[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Epoxyketones. III.[1] Stereochemistry of *cis*- and *trans*-*o*-Nitrobenzalacetophenone Oxide

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A *trans* configuration has been assigned to the low melting α-form of *o*-nitrobenzalacetophenone oxide which results from the peroxide oxidation of *trans*-*o*-nitrochalcone, and from the Darzens condensation of *o*-nitrobenzaldehyde with phenacyl bromide. The assignment of configuration is based upon a rationalization of the steric controls expected to operate in the Darzens-type condensation, upon the relative reactivities of the α- and β- forms of the oxide with phenylhydrazine, and upon the fact that the higher melting *cis*-β-form, which is prepared by a base-catalyzed rearrangement of the *trans*-α-form, shows a slightly lower general absorption of ultraviolet light. The infrared absorption spectra studies of these geometrical isomers show no significant electrical interaction in the ground states between the carbonyl group and the α,β-epoxide ring for either case. The catalytic hydrogenation of either *cis*- or *trans*-*o*-nitrobenzalacetophenone oxide to 2-phenyl-3-hydroxyquinoline provides a new method of synthesis of such materials.

In a previous publication[2] from this Laboratory it was pointed out that interrelated studies of the stereochemistry of *cis* and *trans* forms of analogous series of three-ring carbonyl compounds, R–CH–CH–COR′, where X is CH_2, O and N–R″, (X) are being carried out. The present article describes such a study with the known,[3] but structurally unassigned, *cis*- and *trans*-*o*-nitrobenzalacetophenone oxides. A following publication will report a similar study with the analogous *cis*- and *trans*-1-cyclohexyl-2-*o*-nitrophenyl-3-benzoylethylenimines.[4]

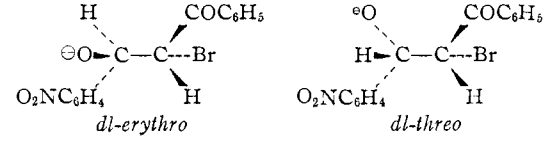
Many years ago Bodforss[3] condensed *o*-nitrobenzaldehyde with phenacyl bromide in the presence of sodium ethoxide to obtain *o*-nitrobenzalacetophenone oxide, α-form, m.p. 110°. On further standing with sodium ethoxide this material was converted to an isomeric substance, β-form, m.p. 175°. As Berson[5] has pointed out, this indicates that the α-form is the kinetically-favored product and is thermodynamically unstable relative to the more slowly formed β-isomer. In the Experimental section we have reported detailed conditions for the precise production of these two isomers, since obviously concentration and time factors are important. Thus in the Darzens[6] condensation of *o*-nitrobenzaldehyde and ω-bromoacetophenone the amount of solvent, the temperature and the contact time in the presence of the sodium methoxide has been held to a minimum to produce the optimum yield of the α-form. This same material resulted when the condensation was carried out in dioxane solution using sodium hydroxide as the condensing agent. We also prepared this α-form by a peroxide oxidation of *o*-nitrochalcone, a reaction which seems to lead to the *trans* forms of aryl aroyl ethylene oxides. Our best samples of this α-form showed a m.p. of 113–115°.

When the α-form was allowed to stand in methanol solution in the presence of sodium methoxide for a considerable length of time the conversion to the higher-melting and much more insoluble β-form, m.p. 175°, was nearly complete.

Ballester and Bartlett[7] have given an excellent discussion of the mechanism of Darzens-type condensations.

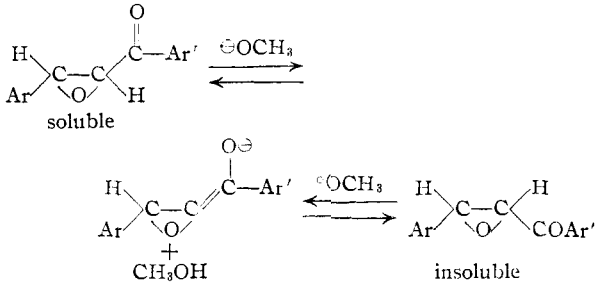
A consideration of the most probable preferred rotational arrangements for the *dl-erythro* and *dl-threo* forms of the intermediate bromohydrin anions suggests that the *dl-threo* form is a less sterically-favored configuration and would be the slower to close the three-ring to form the ethylene oxide.

Preferred rotational arrangements



For the *dl-threo* form to close the ring by an internal SN2 type displacement of the bromine ion it is necessary that a 120° rotation about the central carbon to carbon bond to a still less sterically favored arrangement take place. Consequently reversal to the *o*-nitrobenzaldehyde and the anion $(C_6H_5COCHBr)^{\ominus}$ may be favored and provide for the formation of larger amounts of the *dl-erythro* anion whose preferred rotational arrangement gives a facile ring closure to form the *trans*-*o*-nitrobenzalacetophenone oxide, Bodforss' α-form. Moreover the formation of the *dl-erythro* anion may be kinetically more favored for these same steric reasons than the formation of the *dl-threo* anion from these starting materials.

It seems probable that the rearrangement of the *trans*(α)-form to the *cis*(β)-form proceeds *via* an enolization catalyzed by the alkoxide ion.



(1) (a) For paper I, see N. H. Cromwell and N. G. Barker, THIS JOURNAL, **72**, 4110 (1950); (b) for paper II, see N. G. Barker and N. H. Cromwell, *ibid.*, **73**, 1051 (1951); (c) presented at the 126th meeting of the American Chemical Society, New York, N. Y., Sept., 1954.

(2) N. H. Cromwell, *et al.*, THIS JOURNAL, **75**, 5384 (1953).

(3) S. Bodforss, *Ber.*, **51**, 192 (1918).

(4) Unpublished work with G. Mercer, Dept. of Chemistry, Univ. of Nebraska, 1953–1954.

(5) J. A. Berson, THIS JOURNAL, **74**, 5177 (1952).

(6) G. Darzens, *Compt. rend.*, **139**, 1214 (1904); **141**, 766 (1905).

(7) M. Ballester and P. D. Bartlett, THIS JOURNAL, **75**, 2042 (1953).

The *cis* isomer, being much more insoluble than the *trans* form, precipitates from this reaction mixture in larger amounts.

Studies in the ethylenimine ketone series[8] with phenylhydrazine have shown that the *trans* form of aryl aroyl ethylenimines successfully competes with the *cis* form for one equivalent of the reagent to give a 4-aminopyrazoline which on further heating loses a molecule of amine to produce a pyrazole. The *cis* form reacts more slowly and only the pyrazole can be isolated. Previous investigators[3,9] have shown that certain epoxyketones will react with hydrazines to produce 4-hydroxypyrazolines which are readily converted to the pyrazoles on warming in solution. Thus Bodforss[3] obtained from *m*-nitrobenzalacetophenone oxide 1,3-diphenyl - 4 - hydroxy - 5 - *m* - nitrophenylpyrazoline which readily produced the corresponding pyrazole on warming. By analogy with the studies of the ethylenimine ketones these results suggest that those epoxyketones producing the isolable 4-hydroxypyrazolines are *trans* forms.

We were unable to isolate a 4-hydroxypyrazoline from the reaction of the suspected *trans*(α)-form of *o*-nitrobenzalacetophenone oxide with phenylhydrazine, although its presence in the crude reaction product mixture was indicated by positive Knorr[10] and Raiford[11] tests for pyrazolines. The presence of the *o*-nitro group on the 5-phenyl group, because of its powerful electron-attracting power, caused the proton on the 5-position of the pyrazoline ring to be so mobile as to provide for easy loss of water to produce the 1,3-diphenyl-5-*o*-nitrophenylpyrazole which was isolated in good yields even under quite mild reaction conditions. Furthermore, in a competitive experiment in which one equivalent each of the *cis*- and *trans*-*o*-nitrobenzalacetophenone oxide were allowed to compete for one equivalent of phenylhydrazine the higher-melting *cis*(β)-form or the oxide was isolated from the reaction mixture unchanged. The *trans* form was converted to the pyrazole in this experiment. These experiments may be taken as further evidence for the assignment of the *trans* configuration to the lower-melting α-form.

Absorption spectra studies, see Table I for a summary of the results, were made of the higher-melting *cis*(β)-form and the lower-melting *trans*(α)-form, of *o*-nitrobenzalacetophenone oxide, and of the parent *o*-nitrobenzalacetophenone and *o*-nitrobenzylacetophenone. The ultraviolet studies indicated hyperconjugation of the ethylene oxide bent-bond electrons with the π-orbital of the carbonyl group in both the α- and β-forms, with the lower-melting α-form showing a slightly great absorption of light. Based upon the rationalizations given above and those previously published,[12] the lower-melting α-form is assigned the *trans* configuration, the higher-melting form the *cis* arrangement. It had been predicted previously[12] that neither the *cis* nor the *trans* form of an aryl aroyl ethylene oxide would show significant electrical interaction between the bent-bond three-ring electrons and the π-orbital of the carbonyl group in the ground state. The present infrared studies have borne out this prediction, the carbonyl stretching frequencies for both geometrical isomers being identical (1695 cm.$^{-1}$) and even slightly higher than the value obtained (1690 cm.$^{-1}$) for the parent *o*-nitrobenzylacetophenone. This is in sharp contrast with the considerable interaction observed between a carbonyl group and an ethylenimine ring.[12]

TABLE I

SUMMARY OF ABSORPTION SPECTRA OF KETONES

Compound	Ultraviolet max.[a] Molar concn. × 10^5	λ, mμ	ε × 10^{-3}	Infrared C=O stretching freq.[b] wave no.
o-Nitrobenzalacetophenone oxide				
m.p. 175°, *cis*	1.346	252	18.76	1695
m.p. 113–115°, *trans*	2.084	253	20.11	1695
o-Nitrobenzalacetophenone[c]	0.2061	262	17.56	1671
				1650
o-Nitrobenzylacetophenone[d]	0.9924	244	15.84	1690

[a] Determined with a Beckman model DU instrument employing 10-mm. silica cells and 95% ethanol solutions. [b] Determined by Prof. W. C. Robison, Infrared Spectroscopy Laboratory, University of Nebraska, with a Perkin–Elmer model 21 instrument, using CCl_4 solutions (5–12 mg./ml.) and 1.0-mm. NaCl cells. [c] M.p. 125°, see ref. 4. [d] M.p. 59°, see ref. 4.

When the present results are contrasted with the interesting chemical studies done with various *cis*- and *trans*-aryl aroyl ethylene oxides to establish configurations, as reported by Wasserman[13] and Stevens,[14] it seems well-established that spectral methods may be used to assign the configurations to many pairs of *cis* and *trans* three-ring compounds of the type R–CH–CH–COR′.
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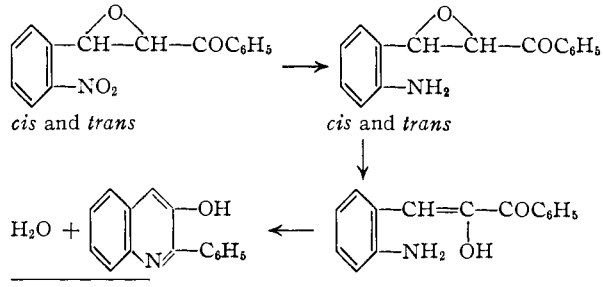
Catalytic hydrogenation of both the *cis* and *trans* forms of *o*-nitrobenzalacetophenone oxide produced 2-phenyl-3-hydroxyquinoline. This constitutes a new method for making 3-hydroxyquinolines and we intend to study its limitations and further possible applications since it seems to offer certain advantages over previously described syntheses of such compounds.

The mechanism for the formation of the 2-phenyl-3-hydroxyquinoline probably involves the prior reduction of the nitro group to give the *o*-aminobenzalacetophenone oxides. Both the *cis* and *trans* forms of this primary reduction product then probably re-



(8) N. H. Cromwell, *et al.*, THIS JOURNAL, **73**, 1044 (1951).

(9) (a) H. Jorlander, *Ber.*, **49**, 2786 (1916); (b) O. Widman, *ibid.*, **49**, 2781 (1916).

(10) L. Knorr, *Ann.*, **238**, 200 (1887).

(11) L. C. Raiford and W. J. Peterson, *J. Org. Chem.*, **1**, 544 (1937).

(12) N. H. Cromwell and M. A. Graff, *ibid.*, **17**, 414 (1952).

(13) H. H. Wasserman and J. B. Brous, *ibid.*, **19**, 515 (1954).

(14) C. L. Stevens, R. J. Church and V. J. Traynelis, *ibid.*, **19**, 522 (1954).

arrange to the enol form of the *o*-aminobenzyl phenyl diketone which can undergo a facile ring closure to give the quinoline.

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Experimental[15]

trans-o-**Nitrobenzalacetophenone Oxide (Low-Melting, α-Form).** (a) **From the Darzens Condensation.**[3]—A 15.1-g. (0.1 mole) sample of *o*-nitrobenzaldehyde and 19.9 g. (0.1 mole) of phenacyl bromide were dissolved in 60 ml. of methanol. Keeping the temperature below 12° a solution of 5.4 g. (0.1 mole) of sodium methoxide in 40 ml. of methanol was added dropwise to the reaction mixture with stirring. After three hours the reaction mixture was brought to a *p*H of 6 with acetic acid. A cream colored precipitate was filtered, washed with water and recrystallized from abs. ethanol; wt. 20.45 g. (76% yield), m.p. 111–113° (literature[3] m.p. 110°).

To 1.52 g. (0.01 mole) of *o*-nitrobenzaldehyde and 1.99 g. (0.01 mole) of phenacyl bromide dissolved in 75 ml. of dioxane, 0.2 g. (0.005 mole) of sodium hydroxide in 20 ml. of dioxane (wet) was added with stirring. After standing for two hours at room temperature the reaction mixture was brought to a *p*H of 6 with acetic acid and diluted with about 300 ml. of water. Cooling in an ice-bath precipitated the product which was recrystallized twice from ethanol; wt. 2.29 g. (85% yield), m.p. 113–115°.

(b) **From *trans-o*-Nitrochalcone.**—A 12.6-g. (0.05 mole) sample of *o*-nitrochalcone[4] was dissolved in 300 ml. of methanol and treated with 10 ml. of 30% hydrogen peroxide (0.09 mole) and 12 ml. of 8% sodium hydroxide all at once. After standing at room temperature for three hours the reaction mixture was diluted with water, cooled and the precipitated product removed by filtration; wt. 8.0 g. (60% yield), m.p. 105–110°, recrystallized from ethanol, m.p. 110–112°.

cis-o-**Nitrobenzalacetophenone Oxide (High-melting, β-Form).**—A 4-g. sample of the *trans*-oxide, m.p. 110–112°, was dissolved in 140 ml. of methanol and 2 ml. of a 10% sodium methoxide solution added. After standing for 30 minutes crystals started to form in the reaction mixture. After standing at room temperature for 14 hours the reaction mixture was made acidic with acetic acid and the product removed by filtration and recrystallized from ethanol; wt. 3.3 g. (83% conversion), m.p. 174–175° (literature m.p. 175°[3]). After the first 30 minutes of standing the extent of conversion in this reaction mixture was only 15%.

Reaction of *cis* and *trans-o*-Nitrobenzalacetophenone Oxides with Phenylhydrazine. (a) **Reaction of the High-melting, β-Form (*cis*, m.p. 175°).**—A 0.45-g. (0.00167 mole) sample of the *cis*-oxide was dissolved in 10 ml. of chloroform and 0.18 g. (0.00167 mole) of pure phenylhydrazine added along with one drop of acetic acid. The reaction mixture was allowed to stand overnight at room temperature. From this reaction mixture 0.12 g. (0.00045 mole) of unchanged colorless *cis*-oxide, m.p. 174°, and 0.20 g. (0.00059 mole) of the yellow colored pyrazole, m.p. 178°, were isolated and separated by fractional recrystallization from methanol.

Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 74.03; H, 4.50; N, 12.14.

(b) **Reaction of the Low-melting, α-Form (*trans*, m.p. 111–113°).**—A 1.35-g. (0.005 mole) sample of the oxide and 0.55 g. (0.005 mole) of phenylhydrazine were dissolved in 5 ml. of chloroform containing two drops of acetic acid. After standing at 6° for six hours the reaction mixture was diluted with petroleum ether. Two fractions resulted, 0.5 g., m.p. 178°, identical with the pyrazole described above, and 0.5 g., m.p. 150–155°, which gave a positive pyrazoline test by the Knorr[10] and Raiford[11] tests. Attempts to obtain the pure pyrazoline from this 150–155° melting material by recrystallization or chromatographic separation techniques resulted in its total conversion to the pyrazole, m.p. 178°. Attempts to obtain this unstable pyrazoline in larger amounts using various solvent media such as benzene, ethyl acetate, chloroform and methanol gave only mixtures of products. Using 20 ml. of chloroform and 40 ml. of methanol with one drop of acetic acid at 8° for 4 hours, 1.46 g. (86%) of pyrazole, m.p. 178°, was obtained from 1.35 g. of the *trans*-oxide.

(c) **Competitive Reaction of the *cis* and *trans* Forms for One Equivalent of Phenylhydrazine.**—A 0.37-g. (0.00137 mole) sample each of *cis*- and *trans-o*-nitrobenzalacetophenone oxide were dissolved in 10 ml. of chloroform and 1 ml. of a chloroform solution containing 0.00137 mole of phenylhydrazine added along with one drop of acetic acid. This reaction mixture was allowed to stand for 14 hours at about 10°. From this solution 0.27 g. (0.00100 mole) of the unchanged colorless *cis*-oxide, m.p. 175°, and 0.44 g. (0.00129 mole) of the yellow pyrazole, m.p. 178°, were isolated and separated by fractional recrystallization from methanol.

Catalytic Hydrogenation of *cis*- and *trans-o*-Nitrobenzalacetophenone Oxides.—*trans*-*o*-Nitrobenzalacetophenone oxide (4.0 g.) was dissolved in 60 ml. of ethyl acetate and shaken with 0.4 g. of Raney nickel for two hours under three atm. of hydrogen. The solvent was removed under vacuum and the residual oil mixed with ether and extracted with 5% sodium hydroxide. This alkaline solution was treated with carbon dioxide (Dry Ice) and the precipitated material recrystallized from abs. ethanol; wt. 2.3 g. (70% yield), m.p. 219–221°; mixed with authentic 2-phenyl-3-hydroxyquinoline,[16] m.p. 220–222°; hydrochloride, m.p. 258–259°.[16]

Anal. Calcd. for $C_{15}H_{11}NO\cdot HCl$: Cl, 13.75. Found: Cl, 13.75.

The infrared spectra of the product from the hydrogenation, and the material synthesized from ω-methoxyacetophenone and isatin *via* 2-phenyl-3-methoxy-4-carboxyquinoline[16] were identical in all respects, both compounds showing bands near 1600, 1520, 1500, 1465, 1390, 1350, 1315, 1280, 1270, 1195, 1145 and 1135 cm.$^{-1}$ when run as Nujol mulls in a Perkin–Elmer model 21 recording spectrophotometer. These curves were very different in appearance from that obtained for 2-phenyl-4-hydroxyquinoline, a sample of which was synthesized[17] from ethyl benzoylacetate and aniline *via* the anil; m.p. 259–260°[17]; infrared bands at 1633, 1597, 1581, 1545, 1507, 1472, 1415, 1380, 1358, 1320, 1255, 1190, 1142 and 1102 cm.$^{-1}$.

cis-o-Nitrobenzalacetophenone oxide, 0.8 g., was dissolved in 60 ml. of ethyl acetate and shaken with 0.2 g. of Raney nickel for two hours under three atm. of hydrogen. A 47.4% yield of 2-phenyl-3-hydroxyquinoline, m.p. 217–219°, resulted as shown by a mixed m.p. experiment with the authentic material. Even after six hours of shaking with hydrogen at three atm. 24% of the starting material remained unchanged, but the amount of 2-phenyl-3-hydroxyquinoline isolated was increased to 58%. No reduction was observed when dioxane was used as a solvent and the above conditions were otherwise unchanged.

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(15) Microanalysis by the Clark Microanalytical Laboratory, Urbana, Ill.

(16) W. Dilthey and O. Thelen, *Ber.*, **58**, 1588 (1925).

(17) C. E. Kaslow and W. R. Lawton, THIS JOURNAL, **72**, 1723 (1950).