Synthesis of p-Isopropyl-α-methylhydrocinnamic aldehyde.

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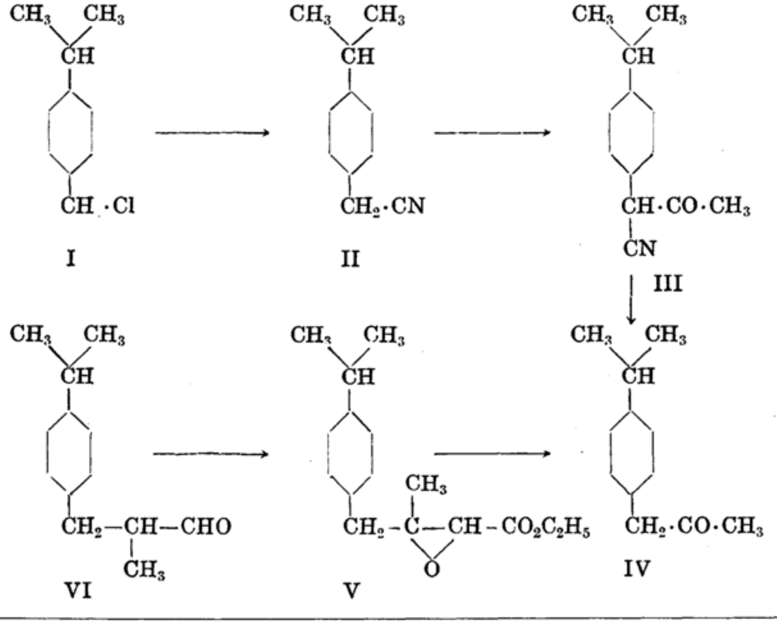
Knorr and Weissenborn⁽¹⁾ synthesised p-isopropyl-α-methylhydrocinnamic aldehyde by condensing cuminaldehyde with propionaldehyde in the presence of alcoholic potash and then reducing the product with hydrogen, using nickel as a catalyser. Since then this compound has been used as perfume. More recently, the compound has been synthesised in the Société des Usines Chimiques⁽²⁾ by heating calcium p-isopropyl-α-methylhydrocinnamate with calcium formate or by heating p-isopropyl-α-methylhydrocinnamic acid with formic acid in the presence of metallic oxides, such as oxide of Ti, Mn, Al, Zn or Th. For this synthesis, p-isopropyl-α-methylhydrocinnamic acid was first synthesised by the condensation of cuminyl chloride with ethyl methylmalonate in the presence of sodium ethoxide and subsequent decomposition of the free acid liberated from the ester.

Two new methods, both starting from cuminyl chloride, of synthesising p-isopropyl-α-methylhydrocinnamic aldehyde have been devised by the present authors.

The first method. Cuminyl chloride (I) was first converted into p-isopropylbenzyl cyanide (II). The cyanide and ethyl acetate were condensed in the presence of sodium ethoxide to form α-p-isopropylphenyl-



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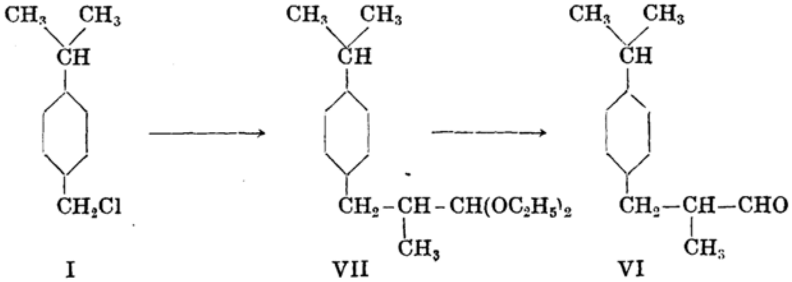
(1) A. Knorr and A. Weissenborn (Winthrop Chemical Co., Inc.), A.P. 1844013 (1932).
(2) F.P. 833644 (1938).

acetoacetonitrile (III), which was converted into *p*-isopropylbenzyl methyl ketone (IV). The ketone and ethyl monochloroacetate were again condensed to yield ethyl α,β-epoxy-γ-*p*-isopropylphenyl-β-methylbutyrate (V), which, on saponification, gave the desired *p*-isopropyl-α-methylhydrocinnamic aldehyde (VI) as shown in the accompanying scheme.

The second method. Cuminyl chloride (I) was converted by the condensation with the diethylacetal of α-bromopropionaldehyde into the diethylacetal of *p*-isopropyl-α-methylhydrocinnamic aldehyde (VII). The acetal, on hydrolysis with dilute hydrochloric acid, yielded the desired *p*-isopropyl-α-methylhydrocinnamic aldehyde (VI), as shown in the following scheme:



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Experimental. p-*Isopropylbenzyl Cyanide* (II). This compound was synthesised by Rossi⁽³⁾ and by Komppa⁽⁴⁾ by heating cuminyl chloride with potassium cyanide in a sealed tube. However, the present authors were able to prepare it with an 85% yield in the following way: Cuminyl chloride (170 g.) and alcohol (170 g.) were added to a solution of potassium cyanide (65 g.) in water (60 c.c.), and the mixture was boiled for 3 hours. On cooling, it separated potassium chloride, which was filtered off and washed with alcohol. The filtrate and the washings were combined and the alcohol evaporated. The residue was extracted with ether and the ethereal extract was washed with water and dried over calcium chloride. After the ether was evaporated, the residual oil was subjected to fractional distillation under reduced pressure, when an oil boiling at 125–128°/9 mm. passed over. The yield was 85% of the theoretical. The oil has n_D^{28} 1.5078, d_4^{28} 0.9619, $[R_L]_D$ 49.28 (Calc. for $C_{11}H_{13}N\ulcorner^{=}_{3}$: 49.22).

α-p-*Isopropylphenylacetoacetonitrile* (III). A mixture of *p*-isopropylbenzyl cyanide (318 g.) and ethyl acetate (264 g.) was added to a solution of sodium (60 g.) in absolute alcohol (700 c.c.) and the whole was heated to boiling for about an hour on a water-bath, until it became a pasty mass. After being heated for an hour more, the mass solidified completely and was allowed to stand for 12 hours. Water (3 kg.) was then added, when unchanged *p*-isopropylbenzyl cyanide separated, which was removed by extraction with ether. The aqueous residue was acidified at about 10° with glacial acetic acid (100 c.c.). The yellow oil, thus obtained was extracted with ether and the ethereal extract was

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(3) A. Rossi, *Ann., Suppl.*, **1** (1861), 139.

(4) G. Komppa, *Ber.*, **68** (1935), 1269.

washed successively with an aqueous solution of sodium carbonate and with water. After the ethereal extract was dried over calcium chloride, the ether was evaporated, and the residual oil solidified. The yield was 290 g. (72% of the theoretical). Although it was pure enough for the next preparation, it was recrystallised from methyl alcohol, from which it separated in colourless needles melting at 84–85°. Found: N, 7.26. Calc. for $C_{13}H_{15}ON$: N, 6.96%.

The semicarbazone crystallised from alcohol in colourless aggregated crystals melting at 156°. Found: N, 21.82. Calc. for $C_{18}H_{18}ON_4$: N, 21.70%.

p-*Isopropylbenzyl Methyl Ketone* (IV).—This compound has already been prepared by Bradfield, Pritchard and Simonsen(5) by condensing cuminaldehyde with ethyl *α*-bromopropionate in the presence of sodium ethoxide, and then hydrolysing the condensation product, namely ethyl *α*,*β*-epoxy-*β*-cuminyl-*β*-methylpropionate, with methyl alcoholic potassium hydroxide.

The present authors synthesised this compound in the following way: Powdered *α*-*p*-isopropylphenylacetoacetonitrile (120 g.) was added, with constant stirring, to concentrated sulphuric acid (170 c.c.), cooled at −10°. After all the nitrile was added, the mixture was warmed to 60° and a brown solution was obtained. After this was cooled to 0°, water (850 c.c.) was rapidly added and the whole was again heated, with constant stirring, for two hours on a water-bath. The green solution thus obtained was cooled, and the supernatant oil was separated. The aqueous solution was extracted several times with ether. The oil and ethereal extracts were combined, washed with water, dried over anhydrous sodium sulphate and evaporated. The residual oil was purified by distillation under diminished pressure, and a fraction, boiling at 125–128°/16 mm., was collected. This fraction has n_D^{28} 1.5033, d_4^{28} 0.9538, $[R_L]_D$ 54.33 (Calc. for $C_{12}H_{16}O\bar{|}_3$: 54.03).

The semicarbazone crystallised from alcohol in colourless prisms melting at 142–143°. Found: N, 18.20. Calc. for $C_{13}H_{19}ON$: N, 18.03%.

*Ethyl α,β-Epoxy-γ-*p*-isopropylphenyl-β-methylbutyrate* (V). Absolute alcohol (55 g.) was added to pieces of sodium (13.8 g.) covered with dry benzene (200 g.). After all the sodium dissolved, the solution was maintained at 0°, and, to this, *p*-isopropylbenzyl methyl ketone (88 g.) and ethyl monochloroacetate (62 g.) were added and stirred for two hours at 0°. The mixture was allowed to stand for 40 hours at the ordinary temperature, poured into ice-cold water (500 g.) and acidified with glacial acetic acid (5 c.c.). The supernatant oily layer was separated and the lower aqueous layer was extracted with benzene. The oil and benzene solution were combined, washed with water, dried over anhydrous sodium sulphate and evaporated. The residual oil was subjected to fractional distillation under reduced pressure of 11 mm., and a fraction distilling at 164–167°, was collected. The yield was 76 g. (58% of the theoretical). Found: C, 73.05; H, 8.62. Calc. for $C_{16}H_{22}O_3$: C, 73.23; H, 8.46%. It has n_D^{23} 1.4987 and d_4^{23} 1.0308.

p-*Isopropyl-α-methylhydrocinnamic Aldehyde* (VI). Ethyl *α*,*β*-epoxy-

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(5) A. E. Bradfield, R. R. Pritchard and J. L. Simonsen, *J. Chem. Soc.*, **1937**, 760.

γ-*p*-isopropylphenyl-β-methylbutyrate (60 g.) was stirred for two hours at 35° with a 10% solution of sodium hydroxide (100 g.), and a lustrous paste was obtained. After this was mixed with a 10% solution of oxalic acid (110 g.), the mixture was distilled in steam. The oil passed over with vigorous effervescence and was extracted with ether. The ethereal extract was dried over anhydrous sodium sulphate and evaporated. The residual oil was distilled under reduced pressure of 10 mm. in a current of carbon dioxide, and a fraction, boiling at 128–131°, was collected. The oil has n_D^{28} 1.5030, d_4^{28} 0.9529, $[R_1]_D$ 58.99 (Calc. for $C_{13}H_{16}O|\!\overline{\,}_3$: 58.64).

The semicarbazone crystallised from alcohol in glazed colourless plates melting at 169–170°. Found: N, 16.24. Calc. for $C_{15}H_{21}ON_2$: N, 16.21%.

Diethylacetal of p-*Isopropyl-α-methylhydrocinnamic Aldehyde* (VII). A mixture of cuminyl chloride (115 g.) and diethylacetal of α-bromopropionaldehyde (140 g.) was gradually added, with constant stirring, to sodium (35 g.), cut into pieces and covered with ether. The stirring was continued, while the temperature rose gradually to boiling. The mixture was cooled with water and allowed to stand for five hours. After the reaction had subsided, the mixture was heated for 6 hours on a water-bath with a reflux condenser. The reaction product was then cooled and the oily part was removed by decantation. The residue left behind in the vessel was extracted with ether. The oily part and ethereal extract were combined, washed with water, dried over anhydrous sodium sulphate and evaporated. The residual oil was distilled under reduced pressure of 13 mm., and a fraction, boiling at 117–122°, was collected. Found: C, 77.01; H, 10.80; Calc. for $C_{17}H_{28}O_2$: C, 72.22; H, 10.92%.

It has n_D^{25} 1.4850, d_4^{25} 0.9376, $[R_L]_D$ 80.69 (Calc. for $C_{17}H_{28}O_2|\!\overline{\,}_3$: 80.39).

The Conversion of the Acetal into p-*Isopropyl-α-methylhydrocinnamic Aldehyde*. The acetal (60 g.) was heated with a 3% solution of hydrochloric acid (600 c.c.) for fifty minutes under a reflux condenser. After the mixture was cooled, the supernatant oily layer was extracted with ether. The ethereal extract was washed with an aqueous solution of sodium carbonate and then with water. The extract was dried over anhydrous sodium sulphate and evaporated. The residual oil was subjected to fractional distillation under reduced pressure of 12 mm. in a current of carbon dioxide, when a colourless oil boiling at 133–135° passed over. The yield was 33 g. (77% of the theoretical). The melting point of the semicarbazone was not depressed by admixture with the specimen synthesised by the first method.

In conclusion, the authors wish to express their hearty thanks to Professor Eiichi Funakubo, Osaka Imperial University, for the assistance in the microanalyses of nitrogen of the substances described above.

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