[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Epoxy Ketones. VI.[1] Stereochemistry of 2-(*p*-Substituted Benzal)-4,4-dimethyl-1-tetralone Oxides

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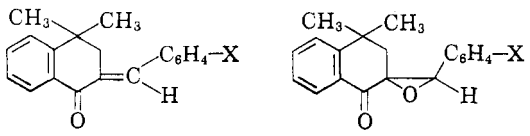
The synthesis of spiroepoxy ketones in the 4,4-dimethyl-2-benzal-1-tetralone oxide series has been extended to include examples with strong electron donating groups (+R) in the benzal-phenyl nucleus, employing either epoxidation of the corresponding 2-benzal-4,4-dimethyl-1-tetralone or a Darzens type condensation of 2-bromo-4,4-dimethyl-1-tetralone and an aromatic aldehyde. The ultraviolet and infrared spectra of these new compounds are reported in connection with a discussion of their stereostructures and conjugation factors. 2-(*p*-Nitrobenzal)-4,4-dimethyl-1-tetralone oxide was found to react with anhydrous hydrogen chloride to produce 2-chloro-2-(α-hydroxy-*p*-nitrobenzyl)-4,4-dimethyl-1-tetralone through a ring cleavage involving inversion at the 2-position. 2-Benzoyl-1-tetralone reacts with phenylhydrazine to give 1,3-diphenylnaphtho(1,2-pyrazole) isomeric with 2,3-diphenylnaphtho(1,2-pyrazole) obtained previously from the phenylhydrazine reaction of 2-benzal-1-tetralone oxide. The spiro-epoxide ring has been found to be resistant to attack by basic nucleophiles.

In an earlier publication[2] the synthesis, absorption spectra and a study of ring cleavage reactions for a series of spiroepoxy ketones was reported. Included in the earlier series were 2-(*p*-chlorobenzal), 2 - (*p* - nitrobenzal) - and 2 - (*m* - nitrobenzal)-4,4-dimethyl-1-tetralone oxide. The series has now been extended to include examples with strong electron donating (+R) groups in the benzal-phenyl nucleus to learn if the reactivity of the three-ring is altered. It was also of interest to determine, spectroscopically, if the conjugative effect of these +R groups is transmitted *via* the benzene ring through the three-ring to the carbonyl group. 2 - (*p* - Methyl -), 2 - (*p* - methoxy-), and 2-(*p*-dimethylaminobenzal) - 4,4 - dimethyl - 1 - tetralone (I, II, III) were prepared in good yields by the base catalyzed condensation of 4,4-dimethyl-1-tetralone with the corresponding substituted benzaldehydes.



I X. *p*-CH_3 IV
II X. *p*-OCH_3 V
III X. *p*-$N(CH_3)_2$ VI
X. *m*-Cl VII

2-(*p*-Methyl-) and 2-(*p*-methoxybenzal)-4,4-dimethyl-1-tetralone oxide (IV, V) were prepared by the epoxidation of the α,β-unsaturated ketones I and II, respectively. A Darzens type condensation of 2-bromo-4,4-dimethyl-1-tetralone with the corresponding substituted benzaldehyde was used to prepare 2-(*p*-dimethylamino-), 2-(*m*-chlorobenzal) - 4,4 - dimethyl - 1 - tetralone oxide (VI, VII), and V.

trans-Chalcone oxide[3] has been shown to react readily with heterocyclic secondary amines by an SN2 type of attack at the β-carbon of the three-ring to produce β-amino-α-hydroxy ketones. The three-ring in 2-benzal-4,4-dimethyl-1-tetralone oxide and the *m*-nitro and *p*-chloro derivatives was shown to be completely resistant to cleavage by various amines.[2] It has now been found that 2-(*p*-nitrobenzal)-4,4-dimethyl-1-tetralone oxide[2] and spiroepoxy ketone V also fail to react even on refluxing with piperidine. Apparently the ring carbons in these three-ring compounds are sterically hindered and an SN2 attack by a large nucleophile is quite difficult if not impossible, regardless of the presence of various types of groups in the benzal phenyl nucleus.

The reaction of α,β-epoxy ketones with hydrogen chloride has been shown to yield α-hydroxy-β-chloro ketones in most instances,[4,5] and 2-benzal-4,4-dimethyl-1-tetralone oxide has been shown to react in this manner.[1,2]

In the present investigation 2-(*p*-nitrobenzal)-4,4-dimethyl-1-tetralone oxide[2] reacted with anhydrous hydrogen chloride in absolute ethanol to produce a chlorohydrin ketone VIII, whose infrared spectrum showed no evidence of intramolecular hydrogen bonding of the hydroxyl group with the carbonyl.[6] Reversal of direction of ring opening with hydrogen chloride in the styrene oxide series when an electron attracting group is present in the benzene ring has been shown by other investigators.[7] When the chlorohydrin ketone VIII was treated with base the epoxide ring closed

(1) For paper V in this series, see N. H. Cromwell and R. E. Bambury, *J. Org. Chem.*, **26**, 997 (1961).

(2) N. H. Cromwell, R. E. Bambury, and R. P. Barkley, *J. Am. Chem. Soc.*, **81**, 4294 (1959).

(3) N. G. Barker and N. H. Cromwell, *J. Am. Chem. Soc.*, **73**, 1051 (1951).

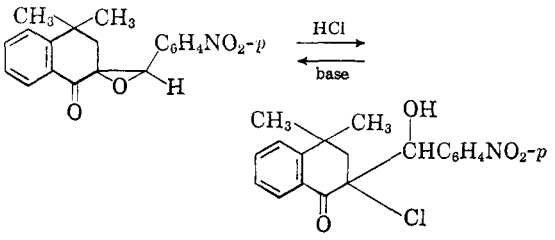
(4) H. H. Wasserman and N. E. Aubrey, *J. Am. Chem. Soc.*, **78**, 1726 (1956).

(5) H. O. House, *J. Org. Chem.*, **21**, 1306 (1956).

(6) It has been shown in several instances, see Ref. 1, that α-hydroxytetralones show intramolecular hydrogen bonding.

(7)(a) F. Arndt, B. Eistert, and W. Partale, *Ber.*, **61**, 1107 (1928). (b) R. Fuchs and C. A. VanderWerf, *J. Am. Chem. Soc.*, **76**, 1631 (1954).

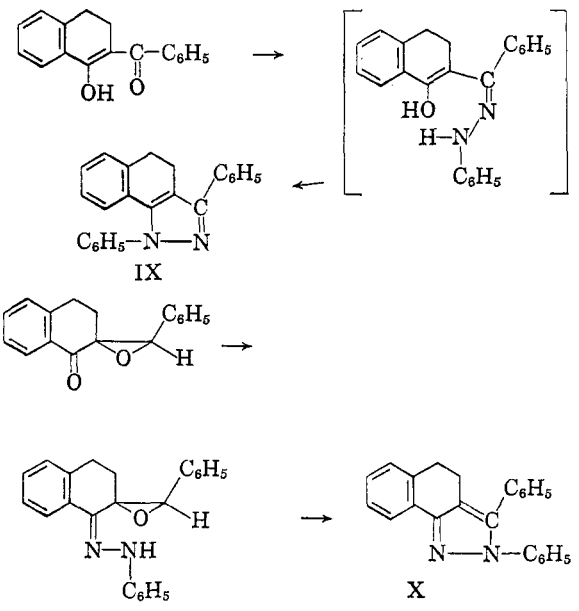
to give a near quantitative yield of the 2-(*p*-nitrobenzal)-4,4-dimethyl-1-tetralone oxide of the same configuration (presumably the *trans* configuration[2]) as the precursor of the chlorohydrin. House[5] has shown that *trans* chalcone oxide will produce both *erythro* and *threo* chlorohydrins and that the *erythro* chlorohydrin reproduces the *trans* chalcone oxide on treatment with base while the *threo* form does not give back an oxide. Our findings described above suggest that the chlorohydrin ketone VIII is *erythro*-2-chloro-2-(α-hydroxy-*p*-nitrobenzyl)-4,4-dimethyl-1-tetralone which is formed from the epoxy ketone by a reaction with hydrogen chloride involving inversion at the 2-position.



VIII

We have reported[2] that 2-benzoyl-4,4-dimethyl-1-tetralone reacts with phenylhydrazine to produce 5,5 - dimethyl - 1,3 - diphenylnaphtho(1,2 - pyrazole). The structure was tentatively assigned to the pyrazole on the basis of analysis, the ultraviolet absorption spectrum, the assumed structure of the diketone enol, and the expected course of the reaction.[8,9] It was expected that the reaction of phenylhydrazine with 2-benzal-4,4-dimethyl-1-tetralone oxide or 2-hydroxy-2-(α-chlorobenzyl)-4,4-dimethyl-1-tetralone would give the isomeric 5,5-dimethyl - 2,3 - diphenylnaphtho(1,2 - pyrazole). Unfortunately it has not been possible to realize these latter two reactions with phenylhydrazine. Reaction appears to be sterically inhibited by the *gem*-dimethyl groups shielding the ring carbonyl group from attack. However 2-benzal-1-tetralone oxide does react with phenylhydrazine to produce a pyrazole which has been assigned[2] the structure, 2,3-diphenylnaphtho(1,2-pyrazole) (X). An isomeric pyrazole, presumably 1,3-diphenylnaphtho-(1,2-pyrazole) (IX), has now been obtained by the reaction of 2-benzoyl-1-tetralone with phenylhydrazine. These pyrazoles all show the expected ultraviolet spectra for such structures.[2] These results lend some support to the assignment of the 5,5 - dimethyl - 1,3 - diphenylnaphtho(1,2 - pyrazole) structure to the phenylhydrazine reaction product of 2-benzoyl-4,4-dimethyl-1-tetralone.[2]

To determine whether or not the carbonyl group had a critical inhibiting effect on the reaction of the 2-benzal-4,4-dimethyl-1-tetralone oxides with



amines, two epoxy alcohols were refluxed with morpholine. Neither 1-hydroxy-2-benzaltetralin oxide[1] nor 1-hydroxy-2-benzal-1,4,4-trimethyltetralin oxide[1] showed any tendency to undergo a ring cleavage. It would appear that the three-ring carbons in all of these spiroepoxy compounds (ketones and alcohols) are sterically inhibited to nucleophilic attack at the ring carbon atoms by organic bases.

Absorption spectra, stereostructure, ana conjugation. A comparison of the ultraviolet spectra of the α,β-unsaturated ketones I, II, and III with those of *trans*-chalcone and *trans*-2-benzal-4,4-dimethyl-1-tetralone[10] clearly indicates these new compounds have *trans* configurations. The cinnamoyl chromophore is extended by resonance with the electron donating groups and bathochromic shifts of 19 mμ for the *p*-methyl, 36 mμ for the *p*-methoxy and 91 mμ for the *p*-dimethylamino groups were observed. The high intensity of the cinnamoyl band is a characteristic of *trans*-chalcones.[10,11]

The ultraviolet spectra of the four new 2-(substituted benzal)-4,4-dimethyl-1-tetralone oxides (IV, V, VI, and VII) indicate that they all have *trans* configurations and that the three-ring is conjugated to a certain extent with the carbonyl group. This is implied by the shift of the benzoyl band from about 250 mμ for the saturated derivative, 2-benzyl - 4,4 - dimethyl - 1 - tetralone,[10] to near 260 mμ for the epoxy ketones IV, V, VI, VII, and 2 - benzal - 4,4 - dimethyl - 1 - tetralone oxide.[10] The mere presence of an oxygen atom in the 2-position of 2-benzyl-1-tetralones is not a sufficient circumstance to cause these bathochromic shifts of 10 mμ. 2-Hydroxy-2-benzyl-4,4-dimethyl-1-

(8) N. H. Cromwell and G. D. Mercer, *J. Am. Chem. Soc.*, 79, 3819 (1957).
(9) S. Bodfors, *Ber.*, 49, 2795 (1916).
(10) A. Hassner and N. H. Cromwell, *J. Am. Chem. Soc.*, 80, 893 (1958).
(11) H. H. Szmant and A. J. Basso, *J. Am. Chem. Soc.*, 74, 4397 (1952).

tetralone has its maximum absorption band (benzoyl) at 250 mμ.[1]

In a previous article[12] it has been reported that ultraviolet spectra studies indicate that the introduction of a *p*-methoxy group into *trans*-chalcone oxide has little effect on the benzoyl chromophore. The present studies with these spiroepoxy ketones indicate that electrical effects of groups present on the benzal-phenyl nucleus do not result in a bathochromic shift of the benzoyl maxima in these cross conjugated systems. In the case of epoxy ketone VI the increased intensity of absorption in the 260-mμ area is probably not to be ascribed to transmission of an electrical effect by the *p*-dimethylamino group to the benzoyl grouping *via* the three-ring since this group also greatly increases the absorption of 2-(*p*-dimethylaminobenzyl) - 4,4 - dimethyl - 1 - tetralone in this area of the spectrum.

The infrared carbonyl stretching vibrations for the 2-(substituted benzal)-4,4-dimethyl-1-tetralones I, II, and III resulted in single absorption bands between 1670 and 1673 cm.$^{-1}$ The position of these bands supports the assignment of an exocyclic α,β-unsaturated ketone structure to these compounds.[10] The constancy of position of the carbonyl maxima for the three unsaturated ketones is expected since conjugation beyond the vinyl group in aryl vinyl ketones has little effect on the carbonyl stretching vibration.[13]

The position of the single infrared carbonyl maxima for the four spiroepoxy ketones IV, V, VI, and VII between 1692 and 1696 cm.$^{-1}$ indicates that in the ground state there is no three-ring carbonyl hyperconjugation[12] with these compounds. In fact the introduction of the three-ring causes a shift of the carbonyl maximum to a higher frequency (2-benzyl-4,4-dimethyl-1-tetralone absorbs at 1686 cm.$^{-1}$). This shift has been ascribed to a reduction in coplanarity between the carbonyl and the adjacent aromatic ring caused by a bond-angle distortion to accommodate the spiroepoxide ring.[10] It is also possible that a dipole-dipole interaction between the carbonyl bond and the α-carbon–oxygen bond may be partially responsible for the elevated frequency.[12]

EXPERIMENTAL[14]

2-(Substituted benzal)-4,4-dimethyl-1-tetralones. These α,β-unsaturated ketones were prepared by the method of Rapson and Shuttleworth[15] using 4,4-dimethyl-1-tetralone[16] and the substituted benzaldehydes.

2-(p-Methylbenzal)-4,4-dimethyl-1-tetralone (I). This colorless compound was obtained in 89% yield, m.p. 92–94°, recrystallized from methanol and water; λ_{max} 238, 265, 326 mμ (ε, 12,600, 9800, 14,900); $\gamma_{C=O}$, 1673/80, γ_{Aro-C}, 1610/80.[21]

Anal. Calcd. for $C_{20}H_{20}O$: C, 86.92; H, 7.29. Found: C, 86.80; H, 7.83.

2-(p-Methoxybenzal)-4,4-dimethyl-1-tetralone (II). Ketone II, was obtained in 96% yield, m.p. 133–135°, recrystallized from benzene and hexane; λ_{max} 250, 343 mμ (ε,14,800, 16,900); $\gamma_{C=O}$, 1670/80, γ_{Aro-C}, 1605/85, γ_{CH_3O-Ar}, 1255/65.

Anal. Calcd for $C_{20}H_{20}O_2$: C, 82.15; H, 6.89. Found: C, 82.03; H, 6.85.

2-(p-Dimethylaminobenzal)-4,4-dimethyl-1-tetralone (III). This orange colored compound was obtained in 85% yield, m.p. 191–193°, recrystallized from dioxane and water; λ_{max} 272, 398 mμ (ε, 18,900, 25,000); infrared spectrum with 5 mg./ml. carbon tetrachloride $\gamma_{C=O}$, 1670/55, γ_{Aro-C} 1600/70.

Anal. Calcd. for $C_{21}H_{23}NO$: C, 82.58; H, 7.59. Found: C, 82.70; H, 7.69.

2-(Substituted benzal)-4,4-dimethyl-1-tetralone oxides. These epoxy ketones were prepared by the direct epoxidation[17] of the corresponding benzaltetralone, method A, or by a Darzens condensation[1,10] of 2-bromo-4,4-dimethyl-1-tetralone with the respective substituted benzaldehyde, method B.

2-(p-Methylbenzal)-4,4-dimethyl-1-tetralone oxide (IV), method A, 73% yield, m.p. 120–121.5°, recrystallized from acetone and water; λ_{max} 260 mμ (ε, 15,600), $\gamma_{C=O}$, 1694/90, γ_{Ar}, 1600/50.

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.15; H, 6.89. Found: C, 82.09; H, 6.88.

2-(p-Methoxybenzal)-4,4-dimethyl-1-tetralone oxide (V), method A, 93% yield and method B, 75% yield, m.p. 130–131°, recrystallized from benzene and hexane; λ_{max} 228, 260, 270 sh. mμ (ε, 12,500, 14,600, 10,000); $\gamma_{C=O}$ 1692/85, γ_{Ar}, 1610/60, γ_{CH_3OAr}, 1250/60.

Anal. Calcd. for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.73; H, 6.57.

2-(p-Dimethylaminobenzal)-4,4-dimethyl-1-tetralone oxide (VI). Attempts to prepare this epoxy ketone by method A returned the starting ketone III. Method B produced the desired product in 81% yield, m.p. 163–165°, recrystallized from benzene and hexane; λ_{max} 285, 292 sh. mμ (ε, 26,700, 5900); infrared spectrum with 5 mg./ml. CCl_4, $\gamma_{C=O}$, 1693/25, γ_{Ar}, 1610/15.

Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21. Found: C, 78.53; H, 7.84.

2-(m-Chlorobenzal)-4,4-dimethyl-1-tetralone oxide (VII), method B, 80% yield, m.p. 176–177°, recrystallized from benzene and hexane; λ_{max} 259, 300 sh. mμ (ε, 16,400, 2000); $\gamma_{C=O}$, 1696/75, γ_{Ar}, 1603/65.

Anal. Calcd. for $C_{19}H_{17}ClO_2$: C, 72.96; H, 5.48. Found: C, 72.98; H, 5.40.

Ring cleavage reactions of spiroepoxy ketones. 1. *With piperidine,* neither epoxy ketone V nor 2-(*p*-nitrobenzal)-4,4-dimethyl-1-tetralone oxide[2] gave any ring cleavage even after refluxing for 8 hr.

2. *With dry hydrogen chloride,* 2-(*p*-nitrobenzal)-4,4-dimethyl-1-tetralone oxide[2] reacted at room temperature after standing for 10 days in absolute ethanol to give an 87% yield

(12) N. H. Cromwell, F. H. Schumacher, and J. L. Adelfang, *J. Am. Chem. Soc.*, **83**, 974 (1961).

(13) N. H. Cromwell *et al.*, *J. Am. Chem. Soc.*, **71**, 3337 (1949).

(14) Melting points are corrected. The ultraviolet spectra were determined between 200 and 400 mμ with a Cary ultraviolet recording spectrophotometer, model 11MS, employing matched 1-cm. fused silica cells and 10^{-4} molar methanol solutions of the compounds. The measurements of the infrared spectra were determined with a Perkin-Elmer model 21 double-beam recording spectrophotometer employing sodium chloride optics over a frequency range of 4000 to 600 cm.$^{-1}$ using 10 mg./ml. carbon tetrachloride solutions (unless otherwise indicated) and matched 1-mm. sodium chloride cells and recorded as γ, cm.$^{-1}$/approximate relative % absorption.

(15) W. S. Rapson and R. G. Shuttleworth, *J. Chem. Soc.*, 636 (1940).

(16) V. L. Bell and N. H. Cromwell, *J. Org. Chem.*, **23**, 789 (1958).

(17) E. Weitz and A. Scheffer, *Ber.*, **54**, 2327 (1921).

of *2-chloro-2-(α-hydroxy-p-nitrobenzyl)-4,4-dimethyl-1-tetralone* (VIII), m.p. 188–189°, recrystallized from benzene and methanol; λ_{max}, 254 mμ (ε, 19,600); infrared spectrum with 5 mg./ml. carbon tetrachloride in a 5 mm. cell, $\gamma_{C=O}$, 1688/65 (1688/60 lithium fluoride optics), γ_{OH}, 3600/20 (3600/15 lithium fluoride optics).

Anal. $C_{19}H_{18}NClO_4$: C, 63.42; H, 5.04; Cl, 9.89. Found: C, 63.63; H, 5.08; Cl, 10.06.

When a 0.36-g. sample of the chlorohydrin VIII was dissolved in 10 ml. of methanol containing 0.1 g. of potassium hydroxide a 97% yield of the 2-(*p*-nitrobenzal)-4,4-dimethyl-1-tetralone oxide was obtained.

Pyrazole formation. 1. *From 2-benzoyl-1-tetralone.* A 1.25-g. (0.05 mole) sample of 2-benzoyl-1-tetralone[18] was mixed with 0.55 g. (0.05 mole) of phenylhydrazine in 10 ml. of 1:1 ethanol-chloroform solution containing 3 drops of glacial acetic acid. After standing at room temperature for 5 hr. a 90% yield of *1,3-diphenylnaphtho(1,2-pyrazole)* (IX), was produced, m.p. 169–171°, recrystallized from benzene and hexane. A mixture of IX and 2,3-diphenylnaphtho(1,2-pyrazole) (X) (m.p.[2] 141–142°) gave m.p. 120–130°. For IX, λ_{max} 257, 270, 280, 300 sh. mμ (ε, 20,000, 20,000, 19,600, 12,000).

Anal. Calcd. for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 86.06; H, 5.64; N, 8.44.

2. Attempts to obtain a pyrazole derivative from the reaction of phenylhydrazine with 2-benzal-4,4-dimethyl-1-tetralone oxide[10] or 2-hydroxy-2-(α-chlorobenzyl)-4,4-dimethyl-1-tetralone[2] returned only starting materials even after refluxing in chloroform solution containing a few drops of acetic acid.

Attempted reaction of 1-hydroxy-2-benzal-tetralin oxide[2] and 1-hydroxy-2-benzal-1,4,4-trimethyltetralin oxide[2] with morpholine. Refluxing these spiroepoxy alcohols with morpholine for 2 hr. returned only the starting materials.

2-(p-Dimethylaminobenzyl)-4,4-dimethyl-1-tetralone. At atmospheric pressure, in the presence of 0.15 g. of Adams catalyst, a solution of 2.0 g. (0.0065 mole) of 2-(*p*-dimethylaminobenzal)-4,4-dimethyl-1-tetralone in 175 ml. of benzene absorbed 0.0057 mole of hydrogen after stirring for 15 hr. After filtration and removal of the solvent the resulting solid was crystallized from ethyl acetate and methanol providing 1.7 g. (85%) of 2-(*p*-dimethylaminobenzyl)-4,4-dimethyl-1-tetralone, m.p. 126.5–129.5°. An analytical sample was prepared by crystallization from methanol, m.p. 128.5–130°; ultraviolet (methanol) λ_{max} 252 and 292 mμ (ε, 26,600, 3620); infrared (carbon tetrachloride) $\gamma_{C=O}$ band, 1691 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.20; H, 7.84; N, 4.46.

Acknowledgment. This investigation was supported in part by a grant from the National Cancer Institute, U. S. Public Health Service, CY 2931.

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(18) C. R. Hauser *et al.*, *J. Am. Chem. Soc.*, 69, 2649 (1947).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Studies of Configuration. IX. The Preparation and Stereochemical Characterization of Some Alkyl-3-hydroxycyclohexanecarboxylic Acids[1,2]

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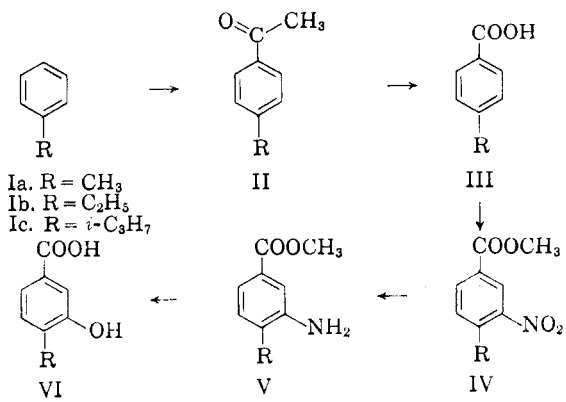
The synthesis of a series of 4-alkyl-3-hydroxycyclohexanecarboxylic acids has been carried out. The all *cis* isomers have been characterized, as well as the corresponding lactones. *trans*-5-Methyl-*cis*-3-hydroxycyclohexanecarboxylic acid and its lactone have been prepared, as well as *cis*-2-methyl-*cis*-3-hydroxycyclohexanecarboxylic acid and the corresponding lactone.

In connection with a quantitative study of the γ-lactone hydroxy acid equilibrium to be discussed in the succeeding paper[4] we have examined the preparation of a variety of alkyl substituted 3-hydroxycyclohexanecarboxylic acids. Our efforts have been directed toward the stereochemical isomers in which the hydroxyl group and carboxyl group are *cis*. In this study we have clarified the stereochemical assignments of several previously reported compounds.

The first group of compounds desired for our study was the 4-alkyl-3-hydroxycyclohexanecarboxylic acids. Chart I summarizes the preparation of 4-methyl-3-hydroxybenzoic acid, 4-ethyl-3-hydrobenzoic acid, and 4-isopropyl-3-hydroxybenzoic acid. The Friedel-Crafts acetylation, hypohalite oxidation, nitration, reduction, and diazotization steps have been reported previously for one or more of the compounds investigated. With attention to the appropriate modification of experimental



(1) Supported in part by the National Science Foundation, G-2387, G-5921.

(2) Presented in part at the 136th Meeting of the American Chemical Society, Atlantic City, September 1959.

(3) Dow Chemical Corp. Fellow, 1958–59.

(4) D. S. Noyce and L. J. Dolby, *J. Org. Chem.*, 26, in press.