[Jour. Indian Chem. Soc., Vol. 34, No. 7, 1957]

A CONVENIENT ROUTE TO αβ-UNSATURATED ALDEHYDES

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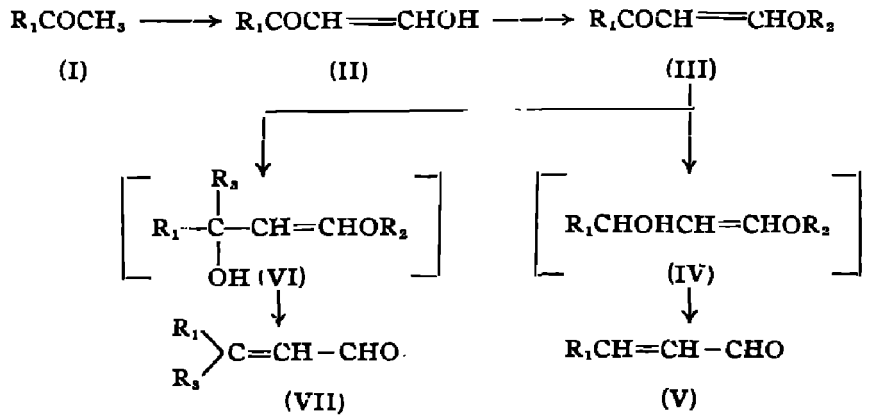
The Seifert and Schinz method for *cyclo*alkenyl aldehydes has been extended to the synthesis of αβ-unsaturated aldehydes of aralkyl as well as aliphatic series. Convenient preparations of cinnamaldehyde, β-methyl-, *p*-methoxy- and β-methyl-*p*-methoxy-cinnamaldehydes, β-methylcrotonaldehyde and β-(6-methoxy-2-naphthyl)-acraldehyde are described.

Our interest in the study of the Michael reaction of αβ-unsaturated aldehydes with ethyl acetoacetate (Mukherji and Bhattacharyya, this *Journal*, 1946, **23**, 451) as a promising route to steroidal hormone derivatives led us to search for a convenient general method for the preparation of αβ-unsaturated aldehydes in the arylalkyl and aliphatic series. Literature records a number of methods for the purpose (Groschientz and Fisher, *J. Amer. Chem. Soc.*, 1941, **63**, 2021; Von Braun and Rudolph, *Ber.*, 1934, **67**, 269, 1735; Wittig and Kethur, *Ber.*, 1936, **69**, 2078; Krõhnke and Börner, *Ber.*, 1936, **69**, 2006; Krõhnke, *Ber.*, 1938, **71**, 2583; Young and Linden, *J. Chem. Soc.*, 1947, 2913; Arens and Van Drop, *Nature*, 1947, **160**, 189; Heilbron *et al.*, *J. Chem. Soc.*, 1949, 737, 291; Seifert and Schinz, *Helv. Chim. Acta*, 1951, **34**, 728). However, the procedure recently elaborated by Seifert and Schinz (*loc. cit.*) appears, because of its simplicity and adaptability, to be eminently suited for the synthesis of a wide variety of αβ-unsaturated aldehydes. The present communication reports the preliminary experiments conducted with a view to seeking a logical extension of Seifert and Schinz's original method (*loc. cit.*). By making use of the modified procedure, a practicable preparative route to a number of αβ-unsaturated aldehydes such, as cinnamaldehyde, β-methyl-, *p*-methoxy-β-methyl- and *p*-methoxy-cinnamaldehydes, β-methylcrotonaldehyde and β-(6-methoxy-2-naphthyl)-acraldehyde has been developed. The reaction sequence employed is schematically represented below.



[a: R_1 = Ph, R_2 = $C_4H_9^t$, R_3 = Me. b: R_1 = OMe.C_6H_4, R_2 = $C_4H_9^t$, R_3 = Me.
c: R_1 = R_3 = Me, R_2 = $C_4H_9^t$. d: R_1 = OMe.$C_{10}H_6$, R_2 = Me]

Acetophenone and *p*-methoxyacetophenone were converted into the corresponding ω-hydroxymethylene derivatives (IIa and IIb) under Birch's conditions (*J. Chem. Soc.*, 1944, 501) in 60% and 35% yield respectively. Claisen and Stylos (*Ber.*, 1889, **21**, 1144) reported acid-catalysed self-condensation of hydroxymethylene-acetophenone, but in our hands it was considerably obviated by avoiding distillation and using the crude hydroxymethylene derivative for the next operation. In the case of other formyl derivatives, excepting formylacetone, no such difficulty was encountered. The formyl compounds, (IIa and IIb), on subsequent treatment with *iso*butanol in the presence of *p*-toluenesulphonic acid in refluxing benzene (Salmi, *Ber.*, 1938, **71**, 1803; cf. Surber and Schinz, *Helv. Chim. Acta*, 1954, **37**, 1239), produced ω-*iso*butoxymethylene-acetophenone (IIIa) and ω-*iso*butoxymethylene-*p*-methoxy-acetophenone (IIIb) in 73% and 74% yield respectively. These underwent smooth reduction with lithium aluminium hydride to the corresponding carbinols, (IVa and IVb) (not isolated) which, on acid hydrolysis under Seifert and Schinz's conditions (*loc. cit.*), furnished cinnamaldehyde (Va) and *p*-methoxycinnamaldehyde (Vb) in 76% and 77% yield respectively.

A variant of the reduction step was sought in the Grignard reaction on the alkoxymethylene ketone, the intermediary carbinol (VI) being capable of undergoing anionotropic rearrangement (cf. Seifert and Schinz, *loc. cit.*). This constitutes another simple approach to ββ-disubstituted-αβ-unsaturated aldehydes. Accordingly, (IIIa) and (IIIb) were allowed to react with methylmagnesium iodide and the Grignard compounds hydrolysed directly, as above, to β-methylcinnamaldehyde (VIIa) and β-methyl-*p* methoxycinnamaldehyde (VIIb) in 55% and 88% yield respectively. The two-stage process *via* the intermediate carbinols (VIa) and (VIb) resulted in diminished yields.

The method was then adapted to the preparation of β-methylcrotonaldehyde. Literature records a few recent syntheses of this important *iso*prenoid aldehyde (Mukherji, this *Journal*, 1948, **25**, 163; Wendler and Slates, *J. Amer. Chem. Soc.*, 1950, **72**, 5341; Heilbron and Weedon, *J. Chem. Soc.*, 1949, 1823; Young and Linden, *loc. cit.*) which, however, are seriously handicapped from the preparative standpoint because of the relative complexity of experimental operations. The present method is only a two-stage process starting from acetone. The dimethylacetal from hydroxymethylene-acetone, prepared according to Royals and Brannock (*J. Amer. Chem. Soc.*, 1953, **75**, 2050), on being allowed to react with methylmagnesium iodide and subsequent hydrolysis of the intermediate carbinol (not distilled) under Wendler and Slates' (*loc. cit.*) conditions, afforded β-methylcrotonaldehyde (VIIc) in 41% yield. Another similar procedure for the preparation of (VIIc) employed *iso*butoxymethylene-acetone (IIIc). Formylacetone was prepared according to the conditions prescribed by Boileau (*Bull. Soc. chim.*, 1954, 761) using chloroacetic acid, thus avoiding self-condensation reported by Claisen (*Annalen*, 1894, **278**, 274). The preparation of *iso*butoxymethylene-acetone by Salmi's method (*loc. cit.*) resulted in a low yield (25%) because of the low boiling point of formylacetone coupled with its insolubility in benzene and possibility of self-condensation. However, *iso*butoxymethylene-acetone (IIIc) could be transformed smoothly in a good yield (59%) to β-methylcrotonaldehyde through

similar reactions. Again, 6-methoxy-2-acetylnaphthalene (Id) was converted into its methoxymethylene derivative (IIId) by a procedure similar to that of Royals and Brannock (*loc. cit.*) in 41% yield. This was then reduced in dioxane with lithium aluminium hydride and subsequently hydrolysed under Seifert and Schinz's (*loc. cit.*) conditions to β-(6-methoxy-2-naphthyl)-acraldehyde (Vd) in 56% yield. The orange-red colour of the 2 : 4-dinitrophenylhydrazone derivative is indicative of the αβ-nature of unsaturation in (Vd).

EXPERIMENTAL

ω-Hydroxymethylene-acetophenone (IIa).—To molecularised sodium (23 g., 1*M*) under anhydrous ether was introduced dropwise a mixture of acetophenone (120 g., 1 *M*) and ethyl formate (84 g., 1.2 *M*), in cold. After the addition was complete, the contents were left standing overnight and then worked up in the usual manner, when a mobile oil was obtained which resisted distillation. The crude material weighed 100 g. (60%). It developed an intense violet coloration with alcoholic ferric chloride.

ω-iso*Butoxymethylene-acetophenone* (IIIa).—A mixture of the above crude formyl compound (56 g.), *iso*butanol (84 g.), and a little *p*-toluenesulphonic acid in anhydrous benzene (200 c.c.) was refluxed using a Dean and Stark water separator till no more water collected. To the contents was then added a little sodium ethoxide to neutralise the excess acid, followed by a sufficient quantity of water. On working up in the customary way, a colorless mobile oil was collected at 150°/6 mm, yield 52 g. (73%). (Found : C, 76.11 ; H, 7.56. $C_{13}H_{18}O_2$ requires C, 76.44 ; H, 7.90%). It gradually developed a violet coloration with alcoholic ferric chloride.

Cinnamaldehyde (V).—To a well-stirred, fine suspension of lithium aluminium hydride (2.44 g.) in anhydrous ether (200 c.c.) was added dropwise ω-*iso*butoxy-methylene-acetophenone (IIIa : 20 g.) at a rate such as to maintain ether at gentle reflux. After the addition was complete, the contents were refluxed for another 15 minutes. Excess hydride was decomposed with 10 c.c. of water. The contents were then treated at 0°-5° with a mixture of sulphuric acid (39.5 c.c.) and ice (30 g.) for one hour. The hydrolysate on working up in the customary manner yielded 10 g. (75.7%) of cinnamaldehyde, b.p. 130°/20 mm.

The 2 : 4-*dinitrophenylhydrazone* derivative, after repeated crystallisations from glacial acetic acid, melted at 251° which remained undepressed on admixture with an authentic sample.

The melting point of the semicarbazone alone as well as when mixed with an authentic sample was 207°.

β-Methylcinnamaldehyde (VIIa).—The Grignard reagent was prepared from magnesium (2.48 g.), methyl iodide (14.5 g.) and dry ether (120 c.c.) and to this was introduced, under ice cooling, ω-*iso*butoxymethylene-acetophenone (IIIa : 20.4 g.) over a period of 20 minutes and the mixture left standing overnight. The contents were decomposed with H_2SO_4 (40 c.c.) and ice (30 g.) at 0°-5°, and the hydrolysate was extracted with

ether. After removal of the solvent the residue was distilled at 130°/12 mm as a colorless oil, yield 8 g. (55%). (Found: C, 82.10; H, 7.09. Calc. for $C_{10}H_{10}O$: C, 82.16; H, 7.09%).

The 2:4-*dinitrophenylhydrazone* derivative was obtained as orange-red needles, which, after crystallisation from glacial acetic acid, melted at 231°. (Found: N, 17.50. $C_{16}H_{14}O_4N_4$ requires N, 17.17%).

The *semicarbazone* was crystallised from ethanol as greyish white needles, m.p. 198; lit. m.p. 201° (Heilbron, "Dictionary of Organic Compounds", 1946, p. 647). (Found: N, 21.2. Calc. for $C_{11}H_{13}ON_3$: N, 20.7%).

ω-*Hydroxymethylene*-p-*methoxyacetophenone* (IIb).—A mixture of *p*-methoxyacetophenone (0.5 *M*, 75 g.), and ethyl formate (0.6 *M*, 42 g.) was dropped with good shaking to powdered sodium (0.5 *M*, 11.5 g.) under anhydrous ether (400 c.c.), in the cold. The contents after being allowed to stand overnight were treated in the manner of (IIa) when 30 g. (34%) of ω-hydroxymethylene-*p*-methoxyacetophenone (IIb) was obtained as a light oil, distilling at 135°/10 mm. It developed a deep violet coloration with alcoholic ferric chloride.

ω-iso*Butoxymethylene*-p-*methoxyacetophenone* (IIIb).—A mixture of the above formyl compound (IIb: 28 g.), *iso*butanol (25 g.) and little *p*-toluenesulphonic acid in benzene (250 c.c.) was treated in the same manner as in the case of (IIIa). The *iso*butoxymethylene derivative (IIIb) distilled at 155°/10 mm as a colorless oil, yield 25 g. (74%). It showed a violet coloration with alcoholic ferric chloride on keeping or warming. (Found: C, 71.60; H, 7.70. Calc. for $C_{14}H_{18}O_3$: C, 71.79; H, 7.69%).

p-*Methoxycinnamaldehyde* (Vb).—ω-*iso*Butoxymethylene-*p*-methoxyacetophenone (IIIb: 10 g.) was reduced with lithium aluminium hydride (1.47 g.) in anhydrous ether (150 c.c.) in the manner analogous to that in the case of (Va), when 5 g. (77%) of *p*-methoxycinnamaldehyde (Vb) was obtained, distilling at 145°/7 mm. (Found: C, 74.51; H, 6.66. Calc. for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22%).

The 2:4-*dinitrophenylhydrazone* was crystallised from ethyl acetate as orange-red needles, m.p. 210°. (Found: N, 16.60. $C_{16}H_{14}O_5N_4$ requires N, 16.37%).

The *semicarbazone* was crystallised from ethanol as colorless needles, m.p. at 196°, Lit. m.p. 199° (Beilstein, "Organische Chemie", 1925, Vol. VIII, p. 130). (Found: N, 19.30. Calc. for $C_{11}H_{13}O_2N_3$: N, 19.15%).

β-*Methyl*-p-*methoxycinnamaldehyde* (VIIb).—To the Grignard reagent, prepared from magnesium (1.2 g.), methyl iodide (7.1 g.) and anhydrous ether (100 c.c.), was introduced, in cold, ω-*iso*butoxymethylene-*p*-methoxyacetophenone (11.7 g.) in dry ether (25 c.c.). The Grignard complex was worked up in the manner of (VIIa) to obtain β-methyl-*p*-methoxycinnamaldehyde (VIIb) as a colorless mobile oil, b.p. 150-52°/10 mm, yield 7.8 g. (8%). (Found: C, 74.22; H, 6.85. $C_{11}H_{12}O_2$ requires C, 74.97; H, 6.86%).

The 2:4-*dinitrophenylhydrazone* derivative was deposited as red needles which, after crystallisation from acetic acid melted at 224°. (Found: N, 15.70. $C_{17}H_{16}O_5N_4$ requires N, 15.72%).

The *semicarbazone* crystallised from ethanol as colorless needles, m.p. 194° (Found: N, 18.20. $C_{12}H_{15}O_2N_3$ requires N, 18.02%).

β-Methylcrotonaldehyde (VIIc).—The dimethylacetal of formylacetone was obtained from acetone exactly according to the method prescribed by Royals and Brannock (*loc. cit.*).

The Grignard reagent was prepared from magnesium (1.67 g.), methyl iodide (9.8 g.) and anhydrous ether (100 c.c.) and to this was introduced, dropwise and under ice-cooling, the above acetal (9.2 g.) in dry ether (25 c.c.). The contents after being allowed to stand overnight were decomposed with saturated ammonium chloride solution and the organic material was taken up in ether. After removal of solvent the residual oil was treated with 5% H_2SO_4 (120 c.c.) and alcohol (10 c.c.), warmed for 5 minutes and then allowed to stand at room temperature for 10 hours. The usual working up of the hydrolysate furnished 2.4 g. (41%) of a colorless oil, b.p. 130-35°. (Found: C, 71.50; H, 9.66. Calc. for C_5H_8O: C, 71.39; H, 9.59%).

The 2:4-*dinitrophenylhydrazone* derivative, after crystallisation from ethyl acetate, melted at 180°. Lit. m.p. 183° (Wendler, *loc. cit.*). (Found: N, 21.40. Calc. for $C_{11}H_{12}O_4N_4$: N, 21.20%).

iso*Butoxymethylene-acetone* (IIIc).—A mixture of formylacetone (35 g.) (Boileau, *loc. cit.*), *iso*butanol (30 g.), a little *p*-toluenesulphonic acid in anhydrous benzene (100 c.c.) was heated to gentle reflux for 2 hours and then refluxed vigorously till there was no more separation of the lower layer in the separator (which consisted of unchanged formylacetone and water). The contents were treated in the manner analogous to that in the case of (IIIa) to obtain 13.3 g. (25%) of (IIIc) as colorless mobile oil, b.p. 102-105°/7 mm. It gradually developed a violet colour with alcoholic ferric chloride. (Found: C, 67.75; H, 9.9. $C_8H_{14}O_2$ requires C, 67.60; H, 9.85%). In certain runs, however, no *iso*butoxymethylene-acetone could be collected.

β-Methylcrotonaldehyde (VIIc).—The above *iso*butoxy compound (6.9 g.) in dry ether (25 c.c.) was treated with the Grignard reagent, prepared from magnesium (1.17 g.), methyl iodide (7 g.) and anhydrous ether (75 c.c.), in cold. On working up in the manner similar to that in the case of dimethylacetal of hydroxymethylene-acetone, 2.4 g. (59%) of β-methylcrotonaldehyde was obtained, b.p. 130-35°.

The 2:4-*dinitrophenylhydrazone* derivative melted at 180° and remained undepressed on admixture with the sample from the above experiment.

ω-Methoxymethyl-6-methoxy-2-acetylnaphthalene (IIId).—6-Methoxy-2-acetylnaphthalene (Id) was prepared according to the procedure of Robinson and Rydon (*J. Chem. Soc.*, 1939, 1399).

A mixture of (Id: 40 g.) and ethyl formate (18 g.) in dry benzene (200 c.c.) was added gradually, under ice-cooling, to powdered sodium (4.6 g.) covered with anhydrous benzene (200 c.c.). After 24 hours' standing, the thick brown mass was filtered and the residue washed repeatedly with anhydrous ether. The dried sodium salt weighed 45 g. (90%). To the cooled suspension of the dry salt (40 g.) in absolute methanol (36 g.) was introduced, with vigorous stirring, a cold solution of dry hydrogen chloride (15 g.) in anhydrous methanol (28 g.). After one hour's additional stirring, the contents were left standing for 4 hours at 20°. Methyl alcoholic potassium

hydroxide was added to make the mass just alkaline whereafter it was filtered and the residue washed with methanol. The filtrate yielded 15 g. (41%) of (IIId), as a highly viscous oil, b.p. 198-200°/7 mm. (Found: C, 74.70; H, 5.93. $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.78%).

β-(6-Methoxy-2-naphthyl)-acraldehyde (Vd).—To a well-stirred suspension of lithium aluminium hydride (1.425 g.) in dry dioxane (150 c.c.) was introduced gradually a solution of (IIId: 10 g.) in dioxane (50 c.c.). After 20 hours' refluxing, the contents were worked up as in (Va) to obtain 5.5 g. (56%) of a colorless immobile oil, b.p. 215-20°/5 mm. (Found: C, 79.10; H, 6.0. $C_{14}H_{12}O_2$ requires C, 79.22; H, 5.70%).

The 2:4-*dinitrophenylhydrazone* derivative was prepared in the customary way and crystallised from ethyl acetate as orange-red needles, m.p. 228°. (Found: N, 14.00. $C_{20}H_{16}O_5N_4$ requires N, 14.28%).

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Received August 3, 1956.