it, and ammonia was condensed until the flask was filled to a predetermined mark. The aniline and trihalobenzene were added, in that order, each dissolved in a small amount of ether, after the KNH_2 solution had been prepared. In Table I, $[C_6H_5NH_2]$ refers to molecular aniline in excess of that which reacted with KNH_2 to form potassium anilide.

Reaction of 1-Chloro-2-fluoro-5-iodobenzene (8) with Potassium Anilide in the Presence of 1-Iodo-2,4,6-trichlorobenzene (15). Reaction of **8** (0.02 *M*), **15** (0.02 *M*), and potassium anilide (0.02 *M*) in 91% ammonia–9% ether medium also containing 0.02 *M* aniline, for 120 min, afforded a grand mixture of products; the glpc tracing showed nine prominent peaks, plus some minor ones. In order of elution these were 1,3,5-trichlorobenzene (46%), **7** (12.4%), **8** (14.3%), unreacted **15** (1.8%), and four different chlorofluorodiiodobenzenes (totaling 10.8%). (Yields of trichloro products are based on **15**, and of chlorofluoro products on **8**.) The ninth peak was unidentified. The first four peaks were identified by the match of infrared and pmr spectra of eluted samples with those of authentic materials. The four chlorofluorodiiodobenzenes were separately identified as to composition by their mass spectra; in the absence of authentic samples of probable isomers, the infrared and pmr spectra of individual fractions, which were obtained, were of no use for assignment of orientation.

Reactions with *tert*-BuOK in DMF or HMPA. DMF was purified by treating it with anhydrous $CuSO_4$ (which complexes both water and dimethylamine) and ultimately by distilling it from a fresh sample of anhydrous $CuSO_4$. *tert*-BuOK was obtained as a dry, powdery solid from MSA Research Corp., Evans City, Pa. Solutions of *tert*-BuOK in DMF or HMPA were prepared in a drybox; aliquots were removed and titrated with standard hydrochloric acid to determine the base concentration. Reactions were initiated by combining a portion of a solution of *tert*-BuOK in DMF or HMPA with a solution of an aryl halide or aryl halides in the same solvent. Reactions were performed at room temperature (about 25°) under a nitrogen atmosphere; great care was taken to prevent access of atmospheric moisture to the reaction mixtures. After a measured period of time, the reaction mixture was poured into water, a measured amount of an internal standard for glpc purposes (usually diphenyl ether) was added, the mixture was extracted with ether, the ether solution was dried over Drierite and evaporated to a small volume, and the residue was analyzed by glpc. In general, a 2.44-m column packed with 5% SE 30 silicone rubber and 5% Bentone 34 on Chromosorb P was used for the glpc work. In many experiments, the halide ion content of the aqueous layer was determined by potentiometric titration against $AgNO_3$. No aryl *tert*-butyl ethers were detected as products.

Unless otherwise stated, the identities of products and recovered reactants were established by the match of their glpc retention times and the infrared spectra of eluted samples with those of authentic samples.

Bromine Scrambling Accompanying Base-Catalyzed Isomerization of 1,2,4-Tribromobenzene[1]

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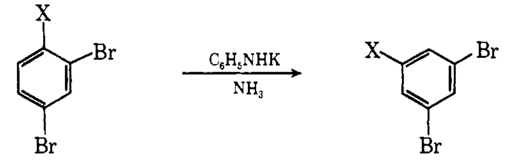
Received February 12, 1970

Abstract: 1,2,4-Tribromobenzene radiolabeled in the 1 position (**1b**) undergoes partial isomerization to 1,3,5-tribromobenzene (**2b**) during 15-min exposure to potassium anilide and aniline in liquid ammonia. Product **2b** and recovered 1,2,4-tribromobenzene are equal in molar radioactivity to each other and to the **1b** introduced. In the recovered 1,2,4-tribromobenzene, the radiolabel is equally distributed among the three bromine positions. For the bromine scrambling, a mechanism is proposed the key step of which is positive bromine transfer from 1,2,4,5-tetrabromobenzene to 2,4,5-tribromophenyl anion, forming products identical with the reactants except for possible differences in the location of the radiolabel.

Although 1,2,4-triiodobenzene, on treatment with potassium anilide in ammonia, undergoes isomerization to 1,3,5-triiodobenzene at a very slow rate,[3] redistribution of the radiolabel of 2-radiolabeled-1,2,4-triiodobenzene occurs more rapidly.[4] Under conditions which effect only 5% isomerization, the radiolabel is statistically redistributed among the 1, 2, and 4 positions.[4]

Isomerization of 1,2,4-tribromobenzene (**1a**) to 1,3,5-tribromobenzene (**2a**) occurs readily in the potassium anilide–ammonia system.[3] We now report that conditions which bring about substantial isomerization of **1a** to **2a** also cause full redistribution of the radiolabel of 1,2,4-tribromobenzene-*1*-^{82}*Br* (**1b**).



1a, X = Br
1b, X = ^{82}Br

2a, X = Br
2b, X = ^{82}Br

In experiments of this type, it is essential to devise a way to degrade the 1,2,4-trihalobenzene in such a way as to remove halogens selectively from at least two of the three positions they occupy. One of the degradation reactions used in the experiment with radiolabeled 1,2,4-triiodobenzene,[4] namely, radical-induced deiodination in alkaline methanol,[5] cannot be used for degradation of **1a** because debromination does not occur under the conditions employed.

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(1) Research supported in part by the National Science Foundation.

(2) (a) University of Auckland; preliminary experiments were performed at Santa Cruz, and the radiochemical experiments at Auckland; (b) to whom inquiries should be addressed, at Santa Cruz.

(3) C. E. Moyer, Jr., and J. F. Bunnett, *J. Amer. Chem. Soc.*, **85**, 1891 (1963); J. F. Bunnett and C. E. Moyer, Jr., **93**, 1183 (1971).

(4) J. F. Bunnett and D. J. McLennan, *ibid.*, **90**, 2190 (1968).

(5) J. F. Bunnett and C. C. Wamser, *ibid.*, **89**, 6712 (1967).

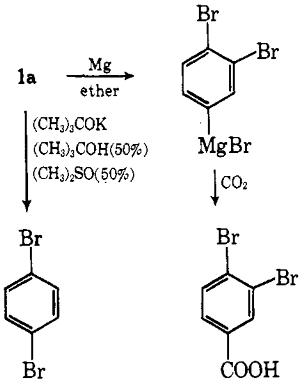
Table I. Radioactivity of Samples

Sample	Cpm[a]	Wt of sample, g	Cpm/g $\times 10^{-4}$	Cpm/mol $\times 10^{-7}$	Time of counting, hr[b]	Decay factor	Cpm/mol (corr) $\times 10^{-7}$	Rel radio-activity[c]
A	11,239	0.0977	11.51	3.627	0	1.00	3.63	1.00
B[d]	7,438	0.0511	14.56	3.435	3	0.943	3.64	1.00
C	10,377	0.1005	10.32	2.891	12	0.790	3.66	1.01
D	10,816	0.1107	9.771	3.078	9	0.838	3.67	1.01
E	9,158	0.0971	9.431	2.971	11	0.806	3.69	1.02
F	7,756	0.0940	8.251	1.947	11	0.806	2.42	0.67
G	4,552	0.0874	5.208	1.458	27	0.588	2.48	0.68
H	2,756	0.0652	4.227	1.332	36	0.493	2.70	0.74
I	Nil	0.1049					Nil	Nil

[a] Counts per minute. [b] Time of counting sample A arbitrarily defined as time zero; times are ±0.3 hr. [c] Counts per minute/mole (corrected), relative to sample A. [d] The aqueous washings from the debromination, which contain Br^-, showed radioactivity no greater than background.

Degradation reactions which were found to be satisfactory and which were employed are outlined in Scheme I. The 4-bromine of **1a** reacts preferentially with magnesium metal to form the Grignard reagent which, on carbonation, affords 3,4-dibromobenzoic acid in high yield. Treatment of **1a** with potassium *tert*-butoxide in 50% *tert*-butyl alcohol-50% dimethyl sulfoxide removes bromine cleanly from the 2 position, giving *p*-dibromobenzene in *ca.* 80% yield.[6] When these degradations are applied to radiolabeled **1a** (*e.g.*, to **1b**), the count rates of the 3,4-dibromobenzoic acid and *p*-dibromobenzene formed represent the radioactivity of the original sample minus that of the 4-bromine and the 2-bromine, respectively. The radioactivity associated with the 1-bromine is then reckoned by simple arithmetic.

Scheme I



A sample of **1b** was prepared from 2,4-dibromoaniline by the Sandmeyer reaction with use of ^{82}Br-enriched HBr. We call this sample A. Portions of sample A were submitted to the following treatments: (i) dehalogenation to *p*-dibromobenzene (sample B) according to Scheme I; (ii) Grignard conversion to 3,4-dibromobenzoic acid (sample C), according to Scheme I; and (iii) reaction (of 0.04 *M* **1b**) with potassium anilide (0.02 *M*) and aniline (0.02 *M*) in 90% ammonia-10% diethyl ether for 15 min at reflux, from which 1,3,5-tribromobenzene (sample D) was obtained in 34% yield, and 1,2-4-tribromobenzene (sample E) was recovered to the extent of 48%.

The recovered 1,2,4-tribromobenzene (sample E) was also degraded according to Scheme I. The *p*-dibromobenzene obtained is called sample F and the 3,4-dibromobenzoic acid is called sample G.

Finally, unlabeled 1,2,4-tribromobenzene (**1a**) (0.02 *M*) and labeled 1,3,5-tribromobenzene (**2b**) (0.0067 *M*) (from sample D) were exposed to 0.02 *M* potassium anilide and 0.02 *M* aniline in 90% ammonia-10% ether solvent. The recovered **2b** is called sample H, and the recovered **1a** is called sample I.

Data concerning the radioactivity of the several samples are set forth in Table I.

The following conclusions can be drawn. First, the sample (A) of **1b** prepared in this work and used in the experiments was labeled exclusively in the 1 position. This follows from the fact that both the *p*-dibromobenzene (sample B) and 3,4-dibromobenzoic acid (sample C) derived from it have molar activity equal to that of the original **1b**. Also, the aqueous washings from degradation to *p*-dibromobenzene, which contain the bromine removed from the 2 position as bromide ion, were not radioactive.

Second, the molar activities of the 1,3,5-tribromobenzene (sample D) from isomerization of **1b** and the 1,2,4-tribromobenzene recovered from exposure to potassium anilide (sample E) are equal to each other, and to that of the **1b** reactant.

Third, the molar radioactivity of the *p*-dibromobenzene (sample F) from degradation of sample E is 65.6% that of sample E, showing the 2-bromine of the recovered 1,2,4-tribromobenzene to contain 34.4% of its activity. The molar activity of the 3,4-dibromobenzoic acid (sample G) derived from sample E is 67.2% of that of sample E, showing the 4-bromine of the recovered 1,2,4-tribromobenzene to contain 32.8% of its radioactivity. By difference, the 1-bromine contains 32.8% of the radioactivity of the recovered 1,2,4-tribromobenzene. Within experimental error, this amounts to an equal distribution of the radiolabel among the three positions.

Discussion

The fact that reversion of **2a** to **1a** occurs in the potassium anilide-ammonia system only if 1,2,3,5-tetrabromobenzene or similar substance is supplied as cocatalyst is compatible with the seven-halogen but not with the six-halogen version of the positive halogen transfer mechanism.[7] Earlier, an adaptation of the six-halogen version had been invoked to interpret the

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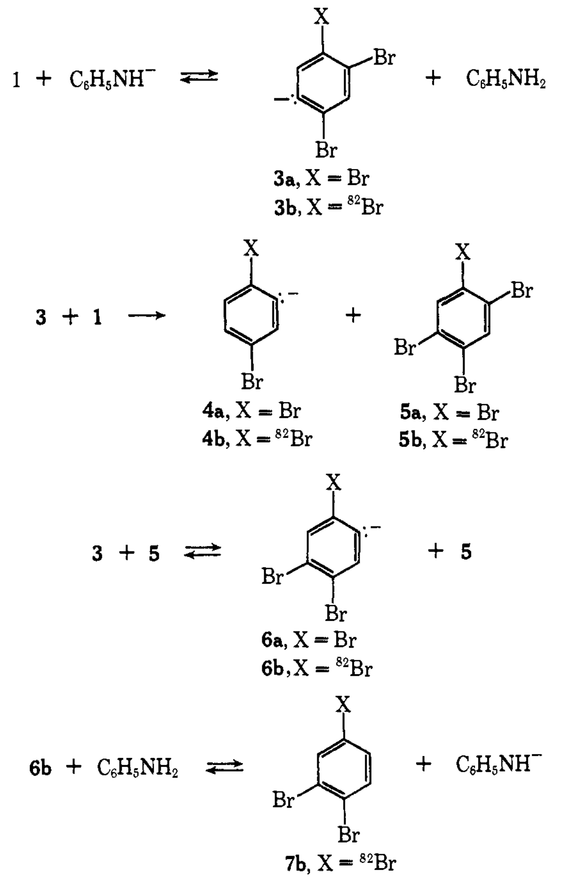
(6) J. F. Bunnett and R. R. Victor, *J. Amer. Chem. Soc.*, **90**, 810 (1968).

(7) J. F. Bunnett and G. Scorrano, *ibid.*, **93**, 1190 (1971).

scrambling of the iodines of 1,2,4-triiodobenzene which occurs on exposure to potassium anilide.[4] Although no need for cocatalysis by 1,2,4,5-tetrabromobenzene in order to achieve redistribution of the label of **1b** has been demonstrated, this tetrabromobenzene is known to be present in this reaction system,[3,7] and a mechanism of the seven-halogen type is attractive by analogy with the mechanism now favored for isomerization of **1a** to **2a**. Such a mechanism is sketched in Scheme II.

Scheme II



The first two steps of Scheme II generate tetrabromobenzene **5a** or **5b** as well as anion **4a** or **4b**; the latter is rapidly protonated to *p*-dibromobenzene. These two steps are thus a mechanism for disproportionation of **1a** to **5a** and *p*-dibromobenzene, a reaction which is known to occur.[3,7] The third step is a positive bromine transfer from a tetrabromobenzene to a tribromophenyl anion, forming a tetrabromobenzene and a tribromophenyl anion. In the absence of the radiolabel, the products and reactants of the third step are indistinguishable. However, anion **6b** differs from anion **3b** in the position of the radiolabel, and protonation of **6b** (the last step) forms **7b** in which the radiolabel is in the 4 position.

Actually, the third step as written is only one of a set of four which can occur. Depending on which bromine of **5b** is seized by **3b**, the by-product tribromophenyl anion may be **6b**, **3b**, **3a**, or a radioisomer of **3b** in which the radiolabel is para to the anionic center. Protonation of these various anions leads to 1,2,4-tribromobenzene radiolabeled in the 1, 2, or 4 position, or unlabeled. All four bromines in **5b** are equivalent and have an equal probability of being seized (except for a negligible isotope effect), and consequently there is an equal probability of the radiolabel showing up in any of the three bromine positions. To the extent that unlabeled **1a** is generated owing to seizure of the radiobromine of **5b**, a doubly labeled tetrabromobenzene is generated, the next round of positive bromine transfer and ensuing proton capture will lead to tribromobenzenes correspondingly richer in radiolabel, and therefore no overall depletion of radiolabel in the 1,2,4-tribromobenzene will occur.[8]

The crux of the mechanism of Scheme II is that in intermediate **5b** all four bromines are equivalent, except for the radiolabel. Since each has an equal probability of being seized, the radiolabel must be equally distributed among the three positions of the ultimate 1,2,4-tribromobenzene.

If this mechanism is correct, the related six-halogen mechanism proposed earlier for scrambling of the radiolabel of 2-labeled 1,2,4-triiodobenzene under similar conditions[4] may nevertheless be valid for that case. One observation reported earlier, namely, that during a short reaction time the 1 position is enriched with radioiodine more than the 4 position, is not intelligible in terms of the seven-halogen type of mechanism.

Experimental Section

1,2,4-Tribromobenzene-*1-^{82}Br* (1b). A solution of 2,4-dibromoaniline (30 g) in 90 ml of 48% hydrobromic acid (in water) was cooled to 0° and 6.3 g of $NaNO_2$ was added cautiously. Meanwhile a solution of CuBr (7.2 g) and 5 ml of Na^{82}Br (5 mCi) in 15 ml of 48% HBr was heated to boiling in a flask equipped for steam distillation. The cold diazonium salt solution was added over a period of 30 min, and about a quarter of the reaction mixture was boiled off. Steam was admitted and distillation was continued until no more steam-volatile product appeared in the distillate. The crude product was collected and washed with a small portion of concentrated sulfuric acid and then with water. It was twice recrystallized from 95% ethanol: yield 12.9 g (34%); mp 43–44°. This is sample A.

Degradation of Sample A. A solution of 0.50 g of sample A in 50 ml of 50% *tert*-butyl alcohol–50% dimethyl sulfoxide which was also 0.5 *M* in potassium *tert*-butoxide was heated 3 hr on the steam bath. The solution was cooled and worked up by standard extraction procedures; the *p*-dibromobenzene product (sample B) was recrystallized twice from 95% ethanol; yield 0.27 g (72%); mp 86.5–87°. The aqueous washings were saved and later examined for radioactivity.

A solution of 0.50 g of sample A in dry diethyl ether was run slowly into a refluxing solution of 0.35 g of ethyl bromide in dry ether in which was suspended 0.115 g of magnesium powder. After spontaneous reflux had ceased, reflux was continued another 30 min by external heating. All operations were carried out under an atmosphere of nitrogen and the reaction mixture was stirred throughout. The solution was poured onto excess solid carbon dioxide, and 3,4-dibromobenzoic acid (sample C) was isolated by conventional procedures: yield 0.405 g (91%); mp 233–234° after one recrystallization from 70% water–30% ethanol.

Isomerization. In a flask equipped with stirrer, gas inlet, and solid CO_2 condenser, and which had been flame-dried during flushing with dry nitrogen, 450 ml of ammonia was condensed. Clean, dry potassium metal (0.391 g) was added, and then a crystal of ferric nitrate. When the blue color had disappeared, 1.86 g of aniline was added and then 6.30 g of sample A dissolved in 50 ml of ether. The mixture was stirred for 15 min under reflux, NH_4Cl was added to neutralize the base, and the neutral organic fraction was chromatographed on 250 g of alumina, with use of petroleum ether (30–60°) as developer and eluent. Obtained were 2.12 g (33.6%) of 1,3,5-tribromobenzene, mp 119–120° (sample D), and

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(8) The fraction of **1b** actually carrying bromine-82 atoms is very small. The probability of an actual doubly labeled 1,2,4,5-tetrabromobenzene molecule is extremely small. However, accounting schemes based on the assumption of 100% labeling give statistically correct predictions as to the ultimate distribution of radiolabel.

3.02 g (48.0%) of 1,2,4-tribromobenzene, mp 44–44.5° (sample E). Both products were then recrystallized from 95% ethanol.

Degradation of Sample E. The methods used were as for degradation of sample A. From 1.0 g of sample E, 0.57 g (76%) of *p*-dibromobenzene, mp 86–87° after two recrystallizations, was obtained. This is sample F. From 1.0 g of sample E, 0.74 g (83%) of 3,4-dibromobenzoic acid, mp 233–234.5°, twice recrystallized from aqueous ethanol, was obtained; this is sample G.

Isomerization of 1a in the Presence of 2b. By the procedure described above, a solution of potassium anilide in ammonia (450 ml) was prepared from 0.391 g of potassium metal and 1.86 g of aniline, a solution of 3.15 g of inactive **1a** and 1.05 g of sample D in 50 ml of ether was added to it, reaction was allowed to occur for 15 min, and the two tribromobenzenes were separated by chromatography on alumina. Obtained were 0.88 g of 1,3,5-tribromobenzene, mp 119.5–120° (sample H), and 2.68 g of 1,2,4-tribromobenzene, mp 43–43.5° (sample I). Both were recrystallized from 95% ethanol.

Counting Procedures. A liquid Geiger-Muller tube (20th Century Electronics, Type M6H) was used. Flatness of the Geiger plateau between applied voltages of 410 and 500 V was established using a ^{32}P sample. Also, the counter was shown to respond linearly to the amount of ^{32}P in the sensitive counter volume (about 8 ml). For ^{82}Br counting, weighed samples were dissolved in an 80% absolute ethanol–20% acetone solvent, which was then washed into the counter. The solution was made up to 8 ml, to a mark on the counter. For counting the dibromobenzoic acid samples, absolute ethanol was used as solvent. At least 20,000 counts were recorded for each sample. All samples were recrystallized to constant specific activity. Counting rates were referred back to an arbitrary zero time, the time of counting sample A. Other count rates were corrected to zero time[9] by means of the first-order decay formula with attention to the 35.3-hr half-life of ^{82}Br. Background counts were about 60–100 cpm, and appropriate corrections were made.

Acknowledgment. We thank Professor A. L. Odell of the University of Auckland for making the facilities of the Urey Radiochemical Laboratory available to us, and for his valuable advice.

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(9) G. Friedlander, J. W. Kennedy, and J. M. Miller, "Nuclear and Radiochemistry," 2nd ed, Wiley, New York, N. Y., 1964, p 541.

Factors Limiting the Extent of Isomerization of 1,2,4-Tribromobenzene in the Potassium Anilide–Ammonia System[1]

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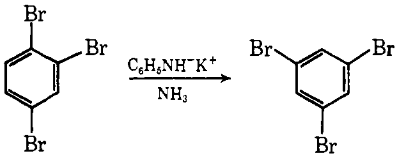
Abstract: Rates of both the potassium anilide catalyzed isomerization of 1,2,4- to 1,3,5-tribromobenzene and of bromide ion forming side reactions are strongly depressed by aniline. This is attributed in part to repression of aryl anion formation in acid-base equilibria, and in part to complexing with anilide ions to form bianilide ions of reduced activity. 1,3,5-Tribromobenzene is much less soluble than its 1,2,4 isomer in liquid ammonia, and isomer proportions at equilibrium may be predominantly determined by solubilities. However, both isomers are quite soluble in 50% ammonia–50% diethyl ether.

Under the influence of potassium anilide in liquid ammonia or 50% ammonia–50% diethyl ether, 1,2,4-tribromobenzene (**1**) isomerizes to its 1,3,5 isomer **2**.[2–4] The latter isomer does not revert to the former under the same conditions, but reversion does occur, at least in 50% ammonia–50% ether, if a small amount of 1,2,3,5-tetrabromobenzene is added as a cocatalyst.[4] These reactions find interpretation in the seven-halogen version of the positive halogen transfer mechanism, as sketched in Scheme II of an accompanying paper.[4]



1 **2** (1)

Except for the original report of Wotiz and Huba,[5] isomerization of **1** to **2** had never been observed to go to completion. Some **1** always remained unconverted. *A priori*, completion of isomerization might be limited either by kinetic factors (such as the consumption of catalyst in side reactions) or by the attainment of a state of equilibrium. Evidence that the transformation of **1** to **2** is reversible providing that 1,2,3,5-tetrabromobenzene or similar substance is supplied as a cocatalyst has been presented,[4] and it is known that disproportionation of **1** to di- and tetrabromobenzenes occurs on exposure to potassium anilide.[3,4] It is therefore plausible that equilibrium between **1** and **2** may be attained with cocatalysis by internally generated tetrabromobenzene.

Nevertheless puzzling was the great variability in the extent of isomerization of **1** to **2** observed in ammonia or ammonia–ether systems. Thus, in experiments of Moyer,[3,6] all seemingly conducive to isomerization, the final ratio of **2**:**1** varied from as low as 0.39 to as high as 9.4. An occasional low conversion (or even complete failure of rearrangement) might be ascribed to the accidental admission of water or CO_2 to the system, but the persistence of variable results despite care to exclude contaminants made that an unlikely cause for the fluctuations observed.

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(1) Support by the National Science Foundation is gratefully acknowledged.

(2) C. E. Moyer, Jr., and J. F. Bunnett, *J. Amer. Chem. Soc.*, **85**, 1891 (1963).

(3) J. F. Bunnett and C. E. Moyer, Jr., *ibid.*, **93**, 1183 (1971).

(4) J. F. Bunnett and G. Scorrano, *ibid.*, **93**, 1190 (1971).

(5) J. H. Wotiz and F. Huba, *J. Org. Chem.*, **24**, 595 (1959).

(6) C. E. Moyer, Jr., Ph.D. Dissertation, Brown University, 1964; *Diss. Abstr.*, **25**, 4412 (1965).