keto-β-dioxolane)-δ-methyl-δ-(*p*-tolyl)-*n*-butyl-dimethyl carbinol* (X)

Grignard reagent was prepared from clean dry magnesium turnings (1·8 g), and methyl iodide (11 g) in dry ether (100 ml). To this was added the ketal-ester (IX, 10 g) dropwise under ice-cooling. The contents were allowed to stand overnight at room temp and then refluxed for an hour. After cooling, the reaction mixture was decomposed with saturated ammonium chloride solution. On subsequent working up the ketal-carbinol (X) was obtained as a colourless viscous oil yield, 7·3 g (76%), b.p. 222–225°/10 mm. (Found: C, 73·5; H, 9·0. $C_{17}H_{26}O_3$ requires: C, 73·34; H, 9·41%).

DL-ar-Turmerone (I)

The above ketal-alcohol (X, 7·3 g) was refluxed for an hour with a solution of ethanol (30 ml), water (100 ml) and four drops of conc HCl. The mixture was then cooled, diluted with water (50 ml) and extracted with ether. The dried ethereal extract was evaporated and the residue was distilled under reduced pressure with a crystal of iodine yielding 4·37 g (64%) of a light oil, b.p. 156–158°/7 mm. η_D^{21} 1·5218. (Found: C, 83·0; H, 9·48. $C_{15}H_{20}O$ requires: C, 83·28; H, 9·32%).

The semicarbazone of I crystallized from dil ethanol in colourless needles, m.p. 105–106.° Lit.[3] m.p. 108° for D-ar-turmerone semicarbazone. (Found: N, 15·1. $C_{16}H_{23}ON_3$ requires: N, 15·37).