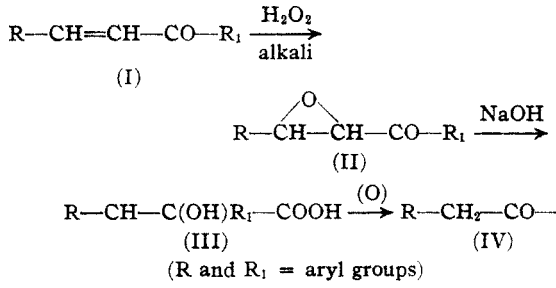
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Use of Chalcones in the Synthesis of Medicinal Intermediates

BY EWALD ROHRMANN, R. G. JONES AND H. A. SHONLE

The relative ease of preparation and the great reactivity of some chalcones makes them a promising starting point for the preparation of a variety of compounds. We have found some of these to be useful intermediates in the synthesis of certain medicinally important compounds.

Weitz and Scheffer[1] observed that many of the chalcones (I) are readily oxidized with hydrogen peroxide in alkaline medium to yield epoxy compounds (II). These epoxy compounds have been shown to undergo a variety of transformations.[2,3] Their reaction with alkali is particularly interesting. On prolonged treatment with alkali, they undergo rearrangement to yield disubstituted glycolic acids (III). Oxidation of the resulting disubstituted glycolic acids with suitable oxidizing agents brings about a simultaneous decarboxylation and oxidation, resulting in the formation of ketones of the desoxybenzoin type (IV). Hutchins, *et al.*,[3] observed that not all chalcones will react with hydrogen peroxide.



This reaction of the epoxy compounds (II) with alkali is one of the most satisfactory methods for the preparation of various disubstituted glycolic acids, which are useful intermediates for the preparation of local anesthetics, antispasmodics, and mydriatics of the basic ester type.[4] The preparation of some of these derivatives will be reported at a later date.

We have applied the above series of reactions to the preparation of desoxyanisoin, which is an important intermediate in the preparation of diethylstilbestrol. All of the reactions involved proceed smoothly, and it has been possible to obtain 50 to 70% over-all yields of desoxyanisoin starting from anisaldehyde and *p*-methoxyacetophenone. In this preparation it is not necessary to isolate intermediates I and II; however, the over-all yields of desoxyanisoin in such cases are somewhat lower. Lead tetraacetate has been found to be by far the most effective oxidizing agent for converting the disubstituted glycolic acids to ketones of the desoxybenzoin type.

Using the same procedure, *p*-methoxybenzyl *p*-ethoxyphenyl ketone was prepared from *p*-methoxybenzaldehyde and *p*-ethoxyacetophenone.

The analyses were made by the late Mr. J. T. Bryant of the Lilly Research Laboratories and by the Arlington Laboratories.

Experimental[5]

Anisyl *p*-Methoxystyryl Ketone.—To a solution of 13.6 g. of anisaldehyde and 15 g. of *p*-methoxyacetophenone in 40 cc. of absolute ethanol was added a solution prepared from 1 g. of sodium and 10 cc. of methanol. After standing at room temperature for twenty minutes the solution had set to a crystalline paste. It was cooled to 0° and the crystals collected and washed with 80% methanol. The product formed fine yellow crystals; m. p. 97–99°; yield 24 g. (92%).

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.20; H, 6.01. Found: C, 76.25; H, 6.04.

***p*-Anisyl α,β-Epoxy-*p*-anisylethyl Ketone.**—To a solution of 20 g. of anisyl *p*-methoxystyryl ketone in 150 cc. of ethanol and 50 cc. of acetone at 40° was added 15 cc. of 4 *N* sodium hydroxide solution and 23 cc. of 28% hydrogen peroxide. The temperature was maintained at 40° for forty minutes. The mixture was then cooled and the crystals collected, washed with aqueous ethanol and recrystallized from ethanol; yield 19.5 g. (92%); m. p. 123–124° (dec.).

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.60; H, 5.6.

***p*-Anisyl *p*-Methoxybenzylglycolic Acid.**[6]—A mixture of 11.5 g. of *p*-anisyl α,β-epoxy-*p*-anisylethyl ketone, 50 cc. of 95% ethanol, and 13 cc. of 30% aqueous sodium hydroxide was refluxed for ninety minutes. The clear red solution was cooled, diluted with 500 cc. of water and filtered. Acidification of the filtrate gave an almost white precipitate of *p*-anisyl-*p*-methoxybenzylglycolic acid; m. p. 173–174° (dec.); yield 11.2 g. (90%).

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.55; H, 5.97. Found: C, 67.85, 67.57; H, 6.04, 5.87.

Desoxyanisoin.—A thick paste of 30.2 g. (0.1 mole) of *p*-anisyl-*p*-methoxybenzylglycolic acid and 90 cc. of glacial acetic acid was stirred while 69 g. (0.1 mole) of red lead (Pb_3O_4) was added in small portions. The temperature was allowed to rise to 65–70° before resorting to external cooling. Gas was evolved and a clear solution obtained. Toward the end of the reaction, crystals began to separate. A few drops of glycerol in 10 cc. of water was added to destroy any excess lead tetraacetate and the mixture was poured into 1 liter of water. The precipitate was collected and washed with dilute alkali and water; yield 25 g. (98%); m. p. 108–110°. After recrystallization from 80% ethanol the product melted at 110–112°; the mixed m. p. with an authentic sample of desoxyanisoin was 110–112°.

Anal. Calcd. for $C_{16}H_{16}O_3$: C, 74.99; H, 6.29. Found: C, 74.94; H, 6.36.

When potassium dichromate in aqueous sulfuric acid was used as the oxidizing agent, the yield was only about 30–40% of the theoretical.

Desoxyanisoin can also be prepared by a procedure in

(1) Weitz and Scheffer, *Ber.*, **54**, 2344 (1921).

(2) Baker and Robinson, *J. Chem. Soc.*, 1798 (1932).

(3) Hutchins, Motwani, Mudbhakal and Wheeler, *ibid.*, 1882 (1938).

(4) Blicke and Maxwell, THIS JOURNAL, **64**, 428, 431 (1942).

(5) All melting points are uncorrected.

(6) Malkin and Robinson, *J. Chem. Soc.*, **127**, 369 (1925), prepared this compound by another method and reported a m. p. of 170°

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]

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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[5] 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).