TABLE III

CALCULATED UNCERTAINTIES OF ANALYSES OF MIXTURES OF ISOBUTANE-d_0 AND -1-d

From ions	59 and 58		59 and 57		44 and 43		30 and 29	
	100% d_0	100% d_1	100% d_0	100% d_1	100% d_0	100% d_1	100% d_0	100% d_1
$\Delta(-d_0)$, %	±1.0	±0.9	±1.0	±0.23	±1.1	±0.9	±1.0	±0.8
$\Delta(-1-d_1)$, %	±0.06	±1.0	±0.12	±1.0	±0.10	±1.0	±0.10	±1.0

the intensities of the pairs of ions, 59 and 57, 44 and 43, and 30 and 29. The mass spectrometric data were obtained in the following order: isobutane, isobutane-1-*d*, the set of products from a given run, isobutane-1-*d* and isobutane. The averages of the isobutane and isobutane-1-*d* calibrations were employed to interpret the set of data in the products of the run. The values of the isobutane-1-*d* concentration estimated from each of the individual pairs of simultaneous equations were averaged after normalization. The results on a typical run, isobutane-1-*d* *vs.* 94.1% H_2SO_4, are shown in Table II.

If it is assumed that errors are random, and that the accuracy of specific intensity measurements is ±1.0%, it is possible to calculate the expected uncertainties of the analyses resulting from the solution of the various pairs of simultaneous equations.[23] The results of such calculations are shown in Table III. It will be noted that the accuracy for a given component varies with the composition of the mixture. This variation is essentially linear with composition.

In the cases of the reaction products resulting from the reaction of isobutane-2-*d* with isobutane-C^{13}, isobutane-C^{13}-2-*d* was directly determinable from the increase in intensity of the ion, $m/q = 60$. After correction of the observed intensities of the ions of $m/q = 59, 58, 57$ for contributions from isobutane-C^{13}-2-*d* (assumed to have a mass spectrum like that of isobutane-2-*d*) a set of simultaneous equations involving the corrected intensities of these three ions was solved for the concentrations of isobutane-d_0, -C^{13} and -2-*d*. A check on the accuracy of the analysis resulting from the solution of the set of simultaneous equations was made through the stoichiometry of the reacting system. Material balance requires

$$\begin{aligned} i\text{-}C_4H_{10} &= (i\text{-}C_4H_{10})_{\text{initial}} + i\text{-}C_4H_{10}\text{-}C^{13}\text{-}2\text{-}d \\ i\text{-}C_4H_{10}\text{-}2\text{-}d &= (i\text{-}C_4H_{10}\text{-}2\text{-}d)_{\text{initial}} - i\text{-}C_4H_{10}\text{-}C^{13}\text{-}2\text{-}d \\ i\text{-}C_4H_{10}\text{-}C^{13} &= (i\text{-}C_4H_{10}\text{-}C^{13})_{\text{initial}} - i\text{-}C_4H_{10}\text{-}C^{13}\text{-}2\text{-}d \end{aligned}$$

Since the composition of the isotopic preparations from which the feed was prepared by blending were accurately known and their mass spectra were well known as well, the synthetic composition could be checked mass spectrometrically by solving only the simultaneous equations involving the intensities of the ions of $m/q = 58$ and 57 in the mass spectrum of the feed. Thus the initial concentrations were known to better than ±0.5%.

The accuracy to be expected for the solution of the three simultaneous equations was calculated under the assumptions that the mass spectral intensities had a relative accuracy of ±1% and the composition of the product was the average of the observed range. The results of these calculations are shown in Table IV, where they are compared with the observed errors taken as the difference between the results of the direct mass spectrometric analyses and the values computed from the stoichiometry.

TABLE IV

ACCURACY OF ANALYSES OF TERNARY MIXTURES OF ISOTOPIC BUTANES

Component	Range of concentration, mole %	Calculated uncertainty, %	Measured error,[a] %
i-C_4H_{10}-C^{13}	25.0–15.0	±0.7	±0.5
i-C_4H_{10}-2-d	50.0–40.0	± .8	± .8
i-C_4H_{10}	25.0–35.0	± .4	± .8

[a] Fourteen analyses.

The agreement between calculated and observed error is satisfactory except in the case of isobutane. It is probable that errors in the determination of isobutane-C^{13}-2-*d* are all reflected in the determination of isobutane, rather than being distributed across all three components. No allowance for such error was made in the calculation.

EMERYVILLE, CALIF.

RECEIVED MAY 28, 1951

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(23) Whitaker and Robinson, "Calculus of Observations," Blackie and Sons, London, 1929, p. 243.

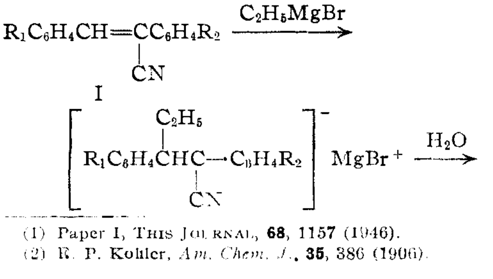
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

Application of the 1,4-Addition of Grignard Reagents to α,β-Unsaturated Acid Derivatives. II. Preparation of 3,4-Diaryl-2-hexanones and 3,4-Diaryl-2-hexanols[1]

BY STANLEY WAWZONEK

3,4-Diaryl-2-hexanones and 3,4-diaryl-2-hexanols have been prepared from α-arylcinnamonitriles for testing as synthetic estrogens. The activity was found to be greatest for the 3,4-di-*p*-anisyl derivatives. The hexanols were found to be unsatisfactory starting materials for the preparation of stilbestrol dimethyl ether and related compounds.

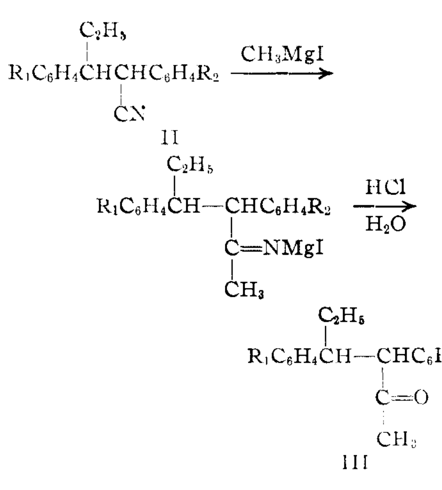
The synthesis of 3,4-diaryl-2-hexanones and 3,4-diaryl-2-hexanols was undertaken to prepare variants of hexestrol and to determine the feasibility of using these compounds in a synthesis of stilbestrol. The ketones were prepared by the reactions devised by Kohler[2] for 3,4-diphenyl-2-hexanone and summarized below.



$R_1C_6H_4CH{=}C(CN)C_6H_4R_2 \xrightarrow{C_2H_5MgBr}$

I

$\left[R_1C_6H_4CH(C_2H_5)\bar{C}(CN)C_6H_4R_2\right]^- MgBr^+ \xrightarrow{H_2O}$



$R_1C_6H_4CH(C_2H_5)CH(CN)C_6H_4R_2 \xrightarrow{CH_3MgI}$

II

$R_1C_6H_4CH(C_2H_5){-}CH(C_6H_4R_2)C(CH_3){=}NMgI \xrightarrow[H_2O]{HCl}$

$R_1C_6H_4CH(C_2H_5){-}CH(C_6H_4R_2)C(=O)CH_3$

III

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[1] Paper I, THIS JOURNAL, **68**, 1157 (1946).

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

The synthesis was carried out with α-phenyl-*p*-methoxycinnamonitrile (I, R_1 = OCH_3, R_2 = H) and α-*p*-anisyl-*p*-methoxycinnamonitrile (I, R_1 = R_2 = OCH_3) and gave as with α-phenylcinnamonitrile[2] (R_1 = R_2 = H) two stereoisomeric nitriles (II) and two stereoisomeric ketones (III). The addition of methylmagnesium bromide to α,β-di-*p*-anisylvaleronitrile (II, R_1 = R_2 = OCH_3) is reported not to occur because the α-hydrogen is sufficiently acidic to attack a Grignard reagent.[3] In this work apparently this difficulty did not occur because of the use of excess Grignard reagent in the reaction.

The lower melting ketone in both series could be isomerized to the higher melting isomer by refluxing with sodium ethoxide in alcohol or with hydrochloric acid. Attempts to demethylate 3,4-di-*p*-anisyl-2-hexanone with either alkali or with hydrobromic acid gave either tarry or water-soluble products which could not be characterized.

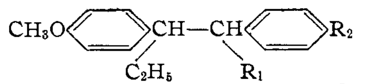
Reduction of the hexanones to the hexanols was accomplished by high pressure catalytic reduction and by means of aluminum isopropoxide. In each method, two isomeric 3,4-diaryl-2-hexanols were obtained.

The hexanols were dehydrated to oily 3,4-diarylhexenes by means of potassium bisulfate. The actual position of the unsaturation in these hexenes is not known but the behavior of the products points to a mixture of possibly the 2-hexene and 1-hexene. Rearrangement of the oil from 3-phenyl-4-*p*-anisyl-2-hexanol by refluxing with iodine in chloroform gave a three per cent. yield of 3-phenyl-4-anisyl-3-hexene. The oil from 3,4-di-*p*-anisyl-2-hexanol gave no isolable stilbestrol dimethyl ether under similar circumstances. 3,4-Di-*p*-anisyl-2-hexene is reported to be converted by such treatment into a quantitative yield of stilbestrol dimethyl ether.[4]

The hexene structure is indicated by the fact that the reduction of the oil from 3-phenyl-4-*p*-anisyl-2-hexanol in the presence of platinum oxide gave a 24% yield of 3-phenyl-4-*p*-anisylhexane. The product from 3,4-di-*p*-anisyl-2-hexanol gave only a trace of *meso*-3,4-di-*p*-anisylhexane.

TABLE I

ESTROGENIC ACTIVITY OF DIARYLHEXANONES, DIARYLHEXANOLS AND RELATED COMPOUNDS



Compound	M.p., °C.	Total dose, mg.	Uterine weight, mg.	Activity	No. of animals
R_1 = CN; R_2 = H	69–71	10[a]	19.4	−	3
R_1 = CN; R_2 = H	118–119	10	23.5	−	3
R_1 = CN; R_2 = OCH_3	131–133	1	64.6	+	3
		1	18.3	−	4
R_1 = $COCH_3$; R_2 = H	108–109	0.1	74.9	+	11
		.01	26.6	−	8
R_1 = $COCH_3$; R_2 = OCH_3	99–101	10	44.0	+	2
		1	24.3	−	3
R_1 = $COCH_3$; R_2 = OCH_3	139–142	0.01	42.0	+	10
		.001	25.5	−	7
R_1 = $CHOHCH_3$; R_2 = OCH_3		.1	66.5	+	4
		.01	25.5	−	7
Estrone		.001	51.6	+	6
Controls		....	18.0	−	8

[a] One injection per day for 4 days.

The results of the testing for estrogenic activity of the various compounds are given in Table I.

Acknowledgment.—The author wishes to express his gratitude to Dr. J. M. Sprague of Sharp and Dohme, Inc., for the estrogenic assays.

Experimental[5]

α-Phenyl-β-(*p*-anisyl)-valeronitrile.—α-Phenyl-*p*-methoxycinnamonitrile (47 g.) when treated with ethylmagnesium bromide in a manner similar to that used by Kohler[2] gave 35.2 g. of solid α-phenyl-β-(*p*-methoxyphenyl)-valeronitrile. This compound after three crystallizations from benzene melted at 118–119°.

Anal. Calcd. for $C_{18}H_{19}ON$: C, 81.5; H, 7.2. Found: C, 81.46; H, 7.69.

The lower melting isomer was isolated from the oil (14 g.) obtained by first distilling at 187–192° (1 mm.) and then fractionally crystallizing from ether. Two recrystallizations from (60–70°) petroleum ether gave a white solid melting at 69–71°.

Anal. Calcd. for $C_{18}H_{19}ON$: C, 81.5; H, 7.2. Found: C, 81.63; H, 7.66.

α,β-Di-(*p*-anisyl)-valeronitrile.—α-(*p*-Methoxyphenyl)-*p*-methoxycinnamonitrile (53 g.) gave 26.5 g. of a solid and 26.2 g. of an oil boiling at 199–200°, at 1 mm. The solid after two crystallizations from ethanol melted at 131–133.5°.

Anal. Calcd. for $C_{19}H_{21}O_2N$: C, 77.28; H, 7.12. Found: C, 77.55; H, 7.54.

The oil gave more solid isomer when treated with ethanol. The residual oil could not be crystallized and probably consists mainly of the other possible isomer. Purification by distillation at 1 mm. at 199–200° gave a pale yellow viscous oil which analyzed correctly for α,β-di-(*p*-methoxyphenyl)-valeronitrile.

Anal. Calcd. for $C_{19}H_{21}O_2N$: C, 77.28; H, 7.12. Found: C, 77.28; H, 7.06.

3-Phenyl-4-*p*-anisyl-2-hexanone.—A solution of α-phenyl-β-*p*-anisylvaleronitrile (6 g.) (m.p. 118–119°) and methylmagnesium iodide (0.4 mole) in benzene (100 ml.) and ether (60 ml.) was refluxed for 24 hours and poured onto a mixture of ice and concentrated hydrochloric acid. Removal of the organic solvents gave an oil which gave white crystals (2.1 g.) when taken up in (60–70°) petroleum ether. The crystals after four crystallizations from (60–70°) petroleum ether melted at 108–109.5°.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.85; H, 7.80. Found: C, 81.05; H, 7.47.

The filtrate gave an oil (3.2 g.) which after distillation at 170° at 1 mm. could be separated by fractional crystallization from (60–70°) petroleum ether into the above isomer and an isomeric ketone. The latter after four crystallizations from (60–70°) petroleum ether melted at 63–66°.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.85; H, 7.80. Found: C, 80.72; H, 7.84.

The low melting α-phenyl-β-*p*-anisylvaleronitrile when treated with methylmagnesium iodide behaved similarly to the higher melting isomer.

3,4-Di-*p*-anisyl-2-hexanone.—α,β-Di-(*p*-anisyl)-valeronitrile (24.5 g., m.p. 131–133.5°) when treated with excess methylmagnesium iodide in a manner similar to that used with α-phenyl-β-*p*-anisylvaleronitrile gave an oil which by fractional crystallization could be separated into two solids. The first (11.0 g.) of these after three recrystallizations from alcohol melted at 139–142°.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.92; H, 7.69. Found: C, 76.49; H, 7.70.

The low melting isomer (7.8 g.) after three crystallizations from ethanol melted at 99–101°.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.92; H, 7.69. Found: C, 76.93; H, 8.13.

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(3) K. Rorig, American Chemical Society Meeting, Boston, Mass. April, 1951.

(4) F. Wessely, E. Kershbaum, A. Kleedorfer, F. Prillinger and E. Zajic, *Monatsh.*, **73**, 127 (1940).

(5) Melting points are not corrected.

The oily isomeric α,β-di-(*p*-anisyl)-valeronitrile likewise gave a mixture of the isomeric hexanones when treated with methylmagnesium iodide.

Isomerization of Hexanones.—3-Phenyl-4-*p*-anisyl-2-hexanone (2.0 g., m.p. 63–66°) was refluxed in ethanol (40 ml.) containing 0.7 g. of dissolved sodium for five hours. The solution was poured into water and the resulting solid filtered. Upon recrystallization from ethanol, the higher melting isomer (105°, 0.93 g.) was obtained.

3-Phenyl-4-*p*-anisyl-2-hexanone (13.5 g., m.p. 63–66°) was refluxed with concentrated hydrochloric acid (100 ml.) for 24 hours, poured into water and extracted with ether. Removal of the ether and addition of petroleum ether (60–70°) gave 4.7 g. of the higher melting isomer (105–107°). The residual oil consisted mainly of starting material.

3,4-Di-*p*-anisyl-2-hexanone (0.48 g.) (m.p. 99–101°) was isomerized by sodium ethoxide to the higher melting isomer (0.24 g.) (m.p. 138–140°).

Attempted Demethylations of 3,4-Di-*p*-anisyl-2-hexanone.—3,4-Di-*p*-anisyl-2-hexanone (2 g.) was refluxed in acetic acid (20 ml.) with 40% hydrobromic acid (10 ml.) for 6 hours. The solution was poured into water and extracted with ether. Extraction of the ether layer with alkali followed by acidification gave a black tar.

3,4-Di-*p*-anisyl-2-hexanone (4 g.) was heated with potassium hydroxide (12 g.) in ethanol (24 ml.) in a steel bomb at 215–220° for 18 hours. The resulting solution was poured into water and extracted with ether. Acidification of the aqueous layer gave no precipitate. The acidified solution smelled strongly of phenol.

3-Phenyl-4-*p*-anisyl-2-hexanol.—3-Phenyl-4-*p*-anisyl-2-hexanone (m.p. 108–109.5°, 8.4 g.) was refluxed with 0.23 mole of aluminum isopropoxide in isopropyl alcohol (100 ml.) for 24 hours. The resulting solution was poured into water, acidified with hydrochloric acid and extracted with ether. Removal of the ether gave an oil (6.0 g.) which could be separated into two fractions by crystallization from petroleum ether (60–70°). The first fraction formed hemispheres which after five crystallizations from petroleum ether (60–70°) melted at 105–109°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.2; H, 8.45. Found: C, 80.24; H, 8.50.

The second more soluble fraction formed needles which after four crystallizations from (60–70°) petroleum ether melted at 95–97°.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.28; H, 8.45. Found: C, 80.35; H, 8.64.

Similar products (10 g.) were obtained by the catalytic reduction of 3-phenyl-4-*p*-anisyl-2-hexanone (m.p. 108–109.5°) 10 g. at 250° in ethanol (100 ml.) at 3000 pounds pressure of hydrogen in the presence of copper chromite.

The structure of the carbinol (105°, 0.852 g.) was demonstrated by oxidation with chromic acid (0.5 g.) in a mixture of acetic acid (10 ml.) and water (1 ml.) at 30° for one hour. The ketone (0.27 g.) was obtained by pouring the resulting solution into water and extracting with ether; m.p. 103–106°. One recrystallization from ethanol gave a sample melting at 107–108° which did not lower the melting point of an authentic sample of the higher melting ketone.

3,4-Di-*p*-anisyl-2-hexanol.—3,4-Di-*p*-anisyl-2-hexanone (10 g.) was reduced at 250° under 3000 pounds of hydrogen in ethanol (100 ml.) and in the presence of copper chromite. The product (10 g.) was separated by fractional crystallization from petroleum ether (60–70°) into two compounds. The rapid-crystallizing isomer after one crystallization from benzene and one from (60–70°) petroleum ether melted at 128.5–130.5°.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.43; H, 8.28. Found: C, 76.53; H, 8.94.

The slow crystallizing isomer after two crystallizations from (60–70°) petroleum ether melted at 112–114°.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.43; H, 8.28. Found: C, 76.22; H, 8.31.

Similar mixture of products was obtained by reducing 3,4-di-*p*-anisyl-2-hexanone with excess aluminum isopropoxide.

Dehydration of 3-Phenyl-4-*p*-anisyl-2-hexanol.—3-Phenyl-4-*p*-anisyl-2-hexanol (22 g.) (mixture of isomers) was heated with freshly fused potassium bisulfate (45 g.) at 200–210° for 45 minutes. Addition of water followed by extraction with ether gave an oil (16.3 g.) which distilled at 145–150° (1 mm.). This sample would not crystallize.

This fraction (5.3 g.) was reduced in ethanol (50 ml.) in the presence of platinum oxide (0.1 g.) at 45 pounds of hydrogen. Removal of the solvent and addition of (30–38°) petroleum ether gave a solid (1.27 g.) melting at 79–82°. After two crystallizations from (30–38°) petroleum ether the white solid melted at 86–88° and did not depress the melting point of 3-phenyl-4-*p*-anisylhexane.[1]

The oil (7.5 g.) was refluxed in chloroform (50 ml.) with iodine (1.0 g.) for four hours and the resulting solution poured into a sodium bisulfite solution. Extraction with ether gave an oil from which crystals (0.28 g.) were obtained by adding ethanol and cooling. The crystals melted at 77–79°. Brownlee[6] reports a melting point of 79–80° for 3-phenyl-4-*p*-anisyl-3-hexene.

Repetition of this process did not give any more solid from the oil.

Dehydration of 3,4-Di-*p*-anisyl-2-hexanol.—3,4-Di-*p*-anisyl-2-hexanol (10 g.) was heated with freshly fused potassium bisulfate (20 g.) at 170–180° for 15 minutes. The reaction mixture was poured into water and extracted with ether. Removal of the ether gave an oil which could be separated by distillation into three fractions. The low boiling fraction (0.9 g.) b.p. 59–166° (1 mm.) was not investigated further. The second fraction (5.3 g.) boiled at 166–170° (1 mm.) while the third fraction (1.4 g.) boiled over a wide range above 170° (1 mm.).

The second fraction upon reduction in ethanol in the presence of platinum oxide at 40 pounds pressure of hydrogen gave a very small amount of a solid melting from 102–130°. The amount was too small to purify. The melting point was not changed materially when mixed with *meso*-hexestrol dimethyl ether.

The second fraction upon refluxing in chloroform with iodine under ultraviolet light gave a product which remained oily and would not crystallize.

Estrogenic Assay. Uterine Weight Method.—The assay was carried out by the Department of Pharmacology of Sharp and Dohme according to the following procedure. The assay was made using immature (21 or 22 day) female albino rats obtained from Blain's, Media, Pa. The rats were given Rockland's diet and water. Bilateral ovariectomy was performed under ether anesthesia and the rats were then used to determine the response of the uterus to the drugs. The compounds were administered by subcutaneous injection. The total dose, either 10 or 1 mg. of the compound in 0.4 cc. of corn oil was divided and given over a period of 4 days. The rats on each compound were kept in a separate cage. A total dose of 0.001 mg. of estrone in 0.4 cc. oil was used as a reference. Ovariectomized rats which received no injection were used as controls. Autopsy was performed on the fifth day and the uterus weighed. When the increase in the uterine weight of rats receiving a compound was significantly larger than the control uterine weight, the dose of compound was decreased until there was no significant difference between the control rats and rats receiving the compound.

IOWA CITY, IOWA RECEIVED JUNE 4, 1951

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[6] G. Brownlee, F. C. Copp, W. M. Duffin and I. M. Tonkin, *Biochemical J.*, **37**, 572 (1943).