The Cleavage of Nonenolizable Ketones

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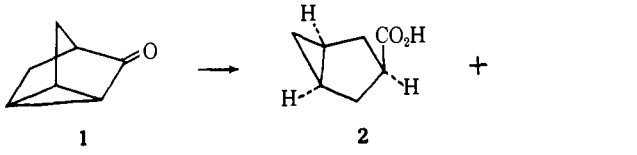
Abstract: A useful method for the cleavage of nonenolizable ketones has been developed. A 10:3 ratio of potassium *t*-butoxide–water in aprotic solvents, such as dimethyl sulfoxide, glyme, hexamethylphosphoramide, hexane, or ether, has been shown to be an exceptionally mild cleavage reagent. Diethyl ether was the most desirable solvent from an experimental point of view. With most ketones, high yields of acids were obtained after a few hours reaction time at room temperature. The stereochemistry of the reaction is such that the acid function undergoes only slight epimerization. The mechanism of this reaction has been shown to involve initial attack by hydroxide ion. The general utility of this cleavage is compared with that of the classical Haller–Bauer reaction.

In the early stages of investigating the base-catalyzed hydrogen–deuterium exchange of nonenolizable bicyclic ketones,[2] we had occasion to use dimethyl sulfoxide–potassium *t*-butoxide as our solvent–base system. It was observed that instead of undergoing hydrogen–deuterium exchange, the nonenolizable bicyclic ketones were rapidly cleaved.[3] This paper presents a detailed evaluation of the mechanism, scope, and limitations of this useful cleavage reaction.

When nortricyclanone (**1**) was treated at room temperature for 2 hr with 10 equiv of potassium *t*-butoxide in dimethyl sulfoxide containing 3 equiv of water, a rapid reaction occurred which produced an acidic and a neutral fraction. The acidic portion, which was obtained in 65% yield, consisted of a mixture of *cis*- and *trans*-bicyclo[3.1.0]hexane-3-carboxylic acids (**2** and **3**, respectively). The presence of **3** was unusually difficult to detect. Reaction of the acidic



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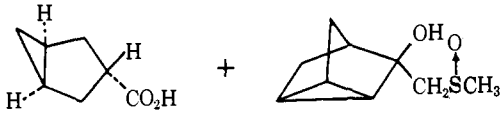
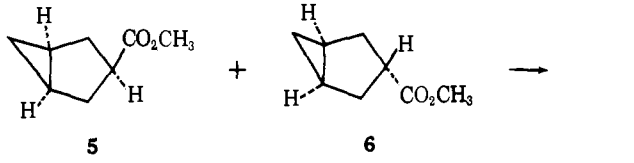


3 **4**

products with diazomethane gave a mixture of the methyl esters **5** and **6** which showed a single sharp peak upon vapor phase chromatography on six columns of widely differing polarity. Reduction of either the acid mixture or the ester mixture with lithium aluminum hydride gave a mixture of the carbinols, **7** and **8**, which were readily separated by vapor phase chromatography. Thus, *via* reduction of the acid mixture with lithium aluminum hydride and vapor phase chromatography of the resultant carbinols, the ratio of **2**:**3** in the cleavage mixture was determined to be approximately 9:1.

The neutral fraction contained the product, **4**, of addition of dimethyl sulfoxide to nortricyclanone.



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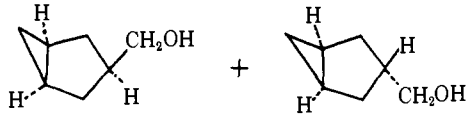
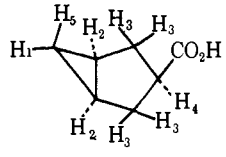


7 **8**

The structure of **4** was substantiated by elemental analysis, combined with nuclear magnetic resonance and infrared spectroscopic data. Since solutions of potassium *t*-butoxide in dimethyl sulfoxide contain an equilibrium mixture of the *t*-butoxide and dimethyl sulfoxide anions, the formation of adducts between **1** and the dimethyl sulfoxide anion was not surprising.[4]

A low-temperature recrystallization of the acidic portion of the reaction product gave pure **2**. The structure of **2** was established on the basis of both spectroscopic and degradative evidence. The near-infrared spectrum of **2** showed a maximum at 1.640 μ characteristic of compounds with cyclopropyl methylene groups.[5] The nuclear magnetic resonance spectrum (in τ) of **2** showed multiplets centered at 10.0 and 9.6 (1 H each), a broad peak at 8.8 (2 H), an intense band at 7.9 (4 H), and a multiplet centered at 7.1 (1 H). These peaks have been assigned to H_1,



2

H_5, H_2, H_3, and H_4, respectively. In a chemical approach to the establishment of the proposed structure, **2** was treated with methyllithium to yield the methyl ketone **9**, which on Baeyer–Villiger oxidation, followed by lithium aluminum hydride reduction, gave the al-

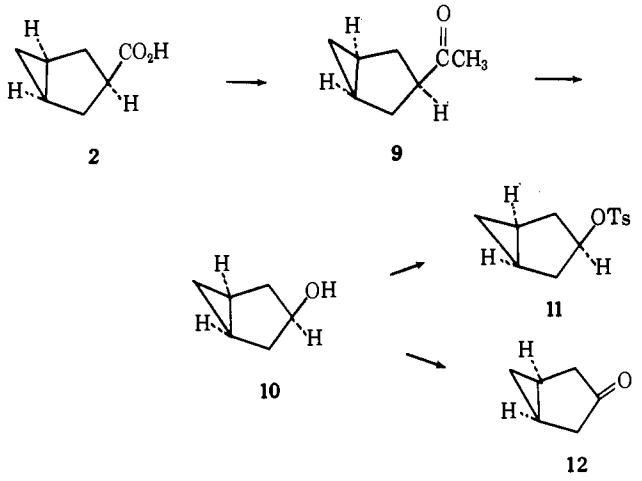
(1) Sinclair Oil Corporation Foundation Fellow, 1964–1965.

(2) P. G. Gassman and F. V. Zalar, *J. Am. Chem. Soc.*, **88**, 3070 (1966).

(3) This work has appeared in preliminary form: P. G. Gassman and F. V. Zalar, *Tetrahedron Letters*, 3031, 3251 (1964).

(4) Ample precedent for formation of adducts from ketones or aldehydes and dimethyl sulfoxide anions has been presented by G. A. Russell and H.-D. Becker, *J. Am. Chem. Soc.*, **85**, 3406 (1963); H.-D. Becker, G. T. Mikol, and G. A. Russell, *ibid.*, **85**, 3410 (1963); and E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1345 (1965).

(5) P. G. Gassman, *Chem. Ind.* (London), 740 (1962); P. G. Gassman and F. V. Zalar, *J. Org. Chem.*, **31**, 166 (1966).

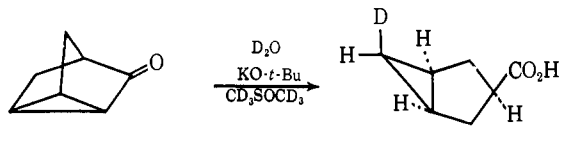


cohol **10**. Reaction of **10** with *p*-toluenesulfonyl chloride gave a product whose melting point agreed with that reported[6] for the tosylate of *cis*-bicyclo-[3.1.0]hexan-2-ol (**11**). Oxidation of **10** with Sarett reagent[7] gave a ketone, **12**, the 2,4-dinitrophenylhydrazone of which did not give a depressed melting point on admixture with an authentic sample[8] and which was spectroscopically identical with the authentic sample.

The mechanism of this cleavage was of prime interest. In order to determine the role played by water, the amount of water in the cleavage mixture was varied. The molar water content was found to be critical, since when water was scrupulously excluded no cleavage occurred. As the water content was increased, the yield of cleavage products increased regularly to a maximum of 65% when the water equaled 30 mole % relative to the amount of potassium *t*-butoxide used. Increase in the mole % of water beyond 30 resulted in a drop in the yield of acids until when the water content was equivalent to the *t*-butoxide essentially no cleavage occurred. The material balance in all these experiments was high; when the water content was low the yield of the adduct, **4**, was high. When the water content was high, starting material **1** was recovered.

In order to determine whether the actual cleavages were taking place during the reaction or during the aqueous work-up, the reaction was worked up by quenching the reaction mixture with deuterium oxide rather than with water. Since no deuterium was incorporated into the cleavage product, it was concluded that placement of the hydrogen at C-6, and therefore cleavage, took place prior to work-up.

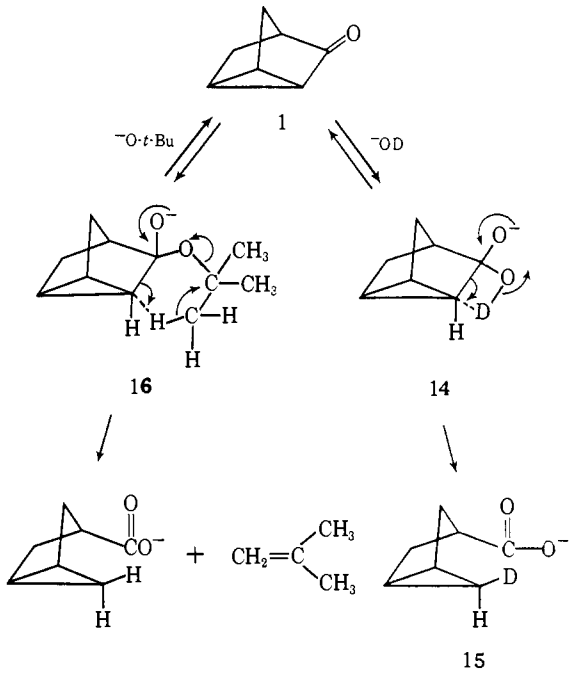
In order to determine the stereochemistry of hydrogen addition at C-6, the cleavage was carried out in perdeuteriodimethyl sulfoxide with added deuterium oxide. It was found that this cleavage gave **13** with the deuterium incorporated at C-6 *cis* to the acid



(6) S. Winstein and J. Sonnenberg, *J. Am. Chem. Soc.*, 83, 3244 (1961).
(7) G. I. Poos, R. E. Beyler, G. E. Arth, and L. H. Sarett, *ibid.*, 75, 422 (1953).
(8) We are grateful to Professor S. Winstein for supplying us with an authentic sample of the 2,4-dinitrophenylhydrazone of bicyclo[3.1.0]-hexan-3-one.

function. This stereospecificity was shown to be complete within the limits of determination by nuclear magnetic resonance spectroscopy.[9] This stereospecificity required either that the cleavage reaction produce a noninverting cyclopropyl carbanion or that the cleavage involve a cyclic mechanism. In evaluating the possible intermediacy of a noninverting cyclopropyl carbanion the studies of Walborsky and co-workers must be considered.[10] These investigators have found that cyclopropyl carbanions are unusually resistant to inversion. They have shown that 1-lithio-1-methyl-2,2-diphenylcyclopropane fails to invert in nonpolar solvents.[10] Even in a polar solvent such as dimethyl sulfoxide, which is known to facilitate electrophilic substitution with inversion,[11] it has been noted that 2,2-diphenylcyclopropylnitrile undergoes base-catalyzed deuterium exchange 60 times faster than inversion.[11b] It would appear, on the basis of these examples, that a noninverting cyclopropyl carbanion may account for the observed stereospecificity in our case.[11c]

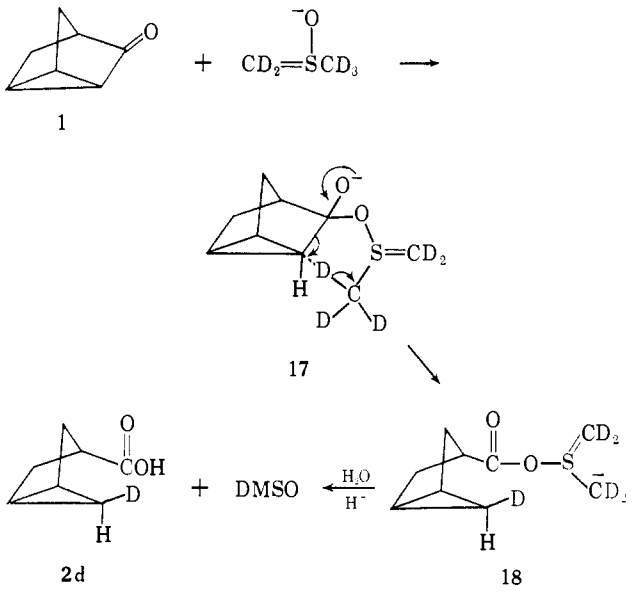
Although a noninverting cyclopropyl carbanion seems to be an attractive explanation for our data, various cyclic mechanisms also merit evaluation. In this category three mechanisms were considered. One explanation would involve initial attack by deuteroxide ion to yield **14**, followed by a four-centered concerted cleavage to yield the carboxylate anion **15**. The absence of cleavage when the *t*-butoxide was completely converted to hydroxide (equivalent amounts of *t*-



(9) For reproduction of the relevant spectra and a discussion of their interpretation, see P. G. Gassman and F. V. Zalar, *Tetrahedron Letters*, 3251 (1964).
(10) H. M. Walborsky and F. J. Impastato, *Chem. Ind.* (London), 1690 (1958); H. M. Walborsky, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), 23, 75 (1962); F. J. Impastato and H. M. Walborsky, *J. Am. Chem. Soc.*, 84, 4838 (1962); H. M. Walborsky, F. J. Impastato, and A. E. Young, *ibid.*, 86, 3283 (1964); and H. M. Walborsky and A. E. Young, *ibid.*, 86, 3288 (1964).
(11) (a) For a leading reference see D. J. Cram, J. L. Mateos, F. Hauck, A. Langemann, K. R. Kopecky, W. D. Nielson, and J. Allinger, *ibid.*, 81, 5774 (1959); (b) see also D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, p 114; (c) *ibid.*, p 148, which presents evidence for the difference between the cyclopropyl carbanion and an acyclic carbanion by showing that 1,2-diphenyl-2-methyl-1-butanone was cleaved under our conditions with 48% net retention of configuration.

butoxide and water) makes this mechanism unlikely. In a similar manner attack by *t*-butoxide ion to yield **16** followed by a concerted cleavage *via* a six-membered transition state to yield the carboxylate anion **15** and isobutylene might be proposed. This can be ruled out on three conditions as follows: (a) low nucleophilicity of *t*-butoxide, (b) absence of cleavage in the absence of water, and (c) complete incorporation of deuterium in the absence of deuterated *t*-butoxide.

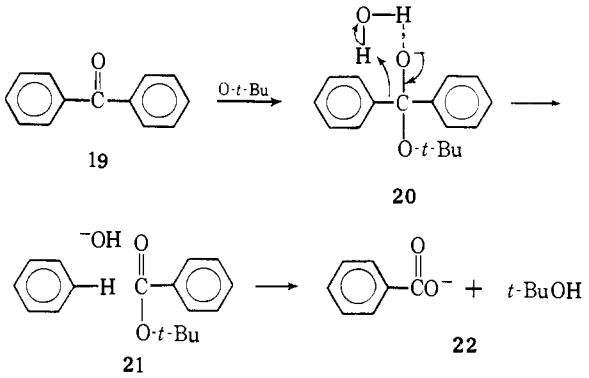
A third cyclic mechanism might involve attack on **1** by the nucleophilic oxygen of the dimethyl sulfoxide anion to yield **17**. This intermediate could undergo



cleavage as shown to produce **18** which on hydrolysis could yield **2d** and dimethyl sulfoxide (DMSO). The discovery that the cleavage could be carried out in solvents other than DMSO made the latter mechanism unacceptable.

When the cleavage was carried out using a 10:3 ratio of potassium *t*-butoxide to water in diethyl ether, the mixture of **2** and **3** was obtained in 89% yield (a yield higher than that obtained in DMSO).[12] When deuterium oxide was substituted for water in the above experiments, only 61% of the product was deuterated.[12] The deuteration had occurred with the same stereospecificity as had been noted when perdeuteriodimethyl sulfoxide was the solvent. In additional experiments we found that hexane, monoglyme, and hexamethylphosphoramide were all suitable solvents for the cleavage of nonenolizable ketones.

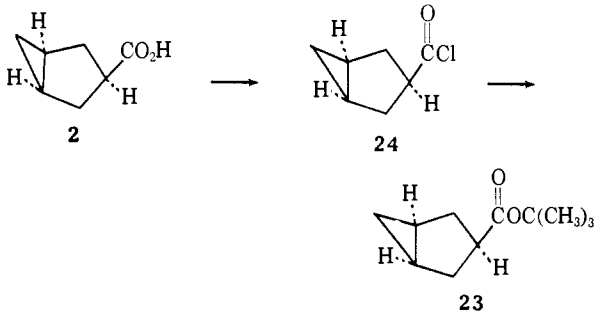
In view of the evidence against a cyclic mechanism, we feel that a nonracemizing cyclopropyl carbanion must be formed. Thus, the only questions which remained to be answered were what was the initial attacking species and why was a mixture of *t*-butoxide and hydroxide needed. Our work in diethyl ether brought to light some earlier work of Swan,[13] who had found that *t*-butoxide–water–ether was an effective reagent for the cleavage of benzophenones to benzoic acids and (presumably) benzenes. He also found that the approximate 3:1 ratio of *t*-butoxide to water was critical. Swan proposed[13] that the mechanism involved initial attack of *t*-butoxide ion on benzophenone (**19**) to yield the hydrated intermediate **20** which then underwent cleavage to yield hydroxide ion, benzene, and *t*-butyl benzoate (**21**). It was suggested that the *t*-butyl benzoate then underwent base-catalyzed hydrolysis to yield benzoic acid (**22**) and *t*-butyl alcohol. It was theorized[13] that water probably was critical



for the cleavage of **20** to **21**, since this mode of cleavage circumvented the necessity of generating a free phenyl anion.

In view of the poor nucleophilicity of *t*-butoxide and because of the unusual *t*-butoxide to water ratio which was necessary for cleavage, we felt that the Swan mechanism required further investigation. Since the Swan proposal requires that a *t*-butyl ester be formed as an intermediate, it would be necessary for the *t*-butyl ester to hydrolyze at a considerably faster rate than the rate of ketone cleavage. We thus decided to synthesize the *t*-butyl ester which would be formed if nortricyclanone were cleaving by the Swan mechanism and to measure its rate of hydrolysis relative to the rate of cleavage of **1**.

The *t*-butyl ester, **23**, was prepared by converting the pure *cis* acid, **2**, into its acid chloride *via* reaction of the sodium salt of **2** with oxalyl chloride at 0°, followed by reaction of the resulting acid chloride, **24**, with *t*-butyl alcohol in pyridine. The resultant ester was shown to be homogeneous by vapor phase chromatography. When a cleavage of nortricyclanone was run for one half-life in ether and the neutral fraction



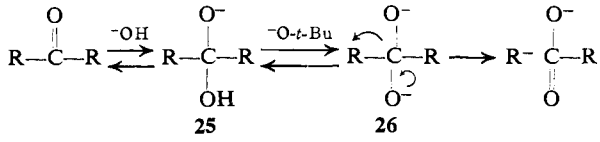
examined for the presence of **23** by vpc, no *t*-butyl ester was detected under conditions which would have indicated as little as 0.5%. This established that if **23** were an intermediate, indeed it would have to hydrolyze at a rate faster than its rate of formation. In addition, the acid recovered from this partial cleavage was the pure *cis* acid, **2**. Therefore, if **23** were an intermediate and if it were rapidly hydrolyzed, the hydrolysis must occur before epimerization at C-3.

(12) For details of these experiments, see P. G. Gassman and F. V. Zalar, *J. Am. Chem. Soc.*, **88**, 2252 (1966).
(13) G. A. Swan, *J. Chem. Soc.*, 1408 (1948).

Since the formation of **23** in the cleavage reaction would reduce the *t*-butyl alcohol content, the composition of the reaction mixture would change as the reaction proceeded. When the reaction was carried to only 10% completion, **23** was still undetectable. Therefore, if **23** were formed it must hydrolyze rapidly under the conditions present *at the start* of the cleavage reaction. Accordingly, a quantity of **23**, equivalent to the amount of acid found when the reaction was carried to only 10% completion, was subjected to the reaction conditions of the cleavage. At a time equivalent to 10% cleavage the small amount of **23** was hydrolyzed only to the extent of 7% and the recovered ester **23** was shown by vpc to be 95% epimerized at C-3. Furthermore, that acid obtained from **23** under the cleavage conditions was shown to consist of 90% of **3** and only 10% of **2** *via* reduction with lithium aluminum hydride followed by vpc of the resulting carbinols. *This unequivocally established that* **23** *could not be an intermediate in the cleavage of nortricyclanone* (**1**).

In order to establish that *t*-butyl benzoate (**21**) was not an intermediate in the cleavage of benzophenone in ether, a series of reactions, analogous to those used with nortricyclanone, were performed. *t*-Butyl benzoate was synthesized according to the procedure of Norris and Rigby.[14] Exposure of **21** to the conditions of the 10% cleavage reaction gave only 50% hydrolysis. Thus, **21** could not be an intermediate in the cleavage of benzophenone.

It would appear that the only feasible mechanism for the cleavage of nonenolizable ketones with potassium *t*-butoxide–water–ether (and by extrapolation in DMSO) must involve initial addition of hydroxide to the carbonyl group. Since complete conversion of *t*-butoxide to hydroxide results in negligible cleavage, some role must be played by the butoxide. It is possible that the function of the *t*-butoxide is to abstract a proton from the initially formed adduct of hydroxide and ketone, **25**. This dianion, **26**, would have significantly



25 **26**

more driving force for cleavage than would **26**. Heterolysis of the carbon–carbon bond in **26** would yield a carbanion and a carboxylate anion.[15]

An alternate role which the potassium *t*-butoxide might be playing is to make the hydroxide formed on the addition of water partially soluble. Whereas potassium *t*-butoxide is somewhat soluble in most organic solvents, potassium hydroxide is insoluble. Indeed, when water is added to a homogeneous solution of potassium *t*-butoxide in DMSO, precipitation occurs. Thus, it is possible that potassium *t*-butoxide–*t*-butyl alcohol–potassium hydroxide in the ratio of 2:1:1, respectively, forms an aggregate which is slightly soluble in organic solvents. In such an aggregate the hydroxide would be only slightly solvated and hence unusually reactive. Substance was given to this idea by the finding that potassium hydroxide could cleave ketones in the absence of potassium *t*-butoxide and *t*-butyl alcohol when the proper solvent was chosen, and the potassium hydroxide was finely dispersed. Thus, when a suspension of potassium hydroxide was prepared by the addition of water to a slight excess of potassium hydride in tetrahydrofuran and the resulting suspension in tetrahydrofuran was treated with nortricyclanone (**1**) for 2 hr at 30°, pure **2** was obtained in 84% yield. Unfortunately, on the basis of present evidence, we cannot determine whether the potassium *t*-butoxide is acting as a base or as a solvating element for hydroxide in the reagent formed from potassium *t*-butoxide–water–ether.

Scope of the Reaction

Although cleavage reactions of nonenolizable ketones have been observed before under a variety of conditions, the only thoroughly investigated general method for ketone cleavage is the classical Haller–Bauer reaction.[17] This reaction generally utilizes sodium amide in refluxing benzene, toluene, or xylene and yields amide and hydrocarbon moieties as products. Since our cleavage in refluxing ether is much less drastic than the Haller–Bauer conditions, it was deemed worthwhile to investigate the scope of this mild method for the cleavage of nonenolizable ketones. In addition to rapid cleavage at low temperature, the system potassium *t*-butoxide–water–ether (or glyme, hexamethylphosphoramide, hexane, or DMSO as solvent) has the advantage of yielding an acid as the cleavage product rather than an amide as is obtained under Haller–Bauer conditions.

Considering the mechanism postulated above, two factors should influence the ease with which various ketones would cleave. First, ketones containing a strained carbonyl should cleave rapidly because addition of hydroxide would occur rapidly and the equilibrium would be shifted from the ketone to **25** owing to relief of *I* strain. In addition, the cleavage of **26** should also be facilitated by the relief of strain. The second factor influencing the ease of cleavage would be the stability of the resulting carbanion. In order to substantiate these ideas a series of ketones has been cleaved.

As previously noted nortricyclanone is readily cleaved in refluxing ether with potassium *t*-butoxide–water. This is to be expected on the basis of the proposal outlined above since the molecule is considerably strained and yields a cyclopropyl carbanion.[18] In view of this facile cleavage, we found the reported stability of **1** to sodium amide in refluxing dioxane rather surprising.[19] We found that reaction of **1** with freshly prepared sodium amide in refluxing benzene for 2.5 hr gave a 90% yield of the amide **27**. The structure of this amide was substantiated by independent synthesis from the acid chloride **24**.

(14) J. F. Norris and G. W. Rigby, *J. Am. Chem. Soc.*, **54**, 2088 (1932). The ester had to be chromatographed on alumina to remove the last traces of benzoyl chloride.

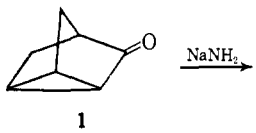
(15) Precedent for this mechanism can be found in recent work of Kenner, *et al.*,[16] on the mechanism of the Haller–Bauer cleavage[17] of fluorenone.

(16) G. W. Kenner, M. J. T. Robinson, C. M. B. Taylor, and B. R. Webster, *J. Chem. Soc.*, 1756 (1962).

(17) For a review see K. E. Hamlin and A. W. Weston, *Org. Reactions*, **9**, 1 (1957).

(18) The acidity of cyclopropyl hydrogens and the related stability of cyclopropyl carbanions has been well documented; see ref 10 and A. I. Shatenshtein, *Advan. Phys. Org. Chem.*, **1**, 176 (1963).

(19) S. J. Cristol and P. K. Freeman, *J. Am. Chem. Soc.*, **83**, 4427 (1961); P. K. Freeman, Thesis, University of Colorado, 1957.



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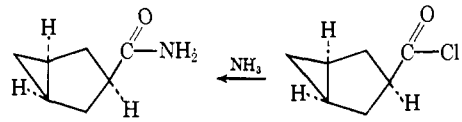
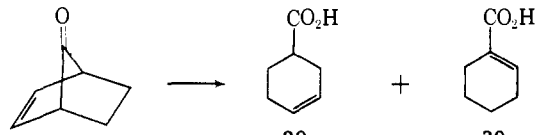


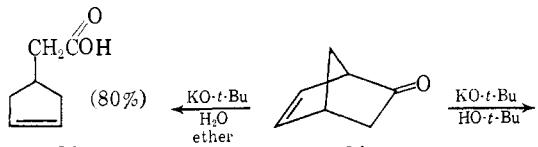
27 24

Other bicyclic nonenolizable ketones were readily cleaved. Thus, 7-ketonorbornene (**28**) gave 32% of cyclohexene-4-carboxylic acid (**29**) and 18% of cyclohexene-1-carboxylic acid (**30**) on cleavage in DMSO. Similarly, the isomeric ketone, dehydronorcamphor

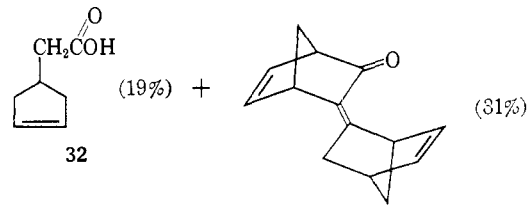


28 29 30

(**31**) was readily cleaved to yield only cyclopentene-4-acetic acid (**32**) in 80% yield. Two factors are interesting in relation to this latter reaction. First, **31** is an enolizable ketone. Secondly, the cleavage of **31** with potassium *t*-butoxide in refluxing *t*-butyl alcohol had previously been investigated by Cristol and Freeman.[19]



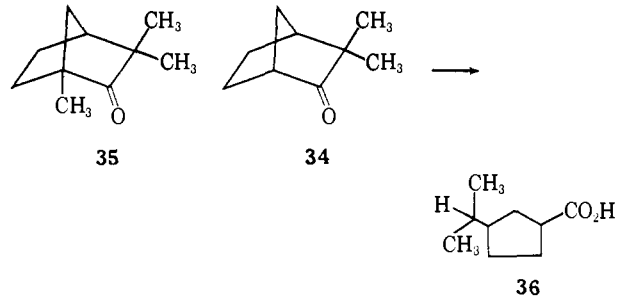
32 31



32 33

These workers found that their conditions gave **32** as the minor product with the self-condensation compound, **33**, being the major product. Under our conditions **33** is not formed. This represents another advantage of the potassium *t*-butoxide–water–aprotic solvent system for ketone cleavage.

The isomeric ketones **28** and **31** would both be expected to cleave easily since they are both strained and both yield allylic carbanions. In contrast, the bicyclic ketones camphenilone (**34**) and fenchone (**35**) have less strained carbonyls and would yield carbanions with little stabilization. Furthermore, the addition of hydroxide would lead to eclipsing of the oxygens with the geminal methyls, thereby leading to an increase in *I* strain. On the basis of the factors listed above, it would be predicted that **34** and **35** would be relatively resistant to cleavage under our conditions. This was substantiated experimentally by the finding that **35** gave no cleavage and **34** gave only 9% camphoceenic acid (**36**) after 6 hr with potassium *t*-butoxide–water–DMSO at 60°. The camphoceenic acid was characterized as its amide.[20]



35 34 36

Diaryl ketones are readily cleaved by our procedure. Benzophenone gave benzoic acid in 90% yield after 4 hr at 30° with potassium *t*-butoxide–water–monoglyme. Fluorenone yielded 90% of biphenyl-2-carboxylic acid after 2 hr at 30° with the same base–solvent reagent. The conditions used in these reactions are significantly milder than previous methods used to cleave these two ketones.[16,17]

A ketone that is known to cleave readily, phenyl triphenylmethyl ketone, also cleaved under our conditions. A quantitative yield of benzoic acid and triphenylmethane was obtained within 2 min at 30° with potassium *t*-butoxide–water–DMSO.

In summary, a very mild method for the cleavage of nonenolizable (and certain enolizable) ketones has been developed. Unusually hindered ketones which form relatively unstable carbanions are resistant to our cleavage conditions. Aryl ketones are readily converted to acidic cleavage products. Although various solvent systems can be used, diethyl ether is the best experimentally.

Experimental Section

Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. Vpc was carried out using a Wilkens Aerograph Hi-Fi Model 600, and an Autoprep Model 700. A Varian A-60 spectrometer was used for nuclear magnetic resonance spectroscopy—all τ values were measured from internal TMS. The dimethyl sulfoxide (Crown Zellerbach) was dried by distillation from calcium hydride followed by storage over Linde 13X Molecular Sieves. Ether and monoglyme (Ansul) were distilled from lithium aluminum hydride and also stored over molecular sieves. In the initial stages of the work, potassium *t*-butoxide purchased from M.S.A. Research Corporation was used, but it was subsequently found that freshly prepared material[13] gave slightly better results.

The Cleavage of Nortricyclanone. a. In Ether. Details of the cleavage of nortricyclanone to a mixture of *cis*- and *trans*-bicyclo[3.1.0]hexane-3-carboxylic acids, reduction of the products with lithium aluminum hydride, and separation of the resulting alcohols have been described previously.[12]

b. In Dimethyl Sulfoxide. A cleavage mixture was prepared from 4.0 g of potassium *t*-butoxide and 0.193 ml of water in 11 ml of dimethyl sulfoxide in a magnetically stirred, side-arm flask under a nitrogen atmosphere. To the mixture, 0.5 g of nortricyclanone was added at 30°, and after a further 2 hr at 30°, 25 ml of water was added. The solution was acidified to pH 1 with concentrated hydrochloric acid and then extracted with ether. The extracts were washed with water, dried, and evaporated, and the residue was distilled to give 313 mg (65%) of the same mixture (9:1) of the acids **2** and **3** as was obtained from the cleavage in ether.[12] In addition, a small amount of **4** was obtained.

When the reaction mixture was quenched with deuterium oxide rather than water, the products were identical with those obtained as described above.

When perdeuteriodimethyl sulfoxide was used as solvent and the acidic products were treated directly with ethereal diazomethane,

(20) F. W. Semmler, *Chem. Ber.*, **39**, 2577 (1906).

the resultant methyl ester **5** was obtained. Purification by preparative vpc gave a sample whose nmr spectrum indicated that deuterium had been incorporated at C-6, *cis* to the carboxyl group (see ref 9 for a reproduction of the spectrum and a discussion of its interpretation).

The Dimethyl Sulfoxide–Nortricyclanone Adduct (4). To a stirred solution of 4 g of potassium *t*-butoxide in 30 ml of dimethyl sulfoxide was added 4 g of nortricyclanone in 25 ml of dimethyl sulfoxide. The solution was maintained at 30° for 4 hr, and then 30 ml of water was added and the solution acidified to pH 1 with concentrated hydrochloric acid. Extraction with ether followed by the usual treatment gave a small amount (0.7 g) of the 9:1 mixture of the acids **2** and **3**. The residual aqueous phase was concentrated *in vacuo* and benzene added to the residue. The potassium chloride was removed by filtration, the benzene evaporated, and the residue chromatographed on basic alumina. Elution with ether–methanol (80:20) gave 4.17 g (59%) of the adduct (**4**). The analytical sample had mp 78–79° (from benzene–hexane).

Anal. Calcd for $C_9H_{14}O_2S$ (mol wt, 186.27): C, 58.03; H, 7.99; S, 17.22. Found: C, 57.99; H, 7.67; S, 17.44.

***cis*-3-Acetylbicyclo[3.1.0]hexane.** An ethereal solution of methyllithium, prepared by adding 13.6 g (0.096 mole) of methyl iodide in 35 ml of ether to 1.4 g (0.2 g-atom) of lithium pieces in 35 ml of ether, was added dropwise to a stirred solution of 2.07 g (0.016 mole) of *cis*-bicyclo[3.1.0]hexane-3-carboxylic acid. The addition took 1 hr and stirring was continued for an additional hour. The mixture was poured onto crushed ice (75 g) and the ethereal layer separated, dried, and evaporated. The residue was distilled to yield 1.69 g (82%) of the methyl ketone, bp 77–78° (16 mm). Purification by preparative vpc gave an analytical sample, $n^{25}D$ 1.4665, λ_{max} 5.85, 7.4, 8.6, 12.3, and 13.4 μ.

Anal. Calcd. for $C_8H_{12}O$ (mol wt, 124.18): C, 77.37; H, 9.74. Found: C, 77.49; H, 9.60.

***cis*-Bicyclo[3.1.0]hexan-3-ol.** To a stirred suspension of 4 g of anhydrous sodium phosphate and 2.07 g (0.016 mole) of 3-acetylbicyclo[3 1.0]hexane in 20 ml of methylene chloride was added slowly the peracid formed from 2.3 ml of trifluoroacetic anhydride and 0.4 ml of 90% hydrogen peroxide in 10 ml of methylene chloride. The mixture was refluxed for 5.5 hr. An infrared spectrum of the reaction mixture indicated that some ketone remained so the mixture was recycled for 8 hr. Even then a small amount of ketone remained. The crude product was treated with 0.6 g of lithium aluminum hydride in 20 ml of ether to give a crude product which was purified by preparative vpc, giving *cis*-bicyclo-[3.1.0]hexan-3-ol (38% yield based on the methyl ketone). A 200-mg portion of the alcohol was converted to a tosylate using 600 mg of *p*-toluenesulfonyl chloride in 10 ml of pyridine in the usual way. After low-temperature recrystallization from pentane, the product had mp 50.9–51.2° (lit.[5] mp 50.6–50.8° for 3-bicyclo[3.1.0]hexyl *p*-toluenesulfonate).

Bicyclo[3.1.0]hexan-3-one. To a cooled solution of 0.5 g of chromium trioxide in 5 ml of pyridine was added 50 mg of *cis*-bicyclo[3.1.0]hexan-3-ol. The solution was stirred at *ca.* 30° for 12 hr. The reaction mixture was poured into water and extracted with ether. The solvent was removed by distillation and the residue treated with 2,4-dinitrophenylhydrazine reagent. Recrystallization gave a product with mp 149–150.5°, which was not depressed on admixture with an authentic sample[8] of the 2,4-dinitrophenylhydrazone of bicyclo[3.1.0]hexan-3-one.

The *t*-Butyl Ester of *cis*-Bicyclo[3.1.0]hexane-3-carboxylic Acid. To 404 mg of *cis* acid (**2**) was added a 5-ml aliquot from a solution prepared from 730 mg of sodium metal and 50 ml of anhydrous methanol. The solvent was removed on a rotary evaporator and the residue suspended in 15 ml of anhydrous benzene. To the stirred suspension was added 1 ml of oxalyl chloride at ice temperature, and stirring was continued for a further 1 hr. Filtration and distillation gave 321 mg of the acid chloride, bp 63–64° (10 mm). The acid chloride was added to a mixture of 2 ml of anhydrous benzene, 2 ml of anhydrous *t*-butyl alcohol, and 0.15 ml of anhydrous pyridine, and the resulting solution stored at 30° for 14 hr. It was then poured into 30 ml of water, the water acidified to pH 1 with hydrochloric acid, and then extracted with ether. The extracts were washed with 10% sodium carbonate and water, dried, and evaporated. Distillation of the residue gave 235 mg of the *t*-butyl ester (**23**), bp 73–74° (4 mm), which was homogeneous to vpc.

Anal. Calcd. for $C_{11}H_{18}O_2$ (mol wt, 182.25): C, 72.49; H, 9.96. Found: C, 72.46; H, 9.85.

It was found that when the *cis* acid (**2**) was treated with thionyl chloride in refluxing benzene, a small amount of epimerization took place and a mixture of *cis* and *trans* acid chlorides was obtained.

Partial Cleavage of Nortricyclanone and Hydrolysis of the *t*-Butyl Ester (23). A cleavage reaction of nortricyclanone, using 3 g of the ketone, 24 g of potassium *t*-butoxide, and 1.15 ml of water in ml of ether, was run for 3 min in an ice bath using the method previously described.[12] The cleavage gave 395 mg (12%) of the pure *cis* acid (**2**) and 2.0 g of recovered nortricyclanone. The stereochemical purity of the acidic fraction was demonstrated *via* reduction with lithium aluminum hydride followed by vpc examination of the product.[12] The product contained only the *cis* alcohol (**7**). Examination of the recovered ketone by vpc failed to reveal the presence of any of the ester (**23**), under conditions where as little as 0.5% would have been detectable. The partial cleavage reaction was then repeated under exactly the conditions described above, except that the ketone was replaced by 580 mg of the ester (**23**) (an amount equivalent to 395 mg of the acid, **2**). The neutral fraction from this reaction, after distillation, amounted to 460 mg. By vpc, it consisted of a 95:5 mixture of the *trans*- and *cis*-*t*-butyl esters of bicyclo[3.1.0]hexane-3-carboxylic acid, respectively. The acidic fraction, which amounted to 30 mg (7%), was reduced with lithium aluminum hydride yielding (according to vpc analysis) a 9:1 mixture of the *trans* and *cis* alcohols, **8** and **7**.

Partial Cleavage of Benzophenone and Hydrolysis of *t*-Butyl Benzoate. A cleavage reaction of benzophenone was run using 2.4 g of the ketone, 4.3 g of potassium *t*-butoxide, and 0.28 ml of water in ether in an ice bath for 17 min by the method previously described.[12] This gave 123 mg (8%) of benzoic acid, mp 118–119°, and 2.2 g of recovered benzophenone. The latter was shown by vpc to contain no detectable amount of *t*-butyl benzoate.[14] The experiment was repeated using 178 mg of *t*-butyl benzoate in place of the benzophenone. The products of this experiment were 62 mg of benzoic acid and 99 mg of unhydrolyzed *t*-butyl benzoate.

All the experiments on the partial cleavage and hydrolyses were run in duplicate. The variation between extents of reaction for corresponding runs was always less than 5%.

Bicyclo[3.1.0]hexane-3-carboxamide. a. From the Haller–Bauer Reaction. A suspension of 610 mg of freshly prepared sodium amide, and 500 mg of nortricyclanone in 10 ml of anhydrous benzene was heated under reflux for 2.5 hr. The mixture was poured onto crushed ice and ether added. The layers were separated, and the aqueous phase was extracted with ethyl acetate, The combined organic phases were dried and evaporated giving 552 mg (90%) of a while solid. After two recrystallizations from benzene, it had mp 199–200°.

Anal. Calcd for $C_7H_{11}NO$ (mol wt, 125.17): C, 67.17; H, 8.86; N, 11.19. Found: C, 67.07; H, 8.80; N, 11.13.

b. From the *cis* Acid (2). A portion of the *cis* acid (**2**) was refluxed with thionyl chloride for 3 hr, and then the solution was fractionated, giving the acid chloride, bp 69–70° (13 mm). The latter was dissolved in dry benzene and ammonia gas bubbled through the solution. Evaporation, followed by recrystallization and sublimation of the product, gave white crystals, mp 200.5–201.5°, which did not depress the melting point of the material prepared in part a above on admixture of the two samples. The two samples of the amide **27** were identical by infrared spectroscopy.

The Cleavage of 7-Ketonorbornene.[21] The cleavage mixture was prepared using 2 g of potassium *t*-butoxide and 0.1 ml of water in 25 ml of dry DMSO. To this was added 2 g of 7-ketonorbornene in 30 ml of dry DMSO. The reaction mixture was stirred at room temperature under nitrogen for 2.5 hr. The reaction mixture was poured into 100 ml of ice water and extracted with two 35-ml portions of ether. The ethereal extracts were dried over anhydrous magnesium sulfate. Removal of the drying agent and the solvent gave 0.28 g of starting ketone.

The aqueous phase was acidified with concentrated hydrochloric acid and extracted with two 35-ml portions of ether. These extracts were dried over anhydrous $MgSO_4$ and filtered, and the ether evaporated. Distillation of the residue gave 1.30 g, bp 90–92° (0.85 mm). The acidic fraction was esterified with excess diazomethane. A mixture of two methyl esters was shown to be present by vpc. Comparison with authentic samples showed that this mixture consisted of 64% cyclohexene-4-carboxylic acid and 36% cyclohexene-1-carboxylic acid.

The Cleavage of Dehydronorcamphor. A cleavage mixture was prepared from 3 g of potassium *t*-butoxide and 0.36 ml of water in 35 ml of dimethyl sulfoxide in the usual manner, and 2.59 g of dehydronorcamphor was added. The cleavage was run for 4 hr at 30°. The reaction mixture was diluted with 50 ml of water, acidified to pH 1 with concentrated hydrochloric acid, and extracted with

(21) P. G. Gassman and P. G. Pape, *J. Org. Chem.*, **29**, 160 (1964).

ether. The ether was dried and evaporated and the residue distilled to yield 2.4 g (80%) of cyclopent-4-enylacetic acid, bp 77–80° (0.5 mm). The acid was converted into the corresponding amide by sequential treatment with thionyl chloride and gaseous ammonia. The amide had mp 129–130° (lit.[19] mp 132.5–133.5° for cyclopent-4-enylacetamide).

The Cleavage of Camphenilone. A cleavage mixture was prepared from 16 g of potassium *t*-butoxide, 0.47 ml of water, and 40 ml of dimethyl sulfoxide in the usual manner, and 2 g of camphenilone was added. The cleavage was run for 6 hr at 50°. The reaction mixture was diluted with water and extracted with ether; the extracts were dried and evaporated. The white solid residue was recrystallized from acetone to give an analytical sample of the camphenilone–dimethyl sulfoxide adduct, mp 173–174°.

Anal. Calcd for $C_{11}H_{20}O_2S$ (mol wt, 216.34): C, 61.07; H, 9.32; S, 14.82. Found: C, 60.87; H, 9.07; S, 14.42.

The aqueous phase was acidified to pH 1 with concentrated hydrochloric acid and extracted with ether. The dried extracts were evaporated giving 200 mg (9%) of a carboxylic acid. Reaction of the acid with thionyl chloride followed by ammonia gave an amide, mp 166–168° (lit.[22] mp 167–168° for 3-isopropylcyclopentane-1-carboxamide).

The Cleavage of Benzophenone. A cleavage mixture was prepared from 1.9 g of potassium *t*-butoxide, 0.07 ml of water, and 10 ml of monoglyme in the usual manner, and 300 mg of benzophenone in 3 ml of monoglyme was added. The cleavage was run for 2 hr at 30°. The reaction mixture was poured into dilute brine and extracted with ether. The extracts were dried and evaporated, leaving no residue. After being acidified to pH 1 with concentrated hydrochloric acid, the aqueous phase was again extracted with ether. The ether was dried and evaporated giving 180 mg (90%) of benzoic acid, mp 119–120°.

The Cleavage of Fluorenone. A cleavage mixture was prepared from 1.94 g of potassium *t*-butoxide, 0.12 ml of water, and 25 ml of monoglyme in the usual manner, and 500 mg of fluorenone in 5 ml of monoglyme was added. The cleavage was run for 2 hr at 30°. The same work-up procedure as described for the benzophenone cleavage was used. No neutral fraction was recovered. The acidic fraction yielded a pale yellow oil which crystallized on trituration under pentane to give 500 mg (90%) of biphenyl-2-carboxylic acid, mp 112–112.5° (lit.[16] mp 112–113°).

The Cleavage of Benzopinacolone. A cleavage mixture was prepared from 4 g of potassium *t*-butoxide, 0.385 ml of water, and 11 ml of dimethyl sulfoxide, and 1.6 g of benzopinacolone in a small amount of dimethyl sulfoxide was added. The cleavage was run for 2 min at 30°. The reaction mixture was poured into water, and the precipitate which formed was filtered off. After drying, 1.1 g (98%) of triphenylmethane was obtained, mp 92–93°. The filtrate was acidified to pH 1 with concentrated hydrochloric acid and extracted with ether. The ether was dried and evaporated giving 560 mg (100%) of benzoic acid, mp 119–120°.

(22) S. S. Nametkin and S. S. Kagan, *J. Gen. Chem. USSR*, **16**, 885 (1946).

The Preparation and Some Reactions of 1,2-Bis(trimethyltin)benzene and Related Compounds

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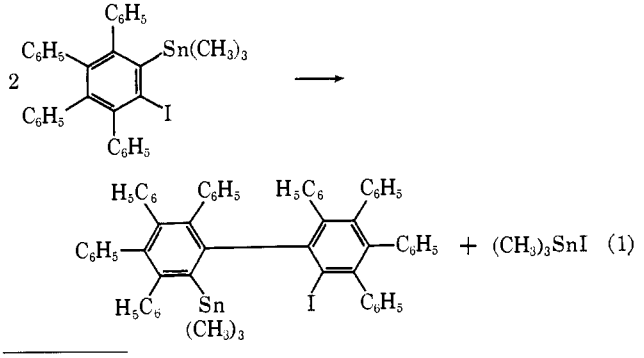
Abstract: The Diels–Alder reaction of bis(trimethyltin)acetylene with the appropriately substituted α-pyrone has been used to prepare 1,2-bis(trimethyltin)benzene, 3,4-bis(trimethyltin)toluene, and methyl 3,4-bis(trimethyltin)-benzoate. Reaction of (phenylethynyl)trimethyltin with α-pyrone gave (2-biphenylyl)trimethyltin. Partial and total cleavage of these tin compounds with iodine and bromine was used to prepare 1-iodo-2-(trimethyltin)benzene, 1-bromo-2-(trimethyltin)benzene, 1,2-dibromobenzene, and a mixture of methyl 3-iodo-4-(trimethyltin)benzoate and methyl 4-iodo-3-(trimethyltin)benzoate. The thermal decomposition of 1-iodo-2-(trimethyltin)benzene was studied; one of the major products was 2-iodo-2′-(trimethyltin)biphenyl.

In a previous communication[2] we reported that the thermal (~230°) decomposition of 1-iodo-2-(trimethyltin)tetraphenylbenzene did not lead, as anticipated, to formation of tetraphenylbenzyne. Instead, a novel coupling reaction (eq 1) was observed. The



possibility that the four phenyl substituents created an abnormal situation[3] and interest in this coupling reaction led us to an examination of routes to less highly substituted *o*-halo(trimethyltin)benzenes. The synthesis of these systems by a Diels–Alder route is the subject of this paper. The system utilized is thought to be of interest since it embodies a general, one-step synthesis of specifically substituted benzene derivatives.

The Diels–Alder reaction of bis(trimethyltin)acetylene with an appropriate diene, followed by monohalodestannation of the product, appeared to us to be an attractive route to the desired *o*-halo(trimethyltin)benzenes. Obviously, bis(trimethyltin)acetylene should be a poor dienophile by classical criteria. The triple bond is not electron deficient; if anything, it is electron rich, since the inductive flow of electrons from the trimethylstannyl groups is probably the predominant elec-

(1) (a) National Institutes of Health Predoctoral Fellow, 1963–1966; (b) Alfred P. Sloan Foundation Fellow, 1962–1966.

(2) D. Seyferth, C. Sarafidis, and A. B. Evnin, *J. Organometal. Chem.* (Amsterdam), **2**, 417 (1964).

(3) Tetraphenylbenzyne could, however, be generated from 1,2-dibromotetraphenylbenzene by treatment with lithium amalgam: D. Seyferth and H. H. A. Menzel, *J. Org. Chem.*, **30**, 649 (1965).