product was filtered and washed with water; yield 4.0 g., 53.5%; m. p. 193–195°, mixed melting point with an authentic sample 193–195°.

3-Indolalhydantoin.—In a 100-cc. round-bottom flask equipped with a mechanical stirrer were placed 6.0 g. of indole-3-aldehyde, 5.0 g. of hydantoin and 18.5 cc. of piperidine. The mixture was heated rapidly to boiling and refluxed for ten to fifteen minutes until a solid cake was formed. The solid was cooled to room temperature, slurried with 500 cc. of distilled water and acidified to litmus paper with glacial acetic acid. The yellow precipitated product was filtered and washed three times with 50-cc. portions of water; wt. 8.5 g., 90.7%; m. p. 325°, mixed melting point with an authentic sample 325°.

Acknowledgment.—The authors are indebted to Drs. R. T. Major and J. R. Stevens for their interest and valuable suggestions.

Summary

Two improved methods for preparing indole-3-aldehyde are described. The first method starting with 2-carbethoxyindole is a modification of a recorded synthesis. The second procedure is a direct conversion of indole to indole-3-aldehyde. In both methods N-methylformanilide is utilized in formylating the indole nucleus.

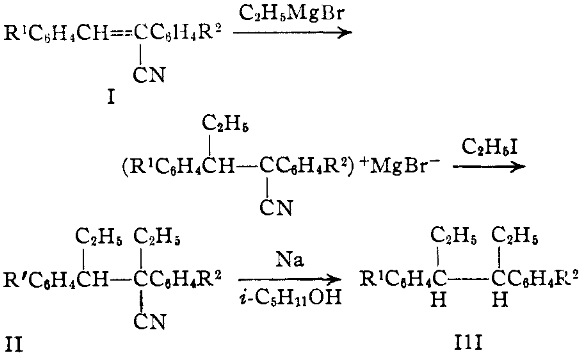
RAHWAY, N. J. RECEIVED MARCH 4, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE, AND THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

Applications of the 1,4-Addition of Grignard Reagents to α,β-Unsaturated Acid Derivatives. I. Synthesis of Compounds Related to Hexestrol

BY STANLEY WAWZONEK

Methods available for the synthesis of hexestrol and related compounds may be divided into four types[1]: reduction of diethylstilbestrol, thermal decomposition of azomethanes, Wurtz-type reactions on anethole hydrobromide or hydrochloride, and formation of free radicals followed by coupling. Reactions carried out by Kohler[2] and summarized below (Ia-IIIa) suggested another possible method for such compounds.



$$R^1C_6H_4CH{=}\underset{\substack{|\\ CN}}{C}C_6H_4R^2 \xrightarrow{C_2H_5MgBr}$$

I

$$(R^1C_6H_4\overset{\substack{C_2H_5\\ |}}{C}H-\underset{\substack{|\\ CN}}{C}C_6H_4R^2)^+MgBr^- \xrightarrow{C_2H_5I}$$

$$R'C_6H_4\overset{\substack{C_2H_5\\ |}}{C}H-\overset{\substack{C_2H_5\\ |}}{\underset{\substack{|\\ CN}}{C}}C_6H_4R^2 \xrightarrow[i\text{-}C_5H_{11}OH]{Na} R^1C_6H_4\overset{\substack{C_2H_5\\ |}}{\underset{H}{C}}-\overset{\substack{C_2H_5\\ |}}{\underset{H}{C}}C_6H_4R^2$$

II III

(a) $R^1 = R^2 = H$
(b) $R^1 = p\text{-}CH_3O$; $R^2 = H$
(c) $R^1 = R^2 = p\text{-}CH_3O$

This method which has the advantage of allowing variations in the alkyl and the aryl groups, has been carried out successfully with α-phenyl-p-methoxycinnamonitrile (Ib) and α-(p-methoxyphenyl)-p-methoxycinnamonitrile (Ic).

Both cinnamonitriles (I) when added to ethylmagnesium bromide in ether behaved in a similar manner to that observed by Kohler[2] with α-phenyl cinnamonitrile (Ia). Treatment of these solutions with a slight excess of ethyl iodide gave an 86% yield of oily nitriles (II) which could be separated into a solid and a liquid isomer. This behavior is different from the 98% yield of one solid isomer reported by Kohler[2] with α-phenylcinnamonitrile. Reinvestigation of Kohler's work gave only a 90% yield of a solid which by fractional crystallization and mechanical picking could be separated into two isomeric nitriles (IIa). The structure of the new isomer thus obtained, was proved by its reduction with sodium and isoamyl alcohol to 3,4-diphenylhexane (IIIa). Varying the conditions by using an excess of ethylmagnesium bromide instead of the theoretical amount, had no effect on the composition of the final product, but increased the yield slightly and greatly reduced the time necessary for the reaction.

The oily mixture of α-ethyl-α-phenyl-β-(p-methoxyphenyl)-valeronitriles (IIa) when treated with a fifteen fold excess of sodium in boiling isoamyl alcohol gave a 76% yield of a mixture of isomeric 3-(p-methoxylphenyl)-4-phenylhexane (IIb) in approximately equal amounts. α-Ethyl-α,β-di-(p-methoxyphenyl)-valeronitrile (IIc) upon similar treatment gave an 80% yield of a mixture of hexestrol dimethyl ethers (IIc). From this mixture a 33% yield of the higher melting isomer could be separated. The pure valeronitriles (II) upon similar treatment gave mixtures of the isomeric hexanes.

Further study of the applications of the 1,4-addition of Grignard reagents to α,β-unsaturated acid derivatives is now in progress.

Experimental[3]

p-Methoxybenzyl Cyanide.[4]—p-Methoxybenzyl cyanide was prepared from p-nitrobenzyl cyanide[5] according to

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[1] (a) Jones, "Annual Reports on the Progress of Chemistry," 1943, p. 137; (b) Kharasch, McBay and Urey, *J. Org. Chem.*, **10**, 401 (1945).

[2] Kohler, *Am. Chem. J.*, **35**, 386 (1906).

[3] Melting points and boiling points are not corrected.

[4] For a better and more recent method, see Shriner and Hull, *J. Org. Chem.*, **10**, 228 (1945).

[5] "Organic Syntheses," Coll. Vol. I, 2nd ed., p. 396.

the directions of Koessler and Hamke[6] with the following modification. The *p*-aminobenzyl cyanide was prepared by the catalytic reduction of *p*-nitrobenzyl cyanide. *p*-Nitrobenzyl cyanide (32.4 g.) when treated in ethyl acetate (150 cc.) with hydrogen at forty-five pounds pressure (3.0 atm.) in the presence of platinum oxide catalyst (0.1 g.) gave pure *p*-aminobenzyl cyanide (21.0 g.), b. p. 147° (1 mm.).

α-Ethyl-α,β-(diphenyl)-valeronitrile.—To a solution of 0.2 *N* ethylmagnesium bromide in ether (350 cc.) solid α-phenylcinnamonitrile[7] (41 g.) was added in small amounts. The resulting red solution after long refluxing became pale brown. Ethyl iodide (25 cc.) was added and the solution refluxed for one hour. Decomposition with ice and ammonium chloride followed by partial removal of the ether gave a white solid (24.4 g.) melting at 102–103°. Kohler[2] reports 105°. The filtrate upon vacuum distillation gave an oil (22.7 g.) boiling at 148–150° (0.07 mm.). This oil upon crystallization from ethanol gave a solid (20.5 g.) melting at 68–78°. Fractional crystallization from ethanol gave a mixture of plates and clusters which could be separated mechanically. The plates melted at 98–99° and were identical with the above isomer (102–103°). The clusters after three crystallizations from ethanol melted at 93–99°. A mixture with the (102–103°) isomer melted at 72–97°. An incomplete separation gave 2.76 g. of the pure (93–99°) isomer.

Anal. Calcd. for $C_{19}H_{21}N$: C, 86.46; H, 8.04. Found: C, 86.46; H, 8.18.

Increasing the ethylmagnesium bromide to 0.4 mole in 400 cc. of ether gave upon similar treatment 26.7 g. of the 102–103° melting isomer together with 22.5 g. of oil boiling at 148–150° (0.07 mm.). The oil when dissolved in ethanol gave a solid (19.4 g.) melting at 70–90°. By fractional crystallization and hand picking 2.69 g. of the 93–99° melting isomer was obtained in a pure form.

Reduction of α-Ethyl-α,β-diphenylvaleronitrile (m. p. 93–99°) (**IIa**).—α-Ethyl-α,β-diphenylvaleronitrile (m. p. 93–99°) (IIa) (5.2 g.) in boiling isoamyl alcohol (150 cc.) was treated with sodium (14 g.) and the resulting solution poured into water. Extraction with ether followed by fractional distillation gave the isomeric 3,4-diphenylhexanes (1.8 g.), b. p. 197–200° (60 mm.). Crystallization twice from ethanol gave 0.6 g. of the solid 3,4-diphenylhexane, m. p. 89–91°. A mixture with 3,4-diphenylhexane prepared from the 102° melting valeronitrile (IIa) gave no lowering in melting point. Starting material was recovered to the extent of 1.2 g.

α-Ethyl-α-phenyl-β-(*p*-methoxyphenyl)-valeronitrile.—(IIb).—Solid α-phenyl-*p*-methoxycinnamonitrile (Ib) (58.7 g.)[8] when added to ethylmagnesium bromide (0.35 mole) in ether (400 cc.) and treated in a similar fashion to the above, gave an oil. Addition of (60–70°) petroleum ether gave a solid (43.7 g.) melting at 81–85°. After three crystallizations from ethanol the nitrile (IIb) melted at 83–87°.

Anal. Calcd. for $C_{20}H_{23}ON$: C, 81.87; H, 7.85. Found: C, 81.50; H, 7.81.

The ligroin filtrate upon removal of the solvent gave an oil distilling at 187–190° (0.07 mm.); yield 20.8 g. The oil could not be crystallized and probably consisted largely of an isomeric nitrile.

Anal. Calcd. for $C_{20}H_{30}ON$: C, 81.87; H, 7.85. Found: C, 81.03; H, 8.18.

α-Ethyl-α,β-di-(*p*-methoxyphenyl)-valeronitrile (IIc).—Solid α-[*p*-methoxyphenyl]-*p*-methoxycinnamonitrile[9] (Ic) (26.5 g.) when added to ethylmagnesium bromide (0.2 mole) in ether (250 cc.) and treated similarly to the above gave an oil which was purified by distillation at 190–195° (0.07 mm.); yield 27.39 g. Addition of (60–68°) petroleum ether gave a solid which upon recrystallization from (90–100°) ligroin melted at 72–74°; yield 11.4 g. After four crystallizations from (60–68°) petroleum ether the valeronitrile (IIc) melted at 73–74°.

Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 78.02; H, 7.74. Found: C, 77.93; H, 7.75.

The ligroin filtrate gave an oil which would not crystallize and probably consists largely of an isomeric nitrile. Redistillation gave an oil, b. p. 190–191° (0.07 mm.) which solidified to a glass at room temperature.

Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 78.02; H, 7.74. Found: C, 78.08; H, 7.73.

3-Phenyl-4-*p*-methoxyphenylhexane (IIIb).—The mixture of isomeric valeronitrile (26.2 g.) (IIb) obtained from the Grignard reaction was treated with sodium (68.0 g.) in boiling isoamyl alcohol (400 cc.). Toward the end of the reaction more isoamyl alcohol (200 cc.) was added. The resulting solution was poured into water and extracted with ether. Removal of the ether followed by fractional distillation gave 15.4 g. of a mixture of isomeric 3-phenyl-4-*p*-methoxyphenylhexane (IIIb); b. p. 147–150° (0.07 mm.). Starting material to the extent of 4.2 g., b. p. 150–188° (0.07 mm.), was recovered. The oily hexanes (IIIb) when taken up in (30–38°) petroleum ether gave 4.56 g. of a solid melting at 85–88°. Three crystallizations from (30–38°) petroleum ether gave white prisms melting at 89–91°. Brownlee and co-workers[10] report 89–90°. A mixture with a sample prepared by the reduction of 3-phenyl-4-*p*-methoxyphenyl-2-hexene[11] melted at the same temperature.

The (30–38°) petroleum ether filtrate gave an oil which distilled at 144° (0.07 mm.) and consisted mainly of the *dl* isomer.

Anal. Calcd. for $C_{19}H_{24}O$: C, 85.09; H, 8.96. Found: C, 85.05; H, 9.36.

The oil (9.8 g.) when heated in acetic acid (120 cc.) with 40% hydrobromic acid (60 cc.) for six hours gave an oil distilling at 152° (0.07 mm.); yield 8.2 g. By crystallization from (30–38°) petroleum ether a white solid (1.06 g.) could be obtained which after two crystallizations from (60–68°) petroleum ether melted at 143–144°. This phenol could be obtained in a quantitative yield in a similar fashion from the 89–91° melting hexane. Brownlee and co-workers[10] report 139–140°. The residual oil was purified by distillation, b. p. 152–153° (0.07 mm.) and consists mainly of the isomeric 3-phenyl-4-*p*-hydroxyphenylhexane.

Anal. Calcd. for $C_{18}H_{22}O$: C, 85.04; H, 8.66. Found: C, 84.62; H, 9.35.

The solid valeronitrile (m. p. 83–87°) (IIb) (26 g.) when treated in a similar fashion with sodium in isoamyl alcohol gave a mixture (15.2 g.) of the isomeric hexanes (IIIb) from which 2.9 g. of the solid isomer was isolated. In addition 4.5 g. of starting material (IIb) was recovered.

The oily valeronitrile (IIb) (13 g.) when treated similarly gave 7.7 g. of the isomeric hexanes (IIIb) together with 3.2 g. of the starting material (IIb). From the hexanes (IIIb) 3.2 g. of the solid isomer could be isolated.

Hexestrol Dimethyl Ether (IIIc).—The oily mixture of α-ethyl-α,β-di-(*p*-methoxyphenyl)-valeronitrile (IIc) (27 g.) when treated similarly to the above gave 14.6 g. of a mixture of the hexestrol dimethyl ethers, b. p. 158–170° (0.07 mm.) (IIIc) and 7.1 g. of starting material, b. p. 170–192° (0.07 mm.) (IIb). The mixture of ethers (IIIc) could be separated by fractional crystallization from alcohol into a solid (4.0 g.), m. p. 136–140°, and a solid (8.1 g.) melting at 54–57°. Mixtures with authentic samples[12] melted at the same temperature.

Summary

1. A synthesis of hexestrol dimethyl ether and related compounds from α-arylcinnamonitriles has been described.

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(6) Koessler and Hamke, *J. Biol. Chem.*, **39**, 585 (1919).

(7) Walther, *J. prakt. Chem.*, [2] **53**, 454 (1896).

(8) Frost, *Ann.*, **250**, 159 (1880).

(9) Niederl and Ziering, THIS JOURNAL, **64**, 885 (1942).

(10) Brownlee, Copp, Duffin and Tonkin, *Biochem. J.*, **37**, 572 (1943).

(11) Unpublished results.

(12) Docken and Spielman, THIS JOURNAL, **62**, 2163 (1940).

2. This method which allows both for the variation of the alkyl and the aryl groups gives mixtures of isomers in all cases tried thus far.

IOWA CITY, IOWA RECEIVED DECEMBER 12, 1945

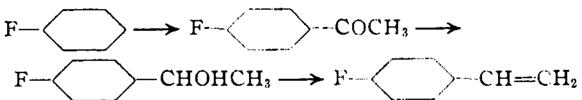
[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT, MONSANTO CHEMICAL COMPANY]

Vinyl Aromatic Compounds. III. Fluorinated Derivatives[1]

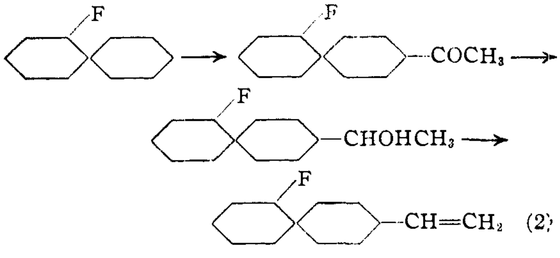
BY MARY W. RENOLL[1a]

As part of a study on substituted styrenes, vinyl derivatives of fluorinated benzene, toluene and biphenyl have been prepared, with the fluorine located in the benzene ring or in a methyl side chain. In all cases a fluorinated hydrocarbon was the starting point of the syntheses and the problem was thus one of introducing the vinyl substituent.

When the fluorine atom is in the ring the fluorinated hydrocarbon can be subjected to acetylation with acetic anhydride in presence of aluminum chloride, without loss of fluorine. This yields a methyl aryl ketone which can be reduced to a secondary carbinol; dehydration of the latter yields the desired vinyl compound. *p*-Fluorostyrene and 2-fluoro-4′-vinylbiphenyl were prepared in this way according to the following series of reactions:

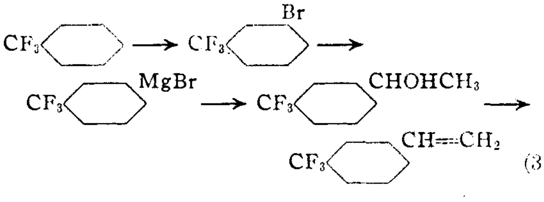


(1)



(2)

When the fluorine is present in a methyl side chain, as in benzotrifluoride, the above procedure cannot be used because of the halogen exchange which occurs between the organic fluoride and aluminum chloride.[2] It is, however, possible to introduce a bromine atom in a position meta to the trifluoromethyl group, transform the bromide into a Grignard reagent[3] and condense the latter with acetaldehyde. This series of reactions gives a methyl aryl carbinol which by dehydration yields the desired vinyl compound, *m*-trifluoromethylstyrene.



(3)

Only in series (2) is there a problem of structure determination. In 2-fluorobiphenyl, acetylation could affect the fluorinated ring but this was conconsidered improbable since the ortho–para-directing influence of the fluorine atom would be hindered by the phenyl group and reaction would be slower than in an unsubstituted ring. Also, it is known that nitration of 2-fluorobiphenyl[4] gives only traces of 2-fluoro-4-nitrobiphenyl, the main products being 2-fluoro-4′-nitrobiphenyl and 2-fluoro-2′-nitrobiphenyl. Oxidation of 2-fluorobiphenyl methyl ketone gave a fluorobiphenyl carboxylic acid. To establish the structure definitely the ketone was hydrogenated under conditions which would simultaneously eliminate fluorine as hydrogen fluoride, and saturate the aromatic ring.[5] The *p*-cyclohexylethylbenzene formed was found to be identical with a sample obtained by the reduction of *p*-phenylacetophenone. That hydrogenation had affected the benzene nucleus which was non-acetylated was confirmed by oxidation to terephthalic acid. It was thus proved that the introduction of the acetyl group in 2-fluorobiphenyl has taken place in the para position of the non-fluorinated ring.

The molecular refractions, MR_D, were calculated by means of the Lorentz-Lorenz formula. The atomic refraction for fluorine, AR_F, was obtained by subtracting from the molecular refraction the increments for C(2.418), H(1.100), Br(8.865), benzene ring (5.199), and O(carbonyl 2.211 or hydroxyl 1.525). The exaltation, EM for MR_D +1.17, for styrene was applied as a correction in calculating AR_F for *p*-fluorostyrene and *m*-trifluoromethylstyrene. A similar correction, EM for MR_D +0.78, for acetophenone was applied in the case of *p*-fluoroacetophenone. The theoretical values used are those reported by Eisenlohr.[6] All the compounds studied show values for AR_F in line with those found in aliphatic compounds.

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[1] The preceding paper of this series, Huber, Renoll, Rossow and Mowry, THIS JOURNAL, **68**, 1109 (1946).

[1a] Present address: Chemistry Department, The Ohio State University, Columbus, Ohio.

[2] Henne and Newman, THIS JOURNAL, **60**, 1697 (1938).

[3] Simons and Ramler, *ibid.*, **65**, 389 (1943).

[4] van Hove, *Bull. classe sci., Acad. roy. Belg.*, [5] **8**, 505 (1922).

[5] Swarts, *ibid.*, **6**, 399 (1920).

[6] Eisenlohr, *Z. physik. Chem.*, **A75**, 585 (1910); Auwers and Eisenlohr, *J. prakt. Chem.*, **84**, 1 (1911).