glycol, glycerol, polyethylene glycol) over the $p$H range 1.5 to 7.0 at 25°.

The observed $\Delta D$ must then actually be caused by the ionization of acid groups. These groups must be carboxyls, since the methylated derivative does not show this indole difference spectrum, but only the phenolic ionization shown in Fig. 10. Since a normal $\beta$- or $\gamma$-carboxyl group with intrinsic $pK$ 4.6 would have an apparent $pK$ of 4.1 because of electrostatic interactions, these carboxyl groups appear to be quite abnormal. However, if the charge effect transfer does not take place through covalent bonds only (see below), the lower $pK$ carboxyl "group" could be the (normal) $\alpha$-carboxyl group.

**The Temperature Dependence of the Difference Spectrum.**—Within the experimental error of about ± 1 kcal., the curves drawn in Fig. 10 give a zero $\Delta H$ of ionization for the lower $pK$ "group," and about 3 kcal. for the higher $pK$ "group." However, no attempt has been made to adjust the values of $\Delta D$ observed at one temperature to the values of $\Delta D$ at the other, that is, the difference absorption coefficient is assumed to be constant with temperature. Although the values of $\delta$ observed for tryptophan do not appear to be a function of temperature,[23] it is still possible that the values of $\delta$ for the indole chromophores in proteins may be a function of temperature. If the estimates of the enthalpies of ionization of these groups are correct, then the abnormality of these groups is probably due to local electrostatic effects.

**The Number of Ionizable Groups which Affect the Spectrum of the Indole Chromophore in Lysozyme.**—The applicability of the assumption of inductive charge effect transfer can be tested for lysozyme by calculating, with the aid of Table II, the number of ionizable groups necessary to cause the observed $\Delta D_{295}$ of 400 per mole at $p$H 5 for one "group." Forty carboxyl groups adjacent to tryptophan residues is the minimum number required. The partial sequence of lysozyme presented by Jollès[41] indicates that, of the nine free carboxyl groups in this lot of lysozyme, seven are not adjacent to tryptophan residues. It appears that inductive effects alone are insufficient to explain the magnitude of the observed effect.

The dependence of $\Delta D_{295}$ for lysozyme on ionic strength (Fig. 7) seems to indicate that at least a large portion of the charge effect transfer is occurring through the solvent, in contrast to model compounds.

The simplest explanation of these effects for lysozyme, which could account for the order of magnitude of $\Delta D$, is that the charge effect takes place through the solvent at small distances between the charged groups (probably few) and the indole chromophores (probably few) producing the difference spectrum. Not *all* the carboxyl groups influence one or more of the indole chromophores, since then: (1) The $\Delta D$–$p$H curve would look very much like the acid portion of the titration curve of the protein. In fact, the titration curve shows no "step" at about $p$H 5, as observed in Fig. 10. (2) The $\Delta D$–$p$H curve for lysozyme lot D638040, which appears to have five more titratable carboxyl groups than lot 381–187, would give a larger $\Delta D$ at any $p$H. In fact, the $\Delta D$ values observed for the complete ionization of each "group" in lot D638040 are the same, within experimental error, as the $\Delta D$ values observed for lot 381–187.

(41) P. Jollès, private communication. See also J. Jollès and P. Jollès, 1° Symp. Internazionale sul Lisozima di Fleming, Milano, April 3–5, 1959.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC., SUMMIT, N. J.]

# Rauwolfia Alkaloids. XXXVI.[1] Non-hypotensive Sedatives Derived from Methyl Reserpate

BY MICHAEL M. ROBISON, ROBERT A. LUCAS, H. B. MACPHILLAMY, R. L. DZIEMIAN, I. HSU AND R. J. KIESEL

RECEIVED JANUARY 16, 1961

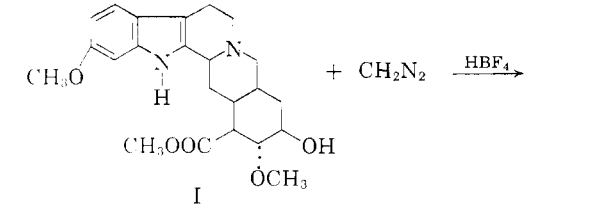
Alkyl ethers of methyl reserpate have been prepared by reactions of the hydroxy compound with diazoalkanes in the presence of fluoroboric acid. Since the products were found to possess potent sedative activity, other methods for their preparation were sought. It was found that alcoholysis reactions with methyl reserpate $p$-bromobenzenesulfonate proceed with inversion to produce ethers of methyl 18-epireserpate, which have comparable sedative activity. The stereochemistry of the epi-ethers was elucidated by relating each series to common intermediates in which all asymmetric centers other than $C_{18}$ are preserved.

Interest in reserpine, the primary sedative and hypotensive principle of the genus Rauwolfia, has stimulated efforts in this Laboratory to separate these two types of physiological action by suitable modification of the structure of the molecule.[2] Isolation of the second type of activity was realized in the preparation of methyl reserpate, 18-(3,5-dimethoxy-4-ethoxyformyloxybenzoate),[2a] a compound which has a hypotensive effect comparable to that of reserpine, but which has greatly diminished sedative properties. Since reserpine itself has an ester group at the 18-position, considerable emphasis in past investigations has been placed on variation of the ester function itself. It seemed desirable, therefore, to extend the study to determine the effects of other substituent types on pharmacological activity. This paper reports the preparation of a number of ethers derived from methyl reserpate, which are potent sedatives with rapid onset of action, but which are essentially devoid of hypotensive effect.

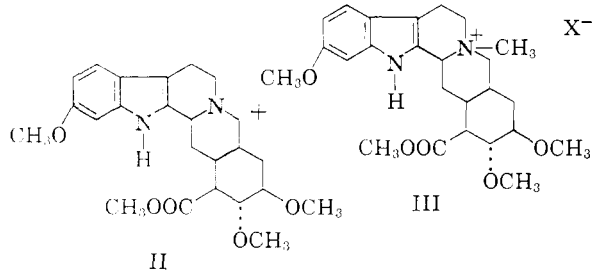
(1) A preliminary account of this investigation was published in *Experientia*, **17**, 14 (1961).

(2) (a) R. A. Lucas, M. E. Kuehne, M. J. Ceglowski, R. L. Dziemian and H. B. MacPhillamy, *J. Am. Chem. Soc.*, **81**, 1928 (1959); (b) R. A. Lucas, R. J. Kiesel and M. J. Ceglowski, *ibid.*, **82**, 493 (1960).

The first series of alkoxy compounds was prepared by reaction of methyl reserpate (I) with the appropriate diazoalkane in the presence of fluoboric acid.[3] In this manner the methyl (II) ethyl and *n*-butyl ethers were produced. The products are formulated as 18$\beta$-alkoxy compounds, since it has been demonstrated in the steroid series that this alkylation proceeds with retention of configuration.[3] As a preparative method the reactions left much to be desired, however, for in spite of numerous attempts to improve the process, the yields remained unsatisfactory. In most cases considerable unreacted starting material remained in the mixtures, but attempts to achieve more nearly complete etherification by increasing the excess of diazomethane resulted in alkylation of Nb as well as oxygen to form the quaternary salt (presumably a complex fluoborate) of the ether III. The structure of this unusual alkylation product[4] was demonstrated by anion exchange to form the quaternary methochloride followed by pyrolysis of this salt. This degradation resulted in the elimination of the N-methyl group, though not without concomitant epimerization at $C_3$, to form methyl 3-isoreserpate methyl ether. To relate the two series the latter was synthesized independently by oxidation of II to the corresponding dehydro compound, followed by sodium borohydride reduction.[5]

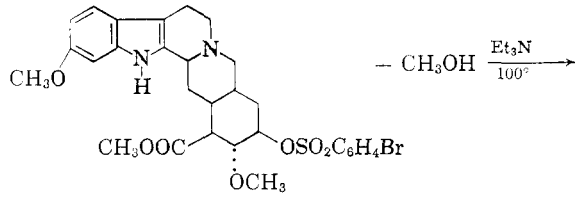



I

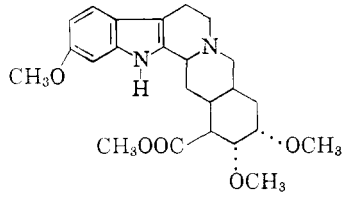



II III

The unusually marked sedative activity of the ethers prompted an intensive search for alternative methods of synthesis. In the course of the investigations a method was discovered by which ethers epimeric at $C_{18}$ could be prepared in high yield. The sedative action of these was comparable to that of the first series. The preparation entailed the alcoholysis of methyl reserpate *p*-bromobenzenesulfonate (IV) under mildly alkaline conditions. Thus, reaction of the brosylate with methanol proceeded at 100° in the presence of triethylamine to produce methyl 18-epireserpate methyl ether (V). The process was applicable to other alcohols and other benzenesulfonate esters under similar conditions.




IV




V

Although it seemed most likely that the reaction course involved a simple inversion at $C_{18}$ with retention of the reserpine configuration at other asymmetric centers, it was necessary to verify this point. Verification was secured by conversion of both epi and normal compounds to common transformation products in which the stereochemistry at positions other than $C_{18}$ was preserved, while at position 18 the asymmetry was eliminated or a common configuration was attained by appropriate reactions. In the first experiment to this end, methyl reserpate brosylate was treated with thiophenol in the presence of triethylamine, to form the corresponding phenylthioether. The assumption was made, in this case, that the stereochemical course of the displacement by thiophenol is the same as that in the methanolysis. (It may be noted that the product was also obtained by treatment of methyl reserpate tosylate with sodium thiophenoxide.) Removal of the phenylthio group by Raney nickel desulfurization produced methyl 18-desoxyreserpate. This substance was identical with a product obtained during this study by platinum-catalyzed hydrogenolysis of "methyl reserpate bromide"[6] (methyl 18$\alpha$-bromo-18-desoxyreserpate, *vide infra*). It was not the same as a substance erroneously described[6] as methyl 18-desoxyreserpate. The latter, prepared by hydrogenolysis of methyl 18-bromo-18-desoxy-3-isoreserpate, is the 3-iso compound, as correctly stated in the Discussion section of the reference.

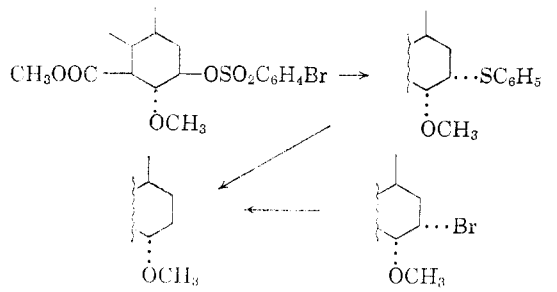
Although the above sequence established that the stereochemistry at positions 16 and 17 is identical in the bromo and phenylthio compounds, it was inconclusive because of the assumption that the stereochemical course of these displacements is the same as that of the methanolysis. Accordingly, a more direct method of relating the epi-ethers to methyl reserpate was sought. Heating methyl reserpate brosylate with aqueous triethyl-

(3) M. Neeman, M. C. Caserio, J. D. Roberts and W. S. Johnson, *Tetrahedron*, **6**, 36 (1959).

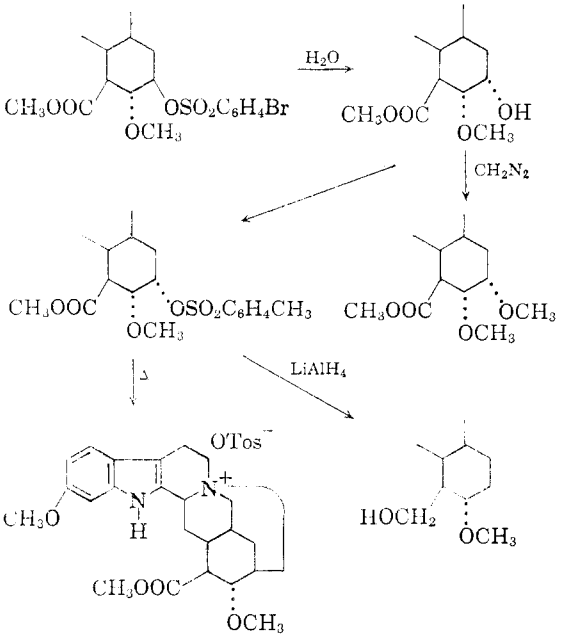
(4) For a similar alkylation of a tertiary amino group by a diazoalkane compare ref. 2b.

(5) It has been found in this Laboratory that sodium dichromate in aqueous acetic acid is an unusually convenient reagent for the oxidation of alkaloids of this type to the corresponding dehydro compounds. The reaction proceeds rapidly and cleanly at room temperature and the isolation procedure is much simpler than with the conventional mercuric acetate reagent; the process is uncomplicated by side-reactions and it is usually possible to isolate the dehydro compounds as the crystalline, free bases, rather than the perchlorate salts.

(6) P. E. Aldrich, *et al.*, *J. Am. Chem. Soc.*, **81**, 2481 (1959).

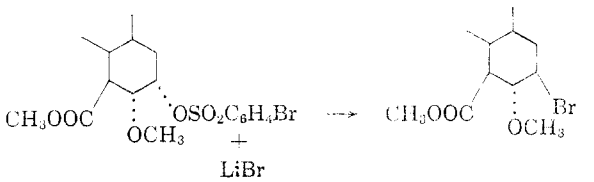


amine resulted in hydrolysis of the brosylate group to form a hydroxy compound isomeric with methyl reserpate. This product could be related directly to methyl epireserpate methyl ether by conversion to the latter on treatment with diazomethane–fluoboric acid. It may be noted that this alkylation proceeded in lower yield than that of methyl reserpate, and it was not possible to separate the ether from the large amount of unchanged starting material. Its presence was demonstrated by paper chromatographic comparison with a standard in six solvent systems. Thus, having established that the methanolysis and hydrolysis took the same steric course, it remained to relate methyl reserpate and its new isomer. The relationship was established by conversion of the latter to methyl epireserpate *p*-toluenesulfonate and treatment of this ester with refluxing collidine. The resulting internal quaternary salt, in which the Nb–$C_{18}$ bond can only be $C_{18}$–$\beta$, was identical with the substance derived from methyl reserpate tosylate on similar treatment.[7] The equivalence of the stereochemistry at $C_{16}$ and $C_{17}$ in the two hydroxy compounds was demonstrated further by reduction of methyl epireserpate tosylate with lithium aluminum hydride. The resulting reserpinol was identical with a sample prepared earlier from the normal tosylate.[8] Having established that the alcoholysis



of the brosylate proceeds with inversion, it was hoped that the process might be repeated with methyl epireserpate brosylate to form members of the first series of ethers, with the reserpine configuration at $C_{18}$. However, treatment of the epibrosylate with methanol, either in the presence of a tertiary amine or without added catalyst, did not result in an uncomplicated displacement as did the earlier process; rather, the two major reactions seemed to be internal quaternary salt formation and elimination of *p*-bromobenzenesulfonic acid. The predominance of these side-reactions, which may be rationalized on the basis of backside attack of Nb on $C_{18}$ or *trans*-diaxial elimination, was such that the methyl ether was only isolated in low yield.

Reaction of methyl epireserpate brosylate with lithium bromide, however, proceeded more readily to yield a bromo compound which was isomeric with the substance obtained from methyl reserpate tosylate.[6] That the only difference in configuration was at $C_{18}$ was again shown by hydrogenolysis to methyl 18-desoxyreserpate. This result was unexpected, since it was previously postulated that the first bromide was the thermodynamically more stable epimer, presumably the 18$\beta$-bromo compound, formed in an equilibrium process. This concept appeared to be reinforced by the report[6] of the preparation of the same 18-iodo compound by reaction of either methyl reserpate tosylate or methyl reserpate bromide (derived from the tosylate) with sodium iodide. The situation was resolved on re-examination of the original sample of product obtained from the latter reaction. It was found to differ from methyl reserpate iodide in analysis and optical rotation and to consist of two major products as well as unchanged starting material. Repetition of the reaction also afforded a mixture of starting material and two products, in approximately equal quantities, as shown by paper chromatography. Finally it was determined that each of the two crude bromo compounds, before recrystallization, contained appreciable quantities of the other. These facts, which lead to the conclusion that equilibration in the halide displacements is far from complete, demonstrate that the methyl reserpate tosylate product should be formulated as the 18$\alpha$-bromo epimer, and the epibrosylate product as the $\beta$-bromo compound.



Pharmacological evaluation of the ethers and their water-soluble hydrochlorides revealed a marked sedative action in dogs without any demonstrable hypotensive effect. The tranquilizing action differed from that of reserpine itself in that the onset of action was within minutes, rather than hours, and the duration of action was considerably shorter

(7) P. A. Diassi, F. L. Weisenborn, C. M. Dylion and O. Wintersteiner, *J. Am. Chem. Soc.*, **77**, 2028 (1955).

(8) C. F. Huebner, H. B. MacPhillamy, A. F. St. André and E. Schlittler, *ibid.*, **77**, 472 (1955).

than that of reserpine; there was no evidence of drug action on the following day. Further, cumulation was not evident on repeated administration. Finally, the ethers did not evoke increased motor activity in the gastrointestinal tract of the dog, unlike reserpine, and their effect on gastric secretion was less than one-tenth as great. Detailed pharmacological studies of the compounds will be reported elsewhere by Drs. W. Barrett and A. J. Plummer of these laboratories.

**Acknowledgments.**—The authors wish to express their sincere appreciation to Dr. E. Schlittler for his interest and encouragement in these studies. They are particularly indebted to Mr. L. Dorfman for his advice and assistance, to his staff for analytical and spectral results and to Mr. B. Korzun and co-workers for the paper chromatographic data. They are also especially appreciative of the valuable coöperation of Drs. W. Barrett and A. J. Plummer of the Macrobiological Division in these studies.

## Experimental[9]

**Methyl Reserpate Methyl Ether (II).**—To a cold solution of 7.44 g. of methyl reserpate in 1200 ml. of methylene chloride a freshly-prepared solution of 2 ml. of fluoboric acid in a mixture of 220 ml. of absolute ether and 60 ml. of methylene chloride was added with stirring. The fluoboric acid had been evaporated[3] to a concentration of approximately 14 *M;* thus the concentration of the ether–methylene chloride solution was about 0.1 *M*. Addition of the solution caused a heavy turbidity to appear. The mixture was cooled to approximately −10° and 200 ml. of 0.35 *M* diazomethane in methylene chloride[10] was added over a 10-minute period, with efficient stirring. During the addition the temperature rose slightly and most of the precipitate redissolved. After stirring for 15 minutes longer, a few milliliters of acetic acid was added to destroy any remaining diazomethane and the methylene chloride solution was washed twice with 5% aqueous sodium carbonate solution and once with saturated sodium chloride. The dried extract was evaporated *in vacuo* to a tan froth. The combined product from three such reactions was stirred for 0.5 hour at room temperature with 450 ml. of benzene, insoluble material (3.2 g.) was separated by filtration and the filtrate was evaporated to dryness *in vacuo*. Trituration with ether and reevaporation yielded approximately 17.5 g. of semi-crystalline solid, m.p. 160–175° dec. In the best isolation procedure 7.5 g. of this material was dissolved as completely as possible in 100 ml. of benzene and adsorbed on a 58 × 110 mm. column (240 g.) of Woelm activity II–III neutral alumina. After washing the column with 500 ml. more benzene, the major part of the product was eluted as rapidly as possible with about 3.5 l. of methylene chloride. A further quantity was obtained on elution with 0.5% methanol in methylene chloride. The combined, oily solids were dissolved in 500 ml. of boiling 1:3 benzene–cyclohexane and the solution was filtered through a pad of 3 g. of Darco. Concentration of the filtrate *in vacuo* and chilling afforded 1.46 g. of white filaments, m.p. 235–236.5° dec. Further recrystallizations from the same solvent-pair produced the analytical sample, m.p. 236–238° dec., $[\alpha]^{25}D$ −111°.

*Anal.* Calcd. for $C_{24}H_{32}N_2O_5$: C, 67.27; H, 7.53; N, 6.54; $OCH_3$, 28.97. Found: C, 67.19; H, 7.61; N, 6.58; $OCH_3$, 29.34.

The water-soluble **methyl reserpate methyl ether hydrochloride**, m.p. 237–242° dec., was prepared by dissolution of the ether in minimum acetone and addition of a solution of concentrated hydrochloric acid in acetone. On stirring, the resulting gel crystallized to form white filaments which were separated by filtration after chilling and washed with more cold acetone.

*Anal.* Calcd. for $C_{24}H_{32}N_2O_5 \cdot HCl \cdot H_2O$: C, 59.68; H 7.30; N, 5.80. Found: C, 60.06; H, 7.30; N, 5.95.

(9) Melting points are uncorrected. All optical rotations were determined in chloroform solution.

(10) R. E. Lutz, *et al.*, *J. Am. Chem. Soc.*, **68**, 1813 (1946).

When a diazomethane reaction was carried out with 7.44 g. of methyl reserpate and 540 ml. of 0.354 *M* diazomethane, the quaternary salt derived from the methyl ether was obtained. In this case the methylene chloride residue was warmed with 75 ml. of ethyl acetate. Filtration afforded 4.91 g. of crude salt. Although this could be recrystallized from ethanol, analytical figures for the salt corresponded to no simple empirical formula. Accordingly, the material was converted to **methyl reserpate methyl ether methochloride** by dissolution of 0.89 g. of the solid in 75 ml. of 4:1 methanol–water and passage through a column of 50 g. of Amberlite IRA-400 anion exchange resin (chloride form). Elution with more of the same solvent, evaporation *in vacuo* and trituration of the resulting froth with acetonitrile afforded 0.85 g. of product, m.p. 280–282° dec. It was purified for analysis by dissolution in a boiling mixture of acetonitrile and methanol, followed by partial evaporation. The resulting white filaments melted at 267–269° dec.

*Anal.* Calcd. for $C_{25}H_{35}N_2O_5Cl$: C, 62.68; H, 7.37; Cl, 7.40. Found: C, 62.48; H, 7.49; Cl, 7.72.

**Methyl 3-Isoreserpate Methyl Ether.**—Pyrolysis of a total of 0.8 g. of the quaternary methochloride was carried out at 350° (0.2 mm.) in four portions. In each case the salt was packed into a sublimation tube which was evacuated, then placed in a pre-heated block. The process was complete in about 2 minutes. The mixture of oil and sublimate was taken up in methylene chloride, the solution was washed with aqueous sodium carbonate and saturated brine, then dried and evaporated. The 0.53 g. of yellow solid was applied to a column of 20 g. of Woelm activity II-III neutral alumina, in benzene. After washing the column with benzene, the product was eluted with about 300 ml. of methylene chloride. The crude product, after washing with ether, weighed 0.23 g. Recrystallizations from 1:3 benzene–cyclohexane (Darco) produced white filaments, m.p. 248.5–251.5° dec., $[\alpha]^{27}D$ −97.5°.

*Anal.* Calcd. for $C_{24}H_{32}N_2O_5$: C, 67.27; H, 7.53; N, 6.54. Found: C, 67.44; H, 7.50; N, 6.63.

**Oxidation of II.**—To solution of 0.8 g. of the methyl ether in a mixture of 16 ml. of glacial acetic acid and 32 ml. of water was added a solution of 0.32 g. of potassium dichromate in 16 ml. of water. The solution darkened at once and a precipitate formed soon after the addition. The mixture was allowed to stand for 1 hour, then chilled, made alkaline with concentrated ammonium hydroxide and extracted with methylene chloride. Evaporation of the dried extracts left a tan foam, which could be crystallized by addition of ethyl acetate. The resulting dehydro compound was white at first, but darkened on standing, even *in vacuo* and in the dark. The material was not recrystallized for analysis; the crude product, m.p. 201–205°, had $[\alpha]^{27}D$ +122°.

As an indication that no other, more profound changes had taken place in the molecule on oxidation, the unpurified solid was reduced with zinc and perchloric acid to reconstitute II. Thus, 0.75 g. of the foam in a mixture of 8 ml. of tetrahydrofuran, 8 ml. of acetone, 7.2 ml. of water and 0.8 ml. of 70% perchloric acid was treated with 0.8 g. of zinc dust, and the mixture was refluxed in a nitrogen atmosphere for 15 minutes. After filtration, the solvent was removed *in vacuo*, 20 ml. of 3:2 acetone–water was added, and the solution was made alkaline and concentrated *in vacuo* to a sticky solid. Addition of water, extraction into methylene chloride, drying, and evaporation were followed by chromatography of the residue (0.7 g.) on 20 g. of Woelm activity II-III neutral alumina by the usual procedure. After removal of 3-iso ether in the benzene eluate, II was eluted. Recrystallization afforded 0.37 g. of product, m.p. 230–233°, $[\alpha]^{25}D$ −108°. It was identical with authentic II as shown by comparison of infrared spectra and mixture melting point.

In a separate experiment the dehydro compound from an oxidation one-half as large as above was dissolved in 35 ml. of methanol and 0.8 g. of sodium borohydride was added. After the initial vigorous reaction the solution was refluxed for 1 hour, then evaporated to dryness. Water was added and the resulting solid was separated by filtration and washed with water. There was obtained 0.37 g. (94%) of methyl 3-isoreserpate methyl ether, m.p. 247–250° dec. This was identical with the methochloride pyrolysis product as shown by mixture melting point, infrared spectra and paper chromatographic comparison.

**Methyl Reserpate Ethyl Ether.**—Reaction of 2.48 g. of methyl reserpate with 113 ml. of 0.212 *M* diazoethane was

carried out in the presence of 66 ml. of fluoboric acid solution, prepared according to the above procedure in ether–methylene chloride. The diazoethane was also prepared in methylene chloride solution. From the reaction 1.87 g. of crude solid was obtained, of which 0.4 g. was insoluble in benzene. The benzene-soluble portion, in this case, was chromatographed on 40 g. of Woelm, activity I neutral alumina. After washing the column with benzene the product was eluted with 0.2% methanol in benzene. The oily eluate was washed with ether to yield 0.29 g. (11%) of tan solid, m.p. 212–215° dec. Recrystallizations from benzene–cyclohexane (Darco) afforded white filaments, m.p. 221–222° dec.

*Anal.* Calcd. for $C_{25}H_{34}N_2O_5$: C, 67.85; H, 7.75; N, 6.33. Found: C, 67.32; H, 7.74; N, 6.65.

**Methyl Reserpate *n*-Butyl Ether.**—Reaction of 4.55 g. of methyl reserpate, 121 ml. of fluoboric acid solution and 150 ml. of 0.3 *M* diazobutane was effected according to the above procedure. In this case the methylene chloride residue was washed with ether before chromatography in an attempt to separate some of the oily impurities. The ether-insoluble material was then extracted with benzene and the benzene-soluble portion (approximately 1 g.) was chromatographed on 40 g. of activity I neutral alumina. In the process gas evolution was noted in the chromatograph column; apparently some impurity from the diazobutane preparation had been carried through. Elution with 0.2% methanol in benzene afforded only 0.19 g. of oily solid. The ether-soluble portion was then chromatographed separately by the same method on 40 g. of alumina. The combined products from both chromatograms were washed with ether to yield 0.26 g. of cream-colored solid, m.p. 213–216° dec. Recrystallizations from benzene–cyclohexane (Darco) raised the melting point to 219–221° dec., $[\alpha]^{26}D$ −90.5°.

*Anal.* Calcd. for $C_{27}H_{38}N_2O_5$: C, 68.91; H, 8.14; N, 5.95. Found: C, 68.94; H, 8.26; N, 6.06.

**Methyl Reserpate *p*-Bromobenzenesulfonate (IV).**—A mixture of 129 g. of methyl reserpate, 200 g. of *p*-bromobenzenesulfonyl chloride and 900 ml. of pyridine was allowed to stand for 3 days in the dark under nitrogen, and was then poured into 1250 ml. of ice-water. The mixture was extracted with about 3.5 l. of methylene chloride in several portions and the extract was washed with two 1200-ml. portions of 5% aqueous sodium carbonate, with 1200 ml. of water and with 1200 ml. of saturated brine. Evaporation of the dried extract *in vacuo* left a dark residue which was washed repeatedly with large volumes of benzene to remove most of the color. The solid was recrystallized by dissolution in a boiling mixture of acetone and methylene chloride, passage through a bed of Darco and evaporation of most of the methylene chloride. By re-processing the mother liquors several times, a total of 124 g. (63%) of product, m.p. 214–215° dec., was obtained. The analytical sample, prepared by further recrystallizations from the same solvent, had m.p. 219–221° dec.

*Anal.* Calcd. for $C_{29}H_{33}N_2O_7BrS$: C, 54.97; H, 5.25; N, 4.42. Found: C, 54.94; H, 5.54; N, 4.23.

**Methyl 18-Epireserpate Methyl Ether (V).**—A suspension of 1.90 g. of methyl reserpate brosylate in 240 ml. of methanol containing 0.36 g. of triethylamine was heated in a sealed vessel with magnetic stirring at 100° for 21 hours. During this period the starting material dissolved. The solvent was removed *in vacuo*, the residue was taken up in methylene chloride and the extract was washed with 5% sodium carbonate solution followed by saturated brine. After drying over sodium sulfate the extract was evaporated *in vacuo* and the residue was triturated with ether. Evaporation left 1.27 g. (99%) of essentially pure, crystalline ether, m.p. 236–238° dec. The analytical sample was prepared by recrystallizations from benzene–cyclohexane (Darco); m.p. 239–241° dec., $[\alpha]^{26}D$ −37.5°.

*Anal.* Calcd. for $C_{24}H_{32}N_2O_5$: C, 67.27; H, 7.53; $OCH_3$, 28.97. Found: C, 67.28; H, 7.57; $OCH_3$, 29.55.

The hydrochloride, m.p. 240–242° dec., was prepared by the method used for the first methyl ether.

*Anal.* Calcd. for $C_{24}H_{32}N_2O_5 \cdot HCl \cdot 1|2H_2O$: C, 60.81; H, 7.23; N, 5.91. Found: C, 61.03; H, 7.15; N, 6.10.

**Methyl 18-Epireserpate Ethyl Ether.**—A mixture of 3.17 g. of methyl reserpate brosylate, 240 ml. of absolute ethanol and 0.6 g. of triethylamine was heated at 100° in a sealed vessel with stirring for 5 days. The reaction was worked up as in the previous case to yield 2.01 g. of crude product, m.p. 220–224° dec. The analytical sample, prepared in the usual manner, had m.p. 229–230° dec., $[\alpha]^{26}D$ −27°.

*Anal.* Calcd. for $C_{25}H_{34}N_2O_5 \cdot HCl$: C, 67.85; H, 7.75; N, 6.33. Found: C, 67.99; H, 7.82; N, 6.14.

The hydrochloride, prepared in the usual manner, had m.p. 233–235° dec.

*Anal.* Calcd. for $C_{25}H_{34}N_2O_5 \cdot HCl$: C, 62.68; H, 7.37; N, 5.85. Found: C, 62.96; H, 7.82; N, 5.42.

**Methyl 18-Epireserpate *n*-Propyl Ether.**—The reaction with *n*-propyl alcohol was carried out by refluxing in a nitrogen atmosphere for 4 days. The analytically-pure compound (benzene–cyclohexane) had m.p. 223–225° dec. and $[\alpha]^{29}D$ −26.5°.

*Anal.* Calcd. for $C_{26}H_{36}N_2O_5$: C, 68.39; H, 7.95; N, 6.14. Found: C, 68.31; H, 8.02; N, 6.17.

**Methyl 18-Epireserpate Isopropyl Ether.**—Reaction with isopropyl alcohol was carried out at 100° in a sealed vessel with stirring. The alcoholysis, as indicated by dissolution of starting material, required 2 weeks for completion. The analytical sample, obtained from benzene–cyclohexane, had m.p. 225–229° dec., $[\alpha]^{24}D$ −23°.

*Anal.* Calcd. for $C_{26}H_{36}N_2O_5$: C, 68.39; H, 7.95; N, 6.14. Found: C, 67.87; H, 7.99; N, 6.42.

**Methyl 18-Desoxy 18α-phenylthioreserpate.**—To a solution prepared by reaction of 1 g. of sodium with 50 ml. of absolute methanol was added 5.5 g. of thiophenol, and the methanol was evaporated *in vacuo*. After addition of dry benzene and re-evaporation, 100 ml. of dry acetonitrile and 2.85 g. of methyl reserpate tosylate[11] were added to the solid and the mixture was refluxed for 1 hour. During this period a new solid precipitated. The residue from evaporation of the solvent was taken up in methylene chloride and the extract was washed with dilute sodium hydroxide solution, with water and with brine, then dried over sodium sulfate and evaporated *in vacuo*. Trituration of the residue with ether, filtration and washing with the same solvent afforded 1.52 g. (60%) of the thioether, m.p. 269–270° dec. Recrystallizations by dissolution in ethanol–methylene chloride and evaporation of the latter produced the analytical sample having the same melting point, $[\alpha]^{25}D$ +99°.

*Anal.* Calcd. for $C_{29}H_{34}N_2O_4S$: C, 68.75; H, 6.77; N, 5.53; S, 6.32. Found: C, 68.55; H, 6.86; N, 5.52; S, 6.57.

In another preparation, a 22-hour reaction of 3.17 g. of methyl reserpate brosylate, 5.1 ml. of thiophenol and 11.1 ml. of triethylamine in 200 ml. of acetonitrile was carried out at 100° with stirring. The product (1.9 g.) was separated directly from the chilled reaction mixture by filtration and washing with more cold acetonitrile. This material m.p. 261.5–262.5° dec., was identical with the above thio compound as shown by infrared spectra and mixture melting point.

**Methyl 18-Desoxyreserpate.**—A mixture of 1.5 g. of methyl reserpate bromide,[6] 28 ml. of purified dioxane, 68 ml. of methanol, 3.5 ml. of 1 *N* methanolic potassium hydroxide and 0.6 g. of platinum oxide was shaken under hydrogen at 3 atmospheres pressure for 2 hours. After filtration of the catalyst the excess base was neutralized with solid carbon dioxide and the solvent was evaporated. Chloroform was added, insoluble salts were separated by filtration, the solvent was evaporated and the foam was caused to crystallize by addition of ether; there was obtained 1.0 g., m.p. 135–139°. For analysis this substance was purified by passage of a methylene chloride solution through a column of Florisil. The product had m.p. 134–137° after trituration with ether, $[\alpha]^{27}D$ −82°. When the substance was recrystallized by dissolution in a large volume of ether and evaporation of most of the solvent, a different crystalline modification, m.p. 197–198.5° dec., was obtained.

*Anal.* Calcd. for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.73; H, 7.72; N, 7.39.

The same product was obtained when 1.9 g. of the phenylthioether, 100 ml. of 95% ethanol, 80 ml. of dioxane and 22 g. of Raney nickel were heated under reflux with stirring for 2 hours. After filtration and washing of the catalyst, the combined filtrates were evaporated and ether was added to the residue. Insoluble material was recrystallized from methanol–water to yield unreacted starting material.

(11) L. Dorfman, *et al.*, *Helv. Chim. Acta*, **37**, 59 (1954).

The methanol–water mother liquor was evaporated to dryness, the residual gum was stirred with methylene chloride and the resulting solid was dissolved in methanol–water. Addition of alkali yielded a gum, which, after recrystallization from methanol–water, had m.p. 127–132°. After recrystallization from ether the substance had m.p. 196.5–197.5° dec., $[\alpha]^{27}D$ −78°. The infrared spectrum was identical with that of the methyl reserpate bromide product.

*Anal.* Calcd. for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.46; H, 7.71; N, 7.09.

**Methyl 18-Epireserpate.**—A mixture of 6.34 g. of methyl reserpate brosylate, 1.2 g. of triethylamine, 100 ml. of water and 300 ml. of dioxane (purified by passage through alumina) was refluxed under nitrogen for 2 days. After evaporation of the solvent the gummy residue was extracted repeatedly with 5% aqueous hydrochloric acid until the extracts no longer gave an appreciable precipitate on basification. Recrystallization of the product from acetonitrile yielded 2.3 g. of stout needles, which became semi-molten at about 180° and decomposed at 222–223°. Further recrystallizations from the same solvent and drying at room temperature afforded the hydrated analytical sample with the same melting-point behavior.

*Anal.* Calcd. for $C_{23}H_{30}N_2O_5 \cdot H_2O$: C, 63.87; H, 7.46; N, 6.48. Found: C, 63.99; H, 7.49; N, 6.45.

Drying at 140° produced an anhydrous sample, but not without slight discoloration. This had m.p. 220–223° dec., $[\alpha]^{25}D$ −80.5°.

*Anal.* Calcd. for $C_{23}H_{30}N_2O_5$: C, 66.64; H, 7.30; $OCH_3$, 22.44. Found: C, 66.45; H, 7.12; $OCH_3$, 22.46.

**Reaction of Methyl Epireserpate with Diazomethane.**—To a solution of 2.58 g. of methyl epireserpate monohydrate in 700 ml. of methylene chloride was added 90 ml. of fluoboric acid solution, prepared as above, and the turbid solution was then treated, by the usual method, with 135 ml. of 0.265 *M* diazomethane in methylene chloride. Paper chromatographic comparison of the total methylene chloride residue with the methyl ether indicated the presence of the methylation product as well as much unchanged starting material. The solvent systems employed and the $R_f$ values of the ether were: chloroform (0.45); 10% pyridine in chloroform (0.80); 2% pyridine in 1:1 benzene–chloroform (0.45); 3:1 xylene–methyl ethyl ketone (0.14); 1:1 benzene–chloroform (0.15); benzene (0.05). The stationary phase in all systems was formamide-impregnated paper. In the first five cases the *pH* of the formamide was adjusted to 5.6. Attempted chromatography of the benzene-soluble portion of the product on alumina did not effect a clean separation of the starting material and product.

**Methyl 18-epireserpate *p*-toluenesulfonate** was prepared by the method used for methyl reserpate brosylate, except that the crude product was washed with acetonitrile, rather than benzene. From 0.9 g. of methyl epireserpate monohydrate there was obtained, after recrystallization from acetonitrile, 0.76 g. of white cubes, m.p. 222–225° dec. Further recrystallizations from the same solvent produced the analytical sample with the same melting point, $[\alpha]^{27}D$ −35.5°.

*Anal.* Calcd. for $C_{30}H_{36}N_2O_7S \cdot 1/2\ H_2O$: C, 62.37; H, 6.46; S, 5.55. Found: C, 62.74; H, 6.50; S, 5.82.

**Quaternization of Methyl Epireserpate Tosylate.**—A suspension of 0.28 g. of the tosylate in 4 ml. of collidine was refluxed for 4 hours, then the collidine was removed by addition of water and vacuum distillation. Methylene chloride was added to the dry residue and the pale-green solid was separated by filtration and washed with more solvent. A sample gave a precipitate with sodium iodide in acetonitrile. Two recrystallizations from acetonitrile produced shiny plates, $[\alpha]^{24}D$ +88° (*c* 0.75, HOAc), m.p. 299° dec., undepressed on admixture with a sample derived from methyl reserpate tosylate. The observed m.p. of the latter was 297° dec. (reported[6] m.p. 290–291° dec.). The infrared spectra of the two samples of quaternary salt were identical.

**Reduction of Methyl Epireserpate Tosylate to Reserpinol.**—The tosylate (0.48 g.) was reduced by the method of Huebner, *et al.*[8] After two recrystallizations from acetone and two sublimations at approximately 225° (0.2 $\mu$) the crystalline product melted at 253–4° dec. alone and at 248–250° dec. on admixture with a sample (observed m.p. 246–248° dec.) derived from methyl reserpate tosylate. The infrared spectra of the two samples were identical.

**Methyl 18-epireserpate *p*-bromobenzenesulfonate** was prepared by the method used for methyl epireserpate tosylate. From 4.32 g. of hydrated methyl epireserpate there was obtained, after recrystallization from acetonitrile, 2.92 g. of product, m.p. 210–212° dec. Further recrystallizations from the same solvent did not change the melting point of the substance, which had $[\alpha]^{26}D$ −32.5°.

*Anal.* Calcd. for $C_{29}H_{33}N_2O_7BrS \cdot 1/2\ H_2O$: C, 54.20; H, 5.33; Br, 12.44. Found: C, 54.05; H, 5.40; Br, 11.98.

**Methanolysis of Methyl Epireserpate Brosylate.**—A mixture of 1 g. of methyl epireserpate brosylate, 80 ml. of methanol and 0.5 ml. of pyridine was heated at 100° under pressure for 121 hours; unreacted starting material (0.25 g.) was separated by filtration and the filtrate was worked up in the usual fashion. An insoluble solid (0.09 g.), apparently internal quaternary salt, was encountered on washing the methylene chloride extract with sodium carbonate. The methylene chloride solution was clarified by filtration through a column of Florisil, then evaporated to yield 0.37 g. of foam. This was chromatographed on 15 g. of grade II-III neutral alumina, eluting with benzene, methylene chloride, and finally pure methanol. Recrystallization of the last fraction from benzene–cyclohexane afforded a mixture, m.p. 175–200°. Evaporation of the mother liquors and trituration with ether produced a solid, m.p. 216–224°, which on recrystallization (Darco) yielded 10 mg. of the methyl ether, m.p. 225–230°, undepressed on admixture with an authentic sample. The substance, $[\alpha]^{25}D$ −101°, had an infrared spectrum identical with that of authentic material.

**Methyl 18β-Bromo-18-desoxyreserpate.**—Methyl epireserpate brosylate (1.24 g.) was treated with 1.1 g. of lithium bromide in 35 ml. of acetonitrile according to the procedure for the preparation of the isomeric bromide.[6] The crude solid from the chloroform was recrystallized first from methanol–water, then from methanol–methylene chloride by evaporation of most of the methylene chloride. The pure product weighed 0.3 g. (33%). The analytical sample, m.p. 234–236° dec., had $[\alpha]^{26}D$ −97°; on admixture with methyl reserpate bromide[5] it melted at 214–217°. The latter isomer, m.p. 224–226° dec., has $[\alpha]D$ −54°.

*Anal.* Calcd. for $C_{23}H_{29}N_2O_4Br$: C, 57.86; H, 6.12; N, 5.86. Found: C, 58.09; H, 6.24; N, 5.98.

Material from the mother liquors of the recrystallizations contained methyl reserpate bromide, according to paper chromatography. Similarly, a recrystallized sample of the latter contained a small amount of the new bromide.

**Hydrogenolysis of the 18β-Bromo Compound.**—The hydrogenolysis was carried out as described above for methyl reserpate bromide, except that 0.5 g. of catalyst was used with 0.95 g. of bromo compound and shaking was continued for 6 hours. The crude product was first recrystallized from cyclohexane to yield a third crystalline modification, m.p. 162–165° dec. It was next dissolved in methylene chloride and the solution was evaporated to a froth. Dissolution in ether followed by seeding with the higher-melting modification yielded crystals, m.p. 196–198° dec., undepressed on admixture with the m.p. 196.5–197.5° material from the phenylthioether. The substance, $[\alpha]^{25}D$ −83.5°, was identical with the other hydrogenolysis products as shown by paper chromatographic comparison and infrared spectra ($CHCl_3$ solution).

**Methyl Reserpate Bromide–Sodium Iodide Reaction.**—It was found that the original sample of the product, thought to be methyl reserpate iodide[6] when first obtained from this reaction, was actually a mixture of approximately equal quantities of unreacted bromide and another substance, as shown by paper chromatography and analysis. In addition, a third substance was present in appreciable amount. The sample, m.p. 216–223° dec., had $[\alpha]^{24}D$ +21° (reported[6] for methyl reserpate iodide, $[\alpha]^{25}D$ +47°).

*Anal.* Calcd. for $C_{23}H_{29}N_2O_4I$: C, 52.68; H, 5.57. Calcd. for $C_{23}H_{29}N_2O_4Br$: C, 57.86; H, 6.12. Found: C, 55.78; H, 5.90.

Repetition of the reaction afforded a crystalline solid, m.p. 205–210° dec., $[\alpha]^{28}D$ +23.5° after recrystallization. The amorphous residue from the mother liquors had $[\alpha]^{28}D$ −53.5°. Both of these new samples were also mixtures of unreacted bromide and other materials according to paper

chromatography. The identification of the product as methyl reserpate iodide was originally based on undepressed mixture melting point and identical infrared spectra. The situation was resolved when it was noted that the infrared spectra of the pure iodide and bromide are identical throughout the whole curve, while the spectrum of the new bromide differs only in very minor respects. It is apparent that the original mistaken identification was caused by the unreliability of mixture melting points in this series, as well as the unusual correspondence of the infrared spectra.

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[CONTRIBUTION FROM FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY, PRINCETON, N. J.]

# The Reactivity of Bridgehead Compounds of Adamantane[1,2]

BY PAUL VON R. SCHLEYER AND ROBERT D. NICHOLAS[3]

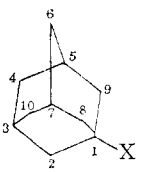
RECEIVED AUGUST 10, 1960

Unexpectedly, bridgehead adamantane compounds are quite reactive. Solvolysis of 1-adamantyl derivatives proceeded at rates only 1000 times slower than the corresponding *t*-butyl compounds, but almost 5000 times faster than 1-bicyclo-[2.2.2]octyl and $10^{11}$ faster than 1-bicyclo[2.2.1]heptyl derivatives. The difference between the reactivity of 1-adamantyl and *t*-butyl compounds appears to be largely due to angle strain in the somewhat flattened but not planar transition states of the former compounds. The impossibility of rearside solvation may play a minor role also, but there is no experimental evidence to support the theory that inhibition of bridgehead hyperconjugation can alter the reaction rate significantly. The difference between the reactivity of 1-adamantyl and 1-bicyclo[2.2.2]octyl compounds, despite their apparently identical arrangements of atoms and bonds in the vicinity of the reaction site, is due to conformational strain in the latter system.

Bartlett[4] first realized that reactions at a bridgehead had important mechanistic implications.[5] Exploitation of this idea has lead to a greater understanding of the stereochemical restrictions of many different reactions.[4,5] Bridgehead compounds are generally difficult to obtain despite the development of ingenious methods for their preparation.[4,5] However, 1-substituted adamantane derivatives have recently become readily available.

Reaction of adamantane (I)[6] with bromine at steam-bath temperature gave excellent yields of 1-bromoadamantane (II).[7-9] Excellent yields of products also resulted from carbonium ion reactions of II. Preparative solvolysis of II in refluxing aqueous solvents readily gave 1-adamantanol (III)[7-9]; II also reacted very satisfactorily in the Friedel–Crafts alkylation[8] and in the Koch carboxylation.[8] Adamantane (I) can be carboxylated directly by a modified Koch procedure involving an intermolecular hydride ion exchange with *t*-butyl carbonium ion.[9c] Treatment of III with thionyl chloride yielded 1-chloroadamantane (IV).[8,10] Both II and III underwent the Ritter amidation smoothly.[8,9] All of these reactions were carried out under mild conditions. These results were especially surprising in view of the well known inertness of bridgehead compounds of other ring systems.[4,5,10]

Very recently, Stetter and co-workers[9] have reported a quantitative study of the reactivity of 1-bromoadamantane (II) in two solvents at one temperature. They noted an unexpected rapidity of reaction, for which they offered no explanation. The results described in the present paper, obtained prior[2] to the publication of the German report, serve to confirm and extend these observations and to offer an interpretation of this behavior.




I, X = H
II, X = Br
III, X = OH
IV, X = Cl
V, X = I
VI, X = OTs

## Experimental Results

**Preparation of Compounds.**—1-Bromoadamantane (II), 1-adamantanol (III) and 1-chloroadamantane (IV) were prepared according to the literature procedures.[7,8] 1-Adamantanol (III) was also prepared by the free radical hydroxylation of adamantane.[1] The literature synthesis of 1-iodoadamantane[7] (V) could not be repeated. Instead, the compound was made by the reaction of III with HI. The m.p. of V so produced, 75.3–76.4°, was at considerable variance with that reported by Landa, Kriebel and Knobloch,[7] 151–152.5°. The

(1) Paper V of a series on Bridged Ring Systems; paper IV, *J. Am. Chem. Soc.*, **83**, 182 (1960). This paper is taken, in part, from the Ph.D. Thesis of R. D. N., Princeton University, 1960.

(2) A preliminary account of this work was presented at the Third Delaware Valley Regional Meeting, Am. Chem. Soc., Feb., 1960, Abstracts, p. 49.

(3) Gulf Research and Development Fellow, 1959–1960. National Science Foundation Summer Fellow, 1960.

(4) P. D. Bartlett and L. H. Knox, *J. Am. Chem. Soc.*, **61**, 3184 (1939); P. D. Bartlett and S. G. Cohen, *ibid.*, **62**, 1183 (1940); P. D. Bartlett and E. S. Lewis, *ibid.*, **72**, 1005 (1950); P. D. Bartlett, *Bull. soc. chim. France*, C100 (1951); P. D. Bartlett in H. Gilman, Ed., "Organic Chemistry," Vol. III, J. Wiley and Sons, Inc., New York, N. Y., 1953, p. 58; also see ref. 5.

(5) For reviews: (a) D. E. Applequist and J. D. Roberts, *Chem. Revs.*, **54**, 1065 (1954); (b) U. Schöllkopf, *Angew. Chem.*, **72**, 147 (1960).

(6) P. von R. Schleyer, *J. Am. Chem. Soc.*, **79**, 3292 (1957); P. von R. Schleyer and M. M. Donaldson, *ibid.*, **82**, 4645 (1960).

(7) S. Landa, S. Kriebel and E. Knobloch, *Chem. Listy*, **48**, 61 (1954); S. Landa and S. Hala, *Coll. Czech. Chem. Comm.*, **24**, 93 (1959).

(8) H. Stetter, M. Schwarz and A. Hirschhorn, *Ber.*, **92**, 1629 (1959); H. Stetter and C. Wulff, *ibid.*, **93**, 1366 (1960).

(9) (a) H. Stetter, J. Mayer, M. Schwarz and K. Wulff, *ibid.*, **93**, 226,[3] (1960); (b) H. Stetter and C. Wulff, *ibid.*, **93**, 1366 (1960); (c) H. Koch and W. Haaf, *Angew. Chem.*, **72**, 628 (1960); (d) W. Haaf, *ibid.*, **73**, 144 (1961).

(10) Contrast the behavior of 1-hydroxybicyclo[2.2.1]heptane (ref. 4) and compare the behavior of 1-hydroxybicyclo[3.2.2]nonane (C. A. Grob, M. Ohta, E. Reuh and A. Weiss, *Helv. Chim. Acta*, **41**, 1191 (1952)) toward this reagent.