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1,3-Elimination–Rearrangement of 2-Acetoxy-6-bromocyclohexanones

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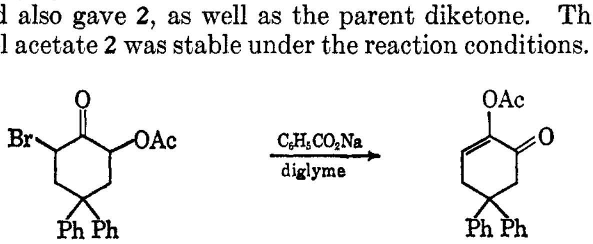
Several additional examples are given to show that the keto–enol acetates (or benzoates) formed by the reaction of *cis*-2,6-dibromocyclohexanones and sodium acetate arise by (a) displacement of bromine to form a *cis*-2-acetoxy-6-bromocyclohexanone, and (b) 1,3-elimination of hydrogen bromide accompanied by acyl migration. Evidence is presented to show that acyl migration does not precede loss of bromide ion. Proton magnetic resonance spectroscopy was used to establish the structures of the resulting keto–enol carboxylates.

In a previous paper[2] we described a new base-catalyzed elimination rearrangement of *cis*-2-acetoxy-6-bromo-4,4-dimethylcyclohexanone in which the overall result was elimination of hydrogen bromide from the 2- and 6-positions (1,3-elimination) accompanied by intramolecular migration of the acyl group from the 2- to the 1-position. We now wish to report some additional examples of this reaction.

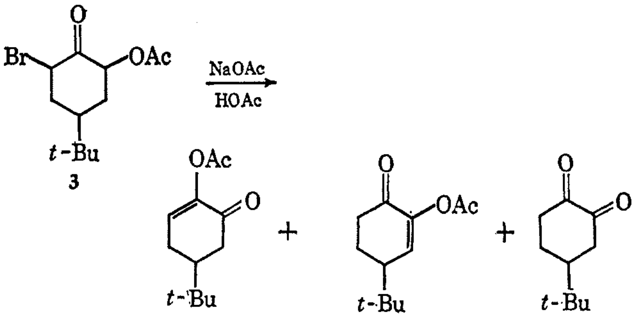
cis-2-Acetoxy-6-bromo-4,4-diphenylcyclohexanone (**1**) was found to undergo the elimination–rearrangement reaction to give 2-acetoxy-5,5-diphenylcyclohex-2-enone (**2**). A 58% yield of **2** was obtained using fused sodium acetate in acetic acid. (No reaction occurred in the absence of the base.) An 82% yield was obtained using sodium benzoate in bis(2-methoxyethyl) ether (diglyme). The latter result provides further evidence for the intramolecular nature of the acyl migration.[2] Reaction of *cis*-2,6-dibromo-4,4-diphenylcyclohexanone with sodium acetate in acetic acid also gave **2**, as well as the parent diketone. The enol acetate **2** was stable under the reaction conditions.



1 **2**

The structure of **2** was assigned on the basis of its pmr and infrared spectra (see Table I). This structure assignment was confirmed by reduction of the C=C bond in **2**. The resulting dihydro derivative was shown to be identical with a compound prepared by reaction of 3,3-diphenylcyclohexanone with lead tetraacetate and to be different from the isomeric compound prepared by the reaction of lead tetraacetate with 4,4-diphenylcyclohexanone.

The reaction of *cis,cis*-2-acetoxy-6-bromo-4-*t*-butylcyclohexanone (**3**) with sodium acetate in acetic acid solution gave 2-acetoxy-5-*t*-butylcyclohex-2-enone (**4**, the analog of **2**), 2-acetoxy-4-*t*-butylcyclohex-2-enone (**5**), and 4-*t*-butylcyclohexane-1,2-dione (**6**) in proportions of 38:11:51 (glpc analysis).



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4 (38%) **5** (11%) **6** (51%)

Almost identical proportions of **4**, **5**, and **6** were obtained under comparable conditions, using *cis,cis*-2,6-dibromo-4-*t*-butylcyclohexanone (**7**) in place of **3**. This is further evidence[2] for the intermediacy of acyloxybromocyclohexanones in the reaction starting from 2,6-dibromocyclohexanones. When treated with sodium benzoate in diglyme, **7** gave a 58% yield of the benzoate corresponding to **4**. Application of this latter procedure on a preparative scale to *cis*-2,6-dibromocyclohexanone gave a 70% yield of 2-benzoyloxycyclohex-2-enone; 63% of 2-acetoxycyclohex-2-enone was obtained when sodium acetate in acetic acid–acetic anhydride was employed.

Reaction of **6** with acetic anhydride gave **4** and **5** in a ratio of about 40:60. Since **4** is obtained in the smaller amount, it must be formed from **3** by a different route (see also ref 2). When the reaction of **7** with sodium acetate was carried out under strictly

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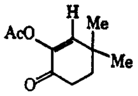
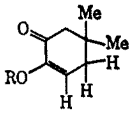
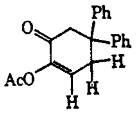
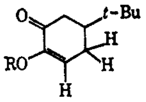
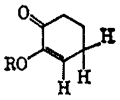
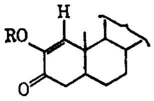
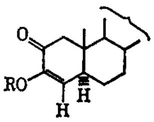
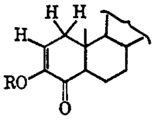
[1] Abstracted from the Ph.D. Dissertation of K. M. Wellman, Northwestern University, June 1963. Eastman Kodak Co. Fellow, 1961–1962.

[2] F. G. Bordwell and K. M. Wellman, *J. Org. Chem.*, **28**, 1347 (1963).

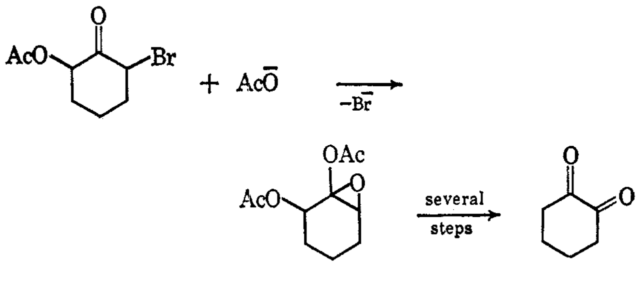
TABLE I

CHARACTERISTIC PMR (60 MC, RELATIVE TO TETRAMETHYLSILANE) AND INFRARED PARAMETERS FOR KETO-ENOL ESTERS

Structure and name	ν, cps (vinylic proton)	M^a	J_{AX}, cps	Infrared bands, μ	
				C=C	C—O—C
					
a: 2-acetoxy-4,4-dimethylcyclohex-2-enone	369	s	. . .	6.05	8.25
					
b: 2-hydroxy-5,5-dimethylcyclohex-2-enone (R = H)	352	t	4.9	. . .	. . .
c: 2-acetoxy-5,5-dimethylcyclohex-2-enone (R = Ac)	379	t	4.3	6.05	8.25
					
d: 2-acetoxy-5,5-diphenylcyclohex-2-enone (2)	394	t	4.4	6.03	8.10
					
e: 2-acetoxy-5-*t*-butylcyclohex-2-enone (R = Ac, 4)	388	Broad multiplet		6.05	8.25
f: 2-benzoyloxy-5-*t*-butylcyclohex-2-enone (R = Bz)	390	Broad multiplet		6.04	7.94
					
g: 2-acetoxycyclohex-2-enone (R = Ac)	383	t	4.0	. . .	. . .
h: 2-benzoyloxycyclohex-2-enone (R = Bz)	387	t	4.0	6.08	7.93
					
i: 2-hydroxycholest-1-en-3-one (R = H, 13)	380	s	. . .	. . .	. . .
j: 2-acetoxycholest-1-en-3-one (R = Ac)	403	s	. . .	6.11	8.31
					
k: 3-hydroxycholest-3-en-2-one (R = H)	339	d	2.0	. . .	. . .
l: 3-acetoxycholest-3-en-2-one (R = Ac)	369	d	1.6	6.08	8.30
m: 3-benzoyloxycholest-3-en-2-one (R = Bz, 11)	375	d	1.6	6.08	7.88
					
n: 3-benzoyloxycholest-2-en-4-one (R = Bz, 12)	390	dd	3.6 4.6	6.03	7.92

[a] The abbreviations for multiplicities are s = singlet, d = doublet, t = triplet, and dd = double doublet.

anhydrous conditions, the ratio **4**:**5**:**6** changed in the manner expected if **6** was formed and acetylated during the reaction. It seems clear from this experiment that **6** is formed even under completely anhydrous conditions. A possible route for the formation of cyclohexane-1,2-diones from 2-acetoxy-6-bromocyclohexanones involves attack by acetate on the carbonyl group.[2] Subsequent ring closure with displacement of bromide would yield the epoxide, which can be visualized as giving rise to the diketone. Hydrogen bonding to the carbonyl in acetic acid solvent might be expected to favor nucleophilic attack at the carbonyl with a corresponding increase in the amount of diketone formed, whereas in an aprotic solvent such as diglyme an increase in the 1,3-elimination–rearrangement product such as **4** could be expected. The increase in yield of **4** to 74% and concurrent decrease of **6** (17%) in diglyme is consistent with such a pathway.

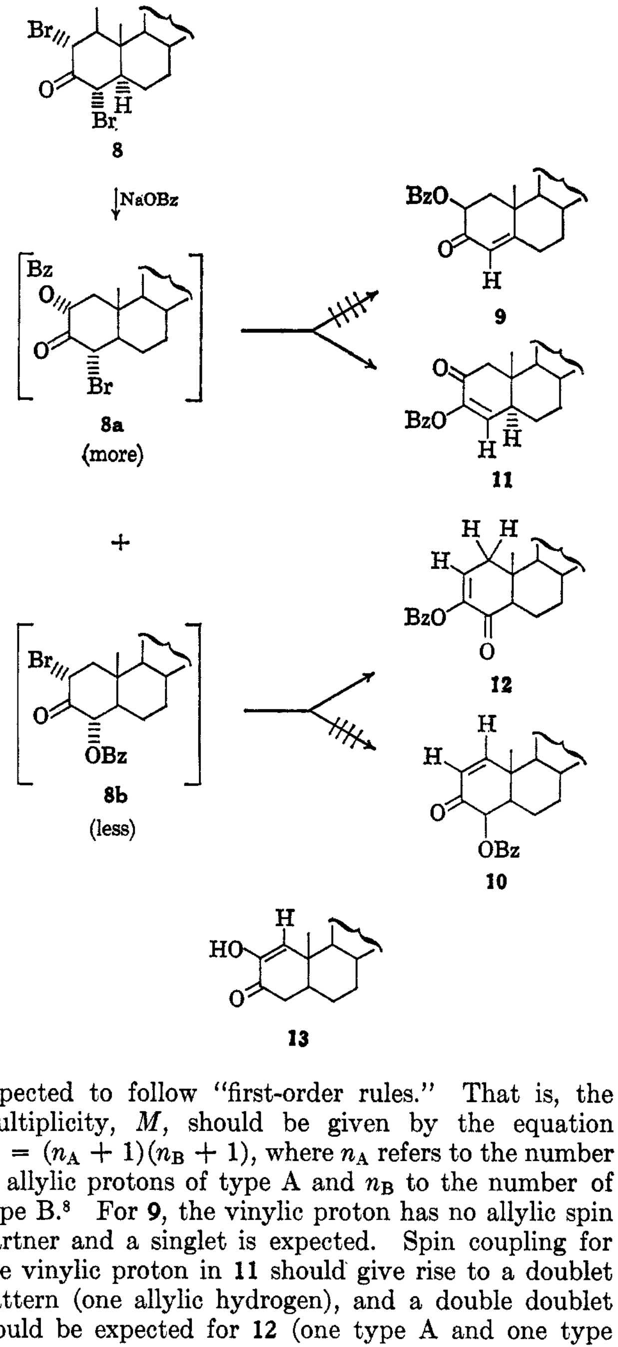


It was of interest to extend the investigation to 2α,-4α-dibromocholestan-3-one (**8**), since Inhoffen[3] found that two unsaturated benzoates are formed in the reaction of **8** with sodium benzoate in butanol–toluene, and tentatively assigned structures **9** and **10** to these products. According to our formulation of the reaction,[2] replacement of the 2- or 4-bromine atoms by an acyloxy group should be followed by elimination–rearrangement, not just elimination, and the products should be **11** and **12** (see Scheme I).

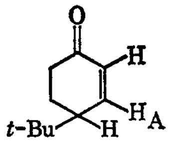
Inhoffen's assignments were based on the formation of cholestane-2,3-dione from his major product,[3,4] and cholestane-3,4-dione from his minor product. The melting point of Inhoffen's major keto–enol benzoate (161–162°) agrees with that of the keto–enol benzoate prepared by Stiller and Rosenheim[5] from "form A" of the two keto–enols of cholestane-2,3-dione obtained on oxidation of cholestan-3-one with selenium dioxide. They tentatively assigned structure **13** to this keto–enol ("form A"), but later Ruzicka, Plattner, and Furrer[6] prepared "form A" by another route and assigned it a structure analogous to **11** on the basis of the reactions of its tosylate. This assignment has now been confirmed by pmr spectra.

A distinction between structures **9**, **10**, **11**, and **12** can be made by examination of the pmr spin-coupling pattern of the vinylic proton. Since there is generally a relatively large chemical shift between vinylic and allylic protons (for example, the chemical shift between these protons in cyclohex-2-en-1-ol is about 200 cps[7]), the interpretation of their spin–spin interactions is expected to follow "first-order rules." That is, the multiplicity, M, should be given by the equation $M = (n_A + 1)(n_B + 1)$, where n_A refers to the number of allylic protons of type A and n_B to the number of type B.[8] For **9**, the vinylic proton has no allylic spin partner and a singlet is expected. Spin coupling for the vinylic proton in **11** should give rise to a doublet pattern (one allylic hydrogen), and a double doublet would be expected for **12** (one type A and one type B allylic proton). Compound **10** has two vinylic protons and each of these should appear as a doublet.[2] Compound **13** will correspond to **9** in type.

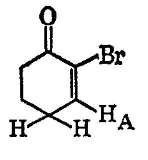
SCHEME I



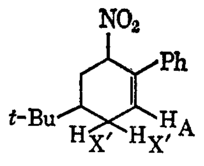
Some idea of the size of the coupling constants to be expected can be gained by considering the coupling constants of a number of related systems shown below.



$J_{AX} \cong 2$ cps (doublet)



$J_{AX} = 4.2$ cps (triplet)



$J_{AX} = 2.3$ cps
$J_{AX'} = 4.6$ cps
(double doublet)[9]

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[3] H. H. Inhoffen, *Ber.*, **70**, 1695 (1937).

[4] He also obtained a small amount of cholestane-3,4-dione, but our results indicate that this arises from contamination of the major benzoate (**11**) by some of the minor benzoate (**12**).

[5] E. T. Stiller and O. Rosenheim, *J. Chem. Soc.*, 353 (1938).

[6] L. Ruzicka, P. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, **27**, 524 (1944).

[7] G. V. D. Tiers, "Tables of T Values for a Variety of Organic Compounds," Minnesota Mining and Manufacturing Co., St. Paul, Minn., Project 737602, 1958.

[8] L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press Inc., New York, N. Y., 1959, p 23.

[9] E. W. Garbisch, Jr., private communication.

Table I summarizes the data obtained for a number of keto–enol acetates and benzoates obtained by elimination–rearrangement reactions described in this and the previous paper.

Examination of Table I shows that the chemical shift for all the vinylic protons covers a reasonably small range of about 370–400 cps. The multiplicities are those expected, except perhaps for e and f, where a broadening of the multiplets occurs. However, this broadening occurs also for the proton α to Br in *cis*-2-bromo-4-*t*-butylcyclohexanone (in contrast to the proton α to Br in *cis*-2-bromo-4-phenylcyclohexanone), and this can be attributed to virtual coupling.[10]

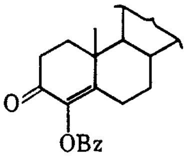
Keto–enol esters have characteristic infrared bands near 5.75 (ester C=O), 5.90 (ketone C=O), 6.05 (C=C), and 8.25–8.31 (C—O) μ. The C=C stretching mode appears at unusually low wavelengths (Table I) compared with that of other α,β-unsaturated alicyclic ketones. For example, Δ^1-3-keto or Δ^4-3-keto steroids have C=C stretching modes at 6.18–6.24 μ.[11] The presence of the 6.05-μ band in combination with the 5.75-, 5.90-, and 8.25–8.31-μ bands is, then, a strong indication of a keto–enol ester grouping. For enol acetates the C-O stretching mode (Table I) appears in the same range as that given by Jones[12] for phenol acetates (8.29–8.32 μ) as contrasted to saturated acetates (8.05–8.09 μ). On the other hand, the enol benzoates have bands below 8.0 μ (Table I) and in the same region as their saturated analogs (the bands for 2-benzoyloxycyclohexanone, *cis*-2,6-dibenzoyloxycyclohexanone, and 1,3-dibenzoyloxypropan-2-one are at 7.87, 7.89, and 7.86 μ, respectively).

The structures of compounds a, b, and c in Table I have been established previously by chemical methods.[2] The structure of d has also been subject to chemical verification (present paper), and that of g and h follow from their mode of preparation. Compounds i and k are the keto–enols of Stiller and Rosenheim[5] ("forms B and A," respectively). The present structure assignments agree with those of Ruzicka, Plattner, and Furrer.[6] Since the structure assignments for these "knowns" in every instance agree with that made from their pmr spectra, the structure assignments made in Table I for the other compounds (e, f, j, l, m, and n) seem secure.

In view of the doublet observed for the vinylic proton of m (**11**), the alternative structure **9**, suggested by Inhoffen,[3] is ruled out. Similarly, the triplet observed for the vinylic proton of n (**12**) rules out the alternative structure **10**.

These structure assignments are consistent with the reaction paths shown (**8** → **8a** → **11** and **8** → **8b** → **12**). The benzoyloxy groups are indicated as having an α configuration by analogy with the formation of *cis*-2-acetoxy-6-bromo-4,4-dimethylcyclohexanone,[2] *cis*-2-acetoxy-6-bromo-4,4-diphenylcyclohexanone (**1**), *cis*,-*cis*-2-acetoxy-6-bromo-4-*t*-butylcyclohexanone (**3**), and *cis*-2,6-dibenzoyloxycyclohexanone from the corresponding *cis*-2,6-dibromocyclohexanones under comparable conditions. The *cis* structure of **1** follows from the large coupling constants of the CHBr and CHOAc (axial) protons.[15] The *cis,cis* structure for **3** and the structure for *cis*-2,6-dibenzoyloxycyclohexanone are less certain, since the α and α' protons in these molecules are virtually coupled,[10] but the width of the signals in both instances indicates that the protons are axial rather than equatorial. No doubt the α-bromo-α'-acetoxycyclohexanones are equilibrated under the experimental conditions. The *cis* isomers are generally more stable and are the products isolated. Further evidence for epimerization under experimental conditions was given by the isolation of some *cis*,-*trans*-2,6-dibromo-4-*t*-butylcyclohexanone from a reaction in which excess **7** reacted with sodium benzoate. In light of this evidence for ready epimerization, it will be difficult to determine the stereochemical preference, if any, of the elimination–rearrangement reaction.

Inhoffen obtained two different isomeric keto–enol benzoates from the reaction of 2,4-dibromocoprostan-3-one with sodium benzoate. The major product gave cholestane-3,4-dione on hydrolysis and was therefore assigned structure **14**. The minor isomer gave an unknown diketone, which Djerassi and Rosenkranz[13] have suggested is coprostane-2,3-dione. If the reaction of 2,4-dibromocoprostan-3-one with sodium benzoate is assumed to follow a course similar to that shown above for **8**, except that displacement at the 4-position predominates over that at the 2-position, the keto–enol benzoates should be **15** and **16**. These products should give coprostane-3,4-dione and coprostane-2,3-dione, respectively, on hydrolysis.



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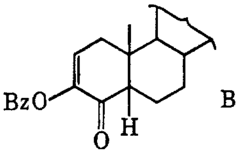

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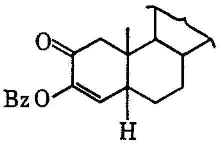

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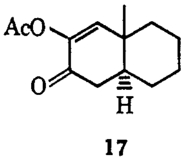
Yanagita and co-workers have found that the 2,4-dibromides of *trans*- and *cis*-9-methyldecalone react with sodium acetate to give keto–enol acetates which were formulated as **17** and **18**, respectively.[14] We would expect **19** and/or **20** from *trans*-9-methyldecalone.



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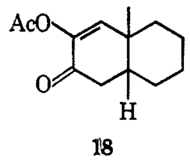

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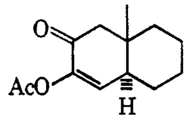

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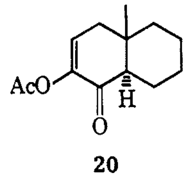

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The acyl migration in the 1,3-elimination–rearrangement was shown previously to be intramolecular,[2] and this was confirmed in the present work (see above).

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[10] J. I. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1962).

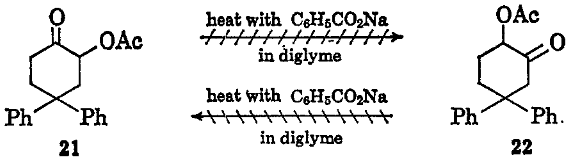
[11] R. N. Jones, P. Humphries, E. Packard, and K. Dobriner, *J. Am. Chem. Soc.*, **72**, 86 (1950).

[12] R. N. Jones, P. Humphries, F. Herling, and K. Dobriner, *ibid.*, **73**, 3215 (1951).

[13] C. Djerassi and G. Rosenkranz, *Experientia*, **7**, 93 (1951).

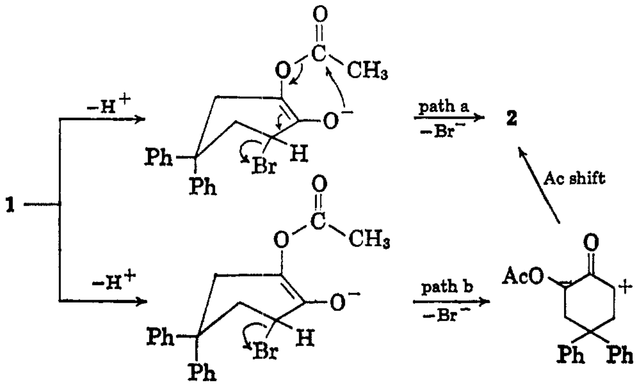
[14] M. Yanagita and A. Tahara, *J. Org. Chem.*, **18**, 792 (1953); M. Yanagita and K. Yamakawa, *ibid.*, **22**, 291 (1957).

Both of the mechanisms proposed earlier[2] assume proton removal as an initial step; they differ only in the order of subsequent steps. Either (a) acyl migration *precedes* loss of bromide ion; (b) acyl migration is subsequent to loss of bromide ion; or (c) the two occur simultaneously. If acyl migration precedes loss of bromide ion, one might expect that acyl migration would occur with 2-acyloxycyclohexanones. However, no rearrangement occurred when either 2-acetoxy-4,4-dimethylcyclohexanone (21) or 2-benzoyloxy-4,4-diphenylcyclohexanone was subjected to reaction conditions leading to elimination–rearrangement, nor was it possible to rearrange 22 to 21 under these conditions.[15]



The failure of either of these transformations to occur is evidence against the mechanism in which acyl migration precedes loss of bromide ion and suggests that removal of bromine is involved in the rate-determining step. It seems likely then that the first step is a rapid proton removal and that this is followed either by a concerted acyl migration and expulsion of bromide ion (path a), or loss of bromide ion followed by acyl migration (path b). (Another variation of path b is to assume a concerted 1,3-elimination of a proton and a bromide ion.) The formation of the dipolar ion by path b is analogous to one of the mechanisms suggested for the Favorskii reaction.[16] (See Scheme II.

SCHEME II



Interestingly enough, the benzoyloxy group can also serve as a leaving group, since 2,6-dibenzoyloxycyclohexanone reacts with sodium benzoate in diglyme to give 2-benzoyloxycyclohex-2-enone.

Experimental Section[17]

***cis*-2-Acetoxy-6-bromo-4,4-diphenylcyclohexanone** (1).—*cis*-2,6-Dibromo-4,4-diphenylcyclohexanone[18] (4.9 g., 0.012 mole), sodium acetate (1.2 g, 0.015 mole), and 30 ml of diglyme were stirred at 52° for 11.5 hr. The mixture was then poured into water and the precipitate was dissolved in ether. The ethereal solution was washed with 5% sodium bicarbonate, dried, and concentrated under reduced pressure to yield an oil, which solidified when triturated with alcohol. The solid was dissolved in 5 ml of benzene, adsorbed onto a 4 × 65 cm column, slurry packed with silica gel, and eluted with 15% ether in hexane. Fraction 1 (4 l, 15% ether) gave 1.77 g (0.0043 mole) of starting material, mp 174–175°, identified by infrared analysis. Fraction 2 (2 l, 20% ether) gave a noncrystalline material which was discarded. Fraction 3 (1 l, 20% ether) and 4 (2 l, 30% ether) were combined to give 1.62 g (0.0042 mole or 35%) of 1, mp 127–128°. A portion of this was recrystallized from ethanol for an analytical sample: mp 129–130°; λ_{max}^{KBr} 5.72, 8.10, 13.3, 14.2 μ; pmr (CCl_4), C*H*Br, δ 4.72 (triplet, J_{aa} = 13.4 cps, J_{ae} = 5.2 cps), and C*H*OAc, δ 5.20 (triplet, J_{aa} = 12.5 cps, J_{ae} = 5.7 cps).

Anal. Calcd for $C_{20}H_{19}BrO_3$: C, 62.02; H, 4.95. Found: C, 62.70; H, 4.92.

Reaction of *cis*-2-Acetoxy-6-bromo-4,4-diphenylcyclohexanone (1) with Sodium Acetate.—A mixture of 0.10 g (0.25 mmole) of 1, 0.10 g (1.2 mmoles) of sodium acetate (fused in the reaction vessel), and *ca.* 2 ml of glacial acetic acid (distilled directly into the reaction vessel) was heated at 99–100° (bath temperature) for 3 hr. The reaction mixture was then cooled and poured into a mixture of 50 ml of water and 50 ml of ether. Solid sodium bicarbonate was added to remove the acetic acid. The organic layer was dried and concentrated to yield 0.044 g (0.15 mmole, 58%) of ether-insoluble keto–enol acetate, mp 173–176°, identified as 2 by comparing its infrared spectrum with that of a pure sample prepared as described below. A reaction run under comparable conditions, except that the sodium acetate was omitted, gave only starting material.

2-Acetoxy-5,5-diphenylcyclohex-2-enone (2).—Under conditions similar to those just described, *cis*-2,6-dibromo-4,4-diphenylcyclohexanone gave 27% of 2: mp 179–181°; λ_{max}^{KBr} 5.69, 5.90, 6.03, 8.10, 8.88, 10.85, 13.2, 13.4, 14.2 μ.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.18, H, 6.00.

The ethereal mother liquor was diluted with 10 ml more of ether and was extracted with 50 ml of 3% sodium hydroxide. The aqueous solution was neutralized with dilute hydrochloric acid and washed with 50 ml of ether, and the ethereal solution was concentrated to give 0.24 g (0.9 mmole, 38%) of a viscous oil which solidified (mp 137–140°) when triturated with a small amount of ether. Recrystallization from ether–hexane gave **4,4-diphenyl-1,2-cyclohexanedione** as yellow-tinged prisms: mp 137–139°; λ_{max}^{KBr} 3.01, 6.01, 6.70, 7.12, 8.10, 11.00, 13.35, 14.5 μ.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.69; H, 6.21.

A mixture of 1 (0.48 g, 0.0012 mole), sodium benzoate (0.72 g, 0.005 mole), and 10 ml of diglyme, when stirred at 105–110° (bath temperature) for 3 hr, gave 0.3 g (0.001 mole, 82%) of 2, mp 174–177°.

2 was recovered (85%) unchanged when heated at 100° for 2 hr with fused sodium acetate and glacial acetic acid.

2-Acetoxy-5,5-diphenylcyclohexanone.—A mixture of 2-acetoxy-5,5-diphenylcyclohex-2-enone (0.09 g, 0.3 mole), 0.014 g of 10% palladium on carbon, and 10 ml of absolute alcohol was stirred magnetically under 2 atm of hydrogen for 5.5 hr, (the reaction was incomplete in 3.5 hr). The mixture was then diluted with 25 ml of acetone, filtered, and concentrated to give 0.0612 g of a glassy solid. Ether (3 ml) was added and the solution was decanted from the small amount of insoluble solid. Evaporation of the ether and recrystallization from hexane gave colorless crystals: mp 129–132°; λ_{max}^{KBr} 5.74 (s), 5.82 (s), 6.63 (m), 6.90 (m), 7.26 (m), 8.08 (s), 8.35 (w), 9.28 (s, br), 9.47 (sh), 9.62 (w), 11.10 (w), 13.20 (s), 14.30 (s) μ.

Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 78.19; H, 6.80.

This compound was found to be identical with a sample prepared by the reaction of 3,3-diphenylcyclohexanone with lead tetracetate according to the general procedure of Cavill and Soloman.[19,20]

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[15] K. L. Williamson and W. S. Johnson [*J. Org. Chem.*, **26**, 4563 (1961)] found that 2α-acetoxycholestan-3-one is not rearranged by potassium acetate (presumably in acetic acid), although rearrangement did occur with tetramethylammonium acetate.

[16] See the discussions by A. W. Fort, *J. Am. Chem. Soc.*, **84**, 2620 (1962), and H. O. House and W. F. Gilmore, *ibid.*, **83**, 390 (1961).

[17] Microanalyses were by Miss Hilda Beck or Micro-Tech Laboratories, Skokie, Ill. Further experimental details may be found in the Ph.D. Dissertation of K. M. Wellman, Northwestern University, June 1963.

[18] F. G. Bordwell and K. M. Wellman, *J. Org. Chem.*, **28**, 2544 (1963).

[19] G. N. K. Cavill and D. H. Soloman, *J. Chem. Soc.*, 4426 (1955).

[20] R. Frame, unpublished results.

2-Acetoxy-4,4-diphenylcyclohexanone.—Following the general procedure of Cavill and Soloman,[19] a mixture of 6.1 g (0.024 mole) of 4,4-diphenylcyclohexanone,[18] 12.5 g (0.03 mole) of dry lead tetracetate, and 27 ml of dry benzene was heated at 71–73° (bath temperature) for 24 hr. Chromatography on silica gel and crystallization gave 4.0 g of solid, mp 116–117°. Recrystallization from ether gave pure 2-acetoxy-4,4-diphenylcyclohexanone as prisms: mp 118–118.5°; $\lambda_{\max}^{\mathrm{KBr}}$ 5.75 (s), 5.82 (s), 8.10 (s), 8.45 (w), 8.90 (w), 9.35 (s, sharp), 10.77 (w), 12.88 (w), 13.33 (m), 14.20 (m), 14.30 (m) μ.

Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.48; H, 6.67.

***cis,cis*-Dibromo-4-*t*-butylcyclohexanone** (**7**).—4-*t*-Butylcyclohexanone (11 g, 0.07 mole) was dissolved in 40 ml of glacial acetic acid and the solution was cooled to 7° with ice cooling. Bromine (22 g, 0.14 mole) was added dropwise over a period of 6 min, with stirring and cooling such that the temperature did not rise above 17°. After 10 min the solution was poured into cold water and extracted with ether to give 22.4 g of partially solid material. Trituration with 15 ml of hot pentane gave 6.4 g of **7**, mp 145–147°.

On standing in the presence of hydrogen bromide, the pentane mother liquors yielded additional material (65% total).

An analytical sample melted at 147.5–149°: $\lambda_{\max}^{\mathrm{KBr}}$ 3.38, 3.65, 5.78, 7.30, 8.05, 15.0 μ; pmr spectrum, CHBr, δ 4.72 (broad signal, $W_v = 19.7$ cps). [W_v is the width between the outer absorption bands in unresolved signals taken at the top of the lowest peak ($W_v \cong J_{aa} + J_{ae}$). Width at half height ($W_{1/2}$)[10] values is difficult to determine in this series because several maxima occur within one signal. W_v values for axial C*H*Br protons were found to be remarkably constant and relatively independent of whether or not the proton was experiencing virtual coupling.]

Anal. Calcd for $C_{10}H_{16}Br_2O$: C, 38.49; H, 5.17. Found: C, 38.69; H, 4.85.

2-Acetoxy-5-*t*-butylcyclohex-2-enone (**4**).—Reaction of 1.6 g (0.005 mole) of **7** with fused sodium acetate in glacial acetic acid and acetic anhydride solution at 100° for 2 hr gave 1.0 g of an oil. Glpc analysis[21] of the crude product indicated the absence of diketone **6** and the presence of the two keto–enol acetates, **4** (57%) and **5** (43%). A small amount of pentane was added to the oil and the solution was placed in the cold room for several days. The solid keto–enol acetate **4** was collected on a filter (0.34 g, mp 45–47°). A second crop raised the total of 2-acetoxy-5-*t*-butylcyclohex-2-enone to 38%. An analytical sample melted at 51°: $\lambda_{\max}^{\mathrm{KBr}}$ 5.70, 5.92, 7.32, 8.25, 8.88, 10.97 μ.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.89; H, 8.66.

4-*t*-Butylcyclohexane-1,2-dione (**6**).—Fifteen grams (0.05 mole) of **7**, 15 g of anhydrous sodium acetate, 150 ml of acetic acid, and 100 ml of water were heated at reflux for 2.8 hr. The solution was added to aqueous sodium bicarbonate and the resulting mixture was extracted with ether. The ethereal solution was washed with 5% sodium bicarbonate and then with ice-cold 10% sodium hydroxide. The cold, basic solutions were acidified immediately and extracted with ether. The residue from the ether was distilled to give 5.3 g (0.03 mole or 61%) of green-yellow oil, bp 74–75° (1.2 mm), $n^{25}\mathrm{D}$ 1.4987; for the middle cut were found $n^{25}\mathrm{D}$ 1.4996 and $\lambda_{\max}^{\mathrm{KBr}}$ 3.00, 6.01, 7.13, 8.20, 8.30, 8.78 μ.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.56; H, 9.64.

Acetylation of 4-*t*-Butylcyclohexane-1,2-dione.—Acetylation 3.7 g of **6** with acetic anhydride and distillation gave 3.5 g (0.013 mole or 74%) of keto–enol acetates, bp 112–115° (1.2 mm), $n^{25}\mathrm{D}$ 1.4796. Glpc analysis indicated two keto–enol acetates, **5** (60%) and **4** (40%).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.50; H, 8.51.

***cis,cis*-2-Acetoxy-6-bromo-4-*t*-butylcyclohexane** (**3**).—A mixture of 8.0 g (0.025 mole) of **7**, 4.6 g (0.03 mole) of silver acetate, and 80 ml of glacial acetic acid was stirred at room temperature for 1 hr and then at 47–50° for 1.5 hr. Chromatography on a silica gel column gave 0.15 g (0.0005 mole or 2%) of **3**, mp 127–129°. An analytical sample melted at 133.5–134°: $\lambda_{\max}^{\mathrm{KBr}}$ 5.74, 5.77, 7.28, 8.05, 8.14, 14.05 μ; pmr spectrum, CHBr, δ 4.72 (broad signal, $W_v = 20.5$ cps), and CHOAc, δ 5.17 (broad signal, $W_v = 20.7$ cps).

Anal. Calcd for $C_{12}H_{19}BrO_3$: C, 49.50; H, 6.58. Found: C, 49.93; H, 6.28.

Reaction of *cis,cis*-2-Acetoxy-6-bromo-4-*t*-butylcyclohexanone (3) with Sodium Acetate.—The acetoxybromo ketone (0.08 g, 0.27 mmole), 0.087 g (1.2 mmoles) of fused sodium acetate, and 0.9 ml of glacial acetic acid were heated at 92–97° (bath temperature) for 3 hr and then worked up in the usual manner to give 0.056 g of liquid. Glpc analysis indicated the ratios **4**:**5**:**6** to be 38:11:51.

Reaction of *cis,cis*-2,6-Dibromo-4-*t*-butylcyclohexanone with Sodium Acetate in Acetic Acid.—A mixture composed of 0.78 g (0.0025 mole) of dibromo ketone **7**, 0.079 g (0.096 mole) of fused sodium acetate, and 0.7 ml of glacial acetic acid was heated at 100° (bath temperature) for 1.3 hr and then processed in the same manner as above to give a liquid. Glpc analysis indicated the amounts of **4**, **5**, and **6** to be 39, 15, and 46%, respectively. In similar runs, heating periods of two to five times as long did not affect the ratio of products.

Reaction of *cis,cis*-2,6-Dibromo-4-*t*-butylcyclohexanone. With Sodium Acetate in Acetic Acid. Anhydrous Conditions.—Sodium acetate (0.4 g, 5.0 mmoles, freshly fused in the reaction vessel) and 3.0 ml of acetic acid (bp 117.1°, distilled from a mixture of 10 ml of acetic anhydride, 90 ml of acetic acid, and about 4 g of sodium acetate) were heated at 86° (bath temperature) for 20 min. The dibromo ketone **7** (0.32 g, 1.0 mmole) was added and heating was continued for 2.5 hr at 84–86°. After processing, glpc analysis indicated the presence of three substances, **4** (57%), **5** (32%), and **6** (11%).

With Acetate–Diglyme Solvent.—A mixture of 2.0 g (0.0064 mole) of the dibromide **7**, 2 g (0.025 mole) of fused sodium acetate, and 40 ml of diglyme was heated (114–118°, bath temperature) with stirring for 3 hr. After processing, glpc analysis indicated the relative amounts of **4**, **5**, and **6** to be 74, 19, and 17%, respectively.

With Sodium Benzoate–Diglyme Solvent.—The dibromo ketone **7** (3.0 g, 0.0096 mole) and sodium benzoate (5.5 g, 0.038 mole) were combined in 50 ml of freshly distilled diglyme and the stirred mixture was heated at 81–82° for 5 hr. After cooling, the solution was poured into 150 ml of water and the precipitate was dissolved in 200 ml of ether. The ethereal solution was diluted with 100 ml of hexane. After washing with 5% sodium bicarbonate, the organic layer was dried and concentrated to give 3.51 g of partially solid material. Crystallization was effected from hexane to give 1.5 g (0.0056 mole or 58%) of **2-benzoyloxy-5-*t*-butylcyclohex-2-enone**, mp 120–123°. An analytical sample melted at 126–126.5°: $\lambda_{\max}^{\mathrm{KBr}}$ 5.79, 5.93, 6.04, 8.88, 9.42, 14.00 μ.

Anal. Calcd for $C_{16}H_{20}O_3$: C, 75.05; H, 7.41. Found: C, 74.88; H, 7.05.

In a similar run using excess **7**, 20% of ***cis,trans*-2,6-dibromo-4-*t*-butylcyclohexanone**, mp 47–48°, identified by mixture melting point and infrared analysis, was isolated along with 12% of 2-benzoyloxy-5-*t*-butylcyclohex-2-enone.

2-Benzoyloxycyclohex-2-enone and *cis*-2,6-Dibenzoyloxycyclohexanone.—Sodium benzoate (115 g, 0.80 mole) and 500 ml of bis(2-methoxyethyl) ether (previously distilled from sodium metal) were combined in a 1000-ml three-neck flask fitted with a stirrer, thermometer, and condenser with a guard tube. The mixture was heated at 95–105° for 15 min, 51.2 g (0.20 mole) of *cis*-2,6-dibromocyclohexanone, mp 107–108.5°, was added, and heating was continued for 4 hr. After processing by ether extraction, a total of 30.1 g (70%) of 2-benzoxycyclohex-2-enone, mp 81–86°, was obtained. An analytical sample was recrystallized from ether–hexane as large, colorless prisms: mp 86.5–87°; $\lambda_{\max}^{\mathrm{KBr}}$ 5.81, 5.96, 6.08, 7.43, 8.48, 8.71, 9.37 μ.

Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.24; H, 5.60. Found: C, 71.78; H, 5.28.

cis--2,6-Dibenzoyloxycyclohexanone (5%), mp 187–188° after crystallization from benzene, was also isolated: $\lambda_{\max}^{\mathrm{KBr}}$ 5.75 (sh), 5.82, 7.89, 8.88, 9.15, 9.33, 9.66, 10.47, 11.27 μ; pmr spectrum, CHOBz, δ 5.60 (broad signal, $W_v = 20.1$ cps).

Anal. Calcd for $C_{20}H_{18}O_5$: C, 70.96; H, 5.36. Found: C, 71.13; H, 5.51.

The dibromo ketone (25.6 g, 0.1 mole) heated with sodium acetate in acetic acid and acetic anhydride gave 9.7 g (0.063 mole, 63%) of **2-acetoxycyclohex-2-enone**, $n^{25}\mathrm{D}$ 1.4847, bp 99.0–102° (3 mm). A middle cut was taken as an analytical sample: $\lambda_{\max}^{\mathrm{CS_2}}$ 5.70, 5.94, 6.07, 8.25, 8.78, 9.05, 10.85 μ.

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[21] Throughout this work an F and M Model 300 vapor phase chromatograph utilizing a 6-ft column packed with 20% diisodecylphthalate on 100–120 mesh firebrick was used at a temperature of 145–175°.

Anal. Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 61.63; H, 6.47.

The keto–enol acetate solidified in the cold room. It crystallized from methyl alcohol as large prisms, mp 32°.

The phenylosazone of cyclohexane-1,2-dione, mp 149–150° (lit.[22] mp 149–150°), was prepared by refluxing 0.9 g of 2-acetoxycyclohex-2-enone with 1.4 g of phenylhydrazine in 10 ml of ethanol for 2.5 hr.

Reaction of *cis*-2,6-Dibenzoyloxycyclohexanone with Sodium Benzoate.—*cis*-2,6-Dibenzoyloxycyclohexanone, mp 187–188°, (0.8728 g, 0.00258 mole) was dissolved in 10 ml of hot diglyme and 1.55 g of sodium benzoate (0.0108 mole) was added. The mixture was stirred at 105–110° (bath temperature) for 4 hr. Processing gave 93% of 2-benzoyloxycyclohex-2-enone, mp 83–84°.

Reaction of 2α,4α-Dibromocholestan-3-one with Sodium Benzoate.—A mixture of 3.0 g (0.0058 mole) of dibromocholestanone, 4.9 g (0.034 mole) of sodium benzoate, and 30 ml of diglyme was stirred and heated (103–107°, bath temperature) 3.5 hr. The reaction mixture was then poured into water and extracted with ether. After drying and concentration, 2.9 g of oily solid was obtained. Trituration of this material with 10 ml of pentane gave 1.36 g of solid, mp 80–110°.[23] The solid was dissolved in 2 ml of benzene and adsorbed onto a slurry-packed silica gel column (3.5 × 120 cm) eluted with 3% ether in hexane initially. Fractions 1 and 2 were blank. Fraction 3 (1000 ml, 6% ether) gave 0.12 g of solid, mp 165–170°. One crystallization from chloroform–ethanol gave 0.10 g (0.19 mmole or 3%) of **3-benzoyloxycholest-2-en-4-one** (**12**): mp 175–177°; $[\alpha]^{26}\text{D}$ +31° (lit.[3] mp 177°; $[\alpha]^{20}\text{D}$ +25.9°); $\lambda_{\max}^{\text{MeOH}}$ 233 mμ (ε 18,800). Fraction 4 (1000 ml, 7% ether) gave 0.13 g of solid, mp 135–140°, which appeared to be a mixture of keto–enol benzoates **11** and **12** by nmr analysis. Fraction 5 (2600 ml, 8–10% ether) yielded 0.52 g of solid. Recrystallization from ethanol–chloroform gave 0.40 g (0.8 mmole) of **3-benzoyloxycholest-3-en-2-one** (**11**), mp 162–163°, further identified by mixture melting point and infrared analysis.

Chromatography of the pentane mother liquors (see above) gave 0.16 g of **11** for a total of 1.111 mmoles (19%).

Attempted Reaction of 2-Acetoxy-4,4-diphenylcyclohexanone with Sodium Benzoate.—A mixture of 2-acetoxy-4,4-diphenylcyclohexanone (0.1 g, 0.37 mmole), sodium benzoate (0.2 g, 1.5 mmoles), and 2 ml of diglyme were heated at 105–115° (bath temperature) for 3 hr with frequent shaking. Only starting material was recovered on processing.

Attempted Rearrangement of 2-Acetoxy-5,5-diphenylcyclohexanone.[24]—A mixture of 2-acetoxy-5,5-diphenylcyclohexanone (0.1 g, 0.35 mmole), sodium benzoate (0.2 g, 1.4 mmoles), and 2 ml of diglyme was heated at 117° (bath temperature) for 3 hr, with magnetic stirring, and then poured into 100 ml of water and 200 ml of ether. The ethereal layer was washed with three 100-ml portions of 5% sodium bicarbonate, dried, and concentrated to about 1 ml. A seed crystal of starting material was added and the solution was cooled to 0°. The first crystalline crop amounted to 0.10 g (mp 116–127°). The infrared spectrum was almost identical with that of the starting material. Thin layer chromatography comparing this crude material with standard mixtures showed that 1% or less of 2-acetoxy-4,4-diphenylcyclohexanone was present. Trituration with hot hexane followed by cooling gave solid material which melted at 130–131°; there was less than a 2% weight loss during this operation.

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[22] A. Kotz, K. Blendermann, R. Rosenbusch, and E. Sirringhaus, *Ann.*, **400**, 55 (1913).

[23] In several preliminary runs it was found that the melting point of the solid depended upon the amount of washing with pentane; when the crude product was triturated with about 25–30 ml of pentane, the melting point was 137–138° (with softening). The nmr spectrum of the product so obtained showed vinyl proton signals corresponding only to the two benzoates (mp 162–163° and 175–177°) obtained when the products were chromatographed.

[24] We wish to thank Mr. Robert Frame for carrying out this experiment.

The Synthesis of 2-Nitrocyclohexanone and the Reaction of Acetyl Nitrate with Cyclohexene

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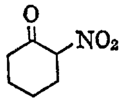
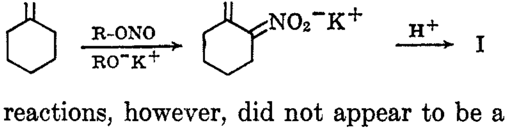
The synthesis of 2-nitrocyclohexanone was accomplished by the chromic acid oxidation of 2-nitrocyclohexanol and by the reaction of acetyl nitrate with cyclohexen-1-ol acetate. The reaction of acetyl nitrate with cyclohexene was shown to produce the previously unreported 4-nitrocyclohexene in addition to the previously reported 2-nitrocyclohexyl acetate, 2-nitrocyclohexyl nitrate, and 3-nitrocyclohexene.

Some of the recent work in this laboratory has centered around the synthesis on a preparative scale of 2-nitrocyclohexanone (I). The only previous synthesis



I

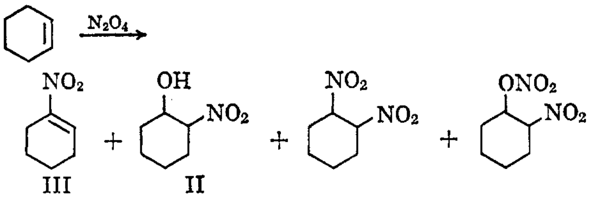
of I was that of Wieland, Garbsch, and Chavan[1] who started with cyclohexanone according to eq. 1.



(1)

These reactions, however, did not appear to be a suitable preparative route owing to the low over-all yield.

The literature indicated that a possible path to I was by direct oxidation of 2-nitrocyclohexanol (II), whose synthesis was accomplished by the reaction of cyclohexene with dinitrogen tetroxide according to the method of Baldock, Levy, and Scaife.[2] The problems[3] associated with this reaction are apparent even though



III II

(2)

II and III are quite easily isolated. The chromic acid oxidation[4] of II provided a 30% yield of I whose physical properties agreed closely with those given by Wieland, Garbsch, and Chavan.[1]

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[1] H. Wieland, P. Garbsch, and J. J. Chavan, *Ann.*, **461**, 295 (1928).

[2] H. Baldock, N. Levy, and C. W. Scaife, *J. Chem. Soc.*, 2627 (1949).

[3] Not only is the number of products excessive, but the reaction temperature must be carefully controlled in order to prevent violent fume-offs in the distillation step.

[4] N. Levy and C. W. Scaife, *ibid.*, 1100 (1946).