A New Ring Enlargement Procedure. IV. The Decomposition of the Magnesium Salts of Various 1-(1-Bromoethyl)-1-cycloalkanols

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A new ring expansion procedure is described. Various ethylidenecycloalkanes were smoothly and easily converted to the halohydrins which in turn were simply transformed to the magnesium salts. The latter were decomposed to the ring enlarged 2-methyl ketones in good yields and high purity.

The utility of the carbocyclic ring expansion reactions in organic synthesis is undeniable. Fortunately, organic chemistry does furnish a variety of excellent methods[1] to effect ring enlargements. The method to be outlined herein, although entailing no new reaction nor reaction type for a ring expansion offers synthetic simplicity for its appeal and merit.

Two preliminary manuscripts[2,3] have demonstrated that the decomposition of the magnesium salts of the appropriate halohydrins unfolded a new procedure for ring expansion (eq 1). An additional preliminary re-

$$n = 4, 5, 6, \text{and } 7$$
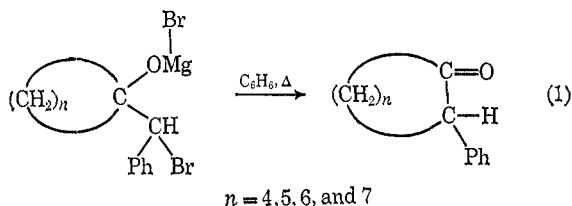
sult[4a] revealed that the magnesium salt of 1-bromomethyl-1-cyclohexanol did not yield the ring expanded ketone, cycloheptanone, but instead produced cyclohexanecarboxaldehyde. Lastly, the decomposition of the magnesium salt of 9-chloro-1-methyl-1-decalol (-O-H and -Cl *cis*) offers a new stereoselective method for the introduction of an angular methyl group.[4b] These results were in accord with the conclusions of Geissman and Akawie[5] who extensively studied the reaction producing ketones *via* the decomposition of the magnesium salts of halohydrins. They observed that primary halides do not rearrange unless a good migrating group is involved and that secondary and tertiary halides do rearrange regardless of the migrating group (eq 2). From their stereochemical studies they concluded that the halo and hydroxyl groups must be

$$(2)$$
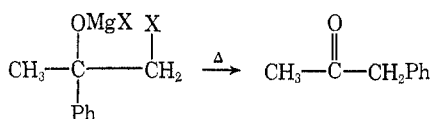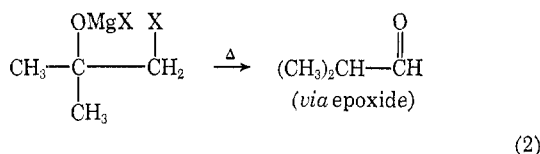
(1) For an excellent recent review, see C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968.

(2) A. J. Sisti, *J. Org. Chem.*, **33**, 453 (1968).

(3) A. J. Sisti, *Tetrahedron Lett.*, **52**, 5327 (1967).

(4) (a) A. J. Sisti, *J. Org. Chem.*, **33**, 3953 (1968); (b) A. J. Sisti and A. Vitale, *Tetrahedron Lett.*, **54**, 2269 (1969).

(5) T. A. Geissman and R. I. Akawie, *J. Amer. Chem. Soc.*, **73**, 1993 (1951).

cis (or can attain the *cis* alignment in nonrigid systems) to effect the rearrangement. The *trans* isomer leads to extensive decomposition, thus, precluding an epoxide interpretation for the reaction and leaving, as plausible, a pinacol-type mechanism (eq 3).


$$(3)$$
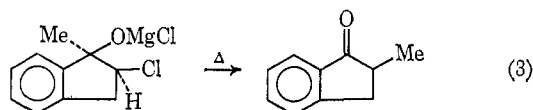
This manuscript extends the synthetic utility of the ring enlargement procedure and further tests the observations of Geissman and Akawie.[5]

Results and Discussion

2-Methylcycloalkanones from Ethylidenecycloalkanes.—The halohydrins, **1**, necessary for the ring expansion were easily prepared by the treatment of the ethylidenecycloalkanes with N-bromosuccinimide and water at room temperature. The halohydrins, **1** ($n = 4$ and 5), were purified and characterized, the remaining

$$n = 4, 5, \text{and } 6$$
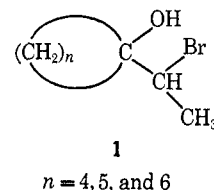
one was used directly without purification. The halohydrins were converted to the magnesium salts (Grignard reagent) and subsequently decomposed producing the 2-methylcycloalkanones, **2**, in good yields (eq 4).

$$(4)$$

$$n = 4, 5, \text{and } 6$$
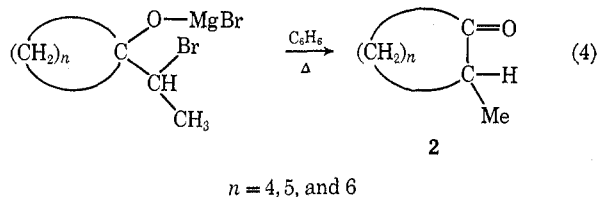
The results are presented in Table I. After distillation of the products, **2**, a polymeric residue remained, most probably due to the decomposition of unreacted halohydrin, **1**.

The structural assignments for the ketones, **2**, were based on the infrared spectra, the nmr spectra, and the 2,4-dinitrophenylhydrazones. The purity of each ketone was determined by vapor phase chromatography revealing that each ketone was no less than 92% pure. The major impurity in each instance was the isomeric carbonyl compound, **3** (vpc analysis). The ketone, **3**, was also detected, in each case, from the nmr spectra

| Compd 1	% yield of ketone 2	2,4-DNP mp, °C (lit.)	ν_{film}, cm^{-1}
4	65 (63)[a]	137–138[b]	1705
5	60 (60)[a]	120–121 (119–121)[c]	1700
6	(61)[a]	140–142 (140–141)[d]	1695

[a] Overall yield, based upon the ethylidenecycloalkane.   [b] Compared with the 2,4-DNP of an authentic sample; no depression in melting point observed.   [c] G. L. Closs and L. E. Closs, *J. Amer. Chem. Soc.*, **83**, 599 (1961).   [d] A. C. Cope and G. L. Woo, *ibid.*, **85**, 3601 (1963).
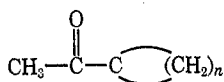
3

n = 4, 5, and 6

(sharp singlet at τ 7.9–8.0, methyl group adjacent to a carbonyl group). Authentic samples of **3** (*n* = 4 and 5) were shown to have the same retention time (vpc) as the minor contaminant from the reaction product. The origin of the production of **3** warrants a brief comment. Two reasonable paths are immediately apparent: first, the production of small amounts of the isomeric halohydrins, **4** (from the reaction of the ethylidenecyclo-
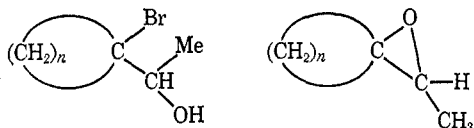

4   **5**

n = 4, 5, and 6

alkanes with NBS and water), whose magnesium salts would yield **3** upon decomposition *via* a hydride shift; second, the formation of small amounts of the epoxides, **5**, from the decomposition of the magnesium salt of **1**, followed by a breakdown to **3**.

10-Methyl-9-phenanthrol from 9-Ethylidenefluorene.
—The halohydrin, **6**, necessary to accomplish the ring expansion was prepared by the new procedure of Dalton[6] (eq 5). It was subsequently converted to the magnesium salt and decomposed to yield 10-methyl-9-phenanthrol (**7**), in good yield (eq 5). The structure of the


(5)
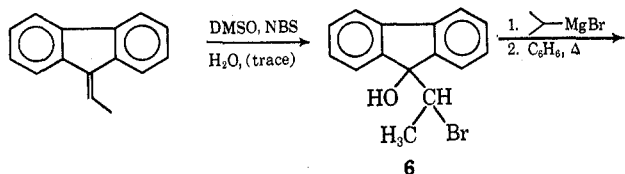
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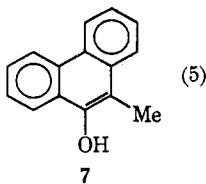
7

latter compound, **7**, was confirmed by its infrared spectrum, melting point, and conversion to a known derivative.

(6) D. R. Dalton, V. P. Dutta, and D. C. Jones, *J. Amer. Chem. Soc.*, **90**, 5498 (1968).

3-Methyl[3.2.1.]bicyclooctanone-2 from 2-Ethylidenenorbornane.—A broad spectrum of reaction types involving alkyl migrations toward incipient electron-deficient centers in the norbornyl system (ring expansion) have been studied. All reactions involving migrations to nitrogen[7] and carbon[8] conspicuously prefer methylene migration (less substituted, C-2–C-3 bond) over methine migration (more substituted, C-1–C-2 bond). Each of the above proceeds as indicated despite the generation of a relatively unfavorable boat transition state. Only the Baeyer–Villiger reaction with 2-norbornanone[9] is electronically controlled (C-1–C-2 bond migration). Sauers[9] has put forth an explanation for these apparent anomalies in the norbornyl system by proposing a third factor. The latter arises from the consideration of the torsional strain produced by nonbonded interactions between the eclipsed groups, on C-2 and the hydrogens on C-3. Thus, the migration of the C-2–C-3 bond produces a considerable easing of the nonbonded interactions. However, the migration of the C-1–C-2 bond would entail much less relief of strain because unfavorable interactions between C-2 and the bridgehead hydrogen are considerably less, since the dihedral angles involved are about 44 and 79°. The ring expansion procedure described herein was successfully tried on the norbornyl system and the results substantiated Sauers' new proposition. A previously communicated result,[3] namely, the decomposition of the magnesium salt of 2-(α-bromobenzyl)-2-norbornanol, (**8**), yielded *exclusively* 3-phenyl[3.2.1]-bicyclooctanone-2 (**9**) (eq 6) which results from the

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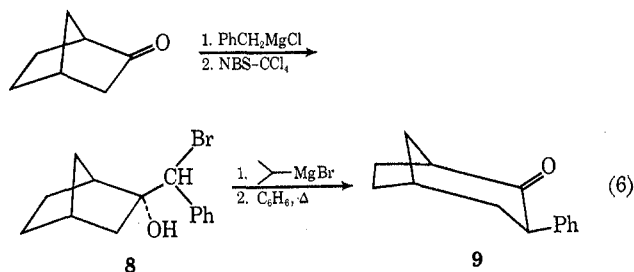
8   **9**

migration of the less substituted C-2–C-3 bond[10] and from the formation of a boat transition state. The present work on 2-ethylidenenorbornane entailed its conversion to the halohydrin,[11] **10** (NBS–H$_2$O method), which when converted to the magnesium salt and decomposed produced only 3-methyl[3.2.1]bicyclooctanone-2 (**11**) (eq 7). Similarly, this compound was produced from the migration of the less substituted, C-2–C-3 bond, which would also involve a boat transition state. The structure indicated for **11** was assigned on the basis of elemental analysis, the infrared spectrum,

(7) R. C. Elderfield and E. T. Losin, *J. Org. Chem.*, **26**, 1703 (1961); C. L. Arcus, R. E. Marks, and R. Vitterlain, *Chem. Ind.* (London), 1193 (1960).

(8) R. R. Sauers and R. J. Tucker, *J. Org. Chem.*, **28**, 876 (1963); J. Berson and D. Willner, *J. Amer. Chem. Soc.*, **84**, 675 (1962).

(9) R. R. Sauers and J. A. Beisler, *J. Org. Chem.*, **29**, 210 (1964).

(10) When the sequence outlined in eq 6 was pursued with 2-methylcyclopentanone, the expected preponderance of the product resulting from the migration of the *more substituted* bond to an electron-deficient center was encountered, namely, 2-phenyl-3-methylcyclohexane (unpublished results of Mr. George Rusch).

(11) The indicated stereochemical assignment for the halohydrin, **10**, was based on the following rationale: the approach of the reagent, NBS, to 2-ethylidenenorbornane to produce the bromonium ion [see E. E. Van Temelen and K. B. Sharpless, *Tetrahedron Lett.*, 2655 (1967)], should be *exo*; thus, the water will attack from the *endo* position.
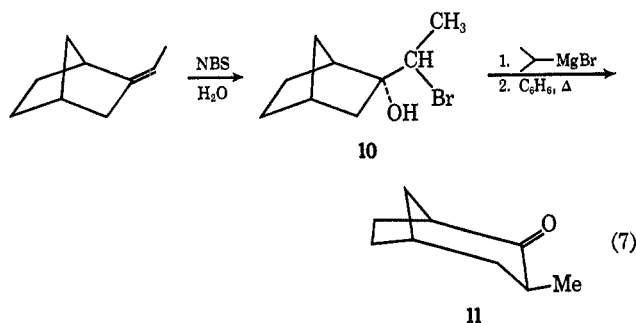
and nmr analysis. The migration of the more substituted carbon atom (C-1–C-2 migration in **10**) would result in the production of 2-methyl[3.2.1]bicyclooctanone-3 and not **11** as indicated (eq 7). The former was discarded on the basis of nmr studies. The nmr in carbon tetrachloride revealed a multiplet at τ 7.3–7.4 assigned to the bridgehead hydrogen α to a carbonyl group, and a multiplet at τ 7.5–7.6 assigned to the bridgehead hydrogen. The previous signal assignments were based upon the following observations. Bicyclo[3.2.1]octanone-2 in carbon tetrachloride exhibits signals at τ 7.3, multiplet corresponding to the bridgehead hydrogen α to a carbonyl group, and τ 7.5 multiplet corresponding to the bridgehead hydrogen, and the following signals reported[3] for **9**, τ 7.25 multiplet corresponding to the bridgehead hydrogen α to a carbonyl group, and τ 7.50 multiplet corresponding to the bridgehead hydrogen. Additional support for the structural assignment was obtained from deuterium exchange studies. The bicyclic ketone, **11**, was subjected to a treatment with trifluoroacetic acid-*d* (10% solution) for 24 hr at 100°. The nmr spectral analysis revealed that essentially one hydrogen was exchanged (the isomeric bicyclic ketone, 2-methyl[3.2.1]bicyclooctanone-3, should have exchanged three hydrogens).

Lastly, it is apparent that all the results herein substantiate the conclusion of Geissman and Akawie[5] that secondary halides rearrange regardless of the migrating group and indicate the simplicity of the conversion of exocyclic ethylidene compounds to the corresponding ring enlarged 2-methyl ketones.

Experimental Section[12]

1-(1-Bromoethyl)-1-cycloalkanols (1) were prepared from the appropriate ethylidenecycloalkanes (Columbia Organic Chemicals Co.) (0.15–0.25 mol), an equivalent amount of N-bromosuccinimide, and 100–150 ml of water according to a procedure previously described.[13] The halohydrins, **1**, were purified by distillation except for **1** (*n* = 6) which was used without purification.

The halohydrin, **1** (*n* = 4): bp 40–41° (0.4 mm) (70%); ir spectrum (film) 3450 cm⁻¹ (-O—H); nmr (CCl₄) τ 5.7–6.1 (q, one hydrogen).

Anal. Calcd for C₇H₁₃BrO: C, 43.54; H, 6.78. Found: C, 43.30; H, 6.50.

For **1** (*n* = 5): bp 45–45° (0.1 mm) (67%); ir spectrum (film) 3500 cm⁻¹ (-O—H); nmr (CCl₄) τ 5.7–6.1 (q, one hydrogen).

Anal. Calcd for C₈H₁₅BrO: C, 46.38; H, 7.25. Found: C, 46.15; H, 7.05.

For **1** (*n* = 6): ir spectrum (film) 3425 cm⁻¹ (-O—H); nmr (CCl₄) τ 5.6–6.0 (q, one hydrogen).

2-(1-Bromoethyl)-2-norbornanol (**10**) was prepared by the procedure presented above except that 12.2 g (0.10 mol) of 2-ethylidenenorbornane (Chemical Samples Co.) was employed. The resultant halohydrin was used without purification: ir spectrum (film) 3450 cm⁻¹ (-O—H); nmr (CCl₄) τ 5.5–6.0 (m, one hydrogen).

9-(1-Bromoethyl-9-fluorenol (6) was prepared with 19.2 g (0.10 mol) of 9-ethylidenefluorene (Aldrich Chemical Co.), 200 ml of DMSO, 2.8 ml of water, and 35 g (0.20 mol) of N-bromosuccinimide according to the method described by Dalton.[6] The halohydrin was not purified but was used directly: ir spectrum (film) 3450 cm⁻¹ (-O—H); nmr (CCl₄) τ 5.6–6.0 (q, one hydrogen).

All the halohydrins gave immediate precipitates with alcoholic silver nitrate.

2-Methylcycloalkanones (2) were prepared by the dropwise addition of an equivalent amount of isopropylmagnesium bromide in ether to a cooled benzene (300 ml anhydrous) solution of the halohydrin, **1** (0.10 mol). After the dropwise addition of the Grignard reagent the solution was gently refluxed overnight and subsequently decomposed (NH₄Cl). The separated organic portion was washed successively with water, 10% sodium bicarbonate solution, and water, and then dried (MgSO₄). The solvent was removed under vacuum (rotary evaporator) and the residue distilled.

For **2** (*n* = 4): bp 50–52° (10–15 mm) (lit.[14] 163°) (65%); ir spectrum (film) 1705 cm⁻¹ (C=O), ir spectrum (film) of an authentic sample of 2-methylcyclohexanone was identical with the preceding ir; nmr (CCl₄) sharp τ 8.9–9.0 [d, -C(=O)C(H)CH₃], τ 8.0 (small sharp s, H₃C—C=O); vpc (20% Carbowax, 150°, 40 spi) showed two peaks, 95% **2** (*n* = 4) and 5% **3** (*n* = 4), an authentic sample, methyl cyclopentyl ketone, had the same retention time as the minor component, **3** (*n* = 4).

For **2** (*n* = 5): bp 53–55° (7–8 mm) (lit.[15] 183°) (60%); ir spectrum (film) 1700 cm⁻¹ (C=O); nmr (CCl₄) τ 9.0–9.1 (sharp d, -C(=O)C(H)CH₃), τ 8.0 (small sharp s, H₃C—C=O); vpc (20% Carbowax, 150°, 40 psi) showed two peaks 93% **2** (*n* = 5) and 7% **3** (*n* = 5), an authentic sample, methyl cyclohexyl ketone, had the same retention time as the impurity, **3** (*n* = 5).

For **2** (*n* = 6): bp 51–52° (0.9 mm) (lit.[16] 86–87° (12 mm) (61%); ir spectrum (film) 1695 cm⁻¹ (C=O); nmr (CCl₄) τ 8.9–9.0 [sharp d, -C(=O)C(H)CH₃], τ 8.0 (small sharp s, H₃C—C=O); vpc (20% Carbowax, 200°, 40 psi) showed two peaks 92% **2** (*n* = 6) and 8% **3** (*n* = 6). The latter structural assignment (methylcycloheptyl ketone) was based on comparison with the preceding verified assignments.

9-Methyl-10-phenanthrol (7).—The halohydrin, **6**, was dissolved in anhydrous benzene (300 ml) and treated with an equivalent amount (0.10 mol) of isopropylmagnesium bromide in ether as described above except that the reflux time was curtailed to 5 hr. The residue was recrystallized from methanol-water, yielding 13 g (62%): mp 122–124° (lit.[17] mp 125°); ir spectrum (CHCl₃) 3580 cm⁻¹ (-O—H). The acetate had mp 148–149° (lit.[17] 150–151°).

3-Methyl[3.2.1]bicyclooctanone-2 (11).—The halohydrin, **10**, was dissolved in 200 ml of anhydrous benzene to which was added an equivalent of isopropylmagnesium bromide in ether (0.10 mol) as previously described above except that the reflux period was for 2 hr. The residue was distilled, bp 59–61° (2.4 mm), yielding 9 g (65%) of a colorless oil: ir spectrum (film) 1710 cm⁻¹ (C=O); nmr (CCl₄) τ 7.3–7.4 (m, bridgehead hydrogen α to a carbonyl group), τ 8.9–9.1 [d, -C(=O)C(H)CH₃]; vpc (20% Carbowax, 200°, 40 psi) showed the compound to be no less than 95% pure.

Anal. Calcd for C₉H₁₄O: C, 78.82; H, 10.21. Found: C, 78.89; H, 10.34.

The 2,4-dinitrophenylhydrazone had a melting point of 144–145.5° (ethanol).

Anal. Calcd for C₁₅H₁₈N₄O₄: C, 56.59; H, 5.70; N, 17.60. Found: C, 56.55; H, 5.64; N, 17.58.

(12) All melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Spectracord infrared spectrophotometer. The nmr spectra were determined with a Varian A-60 instrument.

(13) C. O. Guss and R. Rosenthal, *J. Amer. Chem. Soc.*, **77**, 2549 (1955).

(14) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," Wiley, New York, N. Y., 1964, p 362.

(15) G. L. Closs and L. E. Closs, *J. Amer. Chem. Soc.*, **83**, 599 (1961).

(16) A. C. Cope and G. L. Woo, *ibid.*, **85**, 3601 (1963).

(17) J. W. Cook, J. Jack, J. D. Loudon, G. L. Buchanan, and J. MacMillan, *J. Chem. Soc.*, 1397 (1951).

Before sealing a tube there was inserted 1 g of compound 11, and 2 ml of trifluoroacetic acid-d (10% solution). The tube was placed in an oil bath for 24 hr at 100°, after which the contents were made basic by pouring into 10% sodium carbonate solution followed by extraction with ether. After drying (MgSO₄) and removing the ether, the nmr spectrum of the residue was taken. Upon comparison of the area, τ 7.3–8.2, with the undeuterated

spectrum it was concluded that essentially one hydrogen was exchanged.

Exalted n–π* Transitions for Substituted Phenylacetones

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As the alkyl group in 1-phenylcyclopropyl alkyl ketones was changed in the series Me, Et, i-Pr, t-Bu, strong absorption due to conjugation of the phenyl group with the cyclopropane ring appeared. This conjugation produced absorption tailings which led to false exaltations in the n–π* region. A method is presented which aids in detection of such cases. The stronger acetyl–cyclopropane conjugation is suggested only for the methyl ketone and a value of 2 kcal appeared suitable. Although α'-alkylation of α-phenylacetones did not increase the ketonic absorption, α-alkylation appeared to do so and the possible reasons for this are discussed. The addition of methyllithium to diphenylacetic acids is not a satisfactory synthesis of diphenylacetones.

The fact that α-phenylacetone showed an increase of extinction coefficient (ε 150, EtOH) in the n–π* region (280–290 mμ) has received various interpretations. Cookson[1] originally proposed that such exaltations arose most significantly when the plane of the carbonyl group faced the plane of the benzene ring (θ = ψ = 90° as in Figure 1b). In contrast, it was proposed somewhat later[2] that there was involvement of the n electrons of oxygen. This leads, at least by the LCAO method, to a prediction that the oxygen should nearer the β,γ unsaturation for maximum exaltation. Still later,[3] a computer program, which calculated angular populations as a function of hydrogen–hydrogen repulsions and then evaluated several proposals for explaining exaltations, supported the Cookson view. The best equation (not stated explicitly in ref 3) was ε = 30 + 810 sin² θ sin² ψ, wherein ε is the observed extinction coefficient of an unstrained α-phenyl ketone in ethanol solution and the angles are those defined in Figure 1. Of the ketones examined, only 1-acetyl-1-phenylcyclopropane proved to be an exception. The present paper deals with the source of this difficulty and sets forth additional factors concerning application of the Cookson proposal.

Discussion of Results

The computer program gave no recognition to the fact that the acetyl group and the cyclopropane ring show conjugation in the bisected structure (ψ = 0° or 180°). Such conjugation for cyclopropanecarboxaldehyde was estimated to be in excess of 2 kcal by Bartell.[4a] Such a conjugation term was inserted using the simple expression[4b] E = −2.0 cos² ψ and found to yield acceptable results. Greater or lesser values of the maximum conjugation energy were less satisfactory: 0 kcal (ε_calcd 213.5), 1 (102.9), 1.5 (87.7), 2.0 (76.7), 2.5

(69.4). In an effort to obtain further support for this interpretation, there has been prepared a series of ketones with larger alkyl groups. These were expected to show increasing exaltations of the ketonic absorption due to adoption of conformation 1b (90–90°). The numerical data of Table III (Experimental Section) seem to support such a result. Sought in the following paragraph, however, is a numerical method of deducing the correctness of such a conclusion. Such a method would be of use with literature reports which usually give only spectral values. When complete spectra are at hand, visual examination often suffices for estimation of the existence of a tailings contribution to the n–π* region. For this reason, complete spectra are given in Figure 2 for the four 1-acyl-1-phenylcyclopropanes. This figure suggests that true exaltations of the n–π* region are not obtained in the three new cases. Rather, extinction coefficients in both the benzenoid and carbonyl portions of the spectra are elevated by tailings of strong absorption in the 200–220-mμ region. Absorption in this region increased as R of RCO– was changed in the series Me, Et, i-Pr, t-Bu. This is due to increasing conjugation of the phenyl group with the cyclopropane ring. Thus, it is proposed that the conformation of the methyl ketone lies toward that with angles ψ = 180°, θ = 90° (Ac in the bisected structure), while that for the t-butyl ketone lies heaviest toward that with angles ψ = 90° = 270°, θ = 0° (Ph in the bisected structure). The small bathochromic shift of the ketonic band of the methyl ketone supports the former interpretation. The increased absorption shown by the four ketones in the 200-mμ region is interpreted as being due to increased phenyl–cyclopropane conjugation.[5] This proposal of an angular dependence seems at variance with the conclusion of Eastman[6] who observed little difference in the log ε plots for compounds of fixed geometry. It must be recalled, however, that the angular departures from the bisected structure

(1) R. C. Cookson and N. S. Wariyar, *J. Chem. Soc.*, 2302 (1956).

(2) H. Labhart and G. Wagniere, *Helv. Chim. Acta*, **42**, 2219 (1959).

(3) S. MacKenzie, S. F. Marsocci, and H. C. Lampe, *J. Org. Chem.*, **30**, 3328 (1965).

(4) (a) L. S. Bartell, B. L. Carroll, and J. P. Gillory, *Tetrahedron Lett.*, 705 (1964). (b) A similar equation was used to express the conjugation energy of twisted acetophenones: E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3754 (1955).

(5) S. G. Beech, J. H. Turnbull, and W. Wilson, *ibid.*, 4686 (1952), reported for 1-methyl-2-phenylcyclopropane values of 230 mμ (ε >2500), 254 (1000), and 275 (320, EtOH). The energy of the phenyl-cyclopropane conjugation was given as 1.4 kcal by G. L. Closs and H. B. Klinger, *J. Amer. Chem. Soc.*, **87**, 3265 (1965).

(6) A. L. Goodman and R. H. Eastman, *ibid.*, **86**, 908 (1964).