Ring Enlargements. XI. Structural Influences on the Course of the Intramolecular Diazoalkane–Carbonyl Reaction[1]

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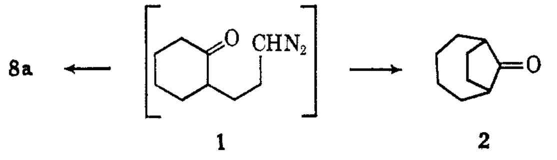
To study the structure–reactivity relationships in intramolecular diazoalkane–carbonyl reactions, a series of methyl-substituted N-nitroso-N-acetyl-3-(2′-ketocycloalkyl)propylamines (**8**) has been subjected to base-catalyzed decomposition. While the parent compound and two of its monomethyl derivatives furnish the bridged ring ketone (a bicyclo[4.2.1]nonan-9-one) as the major product, other of the methylated analogs furnish varying amounts of the oxide (a 6,7-epoxybicyclo[4.3.0]nonane) in addition to or to the exclusion of the bridged ring ketone. For instance, base-catalyzed decomposition of N-nitroso-N-acetyl-3-(1′,3′,3′-trimethyl-2′-ketocyclohexyl)propylamine (**8e**) produces 1,5,5-trimethyl-6,7-epoxybicyclo[4.3.0]nonane (**17**) in at least 85% yield, accompanied by little or none of the corresponding bridged ring ketone. The response of the reaction to the changing patterns of methyl substitution are interpreted in terms of a double-intermediate scheme. This scheme proposes (a) that an association complex precedes the formation of a charge-separated intermediate and (b) that two types of association complexes are possible. One of these is postulated to be the precursor of a carbocyclic intermediate which collapses to ketonic product, and the other is postulated to be the precursor of a heterocyclic intermediate which collapses to epoxide product. The partitioning between the two complexes is interpreted in terms of steric interactions between carbonyl compound and diazoalkane. The present observations as well as others recorded in the literature can be accommodated by this scheme.

A guiding principle for many organic chemical investigations is that of "heuristic homology" which may be defined as a study of a series of homologs in the expectation that patterns of structure–reactivity relationships will emerge. An illustrative example is provided by the present paper which records its application to the intramolecular diazoalkane–carbonyl reaction.

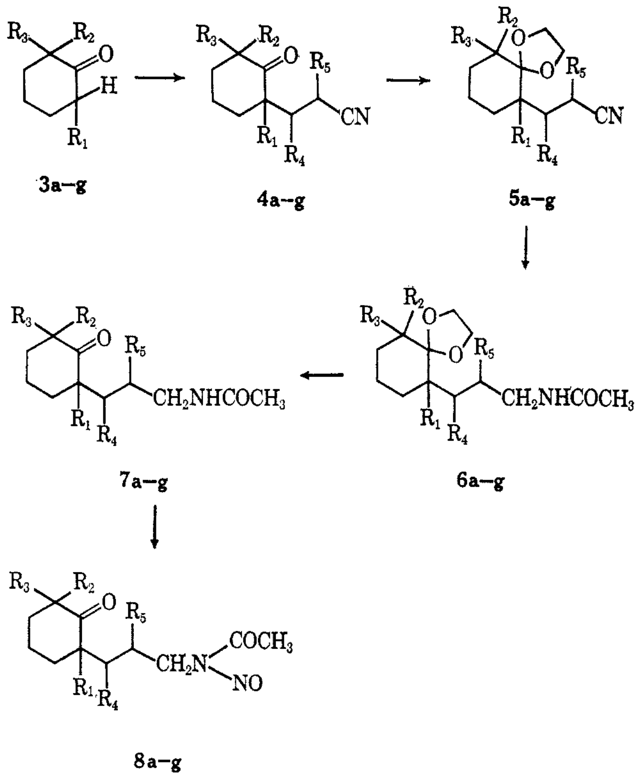
In earlier studies of the intramolecular diazoalkane–carbonyl process[3,4] it was shown that the cleanest reaction occurs with the diazo compound (**1**) from N-nitroso-N-acetyl-3-(2′-ketocyclohexyl)propylamine (**8a**) which gives bicyclo[4.2.1]nonan-9-one (**2**) in over 80% yield (Scheme I). This system was therefore, chosen as the one to which to attach methyl groups in various numbers and at various positions to test the consequences on the course of the reaction. The synthesis of the appropriate nitroso compounds and their fate upon base-catalyzed decomposition constitutes the subject matter for this discussion.

Scheme I



Synthesis of N-Nitroso-N-acetyl-3-(2′-ketocycloalkyl)propylamines (8).—Nitrosoamides **8b** through **8g** were synthesized by the same sequence of reactions that was described earlier[3] for the synthesis of **8a**. By cyanoethylation of ketones **3b**, **3d**, and **3e** and by cyanoethylation of the enamine of **3c**, corresponding ketonitriles **4a** through **4e** were obtained. Ketonitriles **4f** and **4g** were obtained from the reaction of the pyrrolidine enamine of cyclohexanone with 3-butenonitrile and methacrylonitrile, respectively. Protection of the carbonyl group by conversion to ethylene ketal derivative **5**, reductive acetylation to amide **6**, selective hydrolysis to keto amide **7**, and nitrosation to the keto nitrosoamide **8** proceeded smoothly in all cases (Scheme II). The yields in the conversion of **3** to **4** were generally in the range of 60–78% (lower in the case of **3d** and **3g**) and in the over-all conversion of **4** to **8** in the range 65–83%.

Scheme II



a, $R_1 = H; R_2 = H; R_3 = H; R_4 = H; R_5 = H$
b, $R_1 = CH_3; R_2 = H; R_3 = H; R_4 = H; R_5 = H$
c, $R_1 = H; R_2 = CH_3; R_3 = H; R_4 = H; R_5 = H$
d, $R_1 = CH_3; R_2 = CH_3; R_3 = H; R_4 = H; R_5 = H$
e, $R_1 = CH_3; R_2 = CH_3; R_3 = CH_3; R_4 = H; R_5 = H$
f, $R_1 = H; R_2 = H; R_3 = H; R_4 = H; R_5 = CH_3$
g, $R_1 = H; R_2 = H; R_3 = H; R_4 = CH_3; R_5 = H$

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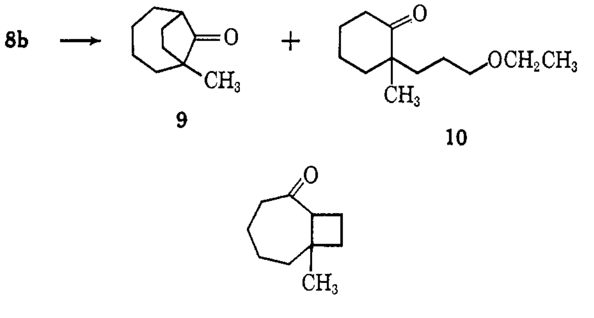
[2] National Institutes of Health Predoctoral Fellow, 1963–1964; National Science Foundation Summer Fellow, 1963.

[3] C. D. Gutsche and D. M. Bailey, *J. Org. Chem.*, **28**, 607 (1963).

[4] D. M. Bailey, J. E. Bowers, and C. D. Gutsche, *ibid.*, **28**, 610 (1963).

Decomposition of N-Nitroso-N-acetyl-3-(2′-ketocycloalkyl)propylamines (8).—The decomposition of the nitroso amides **8b** through **8g** was effected by adding the nitroso amide to a refluxing solution of sodium ethoxide in ethanol. Steam distillation of the resulting mixture yielded a product which was purified by vapor phase chromatography (vpc), column chromatography, or fractional distillation. From the decomposition of **8b** there was obtained a 92% yield of a product possessing a strong camphoraceous odor; analysis by vpc showed it to contain 95% of one component. The identity of this material as 1-methylbicyclo[4.2.1]-nonan-9-one (**9**) is based on an elemental analysis compatible with a $C_{10}H_{16}O$ formula, an infrared carbonyl absorption at 1745 cm^{-1} characteristic of a cyclopentanone moiety,[5,6] an nmr spectrum which shows a singlet at τ 8.96 produced by a methyl group in a quaternary position, its failure to decolorize bromine in carbon tetrachloride solution, and the similarity of this material to bicyclo[4.2.1]nonan-9-one (**2**), the structure of which has been proved by degradation tokn own substances.[7] The minor component is tentatively identified as the keto ether **10** on the basis of its infrared spectrum which shows absorptions at 1710 and 1130 cm^{-1}, characteristic of a cyclohexanone carbonyl group and an ether group, respectively[5] (Scheme III).

SCHEME III

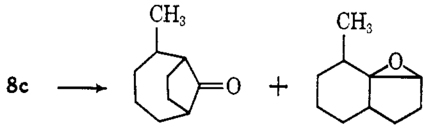


9 10 11

The possibility that the purified sample of **9** might be contaminated with fused ring isomer **11** was excluded on the basis of the following experiment. Admixture of the reaction product with 2,2,6,6-tetramethylcyclohexanone (a nonenolizable and hence difficultly oxidizable ketone) followed by oxidation with refluxing 50% nitric acid containing a catalytic amount of ammonium vanadate yielded a product which showed the same vpc ratio of ketones (*i.e.*, **9** and 2,2,6,6-tetramethylcyclohexanone) as the starting mixture. Had ketone **11** been present it should have been consumed by the oxidizing mixture, thereby changing the ratio of ketones. The nonenolizability of bicyclo[4.2.1]-nonan-9-one (**2**) has been discussed in a previous paper.[7]

Base-catalyzed decomposition of **8c** yielded 78% of a product which was shown by vpc to contain equal amounts of two major components. One of these is identified as 2-methylbicyclo[4.2.1]nonan-9-one (**12**) on the basis of an elemental analysis compatible with a $C_{10}H_{16}O$ formula, an infrared carbonyl absorption at 1750 cm^{-1} characteristic of a cyclopentanone moiety,[5] an nmr spectrum which shows a doublet at τ 9.03 arising from a R_2CHCH_3 moiety, its failure to decolorize bromine in carbon tetrachloride solution or to undergo oxidation with refluxing nitric acid, and the similarity of this material to bicyclo[4.2.1]nonan-9-one (**2**). The other major compound is identified as 5-methyl-6,7-epoxybicyclo[4.3.0]nonane (**13**) on the basis of an infrared spectrum which shows the absence of a carbonyl absorption but bands at 910 and 833 cm^{-1} characteristic of the epoxide grouping,[5] and an nmr spectrum which shows a doublet at τ 9.03 arising from an R_2CHCH_3 moiety and a multiplet at 6.65 accounting for one proton, presumably that attached to the epoxide ring[8] (Scheme IV).

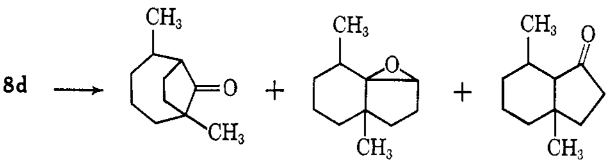
SCHEME IV



12 13

Base-catalyzed decomposition of **8d** yielded 83% of a product which was shown by vpc to contain three components in the ratio 2:6:1. The component present in smallest amount is identified as 1,5-dimethylbicyclo[4.2.1]nonan-9-one (**14**) on the basis of its infrared spectrum and its resistance to bromination and oxidation as described for the previous examples of **9** and **12**. The compound present in next larger amount is identified as 1,5-dimethyl-6,7-epoxybicyclo-[4.3.0]nonane (**15**) on the basis of the infrared and nmr spectra as described for the previous example of **13**. The compound present in largest amount is tentatively identified as 1,5-dimethylbicyclo[4.3.0]-nonan-7-one (**16**) on the basis of an elemental analysis compatible with a $C_{11}H_{18}O$ formula, an infrared carbonyl absorption at 1750 cm^{-1} characteristic of a cyclopentanone moiety, an nmr spectrum which is compatible with the assigned structure, and its reactivity toward bromine in carbon tetrachloride solution and toward refluxing nitric acid (Scheme V).

SCHEME V



14 15 16

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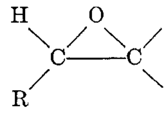
[5] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958.

[6] In addition to the intense absorption at 1745 a less intense band at 1710 cm^{-1} was also observed. This has been noted in numerous other cases and has been ascribed to a "Fermi resonance" between the carbonyl stretching mode and a bending mode of an adjacent C-H or C-C bond; see, for instance, H. O. House and H. C. Muller, *J. Org. Chem.*, **27**, 4436 (1962).

[7] C. D. Gutsche and T. D. Smith, *J. Am. Chem. Soc.*, **82**, 4067 (1960).

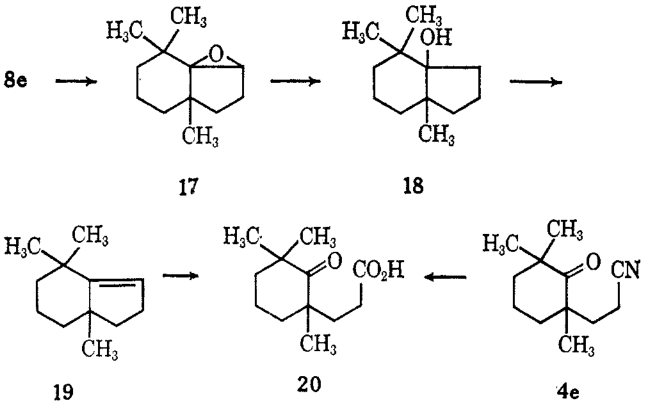
[8] N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1963. The spectra for propylene oxide (No. 32), 3,4-epoxycyclohexylcyanide (No. 173), styrene oxide (No. 193), and indene oxide (No. 524) show resonances for



between τ 7.12 and 5.92.

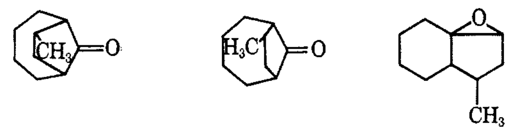
Base-catalyzed decomposition of **8e** yielded 88% of a product which was shown by vpc to contain one major product, present to the extent of 85%, identified as 1,5,5-trimethyl-6,7-epoxybicyclo[4.3.0]nonane (**17**) on the basis of an elemental analysis compatible with a $C_{12}H_{10}O$ formula, infrared absorptions at 830 and 900 cm^{-1} characteristic of the epoxide moiety, an nmr spectrum supporting the presence of three methyl groups and one proton attached to an epoxide ring, and the degradation reactions indicated by the sequence **17** → **20**. Lithium aluminum hydride reduction of **17** produced **18** in 78% yield, dehydration of **18** with thionyl chloride in pyridine gave **19** in 83% yield, and ozonolysis of **19** followed by an oxidative work-up yielded 55% of 3-(1′,3′,3′-trimethyl-2′-ketocyclohexyl)propionic acid (**20**), the identity of which was established by comparison with material obtained by hydrolysis of the nitrile **4e** (Scheme VI).

Scheme VI



Base-catalyzed decomposition of **8f** yielded 97% of a product which was shown by vpc to consist of an equal mixture of two materials, identified as the α and β isomers of 7-methylbicyclo[4.2.1]nonan-9-one (**21**)[9] on the basis of elemental analyses, infrared spectra, and nmr spectra as described for previous examples in this series. Similarly, the base-catalyzed decomposition of **8g** yielded 84% of a product which was shown by vpc to contain three compounds in the ratio 1:2:1. The first of these is identified as 9-methyl-6,7-epoxybicyclo[4.3.0]nonane (**22**) on the basis of its elemental analysis, infrared spectrum, and nmr spectrum as described for previous examples; the second and third components are identified as the α and β isomers of **21** (see Chart I).

Chart I



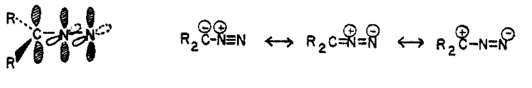
	α-21	**β-21**	**22**
8f →	one part	one part	none
8g →	two parts	one part	one part

Discussion of Results

The diazoalkane moiety contains two nitrogen atoms and a carbon atom joined in a linear fashion[10] and encampassed by a π-bond system resulting from the overlap of the contiguous p orbitals of structure **23** illustrated in Scheme VII. The electron density in this system can be distributed in a variety of ways as represented by the resonance structures in Scheme VII. The partner with which the diazoalkane is reacting will determine which of the resonance structures appears to be the most significant contributor to the resonance hybrid. On the basis of several observations[11] the interaction of diazoalkanes with carbonyl groups is thought to involve a nucleophilic attack on the carbonyl carbon atom, *i.e.*, resonance structure **23a** most important. It seems reasonable to assume that prior to and during the formation of the new C–C bond the preferred orientation of the carbonyl compound and the diazoalkane is the one in which the π-bond systems of the carbonyl group and diazoalkane overlap in a coplanar fashion. This is illustrated by the structure in Scheme VIII designated as a "type A complex."

Scheme VII

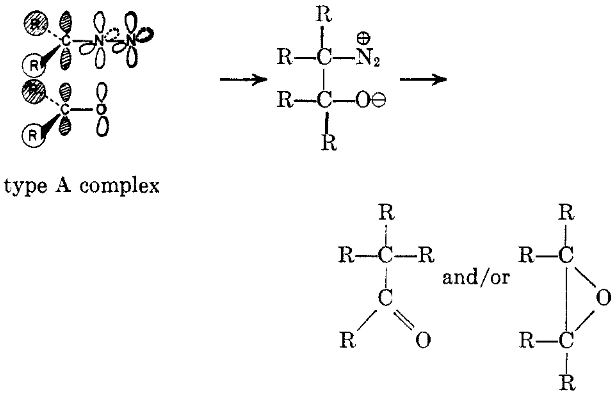
The Structure of Diazoalkanes



23 **a** **b** **c**

Scheme VIII

Diazoalkane Reacting as a Nucleophile at Carbon



The entity formed as the result of the nucleophilic attack at the carbonyl carbon is usually written as a charge-separated structure, the latter subsequently decomposing to homologous carbonyl compounds and/or epoxides. The details of this decomposition are not known, although by analogy to other 1,2-

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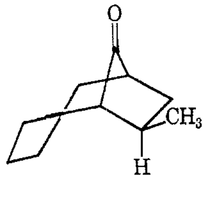
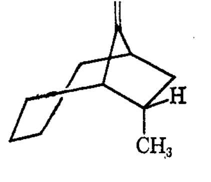
(9) A speculative configurational assignment may be made on the premise that the *exo* form of **21** is more similar to 3-methylcyclopentanone than is the *endo* form of **21**, the nonbonded interactions between the CH_3 and H at the 2 and 6 positions being more severe in the latter. A comparison of the position of the nmr resonance arising from the methyl group of **α-21**, **β-21**, and 3-methylcyclopentanone showed those from **α-21** and 3-methylcyclopentanone to fall at almost the same position, while that from **β-21** to fall at a position downfield by *ca.* 3.7 cps. Accordingly, **α-21** is assigned the *exo* configuration and **β-21** the *endo* configuration.



α-21



β-21

(10) D. A. Ramsay, *J. Chem. Phys.*, **17**, 666 (1949).

(11) C. D. Gutsche, *Org. Reactions*, **8**, 364 (1954).

nucleophilic rearrangements[12] and in explanation of certain diazoalkane–carbonyl reactions,[13] it has been assumed that the reaction takes place in a concerted fashion, *i.e.*, that the nitrogen is expelled by backside displacement of the participating group (carbon in the case of carbonyl products, oxygen in the case of epoxide products).

The mechanism illustrated in Scheme VIII provides a satisfactory explanation for some of the ketone to oxide ratios that have been observed. For instance, carbonyl compounds containing electron-withdrawing groups tend to give low ketone-to-oxide ratios.[11] Thus, *o*-nitrobenzaldehyde[14] and chloral[15] form the epoxide as the predominant reaction product. This is interpreted in terms of a reduced migration aptitude of the R groups of the carbonyl component (*i.e.*, R migrates as a nucleopilic entity) which, thereby, allows the displacement of nitrogen by oxygen (to form epoxide) to take precedence. Unfortunately, however, this mechanism does not easily accommodate a number of cases in which rather subtle changes in the carbonyl component cause marked changes in the ketone-to-oxide ratio. For instance, the ketone-to-oxide ratio for cyclohexanone is 4,[16] while that of 2-methylcyclohexanone is 1.25;[17] the ketone-to-oxide ratio of 3,5-dimethylcyclohexanone is 2.16,[17] while that of 3,3,5-trimethylcyclohexanone is 0.5.[18] That the influences in these instances must be predominately steric rather than electronic in nature is substantiated by the comparison of *cis*-α-decalone (ketone-to-oxide ratio of 25) with *trans*-α-decalone (ketone-to-oxide ratio of 2),[19] compounds in which the electronic environments at the carbonyl group must be virtually identical.

The present work records additional examples of the subtle effects that can be exerted by the presence of methyl groups in the vicinity of the carbonyl function. Inspection of the ketone-to-oxide ratios for the products obtained from the base-catalyzed decomposition of the nitroso compounds **8a** through **8g** (see Table I) shows that the pattern of the methyl substitution may profoundly alter the course of the decomposition, changing the product from all ketone to all oxide in the extreme cases.

In an earlier paper of this series[19] it was postulated that ketonic products and epoxide products *might not arise from the same intermediate, i.e.*, that a double-intermediate system might be operative. A similar suggestion has recently been advanced in interpretation of the kinetics for the reaction of diazomethane with acetone.[20] We believe that the results from the intramolecular reactions reported in the present paper, along with various of the results reported in the literature, are reasonably interpreted on the basis of a double-intermediate scheme.

TABLE I

KETONE-TO-OXIDE RATIO OF PRODUCTS FROM DECOMPOSITION OF **8**

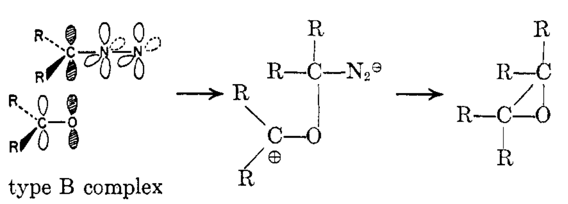
Methyl substitution pattern	Ketone-to-oxide ratio
a	All ketone
b	All ketone
c	1:1
d	1:8[a] (1:2 for oxide and bridged ring ketone)
e	All oxide
f	All ketone
g	3:1

[a] See text for explanation.

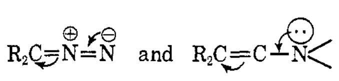
The type A association complex (see Scheme VIII), imputing to the diazoalkane the characteristics of a nucleophile at carbon, is probably preferred over other types of complexes for electrostatic reasons. In this complex, however, the R groups of the diazoalkane and carbonyl compound directly oppose each other and, if sufficiently large, may provide a steric interaction which counteracts the electrostatic attraction of diazoalkane carbon for carbonyl carbon. The steric interaction may be reduced if the complex adjusts along the π-bond plane in such a fashion as to position the diazoalkane carbon above the carbonyl oxygen rather than the carbonyl carbon. In this configuration, represented as the type B complex in Scheme IX, the characteristics of an electrophile at carbon are imputed to the diazoalkane. The charge-separated intermediate ensuing from the type B complex should, most logically, collapse to epoxide product, as illustrated in Scheme IX. Thus, it is postulated that steric interactions between the diazoalkane and the carbonyl compound may result in the shifting from a type A complex (which leads to carbonyl product) to a type B complex (which leads to epoxide product). A somewhat analogous explanation has been advanced for ketene dimerizations. Depending upon the substitution of the ketene, dimerization leads to a lactone, a cyclobutanedione, or a mixture thereof. Which of these routes is followed is thought to be determined by the manner in which the ketene molecules align themselves prior to and during the reaction.[21]

SCHEME IX

DIAZOALKANE REACTING AS AN ELECTROPHILE AT CARBON



The possibility for a diazoalkane to react either as a nucleophile or an electrophile at carbon is anticipated by analogies with enamines and iminium compounds. The structural similarity of


$R_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{N}$ and $R_2C{=}C{-}\ddot{N}{<}$

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(12) C. D. Gutsche and C. T. Chang, *J. Am. Chem. Soc.*, **84**, 2263 (1962); C. Djerassi, B. F. Burrows, C. G. Overberger, T. Takekoshi, C. D. Gutsche, and C. T. Chang, *ibid.*, **85**, 949 (1963).

(13) C. D. Gutsche, H. F. Strohmayer, and J. M. Chang, *J. Org. Chem.*, **23**, 1 (1958).

(14) F. Arndt and W. Partale, *Ber.*, **60**, 446 (1927).

(15) F. Arndt, *Angew. Chem.*, **40**, 1099 (1927).

(16) E. P. Kohler, M. Tishler, H. Potter, and H. T. Thompson, *J. Am. Chem. Soc.*, **61**, 1057 (1939).

(17) D. W. Adamson and K. Kenner, *J. Chem. Soc.*, 181 (1939).

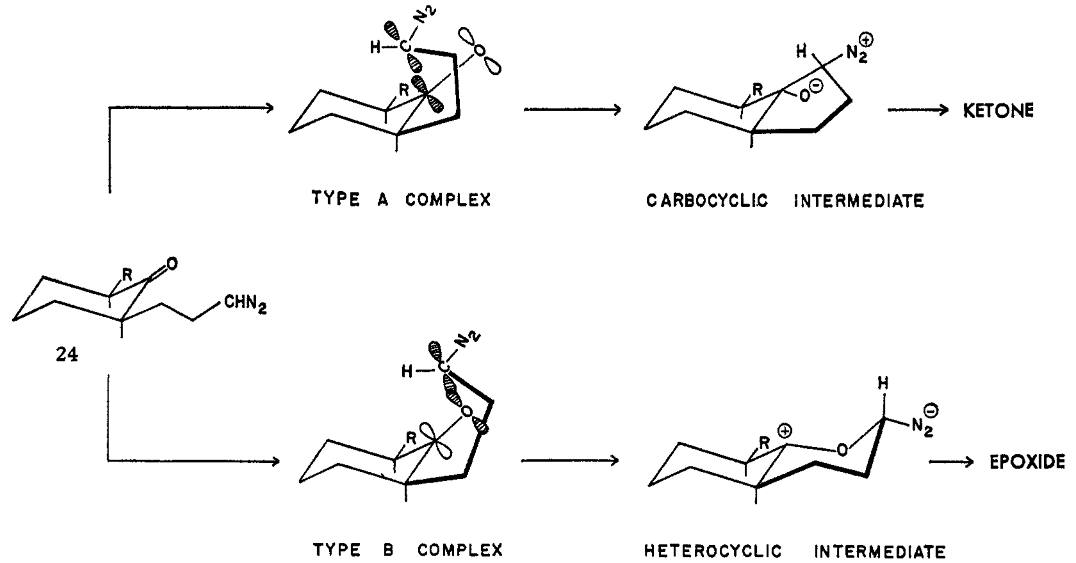
(18) M. Stoll and W. Scherrer, *Helv. Chim. Acta.*, **23**, 941 (1940).

(19) C. D. Gutsche and H. H. Peter, *J. Am. Chem. Soc.*, **77**, 5971 (1955).

(20) J. N. Bradley, G. W. Cowell, and A. Ledwith, *J. Chem. Soc.*, 3433 (1964).

(21) R. B. Woodward and G. Small, Jr., *J. Am. Chem. Soc.*, **72**, 1297 (1950).

Scheme X
Type A and B Complexes from Ketodiazoalkanes

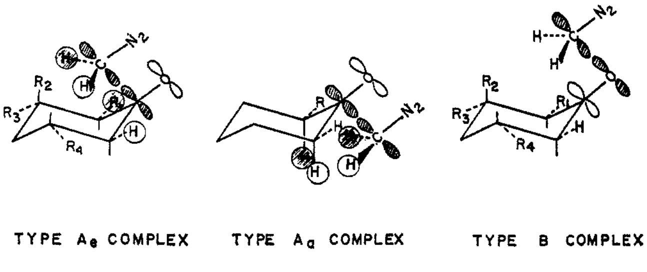


suggests, as with enamines, nucleophilic characteristics at carbon; the structural similarity of $R_2C{=}\overset{\oplus}{N}{=}\overset{\ominus}{N}$ and $R_2C{=}\overset{\oplus}{N}R_2$ suggests, as with iminium cations, electrophilic characteristics at carbon. The highly polarizable π-bond system of diazoalkanes should allow either of these reactivities to be manifested, depending upon the structure of the particular diazoalkane and carbonyl compound. It remains now to define the nature of the steric interactions that are sufficient to cause a shift from a type A complex to a type B complex, *i.e.*, to change the diazoalkane from enamine like reactivity to iminium ion like reactivity.

If it is assumed that diazoalkanes **24** (from nitroso compounds **8**) carry the diazoalkyl side chain in the equatorial position, two association complexes of interest are those represented in Scheme X. In the case of **24** with R = H (*e.g.*, substitution patterns **a** and **b**), little interference is encountered by either the H or the N_2 of the diazoalkyl group as it forms the type A complex and proceeds on to the charge-separated intermediate (carbocyclic intermediate). The products from these two systems are predominately the bridged ring ketones. In the case of **24** with R = CH_3 (*e.g.*, substitution patterns **c**, **d**, and **e**), however, there is a certain amount of interference between (a) the methyl group and the N_2 group as the side chain swings into position to assume the configuration of the type A complex and (b) the methyl group and the hydrogen of the diazoalkyl group as the type A complex proceeds to the carbocyclic intermediate. Both of these interactions are relieved in the type B complex and in the ensuing heterocyclic intermediate. It is in these cases that oxide is formed in considerable amount or, as in series **e**, as the predominant product. Molecular models of the Dreiding type and the Stuart-Briegleb type support the fact of hindrance but suggest that it is considerably less severe than is ordinarily the case where steric interferences are product determining. It is possible, however, that type A and type B complexes form with comparable ease and that unusually small steric encounters between the groups of the carbonyl compound and the diazoalkane are sufficient to shift the balance in favor of B.

The theory that carbonyl product arises from a carbocyclic intermediate *via* a type A complex and that epoxide product arises from a heterocyclic intermediate *via* a type B complex provides an explanation for certain of the puzzling results reported in the literature for intermolecular diazoalkane–carbonyl reactions. In the formation of a type A complex from cyclohexanone and diazomethane the approach may be at the face of the carbonyl which involves encounter with the α protons in (a) an equatorial attachment (type A_e complex) or (b) an axial attachment (type A_a complex), as illustrated in Scheme XI. It is reasonable to assume that the type A_e complex will be the more favorable. If, however, a methyl group is substituted for one of the equatorial hydrogens, type A_e complex should form somewhat less readily, type A_a complex remains a less preferred one, and the tendency to form a type B complex should be increased. It is, in fact, observed that the ketone-to-oxide ratio falls from 4 in the case of cyclohexanone to 1.25 in the case of 2-methylcyclohexanone. Similarly, in 3,5-dimethylcyclohexanone (R_3 = R_4 = CH_3 in Scheme XI), little hindrance is encountered in the formation of a type A_e complex, but in 3,3,5-trimethylcyclohexanone (R_2 = R_3 = R_4 = CH_3 in Scheme XI), the axial methyl group at R_2 hinders the formation of the type A_e complex, the type A_a complex remains less favorable, and again the result should be to facilitate the formation of a type B complex. In accordance with this rationalization, 3,5-dimethylcyclohexanone gives a ketone-to-oxide ratio of 2.16, while 3,3,5-trimethylcyclohexanone gives a ratio of 0.5. Still another

Scheme XI
Type A_e, A_a, and B Complexes from Cyclohexanones and Diazomethane

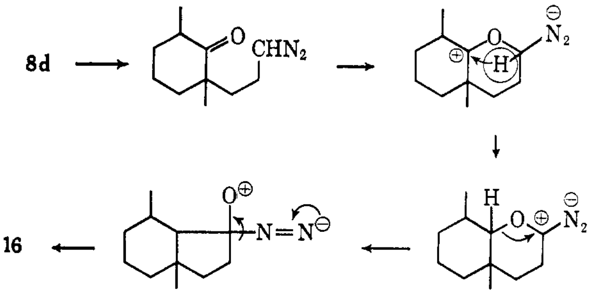


case, that of *cis*- and *trans*-α-decalone, can be interpreted in a comparable fashion. While *cis*-α-decalone possesses a carbonyl face at which the only interference is from equatorial hydrogens in the α position (*i.e.*, an association complex comparable to A_e), the *trans* isomer can only present a carbonyl face at which one of the equatorial positions is the carbon atom of the adjacent ring (*i.e.*, comparable to 2-methylcyclohexanone). Thus, *cis*-α-decalone might be expected to form less epoxide than *trans*-α-decalone; this prediction is in accord with observation.

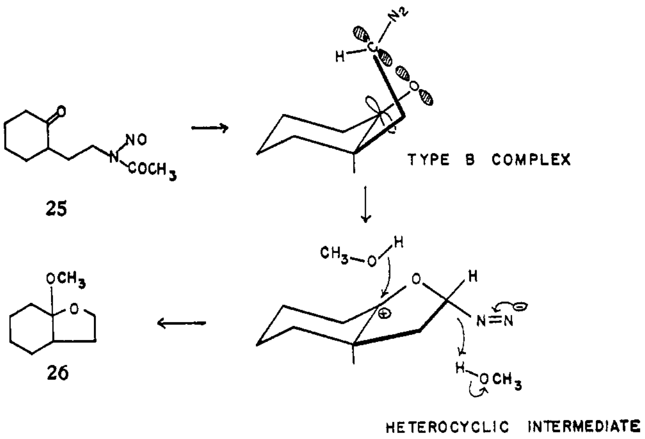
With the plausibility of the double-intermediate scheme supported by several examples, some of the finer points of the results recorded in Table I can now be considered. The fact that series **c** furnishes a 1:1 mixture of ketone and oxide while series **e** gives only oxide may be attributed to the buttressing effect of the second methyl group in the 6 position in series **e**. The methyl group in the equatorial position is less easily repelled in the formation of type A complex if it has to be thrust against another methyl group rather than against an hydrogen atom. The fact that series **g** furnishes a 3:1 mixture of ketone and oxide while series **f** gives only ketone can be attributed to an interaction between the methyl group in the side chain of series **g** with hydrogen atoms of the six-membered ring as the type A complex forms. Although it does not appear that this interference is significantly relieved in the formation of the type B complex, the decreased strain associated with the six-membered heterocyclic intermediate as compared with the five-membered carbocyclic intermediate may magnify the importance of nonbonded interactions in the latter. The formation of bicyclic fused ring ketone **16** from **8d** is surprising, for it has been shown that it is not simply the result of a rearrangement of epoxide **15** during the reaction or work-up. Possibly, a type B complex forms in such a fashion that the hydrogen atom of the diazomethyl carbon is suitably positioned to undergo a transannular migration, thus setting in motion the sequence of transformations illustrated in Scheme XII.[22]

In addition to the intramolecular modes of collapse of a type B complex (as represented by the formation of epoxide or ketone), an intermolecular mode also appears to exist. The major product of base-catalyzed treatment of nitrosoamide **25** (an example of the α-6-2 series[4]) is semicyclic ketal **26**. This result may be interpreted in terms of a type B complex (formed in preference to a type A complex because of the comparative strains present in four- and five-membered rings) which cannot easily collapse by either of the intermolecular routes because of the strain associated with a four-membered ring. Instead, it reacts intermolecularly with methanol, the methanol acting as a nucleophile toward the carbonium ion center and as a proton donor at the incipient carbanion center, as illustrated in Scheme XIII.

SCHEME XII
COLLAPSE OF TYPE B COMPLEXES *via* TRANSANNULAR HYDROGEN MIGRATION



SCHEME XIII
COLLAPSE OF TYPE B COMPLEX
via AN INTERMOLECULAR PATHWAY



The decrease in the ketone-to-oxide ratio that is observed when carbonyl compounds containing electron-withdrawing groups are employed[11] is satisfactorily explained by the nucleophilic mechanism (see Scheme VIII); it may also be interpreted on the basis of the double-intermediate mechanism. If it is assumed that carbonyl product can come only from a carbocyclic intermediate *via* a type A complex, the result of electron-withdrawing groups in the carbonyl compound would be (a) to promote the formation of the complex and the intermediate, but (b) to hinder the collapse of the intermediate because of the reduced electron-releasing properties of the migrating carbon groups. Instead of leading to product, therefore, the type A complex would collapse to starting materials. If it is assumed that epoxide product can come only from a heterocyclic intermediate *via* a type B complex, the result of electron-withdrawing groups in the carbonyl compound would be (a) to hinder the formation of the complex and the intermediate by reducing the basicity of the oxygen, but (b) to promote the collapse of the intermediate by enhancing the electron deficiency of the carbonyl carbon. The intermediate, once formed, would collapse to epoxide rather than starting materials.

The observation that epoxides are less likely to form when substituted diazomethanes are used (*i.e.*, $RCHN_2$) may also be accommodated by the double-intermediate scheme. In alkyl-substituted diazomethanes the elec-

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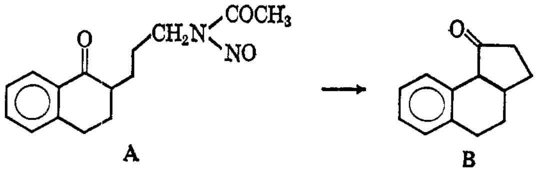
[22] A comparable product has also been isolated from the base-catalyzed decomposition of 2-(N-acetyl-N-nitroso-γ-aminopropyl)-1,2,3,4-tetrahydronaphthalene (A) (see the Experimental Section for description of preparation). The volatile product from this reaction (56% yield) consisted of two



components present in approximately equal amounts. One of these was isolated as a crystalline solid and has been identified as 2,3,3a,4,5,9b-hexahydro-1H-benz[*e*]inden-1-one (B) (see the Experimental Section for structure proof).

tron-releasing effect of the alkyl group (as compared with hydrogen) increases the electron density on the diazoalkyl carbon atom. The result is to facilitate the formation of the carbocyclic intermediate *via* a type A complex by allowing the transition state to be reached at a point where the newly forming C–C bond is longer than that present in the transition state from diazomethane itself, thus reducing steric interferences.

Experimental Section[23]

Preparation of N-Nitroso-N-acetyl-3-(ketocycloalkyl)propylamines (8). N-Nitroso-N-acetyl-3-(1′-methyl-2′-ketocyclohexyl)-propylamine (8b).—Following the general procedure of Bruson,[24] a stirred solution containing 300 ml of *t*-butyl alcohol, 224 g (2.0 moles) of 2-methylcyclohexanone, and 2 ml of benzyltrimethylammonium hydroxide solution (40% in methanol) was treated, dropwise over a period of 15 min, with 35.4 g (0.67 mole) of anhydrous acrylonitrile (redistilled and stored over 5-A Linde seives). After standing for 2 hr at 0–5°, the reaction mixture was warmed to room temperature, poured into 300 ml of ice water, and made acidic with 6 *N* hydrochloric acid. Distillation of the neutral material gave 86 g (78%) of a colorless oil which was indicated by vpc analysis to be a single component: bp 103–105° (0.1 mm); $\tilde{\nu}_{\max}^{\text{liquid}}$ 2300 (nitrile), 1715 cm^{-1} (carbonyl). The **2,4-dinitrophenylhydrazone of 2-methyl-2-(β-cyanoethyl)cyclohexanone (4b)** was obtained, after three recrystallizations from aqueous ethanol, as yellow needles, mp 127–128°.

Anal. Calcd for $C_{16}H_{19}N_5O_4$: C, 55.64; H, 5.55. Found: C, 55.97; H, 5.38.

A mixture of 86 g (0.52 mole) of 2-methyl-2-(β-cyanoethyl)-cyclohexanone, 40 g (0.65 mole) of ethylene glycol, 1.5 g of *p*-toluenesulfonic acid, and 500 ml of dry, thiophene-free benzene was placed in an apparatus equipped with a water-separator tube and refluxed for 12 hr during which time 11.4 ml of water was collected. The solution was cooled, made basic with 1 *M* sodium methoxide solution, poured into water, and processed to yield the ethylene ketal product as a pale yellow oil. Following the procedure of Gould, Johnson, and Ferris[25] for reductive acetylation, the crude ethylene ketal was treated with 25 g of W-2 Raney nickel,[26] 25 g of anhydrous sodium acetate, and 300 ml of acetic anhydride, and the mixture was heated to 100° and subjected to hydrogenation at a pressure of 25 psi. The absorption of hydrogen ceased after 4 hr, at which time the mixture was cooled, filtered, concentrated to 150 ml, and treated with 200 ml of 1:25 aqueous sulfuric acid along with sufficient acetic acid to give a homogeneous solution. This solution was allowed to stand at room temperature for 12 hr (selective hydrolysis of ethylene ketal group) and was then poured into 1 l. of water saturated with sodium chloride. The usual work-up by extraction and distillation gave 74 g (68%) of a colorless oil, bp 162–170° (0.3 mm). A sample of **N-acetyl-3-(1′-methyl-2′-ketocyclohexyl)propylamine (7b)** was obtained by redistilling a portion of this material through a short-path apparatus at 120° (0.001 mm); $\tilde{\nu}_{\max}^{\text{liquid}}$ 3400 and 3300 (NH), 1710 (cyclohexanone carbonyl), 1670 cm^{-1} (amide).

Employing the nitrosation method of White,[27] a solution of 57 g (0.27 mole) of the keto amide in 500 ml of dichloromethane was cooled to −10° and poured into a stirred and cooled (to −30°) solution of 0.41 mole of nitrogen dioxide and 72 g (0.82 mole) of anhydrous sodium acetate in 500 ml of dichloromethane. The temperature was maintained between 0 and −10° (reaction quite exothermic) for 20 min, and the mixture was poured into 1 l. of ice-cold 10% potassium carbonate solution. After thorough agitation, the organic phase was separated, the carbonate solution was twice extracted with 100-ml portions of dichloromethane, the combined extract was dried over anhydrous potassium carbonate, and the solvent was removed to leave the nitroso compound (**8b**) as a red oil.

N-Nitroso-N-acetyl-3-(3′-methyl-2′-ketocyclohexyl)propylamine (8c).—Following the procedure of Stork and co-workers,[28] 2-methyl-6-(β-cyanoethyl)cyclohexanone was obtained in 60% yield from the pyrrolidine enamine of 2-methylcyclohexanone and acrylonitrile. A 39-g sample of this material was converted to the ethylene ketal, subjected to reductive acetylation, and selectively hydrolyzed as described above to yield 38.8 g (78%) of N-acetyl-3-(3′-methyl-2′-ketocyclohexyl)propylamine (**7c**) as a colorless oil: bp 155–159° (0.3 mm); $\tilde{\nu}_{\max}^{\text{liquid}}$ 3400 and 3200 (NH), 1715 (cyclohexanone carbonyl), 1660 cm^{-1} (amide). Nitrosation was effected as described above to yield the nitroso compound (**8c**) as an orange oil which was used without purification.

N-Nitroso-N-acetyl-3-(1′,3′-dimethyl-2′-ketocyclohexyl)propylamine (8d).—Using the Bruson cyanoethylation procedure[24] described above for 2-methylcyclohexanone, a 25-g sample of 2,6-dimethylcyclohexanone[29] was converted to 4.56 g (20%) of **2-(β-cyanoethyl)-2,6-dimethylcyclohexanone (4d)**, obtained as a colorless oil: bp 155–158° (7 mm); $\tilde{\nu}_{\max}^{\text{liquid}}$ 2300 (nitrile), 1705 cm^{-1} (carbonyl).

A 3.90-g sample of this material was converted to the ethylene ketal, subjected to reductive acetylation, and selectively hydrolyzed by the procedures described above to yield 4.09 g (83%) of N-acetyl-3-(1′,3′-dimethyl-2′-ketocyclohexyl)propylamine (**7d**) as a pale yellow oil: bp 165–170° (0.1 mm); $\tilde{\nu}_{\max}^{\text{liquid}}$ 3400 (NH), 1710 (carbonyl), 1670 cm^{-1} (amide). Nitrosation was effected as described above to yield the nitroso compound (**8d**) as an orange oil which was used without purification.

N-Nitroso-N-acetyl-3-(1′,3′,3′-trimethyl-2′-ketocyclohexyl)propylamine (8e).—Using the cyanoethylation procedure described above for 2-methylcyclohexanone, a 95-g sample of 2,2,6-trimethylcyclohexanone[30] was converted to 86 g (61%) of 2-(β-cyanoethyl)2,6,6-trimethylcyclohexanone, bp 122° (1.0 mm). A 79-g sample of the ketonitrile was converted to the ethylene ketal, subjected to reductive acetylation, and selectively hydrolyzed by the procedures described above to yield 72 g (73%) of **N-acetyl-3-(1′,3′,3′-trimethyl-2′-ketocyclohexyl)propylamine (7e)** as a pale yellow oil: bp 145–148° (0.01 mm); $\tilde{\nu}_{\max}^{\text{liquid}}$ 3400 and 3200 (NH), 1700 (carbonyl), 1660 cm^{-1} (amide).

Nitrosation was effected as described above to yield the nitroso compound (**8e**) as an orange oil which was used without purification.

N-Nitroso-N-acetyl-2-methyl-3-(2′-ketocyclohexyl)propylamine (8f).—A 50-g sample (0.51 mole) of cyclohexanone was converted to the pyrrolidine enamine, dissolved in 300 ml of absolute ethanol, treated with 40 g (0.60 mole) of methacrylonitrile,[31] and refluxed for 12 hr to yield 56.7 g (75%) of **2-(β-methyl-β-cyanoethyl)cyclohexanone (4f)** as a colorless oil: bp 98–100° (0.5 mm); $\tilde{\nu}_{\max}^{\text{liquid}}$ 2300 (nitrile), 1715 cm^{-1} (carbonyl).

The **semicarbazone of 2-(β-methyl-β-cyanoethyl)cyclohexanone (4f)** was obtained, after three recrystallizations from water, as white needles, mp 158.5–160°.

Anal. Calcd for $C_{11}H_{18}N_4O$: C, 59.43; H, 8.16. Found: C, 59.67; H, 7.87.

A 53-g sample of the ketonitrile was converted to the ethylene ketal, subjected to reductive acetylation, and selectively hydrolyzed to yield 58 g (65%) of N-acetyl-2-methyl-3-(2′-ketocyclohexyl)propylamine (**7f**) as a pale yellow oil: bp 147–150° (0.05

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[23] Melting points are corrected; boiling points are uncorrected. The infrared spectra were recorded on a Perkin–Elmer Model 21 spectrometer or a Perkin-Elmer Infracord spectrometer; the nuclear magnetic resonance spectra were recorded on Varian HR-60 or A-60 spectrometers. Vapor phase chromatographic analyses were performed on (a) an F and M Model 721 instrument containing a 0.25 in. × 6 ft column packed with 20% by weight of Carbowax 20M on 30–60 mesh firebrick, (b) a homemade apparatus containing a 0.25 in. × 16 ft column packed with 3% or with 15% by weight of A3 neopentylglycol sebacate on 40–50 mesh type ABS Anakrom (products of Analytical Engineering Labs, Inc., Hamden, Conn.). All solvent evaporations were carried out with a rotating evaporator manufactured by the Rinco Instrument Co., Greenville, Ill. The short-path apparatus used for the distillation of small amounts of materials consisted of a two-bulb unit blown from 8–10-mm-diameter glass tubing, the terminal bulb containing the sample and being heated in an electrically controlled air bath and the second bulb acting as a collector and being cooled by air or by pieces of wet cotton. Microanalyses were performed by Mikroanalytisches Laboratorium, Vienna, Austria.

[24] H. A. Bruson, *Org. Reactions*, **5**, 79 (1949).

[25] F. E. Gould, G. S. Johnson, and A. F. Ferris, *J. Org. Chem.*, **25**, 1658 (1960).

[26] R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 181.

[27] E. H. White, *J. Am. Chem. Soc.*, **77**, 6008 (1955).

[28] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

[29] G. Stork and S. R. Dowd, *ibid.*, **85**, 2178 (1963).

[30] C. L. Stevens and A. L. Weinheimer, *ibid.*, **80**, 4072 (1958).

[31] D. T. Mowry and R. R. Morner, *ibid.*, **69**, 1831 (1947).

mm); $\tilde{\nu}_{\max}^{\text{liquid}}$ 3420 and 3210 (NH), 1710 (carbonyl), 1650 cm^{-1} (amide). A **2,4-dinitrophenylhydrazone of 7f** was obtained, after three recrystallizations from aqueous ethanol, as yellow needles, mp 128–129°.

Anal. Calcd for $C_{18}H_{25}N_5O_5$: C, 55.23; H, 6.44. Found: C, 55.42; H, 6.33.

Nitrosation was effected as described above to yield the nitroso compound (**8f**) as a red oil which was used without purification.

N-Nitroso-N-acetyl-3-(2′-ketocyclohexyl)butylamine (8g).—A 98-g sample (1.0 mole) of cyclohexanone was converted to the pyrrolidine enamine, and this was treated with 67 g (1.0 mole) of 3-butenonitrile in ethanol solution. The distilled product consisted of 72.5 g (44%) of **2-(α-methyl-β-cyanoethyl)cyclohexanone (4g)**: bp 98–100° (0.5 mm); $\tilde{\nu}_{\max}^{\text{liquid}}$ 2225 (nitrile), 1705 cm^{-1} (carbonyl).

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15. Found: C, 72.95; H, 9.27.

The **2,4-dinitrophenylhydrazone of 4g** was obtained as yellow needles after recrystallization from aqueous ethanol, mp 152–153°.

Anal. Calcd for $C_{16}H_{19}N_5O_4$: C, 55.64; H, 5.55. Found: C, 55.91; H, 5.52.

A 72.5-g sample of the ketonitrile was converted to the ethylene ketal, subjected to reductive acetylation, and selectively hydrolyzed by the procedures described above to yield 58 g (65%) of **N-acetyl-3-(2′-ketocyclohexyl)butylamine (7g)** as a yellow oil: bp 147–150° (0.05 mm); $\tilde{\nu}_{\max}^{\text{liquid}}$ 3300 and 3200 (NH), 1703 (carbonyl), 1680 cm^{-1} (amide).

Nitrosation was effected as described above to yield the nitroso compound (**8g**) as a red oil which was used without purification.

2-(N-Acetyl-N-nitroso-γ-aminopropyl)-1,2,3,4-tetrahydronaphthalen-1-one.—To a 1-l. flask fitted with a magnetic stirrer and a Soxhlet extractor containing 50 g of calcium carbide[32] was added 84.5 g (0.58 mole) of 1,2,3,4-tetrahydronaphthalen-1-one,[33] 170 g (2.4 moles) of pyrrolidine, 300 ml of toluene, and 2 g of Amberlite IR-120 (acid form). The mixture was refluxed for a 2-week period during which time five additional 2-g portions of Amberlite IR-120 were added. The product consisted of 79.3 g (80% based on recovered starting material) of the pyrrolidine enamine of 1,2,3,4-tetrahydronaphthalen-1-one, obtained as a yellow oil, bp 109–112° (0.3 mm). A 79.3-g (0.4 mole) sample of the enamine was dissolved in 300 ml of absolute ethanol, treated with 29 g (0.55 mole) of acrylonitrile, and refluxed for 4 hr. The crude product consisted of 75 g (94%) of a brown solid, mp 50–54°, which, after one recrystallization from aqueous ethanol, gave 58.5 g (74%) of light tan needles, mp 58–58.5°. An analytical sample of **2-(β-cyanoethyl)-1,2,3,4-tetrahydronaphthalen-1-one** was obtained after a second recrystallization as colorless needles: mp 58–59°; $\tilde{\nu}_{\max}^{\text{CCl}_4}$ 2270 (nitrile), 1680 cm^{-1} (carbonyl).

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58. Found: C, 78.45; H, 6.58.

A 48-g sample of the ketonitrile was converted to the ethylene ketal, subjected to reductive acetylation, and selectively hydrolyzed to give 59.2 g (100%) of **2-(N-acetyl-γ-aminopropyl)-1,2,3,4-tetrahydronaphthalen-1-one**, mp 70–74°. Recrystallization from isopropyl ether containing a small amount of chloroform gave 27 g (46%) of material in the first crop, mp 88–89°, and 7 g (12%) of material in the second crop, mp 85–87°. An analytical sample was obtained by two additional recrystallizations as colorless, thick needles: mp 92–92.5°; $\tilde{\nu}_{\max}^{\text{mull}}$ 3400 and 3200 (NH), 1690 (carbonyl), 1650 cm^{-1} (amide).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81. Found: C, 73.32; H, 8.00.

Nitrosation was effected as described above to yield the nitroso compound as a deep red oil which was used without purification.

Decomposition of N-Nitroso-N-acetyl-3-(ketocycloalkyl)propylamines. Decomposition of N-Nitroso-N-acetyl-3-(1′-methyl-2′-ketocyclohexyl)propylamine (8b).—A 1-l. three-necked flask equipped with a condenser and two addition funnels was charged with 25 ml of anhydrous ethanol. The ethanol was heated to reflux, and nitroso compound **8b** from 57 g of N-acetyl-3-(1′-methyl-2′-ketocyclohexyl)propylamine (**7b**), obtained as described in the previous section, was added dropwise over a 15-min period. Simultaneously, a 0.4 *M* solution of sodium ethoxide in ethanol was added from the other funnel at a rate which maintained a steady nitrogen evolution (5–10 ml usually required). The reaction mixture was refluxed for an additional 15 min and was then subjected to steam distillation, 1 l. of distillate being collected. The crude product so obtained consisted of 41 g (98%) of a yellow oil which was shown by analytical vpc to be at least 95% pure. A colorless sample of **1-methylbicyclo[4.2.1]nonan-9-one (9)** was obtained by a second distillation of the crude material: bp 118–125° (28 mm); $\tilde{\nu}_{\max}^{\text{liquid}}$ 1745 with a shoulder at 1710 cm^{-1} (cyclopentanone carbonyl); nmr (CCl_4) τ 7.6 (multiplet, one proton), 8.4 (broad doublet, 12 protons), 8.96 (singlet, three protons).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 79.01; H, 10.67.

The **2,4-dinitrophenylhydrazone of 1-methylbicyclo[4.2.1]nonan-9-one** was obtained, after three recrystallizations from aqueous ethanol, as yellow needles, mp 197–198°.

Anal. Calcd for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07. Found: C, 58.11; H, 6.43.

The minor component of the reaction mixture from **8b** was tentatively identified as 2-methyl-2-(γ-ethoxypropyl)cyclohexanone (**10**) on the basis of its greater retention time on vpc analysis (characteristic of keto ethers in related systems) and its infrared spectrum $\tilde{\nu}_{\max}^{\text{liquid}}$ 1710 (carbonyl), 1130 cm^{-1} (CH_2OCH_2).

The absence of any fused-ring ketone in the product was indicated by the following experiment. A 100-mg sample of the crude product was mixed with an equal amount of 2,2,6,6-tetramethylcyclohexanone, and the mixture was assayed on the vpc, treated with 50% nitric acid and a small amount of ammonium vandate, refluxed for 1 hr, and reassayed on the vpc. No change in the ratio of the peaks arising from the 2,2,6,6-tetramethylcyclohexanone and the other ketones in the mixture was observed, indicating that no oxidizable (*i.e.*, fused ring) ketones were present in the reaction product.

Decomposition of N-Nitroso-N-acetyl-3-(3′-methyl-2′-ketocyclohexyl)propylamine (8c).—Following the procedure described above, the nitroso compound (**8c**) from 20 g of N-acetyl-3-(3′-methyl-2′-ketocyclohexyl)propylamine (**7c**), obtained as indicated in the previous section, was subjected to base-catalyzed decomposition to yield 11.2 g (78%) of distilled material. Analysis by vpc indicated the mixture to contain two major components in equal amount and accounting for 85% of the total product. Separation by preparative-scale vpc yielded (a) **5-methyl-6,7-epoxybicyclo[4.3.0]nonane (13)**, the more volatile component, as a colorless oil: $\tilde{\nu}_{\max}^{\text{liquid}}$ 910 and 833 cm^{-1} (epoxide); nmr (CCl_4) τ 6.65 (multiplet, one proton), 8.53 (multiplet, 12 protons), 9.3 (doublet, three protons).

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 77.25; H, 10.41.

For reasons that are not apparent, the carbon analysis was consistently low (analytical data from three different microanalytical laboratories). (b) **2-Methylbicyclo[4.2.1]nonan-9-one (12)**, the less volatile component was obtained as a colorless oil possessing a camphoraceous odor: $\tilde{\nu}_{\max}^{\text{liquid}}$ 1750 cm^{-1} (carbonyl); nmr (CCl_4) τ 7.82 (broad singlet, one proton), 8.2 (multiplet, 12 protons), 9.03 (unsymmetrical doublet, three protons).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.43; H, 10.38.

When the base-catalyzed decomposition was carried out at 0–5° with potassium carbonate and methanol, a 76% yield of distilled material was obtained which consisted of 5-methyl-6,7-epoxybicyclo[4.3.0]nonane (**13**), 2-methylbicyclo[4.2.1]nonan-9-one (**12**), and 2-(γ-methoxypropyl)-6-methylcyclohexanone in the ratio 1:2:1. The structure of the latter compound is based solely on the similarity of its infrared spectrum with those of previously identified keto ethers in this series of compounds.

Decomposition of N-Nitroso-N-acetyl-3-(1′,3′-dimethyl-2′-ketocyclohexyl)propyalmine (8d).—Following the procedure described above, nitroso compound **8d** from 2.09 g of N-acetyl-3-(1′,3′-dimethyl-2′-ketocyclohexyl)propylamine (**7d**), obtained as indicated in the previous section, was subjected to base-catalyzed decomposition with sodium ethoxide in boiling ethanol to yield 1.23 g (83%) of distilled product, bp 95–115° (7 mm). Analysis by vpc indicated the mixture to contain three major components in the ratio 2:6:1 and accounting for 85% of the total product. Separation by preparative-scale vpc yielded (a) **1,5-dimethyl-6,7-epoxybicyclo[4.3.0]nonane (15)**, the most volatile component, as a colorless oil: $\tilde{\nu}_{\max}^{\text{liquid}}$ 900 and 823 cm^{-1} (epoxide); nmr (CCl_4) τ 6.83 (singlet, one proton), 8.5 (broad multiplet, 11 protons), 8.97 (singlet, three protons), 9.30 (unsymmetrical doublet, three protons).

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[32] J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford, and F. W. Heyl, *J. Am. Chem. Soc.*,, **78**, 430 (1956).

[33] C. E. Olson and A. R. Bader, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 898.

(b) **1,5-Dimethylbicyclo[4.3.0]nonan-7-one (16)**, the middle component, was obtained as a colorless oil with a camphoraceous odor decolorizing 10% bromine in carbon tetrachloride solution; it could be oxidized by refluxing nitric acid containing ammonium vanadate catalyst; $\bar{\nu}_{\max}^{\text{liquid}}$ 1750 (carbonyl), 1715 cm^{-1} (carbonyl); nmr (CCl_4) τ 7.95 (multiplet, three protons), 8.50 (broad multiplet, nine protons), 8.95 (unsymmetrical doublet, six protons).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.75; H, 11.07.

(c) **1,5-Dimethylbicyclo[4.2.1]nonan-9-one (14)**, the highest boiling component, was obtained as a colorless oil possessing a camphoraceous odor which failed to decolorize bromine in carbon tetrachloride solution or to undergo oxidation with nitric acid and ammonium vanadate, $\bar{\nu}_{\max}^{\text{liquid}}$ 1745 cm^{-1} (carbonyl).

Decomposition of N-Nitroso-N-acetyl-3-(1′,3′,3′-trimethyl-2′-ketocyclohexyl)propylamine (8e).—Following the procedure described above, nitroso compound **8e** from 58.2 g of N-acetyl-3-(1′,3′,3′-trimethyl-2′-ketocyclohexyl)propylamine (**7e**), obtained as indicated in the previous section, was subjected to base-catalyzed decomposition with sodium ethoxide in refluxing ethanol to give a quantitative yield of crude product which was shown by vpc to consist of 85% of one component. Distillation through a spinning-band column yielded 14.40 g (35%) of material, bp 138° (58 mm) 98% pure in the major component, and 5.51 g (13%) of material, bp 142–146° (58 mm) 92% pure in the minor components. The major component, identified as **1,5,5-trimethyl-6,7-epoxybicyclo[4.3.0]nonane (17)**, was obtained as a colorless oil: $\bar{\nu}_{\max}^{\text{liquid}}$ 900 and 830 cm^{-1} (epoxide); nmr (CCl_4) τ 6.76 (broad singlet, one proton), 8.5 (broad multiplet, ten protons), 8.92 (doublet, six protons), 9.3 (singlet, three protons).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.63; H, 11.13.

Decomposition of N-Nitroso-N-acetyl-2-methyl-3-(2′-ketocyclohexyl)propylamine (8f).—Following the procedure described above, nitroso compound **8f** from 39.5 g of N-acetyl-2-methyl-3-(2′-ketocyclohexyl)propylamine (**7f**), obtained as indicated in the previous section, was subjected to base-catalyzed decomposition with sodium ethoxide in refluxing ethanol to give 24 g (86%) of colorless, distilled product, bp 118–124° (28 mm), which was shown by vpc to consist of two components present in equal amount. These were separated by preparative-scale vpc and obtained as the **α and β isomers of 7-methylbicyclo[4.2.1]nonan-9-one (21)**, both colorless oils resistant to oxidation with nitric acid and ammonium vanadate and identical with samples prepared by the decomposition described below.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found (for α isomer): C, 78.74; H, 10.66. Found (for β isomer): C, 78.75; H, 10.79.

Decomposition of N-Nitroso-N-acetyl-3-(2′-ketocyclohexyl)-butylamine (8g).—Following the procedure described above, nitroso compound **8g** from 57 g of N-acetyl-3-(2′-ketocyclohexyl)butylamine (**7g**), obtained as indicated in the previous section, was subjected to base-catalyzed decomposition with sodium ethoxide in refluxing ethanol to give 35 g (84%) of a yellow oil which was shown by vpc to contain three major components in the ratio 1:2:1. Separation was effected by distillation through a 36-in. spinning-band column and further purification by passage through a preparative-scale vpc unit. The lowest boiling component, tentatively identified as 9-methyl-6,7-epoxybicyclo[4.3.0]nonane (**22**), was obtained as a colorless oil:, $\bar{\nu}_{\max}^{\text{liquid}}$ 820 cm^{-1} (epoxide); nmr (CCl_4) τ 7.0 (singlet, one proton), 8.5 (broad multiplet, 12 protons), 9.2 (unsymmetrical doublet, three protons). The middle component, identified as the α isomer of 7-methylbicyclo[4.2.1]nonan-9-one (α-**21**), was obtained as a colorless oil: $\bar{\nu}_{\max}^{\text{liquid}}$ 1740 cm^{-1} (carbonyl); nmr (CCl_4) τ 7.6 (multiplet, one proton), 8.3 (broad multiplet, 12 protons), 8.95 (unsymmetrical doublet, three protons). The **2,4-dinitrophenylhydrazone of α-21** was obtained as orange needles after three recrystallizations from ethanol, mp 142–143°.

Anal. Calcd for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07. Found: C, 58.22; H, 5.99.

The highest boiling component, identified as the β isomer of 7-methylbicyclo[4.2.1]nonan-9-one (β-**21**), was obtained as a colorless oil: $\bar{\nu}_{\max}^{\text{liquid}}$ 1740 cm^{-1} (carbonyl); nmr (CCl_4) τ 7.70 (unsymmetrical doublet, three protons), 8.4 (broad singlet, ten protons), 8.92 (unsymmetrical doublet, three protons). The **2,4-dinitrophenylhydrazone of β-21** was obtained as orange needles after three recrystallizations from ethanol, mp 145–146°. Upon admixture with the 2,4-dinitrophenylhydrazone of the α isomer, the melting point was depressed to 138–139°.

Anal. Calcd for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07. Found: C, 57.80; H, 5.86.

Decomposition of 2-(N-Acetyl-N-nitroso-γ-aminopropyl)-1,2,3,4-tetrahydronaphthalen-1-one (26).—Following the procedure described above, the nitroso compound from 27 g of 2-(N-acetyl-γ-aminopropyl)-1,2,3,4-tetrahydronaphthalen-1-one (**25**), obtained as indicated in the previous section, was subjected to base-catalyzed decomposition with sodium ethoxide in refluxing ethanol to give 10.5 g (56%) of distilled material, bp 140–150° (0.5 mm), which was shown by vpc to consist of two major components present in the ratio 4:5. Upon dissolving a portion of the product in a small amount of ethanol and allowing the solution to stand for 2 days, one of the components separated as a solid. Recrystallization from aqueous ethanol yielded 2,3,3a,4,5,9b-hexahydro-1H-benz[*e*]inden-1-one (**27**) as white needles: mp 64–65°; $\bar{\nu}_{\max}^{\text{liquid}}$ 1745 (carbonyl), 765 and 735 cm^{-1} (*ortho*-disubstituted benzene). The **2,4-dinitrophenylhydrazone of 27** was obtained, after recrystallization from ethanol–butanol, as yellow needles, mp 221–222°.

Anal. Calcd for $C_{19}H_{18}N_4O_4$: C, 62.28; H, 4.95. Found: C, 62.12; H, 4.88.

Proof of Structure of Products from Decomposition of Nitroso Compounds. 1,5,5-Trimethyl-6,7-epoxybicyclo[4.3.0]nonane (17). A. Lithium Aluminum Hydride Reduction.—A 1.01-g (0.0055 mole) sample of 1,5,5-trimethyl-6,7-epoxybicyclo[4.3.0]nonane (**17**) was dissolved in 10 ml of anhydrous ether, and the solution was added dropwise to a suspension of 0.6 g (0.015 mole) of lithium aluminum hydride in 50 ml of refluxing ether.[34] The mixture was refluxed for 24 hr and then worked up to give, after short-path distillation, 0.780 g (78%) of 1,5,5-trimethylbicyclo[4.3.0]nonan-6-ol (**18**) as a waxy, low-melting solid: mp *ca.* 30° $\bar{\nu}_{\max}^{\text{liquid}}$ 3690 cm^{-1} (hydroxyl).

B. Dehydration of 1,5,5-Trimethylbicyclo[4.3.0]nonan-6-ol (18).—A 0.516-g (0.00284 mole) sample of 1,5,5-trimethylbicyclo[4.3.0]nonan-6-ol (**18**) was dissolved in 15 ml of pyridine, cooled to 0°, and treated with 5 ml of thionyl chloride. After warming to room temperature and standing for 15 min the mixture was added to ice and water and worked up to give, after short-path distillation of the residue, 0.380 g (83%) of **1,5,5-trimethylbicyclo[4.3.0]non-6-ene (19)** as a colorless oil: $\bar{\nu}_{\max}^{\text{liquid}}$ 1660, 1640 cm^{-1} (olefin).

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.71; H, 12.19.

C. Ozonolysis of 1,5,5-Trimethylbicyclo[4.3.0]non-6-ene (19).—A 0.200-g (0.00122 mole) sample of 1,5,5-trimethylbicyclo[4.3.0]non-6-ene (**19**) was dissolved in 20 ml of dichloromethane and ozonized until the absorption of ozone ceased. The solvent was evaporated, 10 ml of formic acid was added, the solution was heated on the steam bath, and 2 ml of 30% hydrogen peroxide solution was added. The reaction mixture was cooled, concentrated to 3 ml, diluted with 10 ml of water, and continuously extracted with ether for 24 hr. The product was obtained, after short-path distillation, as 0.138 g (55%) of solid, mp 43–45°, which was shown to be identical with 3-(1′,3′,3′-trimethyl-2-ketocyclohexyl)propionic acid (**20**), obtained by an alternate synthesis (see next section).

D. Epoxidation of 1,5,5-Trimethylbicyclo[4.3.0]non-6-ene.—A 60-mg sample of 1,5,5-trimethylbicyclo[4.3.0]non-6-ene was oxidized with monoperphthalic acid,[35] and the product was chromatographed on alumina and purified by passage through a preparative-scale vpc column to yield 21 mg (29%) of a colorless oil, $\bar{\nu}_{\max}^{\text{liquid}}$ 900 and 830 cm^{-1} (epoxide). Analytical vpc indicated the product to be a mixture of two compounds, presumably the *cis* and *trans* isomers of 1,5,5-trimethyl-6,7-epoxybicyclo[4.3.0]-nonane; one of the components had a retention time identical with that of the product obtained from the decomposition of N-nitroso-N-acetyl-3-(1′,3′,3′-trimethyl-2′-ketocyclohexyl)propylamine (**17**), *i.e.*, the oxide which provided the starting material for this series of reactions.

2,3,3a,4,5,9b-Hexahydro-1H-benz[*e*]inden-1-one (28).—A 114-mg sample of **27** was subjected to a Clemmensen reduction,[36] and the resulting product was purified by passage through an alumina column followed by short-path distillation to yield 76 mg (72%) of 2,3,3a,4,5,9b-hexahydro-1H-benz[*e*]indene (**28**) as a

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[34] W. G. Brown, *Org. Reactions*, **6**, 469 (1951).

[35] H. Bohme, ref 26, p 619.

[36] E. L. Martin, *Org. Reactions*, **1**, 155 (1942).

colorless oil. A comparison of the infrared spectrum of this material with a sample prepared by a different route[37] showed the two compounds to be identical. Dehydrogenation of **28** was effected by heating with 10% palladium on charcoal at 250° for 1.5 hr and 350° for 0.5 hr. From 60 mg of meterial there was obtained 25 mg (43%) of 2,3-dihydro-1H-benz[*e*]indene (**29**) as a colorless oil possessing an infrared spectrum identical in every detail with that of a sample prepared by a different method.[37]

3-(1′,3′,3′-Trimethyl-2′-ketocyclohexyl)propionic Acid (20).—A 500-mg sample of 2-(β-cyanoethyl)-2,6,6-trimethylcyclohexanone (**4e**) was refluxed for 2 hr with 25 ml of 2.5 *N* sodium hydroxide solution, and the resulting product was purified by short-path distillation to yield 450 mg (82%) of **20** as a colorless, crystalline solid, mp 45–47°.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.87; H, 9.50. Found: C, 67.99; H, 9.71.

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[37] D. Lipkin and F. R. Galiano, unpublished observations; see F. R. Galiano, Ph.D. Dissertation, Washington University, 1961.

Registry No.—**4b** 24,-DNPH, 7688-07-5; **7b**, 7647-20-3; **7c**, 7647-21-4; **4d**, 7647-22-5; **7d**, 7647-23-6; **7e**, 7647-24-7; **4f** 7647-25-8; **4f** semicarbazone, 7647-26-9; **7f** 2,4-dinitrophenylhydrazone, 10035-80-0; **4g**, 7647-27-0; **4g** 2,4-dinitrophenylhydrazone, 7647-28-1; **7g**, 7647-29-2; 2-(β-cyanoethyl)-1,2,3,4-tetrahydronaphthalen-1-one, 7647-30-5; 2-(N-acetyl-γ-aminopropyl)-1,2,3,4-tetrahydronaphthalen-1-one, 7678-11-7; **9**, 7688-08-6; **9** 2,4-dinitrophenylhydrazone, 7678-12-8; **13**, 7647-31-6; **12**, 7647-32-7; **15**, 7647-33-8; **16**, 7647-34-9; **14**, 7647-35-0; **17**, 7647-36-1; α-**21**, 7647-37-2; β-**21**, 7647-38-3; **22**, 7647-39-4; α-**21** 2,4-dinitrophenylhydrazone, 7647-40-7; β-**21** 2,4-dinitrophenylhydrazone, 7647-41-8; **27**, 7647-42-9; **27**, 2,4-dinitrophenylhydrazone, 7647-43-0; **18**, 7647-44-1; **19**, 7647-45-2; **20**, 7647-46-3; **28**, 7647-47-4.

Friedel–Crafts Alkylation of Pentafluorobenzene[1,2]

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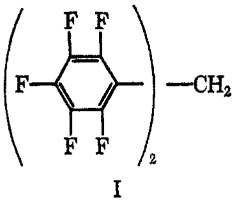
Bis(pentafluorophenyl)methane and tris(pentafluorophenyl)methane were prepared in 77 and 92% yields, respectively, by a Friedel–Crafts reaction of pentafluorobenzene with methylene chloride and chloroform using aluminum chloride as the Lewis acid. Pentafluorotoluene (8% yield) was the sole product isolated in the reaction of methyl chloride with pentafluorobenzene. Pentafluorobenzyl chloride was treated with pentafluorobenzene and benzene to produce bis(pentafluorophenyl)methane and pentafluorophenylphenylmethane, respectively. Spectral properties of the new compounds were consistent with the proposed structures. Addition of small amounts of copper metal and cupric chloride did not drastically change the yields.

Previous investigators have prepared alkyl- or aryl-substituted fluoro aromatics by Grignard synthesis[3] or by the interaction of alkyl- or aryllithium reagents[4] with hexafluorobenzene. To eliminate the handling of air-sensitive organometallics, it was of interest to explore the Friedel–Crafts reactions of pentafluorobenzene as source of pentafluorophenylalkanes.

Initial attempts to alkylate pentafluorobenzene by standard Friedel–Crafts methods were abortive. Refluxing of an excess of pentafluorobenzene with methylene chloride or chloroform for 4 hr in the presence of catalytic or stoichiometric amounts of aluminum chloride[5] gave the starting materials, traces of unidentified oils, and small amounts of a crystalline compound which was identified as hexachlorobenzene.[6] Under these reaction conditions, the change of the solvent to carbon disulfide or nitrobenzene did not give the desired results. A 33% yield of tris(pentafluorophenyl)methane, however, could be obtained from chloroform, aluminum chloride, and excess pentafluorobenzene when the refluxing time was prolonged to 21 hr.

Better results were obtained when the experiments were carried out in a steel bomb at 150°, using excess pentafluorobenzene as solvent. Under these conditions, methylene chloride and chloroform reacted readily with pentafluorobenzene in the presence of aluminum chloride to form bis(pentafluorophenyl)methane (I) and tris(pentafluorophenyl)methane (II) in 77 and 92% yield, respectively.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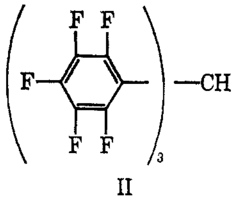
II

The over-all effect of reaction time and ratio of aluminum chloride to haloalkane can be observed from the data in Table I.

A reaction which employed methyl chloride as the alkylating agent produced 8% of pentafluorotoluene (III). The low yield of III is not surprising as methyl halides are the least reactive ones in the series of primary halides,[9] and halogenated aromatics are alkylated only with difficulty.[10] Similar reactions using 1,2-di-

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[1] This work was supported by the Foundational Research Program of the Naval Ordnance Systems Command.

[2] Presented in part at the 3rd International Fluorine Chemistry Symposium, Munich, Germany, Sept 1965.

[3] W. J. Pummer and L. A. Wall, *Science*, **127**, 643 (1958); R. J. Harper, Jr., and C. Tamborski, *Chem. Ind.* (London), 1824 (1962); A. K. Barbour, M. W. Buxton, P. L. Coe, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 808 (1961).

[4] J. M. Birchall and R. N. Haszeldine, *ibid.*, 3719 (1961); J. M. Birchall, T. Clarke, and R. N. Haszeldine, *ibid.*, 4977 (1962); M. T. Chaudhry and R. Stephens, *ibid.*, 4281 (1963).

[5] Refer to Experimental Section for detailed information concerning the quality of the aluminum chloride used and the handling conditions.

[6] Hexachlorobenzene was isolated as a by-product from all Friedel–Crafts reactions in low yields in which pentafluorobenzene was used as the aromatic component. Halogen interchange reactions have been noted in the fluorobenzenes by Olah, *et al.*,[7] and in fluoronaphthalene by Vorozhtsov, *et al.*[8]

[7] G. A. Olah, W. S. Tolgyesi, and R. E. A. Dear, *J. Org. Chem.*, **27**, 3441, 3449 (1962).

[8] N. N. Vorozhtsov and N. M. Przhiyalgorskaya, *J. Gen. Chem. USSR*, **24**, 1787, 1961 (1954).

[9] F. A. Drahowzal in "Friedel–Crafts and Related Reactions," Vol. II, G. A. Olah, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, pp 417–475.

[10] Reference 9, p 435.