endo-proton nuclear spins by interaction with the nickel atom.

The simplicity of the methylene resonance of π-C_5H_5Ni-π-$C_5H_5D_2$ demonstrates the *cis* stereochemistry of the incorporated deuteriums, since a *trans* orientation should afford both *endo* and *exo* resonances analogous to I. The chemical shift of the methylene protons of II corresponds closely to that of the low-field BB′ multiplet of I. The deuterium atoms have replaced the protons giving rise to the high-field resonance, and, therefore, can be assigned the *endo* configuration.

The departure from the usual stereochemistry in catalytic hydrogenation observed in this study may prove to be a general feature of organic ligands coordinated to transition metals. We plan to examine this possibility.

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Studies on the Hepatic Microsomal N-Dealkylation Reaction. Molecular Oxygen as the Source of the Oxygen Atom

Sir:

The TPNH-dependent oxygenases associated with the endoplasmic reticulum of mammalian hepatic cells catalyze the oxidative dealkylation of a wide variety of N- and O-alkyl compounds, including amines, amides, carbamates, sulfonamides, and aromatic ethers.[1] The most likely mechanism[1,2] for this enzymatic reaction involves hydroxylation of the carbon atom adjacent to the heteroatom as the initial reaction step. With a tertiary amine as substrate, a carbinolamine would be produced. This unstable intermediate would then dissociate to form the dealkylated amine and an aldehyde, the observed reaction products (eq 1). Alternatively it has been suggested[3,4] that oxidative dealkylation may proceed by the initial formation of an N-oxide which in turn could rearrange to the carbinolamine intermediate (eq 2). In support of this pathway it can be mentioned that enzymatic N-oxidation is a known reaction[5] and further that the dealkylation of N-oxides to form dealkylated amine and aldehyde is a known chemical reaction.[4]

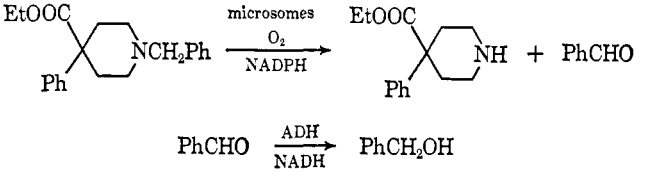
$$R_2NCH_2R \xrightarrow{[O]} [R_2NCHOHR] \longrightarrow R_2NH + O{=}CHR \quad (1)$$

$$R_2NCH_2R \xrightarrow{[O]} R_2\overset{\uparrow}{\underset{O}{N}}CH_2R \longrightarrow [R_2NCHOHR] \quad (2)$$

One difference between these two possible reaction pathways would be the source of the oxygen atom. If the reaction is indeed a typical microsomal hydroxylation (mechanism 1) the carbonyl oxygen in the aldehyde produced should derive from molecular oxygen. This would not be true in the case of mechanism 2. The probable[6] mechanism for the Fe^{II}-catalyzed dealkylation of tertiary amine oxides requires that the oxygen in the carbinolamine be derived from solvent water and not from N-oxide oxygen. The same situation exists for the earlier mechanism suggested by Craig, *et al.*[7] Thus it became of considerable interest to establish the source of carbonyl oxygen in the enzymatic dealkylation reaction.

Oxygen-18 studies, however, present a serious difficulty, *i.e.*, aldehydes in water solution rapidly exchange carbonyl oxygen with solvent water oxygen.[8] For this and other reasons it seemed impractical to investigate either N-demethylation or N-deethylation initially. We therefore turned to enzymatic N-debenzylation with the hope that the benzaldehyde formed would exchange with water slowly enough to allow the oxygen to be trapped as benzyl alcohol by a coupled enzymatic reduction. This possibility was investigated as follows. When benzaldehyde-^{18}O (37 atom %) was dissolved in phosphate buffer (pH 7.4), allowed to stand 15 min, and then reduced by the addition of horse liver alcohol dehydrogenase (LADH) and 1 equiv of NADH the benzyl alcohol recovered contained only 1.1 atom % ^{18}O. When, however, benzaldehyde-^{18}O (37 atom %), LADH, and NADH were added simultaneously to buffer, the resultant benzyl alcohol contained 7 atom % ^{18}O (19% recovery of ^{18}O). Thus, although the exchange reaction readily occurs, ^{18}O can be partially trapped if reduction to benzyl alcohol occurs rapidly enough.

Thus encouraged, we next carried out the following coupled enzymatic dealkylation–reduction sequence using oxygen-18-labeled molecular oxygen.



A solution containing washed liver microsomes[9] from 6 g of rat liver, 5 mg of alcohol dehydrogenase, 100 mg of NADH, 70 mg of $NADP^+$, 200 μmoles of isocitric acid, and 1 mg of isocitric dehydrogenase in 20 ml of 0.1 *M* phosphate buffer (pH 7.4) was prepared in a 125-ml reaction flask. The solution was then frozen in liquid nitrogen and 50 μmoles of N-benzyl-4-phenyl-4-carbethoxypiperidine hydrochloride was added. After evacuation and the addition of 1 mmol of $^{18}O_2$ (95 atom %), the closed flask was heated at 37° with stirring for 0.5 hr. The reaction product, benzyl alcohol, was recovered by extraction, purified by gas–liquid partition chromatography, and found (by mass spectroscopy) to contain 29 atom % of ^{18}O. Repetition of the experiment yielded benzyl alcohol containing 26 atom % ^{18}O. A control experiment in which the substrate was benzaldehyde instead of the N-benzylamine

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yielded benzyl alcohol containing less than 0.5 atom % ^{18}O.

The data presented above clearly establish that the source of oxygen in the microsomal dealkylation reaction is molecular oxygen. This finding provides further support for a reaction pathway involving direct hydroxylation of the carbon atom, a mechanism compatible with other biochemical data.[1,2,10]

The experiments described herein pertain only to the mammalian hepatic microsomal system. Their relationship to other dealkylases of animal or plant origin is at present unknown.

Acknowledgment. The authors are indebted to Mrs. Catherine Cobb for assistance with the enzyme studies.

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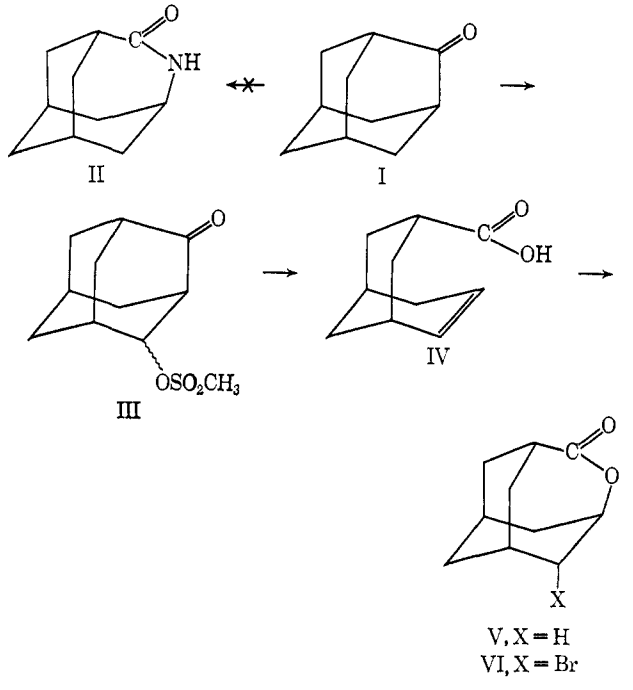
Novel Substitution Reaction of Adamantanone. A Simple Synthesis of Bicyclo[3.3.1]non-2-ene-7-carboxylic Acid[1]

Sir:

In spite of the extensive studies on the substitution reactions of adamantane and its derivatives,[2] there seem



to be no reports on direct substitution reactions of adamantanone (I). We wish to report a new and novel substitution reaction of I at its 4 position.

In view of the expected conversion of I into the ring-enlarged 2-aza-3-oxotricyclo[4.3.1.1^{4,7}]undecane (II) by the Schmidt reaction, I was treated with sodium azide in methanesulfonic acid under the reaction conditions given by Smith and Berry.[3] The product, obtained as colorless crystals, mp 73–75°, in 90% yield, was characterized unexpectedly as 4-methylsulfonoxyadamantanone (III) on the basis of the analytical data (*Anal.* Calcd for $C_{11}H_{16}O_4S$: C, 54.07; H, 6.60. Found: C, 53.82; H, 6.69) and the following spectral data; the infrared spectrum (KBr) exhibited strong bands at 1720 ($\nu_{C=O}$) and 1340 and 1180 (ν_{SO_2}) cm^{-1} but no NH band. In the nmr spectrum (100 MHz, $CDCl_3$) signals at τ 5.20 (1 H, unsymmetrical triplet, J = 3.5 Hz, C-4 proton),[4] 6.95 (3 H, singlet, OSO_2CH_3), 7.11 (1 H, broad singlet, C-3 proton), 7.44 (1 H, broad singlet, C-1 proton), 7.51–8.40 (10 H, complex multiplet, other adamantane ring protons) appeared and the mass spectrum had peaks at *m/e* 244 (5, M$^+$), 149 (58), 121 (17), and 79 (100); 2,4-dinitrophenylhydrazone mp 227–229°; oxime mp 131–133.°.

III was cleaved to the known bicyclo[3.3.1]non-2-ene-7-carboxylic acid (IV)[5] on alkaline hydrolysis (aqueous potassium hydroxide and/or sodium carbonate) in 85% yield; this provided chemical proof of structure III, for if a methylsulfonoxy group is present at C-1 and/or C-5, the hydrolysis product should be noradamantane-1-carboxylic acid[6] and/or 1,7-dehydrobicyclo[3.3.1]nonane-3-carboxylic acid, respectively. The structure of IV was confirmed on the basis of its physical (mp 195–196°, lit.[5] mp 195–198°) and spectral data; the infrared spectrum was superimposable with that of an authentic sample[7] and the nmr spectrum (60 MHz, $CDCl_3$), having signals at τ −1.3 (1 H, singlet, COOH), 4.38 (2 H, unsymmetrical singlet with a weak satellite at τ 4.26 and 4.52, -CH=CH-), and 7.3–8.7 (11 H, complex multiplet, other bicyclononene ring protons), was compatible with the assigned structure IV. For further confirmation of the structure, IV was converted to the known lactone V, mp 296–297° (lit.[5] mp 288–290°), in 90% yield, and to a new bromolactone, VI,[8] mp 139°, in 96% yield.

The fact that a facile quasi-Favorskii reaction of III[9] had occurred to give IV in good yield provides evidence of the presence of the 4-methylsulfonoxy group in an adamantanone ring.

Treatment of adamantane with sodium azide under similar reaction conditions gave only recovered adamantane, indicating a carbonyl function is necessary for the new substitution reaction. Formation of III from I under Schmidt reaction conditions might involve 1,3-hydride transfer,[10] followed by oxidation or disproportionation; furthermore, it should be mentioned that

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