which the intermediary anisyl *p*-methylstyryl ketone and the *p*-anisyl α,β-epoxy-*p*-anisylethyl ketone were not isolated. The following method was used:

To a solution prepared from 4.6 g. of sodium and 80 cc. of 95% ethanol was added a solution of 30 g. of *p*-methoxyacetophenone and 27.2 g. of anisaldehyde in 60 cc. of 95% ethanol. After standing for thirty minutes at room temperature, 360 cc. of 95% ethanol was added and the mixture heated to dissolve the *p*-anisyl *p*-methoxystyryl ketone. The solution was then cooled to 45° and 50 cc. of 14% aqueous hydrogen peroxide added. The mixture was shaken and the temperature maintained at about 40° for forty-five minutes, after which 60 cc. of 30% aqueous sodium hydroxide was added. The mixture was refluxed for two hours during which time about 400 cc. of ethanol was removed. The remaining red solution was diluted with 2 liters of water and filtered from a small amount of solid. The filtrate was acidified with hydrochloric acid and the anisyl *p*-methoxybenzylglycolic acid was collected, washed with water, and dried. The oxidation with lead tetraacetate was carried out as described above. The yield of desoxyanisoin was 26 g. (51%).

p-**Ethoxyphenyl** *p*-**Methoxystyryl Ketone.**—A solution of 33 g. of *p*-ethoxyacetophenone and 27.2 g. of *p*-methoxybenzaldehyde in 60 cc. of 95% ethanol was condensed with sodium methylate as described for anisyl *p*-methoxystyryl ketone. The product formed small yellow crystals, m. p. 106.5–108°.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.59; H, 6.38. Found: C, 76.51, 76.58; H, 6.28, 6.34.

p-**Ethoxyphenyl** *p*-**Methoxybenzyl Ketone.**—A solution of 40 g. of *p*-ethoxyphenyl *p*-methoxystyryl ketone in 300 cc. of ethanol and 100 cc. of acetone was treated with 30 cc. of sodium hydroxide and 46 cc. of 28% hydrogen peroxide as described for *p*-anisyl α,β-epoxy-*p*-anisylethyl ketone. The yellow crystalline product, which melted at 112–114°, was dissolved in 750 cc. of 95% ethanol and a solution of 30 g. of sodium hydroxide in 60 cc. of water added. The mixture was refluxed for four hours. The product was worked up as described for *p*-anisyl *p*-methoxybenzylglycolic acid. The crude acid (34 g.) melting at 153–156° was oxidized with lead tetraacetate as described under desoxyanisoin. The reaction product was recrystallized from ethanol as small almost colorless crystals, m. p. 103–104°. The yield was 17 g., or 42% (based on the *p*-ethoxyphenyl *p*-methoxystyryl ketone used).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.55; H, 6.71. Found: C, 75.41; H, 6.78.

Summary

The use of chalcones as intermediates for the synthesis of desoxyanisoin is discussed.

An effective method of oxidizing disubstituted glycolic acids with lead tetraacetate is described.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Configurations of Some 4,5-Diarylpiperidones[1]

BY C. F. KOELSCH AND ROBERT F. RAFFAUF

It has been noted previously[2] that when a mixture of the diastereoisomeric forms of ethyl γ-cyano-β,γ-diphenylbutyrate is hydrogenated at 165° using Raney nickel, there is formed a mixture of two forms of 4,5-diphenylpiperidone-2. It is now shown that the "α-form" of the piperidone (m. p. 192–194°) is *cis* and the "β-form" (m. p. 177–178°) is *trans*.[3] This assignment of configurations rests on a new synthesis of the piperidones through Beckmann rearrangements of the oximes of the known[4,5] *cis* and *trans* forms of 3,4-diphenylcyclopentanone.

When ethyl β-(*m*-aminophenyl)-γ-cyano-γ-phenyl-butyrate is hydrogenated, it yields a mixture of two forms of 4-(*m*-aminophenyl)-5-phenylpiperidone-2. The configurations of these isomers have been determined by converting the substances, through diazotization and reduction, into the unsubstituted diphenylpiperidones just discussed. Using the *cis* and *trans* aminophenyl compounds, it has been possible to prepare certain other pairs of stereoisomeric piperidones of known configurations, namely 4-(*m*-acetylaminophenyl)-, 4-(*m*-iodophenyl)-, 4-(*m*-hydroxyphenyl)-, and 4-(*m*-methoxyphenyl)-5-phenylpiperidone-2.

It is expected that additional labilizing groups can be introduced into the hydroxylated nucleus of 4-(*m*-hydroxyphenyl)-5-phenylpiperidone-2, rendering this nucleus susceptible to degradation to a carboxyl group. This degradation will establish the configurations of the "α-" and "β-" forms of a number of known[6] 4-alkyl-5-phenylpiperidones.

Experimental

cis-3,4-Diphenylcyclopentanol (b. p. 170–190° at 1–2 mm., m. p. 80–82°, reported[5] m. p. 85–86°) was obtained in yields of over 90% by reducing diphenylcyclopentenone or better anhydracetonebenzil in alcohol at 85° with Raney nickel and hydrogen at 100 atmospheres.

Anal. Calcd. for $C_{17}H_{18}O$: C, 85.7; H, 7.6. Found: C, 85.7; H, 7.9.

The same compound was the sole product when the catalytic reduction was carried out in alcohol containing sodium ethoxide, and it was not inverted when it was boiled for one hour with concentrated alcoholic sodium ethoxide.

cis-3,4-Diphenylcyclopentanone (m. p. 108–109°; reported m. p. 107°,[4] 110°[5]) was obtained in 90% yield by oxidizing the foregoing alcohol with chromic acid in acetic acid at 25°. The ketone formed a 2,4-dinitrophenylhydrazone, m. p. 206–207° (reported[5] 208°); the oxime was obtained in a yield of 95%, m. p. 137° (reported[6] 137–138°). The oxime could not be rearranged satisfactorily under the conditions described by Hildebrand and Bogert[7]

(1) From the Ph.D. Thesis of Robert F. Raffauf, January, 1944.

(2) Koelsch, THIS JOURNAL, **65**, 2093 (1943).

(3) The corresponding "α-" (m. p. 83–84°) and "β-" (m. p. 115–116°) forms of 3,4-diphenylpiperidine are thus, respectively, *cis* and *trans* compounds. The configurations of the derivatives of these compounds previously prepared, are likewise established.

(4) Weidlich, *Ber.*, **71**, 1601 (1938).

(5) Burton and Shoppee, *J. Chem. Soc.*, 567 (1939).

(6) Ref. 2 and unpublished research with Dr. E. J. Prill.

(7) Hildebrand and Bogert, THIS JOURNAL, **58**, 650 (1936).

for certain analogous compounds, but when 4.1 g. of it was added slowly to 10 ml. of 75% sulfuric acid at 150–160° and the mixture was then stirred for thirty minutes, it was converted into a brown tarry product. From this there was isolated 1.2 g. (30%) of *cis*-4,5-diphenylpiperidone-2, m. p. 192–193°. The m. p. was unchanged when the substance was mixed with a sample of the "α-form of 4,5-diphenylpiperidone-2" obtained by the hydrogenation of ethyl γ-cyano-β,γ-diphenylbutyrate.[2]

A mixture of *cis*- and *trans*-3,4-diphenylcyclopentanols, b. p. 185–195° at 2 mm., was obtained in 61% yield by reducing 10 g. of diphenylcyclopentenone in 100 ml. of dry ethanol with 5.8 g. of sodium. Ten grams of this mixture was dissolved in 50 ml. of acetic acid and treated at 25° with 2.8 g. of chromic anhydride in 150 ml. of 90% acetic acid. After it had been kept overnight, the solution furnished 9.5 g. of mixed *cis*- and *trans*-3,4-diphenylcyclopentanones; fractional crystallization from methanol gave 1.6–2.0 g. of *trans*-3,4-diphenylcyclopentanone, m. p. 175–177° (reported[4,5] 177°). The oxime, m. p. 120–122° (reported[5] 121.5°), was obtained in a yield of 80%. When the oxime was heated with 75% sulfuric acid at 125–140° for a few minutes, it was converted into a red oil from which there was isolated *trans*-4,5-diphenylpiperidone-2, yield, 25%, m. p. 177–178°. The m. p. was unchanged when the substance was mixed with a sample of the "β-form of 4,5-diphenylpiperidone-2" obtained by the hydrogenation of ethyl γ-cyano-β,γ-diphenylbutyrate.[2] The only crystalline product isolated from the residues from either Beckmann rearrangement, *cis* or *trans*, other than the piperidone was the unchanged oxime.

Ethyl β-(*m*-Aminophenyl)-γ-phenyl-γ-cyanobutyrate.—When a solution of 2 g. of sodium in 40 ml. of dry ethanol was added to 50 g. of ethyl *m*-aminocinnamate and 46 g. of benzyl cyanide at 25°, the temperature of the mixture rose rapidly to 75°. The condensation product, separated from excess benzyl cyanide by extraction with dilute hydrochloric acid, was an oil (69 g., 86%) which could not be distilled or crystallized. It was analyzed in the form of its **picrate**, yellow needles from dilute alcohol, m. p. 181–182°.

Anal. Calcd. for $C_{25}H_{23}N_5O_9$: C, 55.9; H, 4.3. Found: C, 56.2; H, 4.1.

The cyanoester (69 g.) was hydrogenated with Raney nickel in 100 ml. of alcohol at 150° and 100 atmospheres. Separation of the product (yield 56%) into the *cis* and *trans* forms of the piperidone was effected by repeated crystallization from benzene. ***cis*-4-(*m*-Aminophenyl)-5-phenylpiperidone-2** melted at 183.5–184.5°. The *trans* isomer melted at 173.5–175°.

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.7; H, 6.77. Found: (*cis*) C, 77.1; H, 6.60; (*trans*) C, 76.3; H, 6.56.

The **acetyl derivatives** separated from dilute acetic acid in the form of flat colorless needles; the *cis* compound melted at 206.5–207.5°; the *trans* compound melted at 233–234.5°.

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.0; H, 6.5. Found: (*cis*) C, 74.0; H, 6.6; (*trans*) C, 74.0; H, 6.2.

Nitration of the *cis*-acetylamino compound with excess fuming nitric acid in acetic acid gave a poor yield of ***cis*-4[5 - acetylamino - 2(?) - nitrophenyl] - 5 - phenylpiperidone-2,** yellowish crystals from dilute acetic acid, sint. 245°, m. p. 252–257° dec.

Anal. Calcd. for $C_{19}H_{19}N_3O_4$: C, 64.6; H, 5.4. Found: C, 64.5; H, 5.2.

A solution of the diazonium chloride from 1.33 g. of the *cis* piperidone allowed to stand for twenty hours with 5 equivalents of hypophosphorous acid gave 0.3 g. (25%) of *cis*-4,5-diphenylpiperidone-2, m. p. and mixed m. p. 192–194°; the rest of the product was an orange gum. The *trans* amino compound similarly treated, gave *trans*-4,5-diphenylpiperidone-2, m. p. and mixed m. p. 177–178°.

When a diazonium sulfate solution from 0.5 g. of the *cis* amino compound was treated with excess potassium iodide, it yielded ***cis*-4-(*m*-iodophenyl)-5-phenylpiperidone-2,** small prisms from benzene and ether, m. p. 146–149°; ***trans*-4-(*m*-iodophenyl)-5-phenylpiperidone-2,** irregular plates, m. p. 180–182.5°, was obtained similarly from the *trans* amino compound.

Anal. Calcd. for $C_{17}H_{16}INO$: C, 54.1; H, 4.24. Found: (*cis*) C, 54.5; H, 4.49; (*trans*) C, 54.4; H, 4.48.

When a diazonium sulfate solution from 6 g. of the *cis* amino compound was warmed, nitrogen was evolved and a tar was deposited. From this, by sublimation at 13 mm., there was isolated 2.2 g. (36%) of ***cis*-4-(*m*-hydroxyphenyl)-5-phenylpiperidone-2,** fine white needles from ethyl acetate containing a little alcohol, m. p. 232–233° under nitrogen. The compound retained solvent very tenaciously and required long drying at 100° in nitrogen under reduced pressure before it gave a satisfactory m. p. or analytical figures. ***trans*-4-(*m*-Hydroxyphenyl)-5-phenylpiperidone-2,** obtained analogously in a yield of 38%, had similar properties, m. p. 218–224°.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.4; H, 6.4. Found: (*cis*) C, 76.2; H, 6.2; (*trans*) C, 76.7; H, 6.5.

Treatment of the hydroxy compounds with methyl sulfate and alkali or with ethereal diazomethane yielded **4-(*m*-methoxyphenyl)-5-phenylpiperidone-2;** both products formed fine white needles from ligroin and ether. The *cis* compound melted at 100–102°; the *trans* compound at 184–185°.

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.9; H, 6.8. Found: (*cis*) C, 77.1; H, 6.5; (*trans*) C, 76.6; H, 7.0.

Only one experiment was carried out on the conversion of the piperidones described above into piperidines. The reduction of 2 g. of *cis*-4-(*m*-aminophenyl)-5-phenylpiperidone-2 with 1 g. of sodium according to the usual procedure[2] gave ***cis*-4-(*m*-aminophenyl)-3-phenylpiperidine,** an oil, b. p. 230–235° at 9 mm. The base gained in weight when it was exposed to air; its hydrochloride, chloroplatinate, picrate and acetyl derivative were hygroscopic solids or oils.

Anal. Calcd. for $C_{17}H_{20}N_2$: C, 81.0; H, 7.9. Found: C, 81.2; H, 8.2.

Summary

It has been possible to assign *cis* and *trans* configurations to the two forms of 4,5-diphenylpiperidone-2 by synthesizing the compounds from the known *cis* and *trans* forms of 3,4-diphenylcyclopentanone. Using the diphenylpiperidones as reference compounds, it has been possible to assign configurations to some other 3-phenyl-4-arylpiperidine derivatives.

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