9-Benzyl-1,4-dioxa-9-azaspiro[4.8]tridecane (38).—A solution of 9-benzoyl-1,4-dioxa-9-azaspiro[4.8]tridecane (13.331 g, 0.0462 mole in ether (250 ml) was dribbled into a mixture of lithium aluminum hydride (2.0 g) in ether (100 ml). The mixture was stirred at room temperature for 16 hr and at reflux temperature for 4 hr. The excess hydride was decomposed by the cautious addition of water. The inorganic solids were removed by filtration and washed with ether. The combined ether solution was dried and concentrated to an oil. A simple distillation of the oil gave the product (10.779 g, 0.0392 mol, 85%) as a colorless oil: bp 145–147° (1.5 mm); $n^{26}D$ 1.5302; $\nu_{C=C}$ 1600 w, 1498 m, $\nu_{C_6H_5}$ 750 m, 715 ms, 701 ms cm^{-1} (on the oil).

Anal. Calcd for $C_{17}H_{25}NO_2$ (275.38): C, 74.14; H, 9.15; N, 5.09. Found: C, 74.77; H, 9.66; N, 5.04.

The oil crystallized when kept overnight in the refrigerator, mp 44–46°.

4-Benzyloctahydro-8a-hydroxyindolizinium Perchlorate (39).—Aqueous (70%) perchloric acid (2 ml) was added to a solution of 9-benzyl-1,4-dioxa-9-azaspiro[4.8]tridecane (0.491 g, 0.00178 mole) in ethanol (3 ml). The solution became hot After cooling, ether was added to the point of forming two phases. Crystals formed slowly. The mixture was cooled in the freezer. Colorless crystals (0.456 g, 0.00137 mol, 73%) were obtained, mp 143–145°. Two recrystallizations from ethanol–ether gave colorless crystals: mp 152–153°; ν_{OH} 3420 s, $\nu_{C_6H_5}$ 768 s, 710 s cm^{-1} (in Nujol).

Anal. Calcd for $C_{15}H_{22}NO_5Cl$ (331.80): C, 54.29; H, 6.68; N, 4.22. Found: C, 54.16; H, 6.85; N, 4.48.

1,4-Dioxa-9-azaspiro[4.8]tridecane (40).—A solution of 9-benzyl-1,4-dioxa-9-azaspiro[4.8]tridecane (9.451 g, 0.0344 mol) in methanol (150 ml) was shaken with 5% palladium on carbon (2.5 g) in hydrogen for 45 min at which time uptake of hydrogen appeared complete. The catalyst was removed by filtration and the colorless filtrate was stored overnight in the refrigerator. The solution, now yellow, was concentrated under reduced pressure. The yellow oil product crystallized as it cooled. The solid was dissolved in ether, decolorized with activated charcoal, filtered, and crystallized by addition of Skellysolve B to the ether and by cooling in the freezer. Colorless crystals (4.649 g, 0.0251 mole, 73%) were obtained, mp 55–57°. Recrystallization from ether–Skellysolve B gave colorless, chunky crystals: mp 55–57°; ν_{NH} 3400 mw cm^{-1} (in Nujol).

Anal. Calcd for $C_{10}H_{19}NO_2$ (185.26): C, 64.83; H, 10.34; N, 7.56. Found: C, 64.66; H, 10.40; N, 7.62.

2,3,5,6,7,8-Hexahydro-1H-indolizinium Perchlorate (41).—Aqueous (70%) perchloric acid (2 ml) was added to a solution of 1,4-dioxa-9-azaspiro[4.8]tridecane (0.483 g, 0.00261 mol) in absolute ethanol. The solution became hot and, after cooling, ether was added to the point of separation of two phases. The solution was placed in the freezer and crystals slowly formed. Colorless crystals (0.350 g, 0.00157 mol, 60%) were collected by filtration, mp 212–220°. Three recrystallizations from ethanol–ether gave colorless flakes: mp 227–228° dec (lit.[15] mp 218–219° dec); $\nu_{C=N^+}$ 1690 cm^{-1} (in Nujol) [lit.[15] 1689 cm^{-1} (in Nujol)].

Registry No.—**8,** 16803-02-4; **10,** 16803-03-5; **12,** 15923-40-7; **12a,** 16803-05-7; **13,** 16803-06-8; **14,** 16803-07-9; **16,** 16803-08-0; **18,** 16803-09-1; **19,** 16803-10-4; **20,** 16803-11-5; **21,** 16803-12-6; **22a,** 16853-06-8; **22b,** 16853-07-9; **23,** 16853-08-0; **24b,** 16353-09-1; **25,** 16803-13-7; **26,** 16853-10-4; **30,** 16803-14-8; **31,** 16803-15-9; **32,** 16853-11-5; **33,** 16803-16-0; **35,** 16803-17-1; **36,** 16803-18-2; **37,** 16803-19-3; **38,** 16803-20-6; **39,** 16853-12-6; **40,** 16803-21-7; **41,** 14594-57-1.

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The Microbiological Oxygenation of Some Azabicycloalkanes

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The microbiological oxygenation of 3-benzoyl-3-azabicyclo[3.3.1]nonane (**1**) and 3-benzoyl-3-azabicyclo[3.2.2]nonane (**11**) with *Sporotrichum sulfurescens* has been shown to give 3-benzoyl-*endo*-3-azabicyclo[3.3.1]nonan-6-ol (**2**) in the first case and a mixture of 3-benzoyl-*endo*-3-azabicyclo[3.2.2]nonan-6-ol (**12**) and 3-benzoyl-3-azabicyclo[3.2.2]nonan-6-one (**13**) in the second case. Reduction of ketone **13** with sodium borohydride gave 3-benzoyl-*exo*-3-azabicyclo[3.2.2]nonan-6-ol (**14**), which underwent acyl migration in acidic solution. The major and minor hydroxylated products obtained from microbiological oxygenation of 2-benzoyl-2-azabicyclo[2.2.2]octane (**23**) were assigned *endo*-5-ol (**24**) and *endo*-6-ol (**25**) structures, respectively, based on the patterns of oxygenation observed in the above and in related molecules.

The oxygenation of saturated organic molecules by microorganisms is of particular importance because of the introduction of functionality at positions inaccessable to many methods of organic chemistry. Examples of interest are the numerous oxygenations of the steroid nucleus by a variety of microorganisms.[1] Recent extensions include oxygenations of macrocyclic alcohols[2] and the amide derivatives of cyclic amines[3] by the microorganism, *Sporotrichum sulfurescens*. As yet there is considerable uncertainty as to the position of oxidative attack by microorganisms. A proposal that such attack by *S. sulfurescens* will occur at a saturated carbon approximately 5.5 Å from an electron-rich center, such as a ketone or an amide carbonyl oxygen,[2,3] provides a working hypothesis with which to consider this question. Continued expansion of the varieties of molecules submitted to microbiological oxygenation aids in testing this proposal as well as in determining the limits of the reaction with respect to chemical structure. The successful microbial oxygenation of the amides of azacycloalkanes[4] suggested the further extension to the amides of azabicycloalkanes. The oxygenation of 3-benzoyl-3-azabicyclo[3.3.1]nonane (**1**), 3-benzoyl-3-azabicyclo[3.2.2]nonane (**11**), and 2-benzoyl-2-azabicyclo[2.2.2]octane

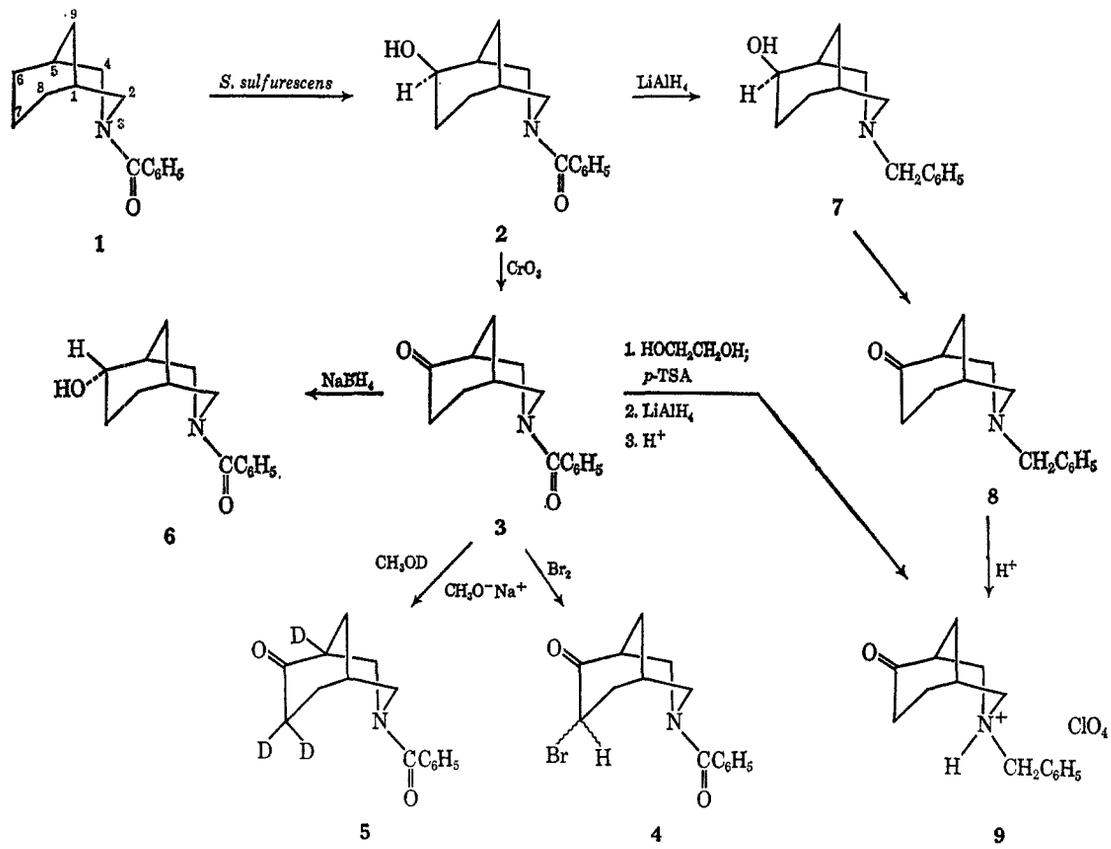
(1) *Cf.* S. H. Eppstein, P. D. Meister, H. C. Murray, and D. H. Peterson, "Vitamins and Hormones," Vol. XIV, Academic Press Inc., New York, N. Y., 1956, pp 359–432.

(2) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Amer. Chem. Soc.*, **89**, 672 (1967).

(3) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Org. Chem.*, **33**, 3182 (1968).

(4) R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *ibid.*, **33**, 3187 (1968).

SCHEME I



(23) by *S. sulfurescens* and the structure determination of the products provide the subjects for this paper.

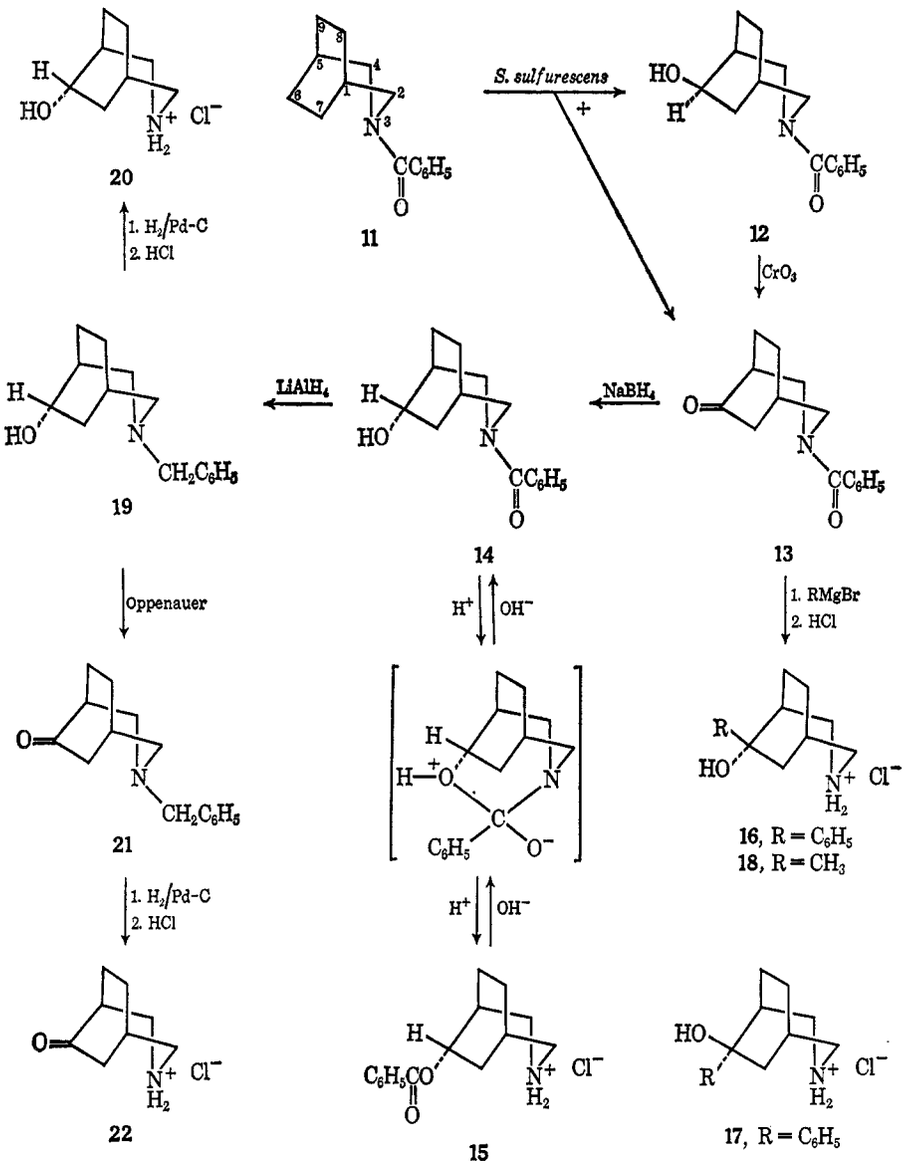
3-Benzoyl-3-azabicyclo[3.3.1]nonane (1).—The bicyclic amide **1** served as an excellent substrate, giving a single monohydroxylated product (**2**) in yields of 60–70% when oxygenated with *S. sulfurescens*. Dissimilation of the substrate (**1**) was rapid and was successful at a substrate level of 0.5 g/l. of medium (which may be compared with a level of 0.2 g/l. with the other above substrates). There are five chemically different saturated carbon atoms[5] in the substrate molecule (**1**) at which hydroxylation could occur. These are C-1 (equivalent[5] to C-5), C-2 (equivalent to C-4), C-6 (equivalent to C-8), C-7, and C-9. Formation of a ketone (**3**) (Scheme I) when **2** is oxidized with chromic acid eliminated the possible sites at C-1 and C-2 since a hydroxyl group at the former position would be tertiary and not oxidizable and at the latter position would give an imide rather than a ketone if oxidized. An imide would have characteristic reactions and spectral properties, which were not observed. Position C-9 may be eliminated by the observation that ketone **3** is rapidly brominated at room temperature in chloroform solution, giving a monobromo ketone (**4**). A ketone at C-9 in **3** would be flanked by two bridgehead carbons and bromination under such mild conditions is improbable. This conclusion was supported, and the position of the oxygen was disclosed by a deuterium exchange experiment. Exchange of the protons α to the carbonyl in **3** was catalyzed by sodium methoxide in deuteriomethanol. The resulting ketone (**5**) showed an increase of three mass units to a molecular weight of 246 as determined by mass spectrometry. Introduction of three deuterium atoms was nearly complete. A small amount of material of mass 245 was detected, which could result from incomplete exchange at a bridgehead position owing to a slower rate of exchange. No peak at 247 mass units other than that due to the natural isotopic distribution was observed. Only a ketone at the 6 position in molecule **3** has three exchangable α protons. The nmr spectrum of **3** is consistent with this assignment in that it has a triplet (J = 6.0 cps) at δ 2.53 superimposed on a second broad signal. These signals correspond to three protons, which are those on the tertiary C-5 carbon and the secondary C-7 carbon atoms. It is concluded that compound **3** contains a ketone at the 6 position and that hydroxylation of bicyclic amide **1** has occurred at the 6 position. The hydroxylating enzyme does not appear to be stereoselective, since the product has an optical rotation of only $-1°$ at the sodium D line, indicating that the product is a *dl* pair.

The configuration of the hydroxyl group[6] in **2** was determined as follows. Examination of a Dreiding model of the ketone **3**, derived from **2**, predicts that axial hydride attack on the ketone carbonyl would be less hindered sterically than would be equatorial attack. The ketone **3** therefore was reduced with sodium borohydride. A single alcohol (**6**) was isolated from the reduction and was isomeric with alcohol **2**. The hydroxy group in **6** is predicted to be equatorial and so the hy-

(5) It should be realized that the chemically equivalent positions of the bicyclic rings are not stereochemically equivalent when approached by hydroxylating enzyme.

(6) In considering the configuration of the hydroxyl group, we assume that the bicyclic molecule will prefer to be in a chair–chair conformation. Support for this assumption may be found in R. Lygo, J. McKenna, and I. O. Sutherland, *Chem. Commun.*, 356 (1965). In this conformation an axial 6-hydroxyl group will be considered *endo* and an equatorial 6-hydroxyl group will be *exo*.

SCHEME II



droxyl group in **2**, whose isomeric relationship with **6** is due only to a different alcohol conformation, can be assigned the axial configuration. A second piece of evidence supporting this conclusion is found in the nmr spectrum of the amino alcohol **7**, obtained when amido alcohol **2** is reduced with lithium aluminum hydride. Of interest here is the signal of the single C-6 proton, which is shifted downfield to δ 3.98 by the C-6 hydroxyl group. The half-band width of this signal is 8 cps, characteristic of equatorial carbinol protons.[7] It is concluded that the hydroxyl group of product **2** has an axial configuration with respect to the six-membered ring on which it is found.

Of interest to us was the possibility of interaction between the nitrogen and either the oxygen or carbon at position 6. However, neither **2** nor **6** underwent acyl migration[8] in acidic media. Likewise, amino ketone **8**, obtained from **7** by oxidation or from **3** *via* the ketal and hydride reduction, did not exhibit transannular interactions. A keto amine salt (**9**) formed when **8** was allowed to react with acid.

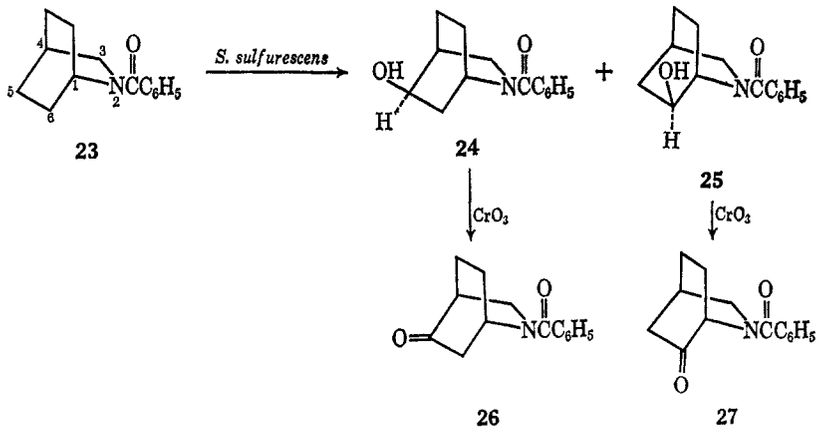
(7) *Cf.* R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, **80**, 6098 (1958).

(8) G. Fodor and K. Nador, *J. Chem. Soc.*, 721 (1953).

3-Benzoyl-3-azabicyclo[3.2.2]nonane (11).—Two products were isolated when the bicyclic amide **11** was oxygenated with *S. sulfurenscens*. These were readily identified as an alcohol (**12**, 50%) and a ketone (**13**, 22%) and were found to be substituted at the same position when oxidation of the alcohol **12** gave ketone **13**. As in the previous series, formation of a ketone eliminates positions 1, 2, 4, and 5 of the bicyclo[3.2.2]-nonane ring as sites of oxygenation. The remaining positions are chemically equivalent[5] and therefore **12** and **13** are the 6-hydroxy and 6-keto derivatives, respectively. (See Scheme II.)

The configuration of the hydroxyl group of **12** may be *endo* or *exo* with respect to the six-membered ring and was determined as follows. Reduction of ketone **13** with sodium borohydride gave a crystalline alcohol (**14**), which was isomeric with the alcohol **12**. The individual alcohols were shown to be homogeneous by both thin layer and paper chromatography and, additionally, when in admixture, they were separated by the same chromatography systems used to determine their purity. When alcohol **14** was dissolved in a dilute solution of hydrochloric acid in tetrahydrofuran, the benzoyl group migrated from the nitrogen to the oxy-

SCHEME III



gen, giving the benzoate–amine hydrochloride **15** (see Scheme II) in high yield. The direction of migration was reversed by placing **15** in an alkaline solution. Analogous acyl migration reactions were first studied and discussed in detail by Fodor and coworkers.[8] In the present system migration from N to O requires that the hydroxyl group of **14** be *exo* with respect to the six-membered ring. Since **14** is isomeric with the microbiological oxygenation product **12** at the alcohol carbon, the configuration of the hydroxyl group in **12** must be *endo* with respect to the six-membered ring.

Formation of the *exo* alcohol (**14**) from reduction of the ketone must result from *endo* attack of the hydride on the carbonyl function. It may be suggested then that nucleophilic attack from the *endo* direction in general is less sterically hindered than from the *exo* direction. Examination of a Drieding model supports this idea. We have assigned structures to the products of Grignard addition to the ketone (**13**) on the basis of this reasoning. Addition of phenylmagnesium bromide to **13** gave two isomeric alcohol–amine salts. The product mixture (73% yield) was separated into a major product (**16**, 36%) and a minor product (**17**, 10%) by fractional crystallization. The phenyl group in alcohol **16** is assigned the *endo* configuration, while the phenyl group of **17** is assigned the *exo* configuration. Reaction of methyl magnesium bromide with ketone **13** gave a single alcohol–amine salt (**18**). The methyl group in **18** is assigned the *endo* configuration.

Several other reactions were carried out so that oxygenated derivatives of the unsubstituted 3-azabicyclo[3.2.2]nonane ring system could be obtained. Reduction of **14** with lithium aluminum hydride gave the amino alcohol **19**, characterized as the hydrochloride. Hydrogenolysis of the benzyl group of **19** over palladium-on-carbon catalyst proceeded readily, giving *exo*-3-azabicyclo[3.2.2]nonan-6-ol, which was characterized as the hydrochloride (**20**). Finally, Oppenauer oxidation of amino alcohol **19** gave amino ketone **21**. Hydrogenolysis of the benzyl group of **21** gave 3-azabicyclo[3.2.2]nonan-6-one, characterized as the hydrochloride (**22**).

2-Benzoyl-2-azabicyclo[2.2.2]octane (23).—Oxygenation of **23** with *S. sulfurescens* gave two alcohols, **24** (45%) and **25** (6%). Both alcohols were oxidizable with Jones reagent, giving two ketones **26** and **27**, respectively. Formation of two ketones in this manner identifies the positions of oxygenation as the 5 and 6 atoms of the bicyclic systems. Lack of ample substrate prevented complete chemical characterization of the products. However, we suggest that the alcohol (**24**) formed in higher yield is the 5-hydroxy compound (see Scheme III) since the distance between the amide carbonyl and the 5-carbon atom more nearly fits the ~5.5-Å spacing of the enzyme–substrate interaction referred to previously.[2] The position of the hydroxyl group in the minor product (**25**) will then be at the C-6 atom.

In a companion paper,[9] a number of stereochemical relationships observed in the patterns of substitution found in a variety of microbiological oxygenated products have been discussed. One set of observations suggested that the hydroxyl group and the electron-rich center of the substrate (the amide group in the present case) will be spatially oriented in opposite directions. It is therefore suggested that the hydroxyl groups in **24** and **25** will be oriented in an *endo* configuration with respect to the N-containing bridge, as shown in Scheme III.

Experimental Section[10]

Biotransformation Process.—The process used has been described previously,[4] the only exception being that substrate **1** could be used at a level of 0.5 g/l.

Isolation of the Product from the Bioconversion of 3-Benzoyl-3-azabicyclo[3.3.1]nonane (1). 3-Benzoyl-*endo*-3-azabicyclo[3.3.1]nonan-6-ol (2).—The oily methylene chloride extracts from the 125-l. bioconversion of 3-benzoyl-3-azabicyclo[3.3.1]-nonane (25 g, 0.109 mol) with *Sporotrichum sulfurescens* was chromatographed on Florisil (2.0 kg) packed with Skellysolve B. Elution with 25 and 50% (v/v) acetone–Skellysolve B gave crystalline material (19.645 g). Recrystallization from acetone preceded by decolorization with activated charcoal gave colorless crystals. From the several crops collected, a total of 16.894 g (0.0689 mol, 63%) of product was obtained, mp 137–141°. Three recrystallizations from acetone gave colorless crystals: mp 139–141°; $[\alpha]_D$ −1° (*c* 0.860, chloroform); ν_{OH} 3460, 3420 sh cm^{-1}; $\nu_{C=O}$, $_{C=C}$ 1610, 1575, 1525, 1495 cm^{-1}; $\nu_{C_6H_5}$ 785, 740, 705 cm^{-1} in Nujol.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.66; H, 7.96; N, 6.07.

In a similar experiment, the combined extracts from a 10-l. (5.0 g of substrate **1**) and a 125-l. (62.5 g of substrate) bioconver-

(9) R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *J. Org. Chem.*, **33**, 3217 (1968).

(10) Melting points were determined on a calibrated Fisher-Johns hot stage and are corrected. Magnesium sulfate was used as the drying agent unless indicated otherwise. Infrared spectra were determined with either a Perkin-Elmer Infracord or Model 421 spectrophotometer. The nmr spectra were determined at 60 Mc with a Varian Model A-60 spectrometer, using tetramethylsilane as an internal standard in chloroform solution unless indicated otherwise. Mass spectra were determined on an Atlas CH14 instrument.

sion (total substrate 67.5 g, 0.293 mol) gave a total of 51.20 g (0.208 mol, 71%) of crystalline product, mp 140–143°.

3-Benzoyl-3-azabicyclo[3.3.1]nonan-6-one (3).—A solution of **2** (1.543 g, 6.30 mmol) in acetone (150 ml) was cooled on an ice bath and treated with an excess (1.8 ml) of Jones reagent.[11] After 30 min at room temperature, the excess oxidant was consumed with isopropyl alcohol. The solution was decanted, filtered through sodium sulfate, and concentrated. The green residue was dissolved in water and extracted with methylene chloride. The combined organic solutions were dried, Celite was added, and the mixture again filtered. The filtrate was concentrated under reduced pressure and cooled. Crystallization gave 0.882 g (3.63 mmol, 57%) of product, mp 158–160°. Two recrystallizations from acetone gave colorless crystals: mp 159–161°; $\nu_{C=O}$ 1705, 1620 cm^{-1}; $\nu_{C=C}$ 1600, 1580, 1570, 1490 cm^{-1}; $\nu_{C_6H_5}$ 785, 775, 735, 700 cm^{-1} in Nujol; δ 7.36 (5 H, aromatic), 4.37 (2 H, broad, equatorial N-CH), 3.18 (2 H, quartet, J_{gem} = 13 cps, J_{ae} = 3.5 cps, axial N-CH), 2.53 (3 H, triplet over broad signal, J = 6 cps, -CH-CO-CH$_2$-), 2.08 ppm (5 H, multiplet); m/e 243 (M$^+$), 242, 215, 214, 186, 138, 105, 77.

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.21; H, 6.82, N, 5.74.

3-Benzoyl-7-bromo-3-azabicyclo[3.3.1]nonan-6-one (4).—A solution of bromine in chloroform was added in small portions to a cold (5–15°) solution of **3** (2.489 g, 10.2 mmol) in chloroform (50 ml) until the solution retained a light yellow color longer than 1–2 min. The solution was washed with water, 5% aqueous sodium bicarbonate (remained basic to pH paper), and again with water. The solution was dried and concentrated to an oil. The oil was crystallized from acetone–Skellysolve B, giving 2.381 g (7.40 mmol, 72%) of product, mp 141–144°. Two recrystallizations, the last preceded by decolorization with activated charcoal, from acetone–Skellysolve B gave colorless crystals: mp 147–149°; $\nu_{C=O}$ 1715, 1630 cm^{-1}; $\nu_{C=C}$ 1590, 1575, 1490 cm^{-1}; $\nu_{C_6H_5}$ 730, 715, 700 cm^{-1} in Nujol; δ 5.00 (>CHBr, doublet, J = 11.0 cps), 4.87 (>CHBr, doublet, J = 11.0 cps), 4.38 [-CH(-H)N, broad doublet, J = 13.0 cps, 2 H], 3.22 ppm [doublet (J = 14.0 cps) of doublets (J = 3.5 cps), 2 H].

Anal. Calcd for $C_{15}H_{16}BrNO_2$: C, 55.91; H, 5.01; N, 4.35; Br, 24.80. Found: C, 56.09; H, 5.28; N, 4.59; Br, 25.05.

3-Benzoyl-3-azabicyclo[3.3.1]nonan-6-one-$d_5d_7d_7$ (5).—A solution of **3** (0.035 g) and sodium (0.010 g) in methyl alcohol-*d* was kept at room temperature for 20 hr. Acetic acid-*d* in D_2O was added to neutralize the base. The solution was concentrated under reduced pressure. Water (25 ml) was added to the residue, and the mixture was extracted with three 20-ml portions of methylene chloride. The organic solution was dried and concentrated to an oil, m/e 246 (M$^+$).

3-Benzoyl-*exo*-3-azabicyclo[3.3.1]nonan-6-ol (6).—A solution of sodium borohydride (1.0 g, 0.0265 mol) in 0.1 *M* aqueous sodium hydroxide (10 ml) was added to a solution of **3** (1.017 g, 4.18 mmol) in methanol (40 ml). Thin layer chromatography (silica gel, 10% methanol in benzene) after 0.5 hr showed reaction to be complete. The solution was partially concentrated under reduced pressure and then was diluted to 150 ml with water. The solution was made acidic (pH 5–6) with acetic acid and was concentrated under reduced pressure over a hot water bath until crystals began to form. The mixture was extracted with three 50-ml portions of methylene chloride. From the dried extract solution, an oil was obtained following concentration. The oil crystallized and the solid was recrystallized from acetone–Skellysolve B, giving 0.695 g (2.84 mmol, 67%) of crystals, mp 135–138°. Two recrystallizations from acetone–Skellysolve B gave colorless, shiny flakes: mp 139–141°; ν_{OH} 3360 cm^{-1}; $\nu_{C=O}$ 1600 cm^{-1}; $\nu_{C=C}$ 1590, 1575, 1530, 1490 cm^{-1}; ν_{C-O} 1060 cm^{-1}; $\nu_{C_6H_5}$ 790, 780, 735, 705 cm^{-1} in Nujol.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.92; H, 7.95; N, 6.08.

3-Benzyl-3-*endo*-azabicyclo[3.3.1]nonan-6-ol (7).—A solution of **2** (5.0 g, 0.0204 mol) in tetrahydrofuran (100 ml) was poured into a mixture of lithium aluminum hydride (3.0 g) and tetrahydrofuran (150 ml). The whole mixture was heated at reflux temperature for 5 hr; then the excess hydride was consumed with ethyl acetate and water. The inorganic solids were removed by filtration through Celite and washed with hot tetrahydrofuran. The tetrahydrofuran solution was dried and concentrated under reduced pressure to an oil. The oil was transferred with ether to a distillation flask. After a few minutes at low pressure, the oil solidified. The solid crystallized from cold hexane, giving crystals, mp 67–69°. Three recrystallizations from cold hexane, the last preceded by decolorization with activated charcoal, resulted in colorless crystals: mp 70–71°; ν_{OH} 3320, 3220 cm^{-1}; $\nu_{C=C}$ 1600, 1495 cm^{-1}; $\nu_{C_6H_5}$ 730, 695 cm^{-1} on the oil; δ 7.29 (5 H, singlet, aromatic), 3.98 [1 H, multiplet half-band width = 8 cps, >C(-O)H], 3.38 (2 H, singlet, benzylic), 2.87 (2 H, doublet, J_{gem} = 11 cps, equatorial -N-CH), 2.18 (2 H, quadruplet, J_{gem} = 11 cps, J_{ae} = 3 cps, axial -N-CH).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 78.01; H, 9.54; N, 6.33.

3-Benzyl-3-azabicyclo[3.3.1]nonan-6-one (8).—A solution of 7.457 g of **7** in toluene (120 ml) and cyclohexane (30 ml) was heated to boiling and the toluene–water azeotrope distilled off. Aluminum isopropoxide (10 g) and cyclohexanone (10 ml) were added to the solution, and the mixture was heated at reflux temperature for 2 hr. The mixture was poured into ice–aqueous hydrochloric acid and stirred. The aqueous layer was separated, extracted with three 100-ml portions of ether, and made alkaline with concentrated sodium hydroxide solution. A heavy precipitate formed at the neutralization point but disappeared, and an oil formed as additional base was added. The solution and oily phase were extracted with three 100-ml portions of ether; the ether was dried and concentrated under reduced pressure to a reddish brown oil. The oil was transferred with ether to a 10-ml distillation flask and distilled, bp 126–129° (0.04 mm), giving 4.171 g (0.0182 mol, 60% from hydroxy amide) of a colorless oil: n_D 1.5499; $\nu_{C=O}$ 1700 cm^{-1}; $\nu_{C=C}$ 1600, 1580, 1490 cm^{-1}; $\nu_{C_6H_5}$ 735, 695 cm^{-1} on the oil.

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.90; H, 8.56; N, 6.05.

3-Benzyl-3-azabicyclo[3.3.1]nonan-6-one Perchlorate (9). A. From Ketone 3 *via* the Ketal.—A mixture of **3** (0.550 g, 2.26 mmol) in benzene (100 ml), *p*-toluenesulfonic acid hydrate (0.090 g, 0.473 mmol), and ethylene glycol (10 ml) was heated to reflux for 18 hr. The condensate was dried by passing through a calcium carbide trap. A few drops of pyridine were added, and the mixture was cooled to room temperature. The mixture was extracted with 5% aqueous sodium bicarbonate solution (50 ml) and with two 25-ml portions of water. The benzene layer was dried over magnesium sulfate and concentrated under reduced pressure to an oil: $\nu_{C=O}$ 1630 cm^{-1}; $\nu_{C=C}$ 1605, 1580, 1500 cm^{-1}; $\nu_{C_6H_6}$ 708 cm^{-1} on the oil.

A solution of the above oil in ether was reduced with lithium aluminum hydride (0.5 g) in ether. After refluxing 4 hr, the excess hydride was decomposed with ethyl acetate and water, the solids were filtered off, the ether solution was dried and concentrated to an oil: ν_{CH} 2390, 2900, 2875 cm^{-1}; $\nu_{C=C}$ 1600, 1580, 1495 cm^{-1}; $\nu_{C_6H_5}$ 736, 700 cm^{-1} on the oil.

Aqueous perchloric acid (70%, 15 drops) was added to a solution of the above oil (0.25 g, 0.915 mmol) in absolute ethanol (5.0 ml). The solution was heated on the steam bath for 3 min. Addition of ether slowly precipitated an oily solid, which crystallized into colorless crystals (0.251 g, 0.763 mmol, 83%), mp 210–215°. Two recrystallizations from ethanol containing a few drops of water gave crystals: mp 213–216°; ν_{NH^+} 3080 cm^{-1}; $\nu_{C=O}$ 1695 cm^{-1}; $\nu_{C=C}$ 1500 cm^{-1}; $\nu_{C_6H_5}$ 770, 745, 705 cm^{-1} in Nujol.

Anal. Calcd for $C_{15}H_{20}NO_5Cl$: C, 54.63; H, 6.11; N, 4.25. Found: C, 54.51; H, 5.87; N, 4.33.

B. From Ketone 8.—Aqueous perchloric acid (70%, 10 drops) was added to a solution of **8** (0.236 g, 1.03 mmol) in absolute ethanol (3 ml). Crystals formed after 10 min. A first crop of 0.157 g of colorless crystals was collected by filtration. A second crop of 0.042 g (0.199 g total, 6.05 mmol, 58%) was obtained from the mother liquor. The infrared spectrum of the crystal is identical with that of the above salt.

Isolation of Products from the Bioconversion of 3-Benzoyl-3-azabicyclo[3.2.2]nonane. 3-Benzoyl-3-azabicyclo[3.2.2]nonan-6-one (13). A. From Direct Oxidation of Bioconversion Products.—The residue from the beer extract of a 25.0-g conversion of 3-benzoyl-3-azabicyclo[3.2.2]nonane with *Sporotrichum sulfurescens* was dissolved in 500 ml of acetone and oxidized by the Jones method. After 10 min, excess oxidant was destroyed by the addition of 10 ml of isopropyl alcohol. The mixture was diluted with 1 l. of water and extracted three times with 250 ml of methylene chloride. The combined extract was washed once with water and dried over sodium sulfate. The filtered solution was concentrated under reduced pressure, the residue was dis-

(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

tilled through a 4-in. Vigreux column, and the product was collected at 190–195° at 0.3 mm, yield 12.17 g. The infrared spectrum of this product was identical with the product obtained upon oxidation of pure alcohol (**12**).

B. From Oxidation of Alcohol 12.—Oxidation of pure **12** with Jones reagent[11] gave ketone **13** as colorless crystals, mp 59–62°.

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.32; H, 7.13; N, 5.87.

The semicarbazone of 13 was prepared by heating at reflux a mixture of 1.0 g of ketone, 1.0 g of semicarbazide hydrochloride, 1.5 g of sodium acetate, 1.6 ml of water, and 20 ml of methanol. The analytical sample was obtained by recrystallization from aqueous methanol, mp 197–200°.

Anal. Calcd for $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 64.06; H, 6.82; N, 18.29.

The oxime of 13 was prepared by heating at reflux a mixture of 0.3 g of ketone, 0.5 g of hydroxylamine hydrochloride, 5.0 ml of 5% sodium hydroxide solution, and 3 ml of methanol. The product was recrystallized from aqueous methanol, mp 156–158°.

Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.71; H, 7.16; N, 10.87.

2,4-Dinitrophenylhydrazone of 13 was prepared from a mixture of 2,4-dinitrophenylhydrazine, hydrochloric acid, and ethanol. The product was recrystallized from methylene chloride–ethanol, mp 198–201°.

Anal. Calcd for $C_{21}H_{21}N_5O_5$: C, 59.56; H, 5.00; N, 16.54. Found: C, 59.57; H, 4.94; N, 16.65.

3-Benzoyl-*endo*-3-azabicyclo[3.2.2]nonan-6-ol (12).—The residue from the methylene chloride extraction of the beer from a 4.0-g bioconversion of 3-benzoyl-3-azabicyclo[3.2.2]nonane was chromatographed over silica gel. The column was prepared from 200 g of silica gel (0.05–0.20 mm) and ethyl acetate–Skellysolve B hydrocarbons (5:1). The crude residue was placed on the column and eluted in 55-ml cuts with the same solvent mixture. Fractions 13–18 contained 0.950 g (22%) of ketone which was idential by comparison of infrared spectra and thin layer and paper chromatographic analysis with 3-benzoyl-3-azabicyclo-[3.3.2]nonan-6-one (**13**) described above. Fractions 29–50 contained 2.464 g (56%) of hydroxybenzamide (**12**). This product was shown by thin layer and paper chromatographic analysis to be a single entity and different than the hydroxyamide (**14**) described below. Treatment in acetone with activated carbon' produced a colorless oil which eventually crystallized, $[\alpha]_D$ 0° (95% ethanol), mp 73–75°.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.08; H, 7.81; N, 6.00.

3-Benzoyl-*exo*-3-azabicyclo[3.2.2]nonan-6-ol (14).—Crude **13** (20 g) dissolved in 350 ml of methanol was treated with a solution of 16.0 g of sodium borohydride in 100 ml of 0.1 *N* sodium hydroxide for 30 min when thin layer chromatography indicated complete reaction. The mixture was diluted with 300 ml of water, allowed to stand in the hood for 18 hr, and, with chilling, adjusted to pH 6 by the cautious addition of 50% acetic acid. The solid product was recovered by filtration, washed with water, and dried: yield, 12.75 g; mp 131–135°. The analytical sample from acetone melted at 135–137°.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.31; H, 7.87; N, 5.89.

***exo*-6-Benzoyloxy-3-azabicyclo[3.2.2]nonane Hydrochloride (15).**—The hydroxybenzamide (**14**), 2.14 g, was dissolved in 50 ml of tetrahydrofuran by warming. To the warm (50°) solution was added 4.0 ml of concentrated hydrochloric acid, and the mixture was allowed to stand at 25°. The solution was examined at intervals by thin layer chromatogaphy, and after complete reaction (23 hr) it was concentrated under reduced pressure to an oil. This was triturated twice with ether, decanting off the ether each time, and the hydrochloride salt was precipitated by adding 25 ml of acetone and 50 ml of ether: yield 2.16 g; mp 205–208°. This was recrystallized from methanol–methyl ethyl ketone: yield, 2.06 g; mp 205–208°; ν_{NH^+} 2250–2700 cm^{-1}; $\nu_{C=O}$ 1710 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}NO_2Cl$: C, 63.93; H, 7.15; N, 4.97. Found: C, 63.92; H, 7.44; N, 5.24.

Reverse Reaction to Regenerate Hydroxybenzamide (14).—The salt (**15**) (200 mg) in 5 ml of water was treated with a few drops of 50% sodium hydroxide solution and stirred. After the resulting product had solidified, the mixture was acidified with hydrochloric acid, the product recovered, washed with water and dried: mp 135–137°. The infrared spectrum was identical with the hydroxybenzamide (**14**) described above. The filtrate from the above upon retreatment with base produced a second crop of the same product.

6-Phenyl-*exo*-3-azabicyclo[3.2.2]non-6-ol Hydrochloride (16).—A solution of 20 g of **13** in 400 ml of tetrahydrofuran was added to a stirred solution of 200 ml of 3 *M* phenylmagnesium bromide in ether. Solvent was removed by distillation until the boiling temperature was 60°, and the mixture was heated at reflux for 4.5 hr. After cooling, it was poured onto ice and stirred and acidified with concentrated hydrochloride while continuing to add ice. This mixture was extracted several times with ether. The neutral product from this ether extracted proved to be benzophenone. The aqueous acid solution was made basic with 50% sodium hydroxide solution, and the resulting mixture was extracted several times with ether. The extract was dried, treated with ethereal hydrogen chloride, and the insoluble salt was recovered and washed with ether: yield, 15.32 g. This was fractionally crystallized from methanol–methyl ethyl ketone to give about 7.5 g of a less soluble, higher melting isomer; mp 238–240° dec.

Anal. Calcd for $C_{14}H_{20}NOCl$: C, 66.26; H, 7.94; N, 5.52; Cl, 13.97. Found: C, 66.51; H, 8.17; N, 5.49; Cl, 13.90.

6-Phenyl-*endo*-3-azabicyclo[3.2.2]nonan-6-ol Hydrochloride (17).—From the filtrates of the above experiment 2.0 g of a more soluble, lower melting isomer were isolated, mp 218–220° dec.

Anal. Calcd for $C_{14}H_{20}NOCl$: C, 66.26; H, 7.94; N, 5.52; Cl, 13.97. Found: C, 66.09; H, 8.33; N, 5.36; Cl, 13.70.

6-Methyl-*endo*-3-azabicyclo[3.2.2]non-6-ol Hydrochloride (18).—Ketobenzamide **13** (10 g) in 200 ml of tetrahydrofuran was added to a stirred solution of 100 ml of 3 *M* methylmagnesium bromide in ether. The mixture was distilled until the vapor temperature was 60° and then heated at reflux for 4.5 hr. The stirred mixture was chilled and treated with 60 ml of water, followed by 50 ml of acetic acid, and extracted several times with ether. The ether solution, after washing with dilute HCl, water, and sodium bicarbonate solution, was dried (Na_2SO_4), and the solvent was removed to give an oil which proved to be acetophenone. The aqueous solution remaining from the ether extraction was made basic with 50% sodium hydroxide, and the resulting gelatinous mixture was continuously extracted with ether. The extract was dried (Na_2SO_4) and treated with hydrogen chloride. The resulting HCl salt was recovered and washed with ether: yield 3.29 g; mp 228–230°. Recrystallization from methanol–ether gave a product, mp 230–232°.

Anal. Calcd for $C_9H_{18}NOCl$: C, 56.38; H, 9.46; N, 7.30; Cl, 18.50. Found: C, 56.67; H, 9.97; N, 7.09; Cl, 18.63.

3-Benzyl-*exo*-3-azabicyclo[3.2.2]nonan-6-ol (19).—The hydroxy amide **14** (6.69 g) was dissolved in 80 ml of tetrahydrofuran and added with stirring to a mixture of 6.0 g of lithium aluminum hydride in 100 ml of ether. The mixture was refluxed for 1 hr, chilled in a cold bath, and carefully decomposed by the addition of 25 ml of water. After dilution with 300 ml of ether and filtering, the filtrate and ether wash was dried and the solvent removed under reduced pressure to give 5.90 g of straw-colored oil. Part of the oil (1.33 g) was dissolved in ether and treated with ethereal hydrogen chloride to precipitate the salt which was recrystallized from methanol ether: yield, 1.07 g; mp 185–187°.

Anal. Calcd for $C_{15}H_{22}NOCl$: N, 5.23; Cl, 13.24. Found: N, 5.47; Cl, 13.74.

***exo*-3-Azabicyclo[3.2.2]nonan-6-ol Hydrochloride (20).**—The hydroxybenzylamine **19** (9.17 g) dissolved in 120 ml of ethanol was shaken with 1.0 g of 10% palladium–carbon and hydrogen (44 psig starting pressure) for 20 hr. The mixture, freed of catalyst and concentrated *in vacuo*, gave the free amine as a solid, 5.60 g. A portion of the free base was dissolved in ether and treated with ethereal hydrochloric acid to precipitate the amine hydrochloride, which was recrystallized from methanol–methyl ethyl ketone, mp 280° dec.

Anal. Calcd for $C_3H_{16}NOCl$: C, 54.07; H, 9.08; N, 7.88; Cl, 19.96. Found: C, 54.17; H, 9.05; N, 8.01; Cl, 19.99.

3-Benzyl-3-azabicyclo[3.2.2]nonan-6-one (21).—The crude benzylamine **19**, resulting from the hydride reduction of 10 g of **14**, dissolved in 600 ml of toluene and 150 ml of cyclohexanone was distilled to remove *ca.* 100 ml of toluene. Aluminum isopropoxide (20 g) was added; the mixture was distilled to remove *ca.* 50 ml of solvent and then heated at reflux for 60 min. After cooling it was poured onto an ice mixture containing excess hydrochloric acid and stirred, and the layers were separated. The aqueous acid layer was extracted several times with ether and then made basic with 50% sodium hydroxide solution. The

resulting emulsion was well extracted with ether, and the ether extract was washed once with water and dried. The ether solution was made up to 650 ml and 100 ml of this was treated with ethereal HCl to precipitate the salt of **21**. This was recrystallized from methanol–ethanol–ether: yield, 0.744 g; mp 222° dec.

Anal. Calcd for $C_{15}H_{20}NOCl$: C, 67.78; H, 7.59; N, 5.27; Cl, 13.34. Found: C, 68.13; H, 7.77; N, 5.42; Cl, 13.17.

3-Azabicyclo[3.2.2]nonan-6-one Hydrochloride (22).—The ether solution of free base remaining from the above experiment was taken to dryness to yield 4.55 g of oil. This was dissolved in 90 ml of ethanol and shaken with 1.0 g of 10% palladium on carbon and hydrogen (50 psig) for 180 min. The catalyst was removed by filtration; the filtrate and wash were concentrated *in vacuo* to a small volume, diluted with ether, and treated with ethereal HCl. The hydrochloride of **22** was recovered, washed with ether, and dried: yield, 3.12 g; mp 218–220° dec. A sample from methanol–ether melted at 227–229° dec.

Anal. Calcd for $C_8H_{14}NOCl$: C, 54.70; H, 8.03; N, 7.98; Cl, 20.19. Found: C, 54.22; H, 8.14; N, 7.98; Cl, 20.64.

Bioconversion of 2-Benzoyl-2-azabicyclo[2.2.2]nonane (23). 2-Benzoyl-*endo*-2-azabicyclo[2.2.2]octan-5-ol (24) and 2-Benzoyl-*endo*-2-azabicyclo[2.2.2]octan-6-ol (25).—The methylene chloride extract residue from the bioconversion of **23** (25.0 g, 0.116 mol) was chromatographed over 1000 g of Florisil. Elution with 4 l. each of Skellysolve B containing 10, 15, and 20% acetone and with 12 l. of Skellysolve B containing 25% acetone by volume was carried out with collection of 800-ml fractions. The fractions were pooled as follows on the basis of tlc. Fractions 7–11 were 3.98 g (16%) of unchanged starting material. Fractions 17, and 18 gave, after recrystallization from acetone, 1.61 g (6.97 mmol, 6% **25**, mp 200–205°).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.03. Found: C, 72.70; H, 7.64; N, 5.82.

Fraction 19 was a mixture, 2.14 g (8%). Fractions 20–27 gave 12.16 g of solid. Recrystallization from acetone gave 10.62 g (0.0460 mol, 40%) of crystalline **24**, mp 146–148°.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.03. Found: C, 72.52; H, 7.19; N, 6.18.

2-Benzoyl-2-azabicyclo[2.2.2]octan-6-one (26).—2-Benzoyl-*endo*-2-azabicyclo[2.2.2]octan-6-ol (2 g) in 100 ml of acetone was oxidized by the Jones method[11] to give the ketone (1.95 g) as an oil which eventually crystallized: mp 67–72°; $\nu_{C=O}$ 1740, 1610 cm^{-1} in Nujol.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 72.82; H, 6.94; N, 6.08.

2-Benzoyl-2-azabicyclo[2.2.2]octan-5-one (27).—2-Benzoyl-*endo*-2-azabicyclo[2.2.2]octan-5-ol (300 mg) was oxidized[11] to the ketone which was recrystallized from acetone–hexane: mp 99–101°; $\nu_{C=O}$ 1740, 1610 cm^{-1} in Nujol.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.15; H, 6.70; N, 5.99.

Registry No.—**2**, 16780-54-4; **3**, 16780-67-9; **4**, 16780-68-0; **6**, 16780-69-1; **7**, 16780-70-4; **8**, 16780-71-5; **9**, 16780-72-6; **12**, 16780-73-7; **13**, 16780-74-8; semicarbazone of **13**, 16780-75-9; oxime of **13**, 16808-42-7; 2,4-dinitrophenylhydrazone of **13**, 16780-76-0; **14**, 16780-77-1; **15**, 16780-78-2; **16**, 16780-79-3; **17**, 16780-80-6; **18**, 16780-81-7; **19**, 16808-43-8; **20**, 16808-44-9; **21** HCl, 16808-45-0; **22**, 16808-46-1; **24**, 16785-68-5; **25**, 16785-69-6; **26**, 16785-70-9; **27**, 16808-47-2.

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The Microbiological Oxygenation of Acylated 1-Adamantanamines. Stereochemistry and Structural Determinations

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Microbiological oxygenation of N-acetyl-1-adamantanamine with *Sporotrichum sulfurescens* produced C-4 hydroxylation as the major reaction along with a minor quantity of C-3 hydroxylation. The reaction of the same organism with N-benzoyl-N-methyl-1-adamantanamine led to C-4 and C-6 dihydroxylation as the major conversion entity with a lesser quantity of C-4 monohydroxylation. Oxygenation occurred primarily on the methylene carbons and resulted in *trans* hydroxylation with respect to the N substituent; lipophilicity led to dihydroxylation, whereas hydrophilicity led to monohydroxylation. The products obtained from the biotransformations of some other N-acetylated adamantanamines are described.

In recent papers[1] we have described the microbiological oxygenation of macrocyclic alcohols,[1a] heterocyclic ring systems,[1b] and alicylic amides.[1c] When various substrates were dispersed in the active fermentation medium of *Sporotrichum sulfurescens*, oxygenation was shown to occur at an optimal distance of about 5.5 Å from an electron-rich center to the position of attachment at an unactivated methylene site. The authors have now studied the action of *S. sulfurescens* on some N-acylated 1-adamantanamines (Charts I, II, and III). The structures of the products, including the stereochemistry, have been determined by chemical and spectroscopic methods. The proposed enzyme–substrate model described previously[1a] was helpful in predicting the most favorable position for oxygenation of this rigid cage molecule, and the products obtained were compatible with the hypothesis.

Bioconversion products of N-acetyl-1-adamantanamine[2] (**1**) (Chart I) unexpectedly were found to be quite water-soluble compounds and could not be extracted with methylene chloride. The compounds were readily absorbed on carbon from which they were recovered and further purified. Two monohydroxylated compounds were isolated from this conversion. The one produced in minor quantity could not be oxidized to ketone and was assigned a tertiary alcohol structure (**3**).[3] Heating at reflux in aqueous base produced the

(1) (a) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *J. Amer. Chem. Soc.*, **89**, 672 (1967); (b) R. A. Johnson, M. E. Herr, H. C. Murray, L. M. Reineke, and G. S. Fonken, *J. Org. Chem.*, **33**, 3195 (1968); (c) G. S. Fonken, M. E. Herr, H. C. Murray, and L. M. Reineke, *ibid.*, **33**, 3182 (1968).

(2) H. Stetter, M. Schwarz, and A. Hirschborn, *Chem. Ber.*, **92**, 1679 (1959).

(3) Since our isolation of this compound its chemical preparation has been reported: H. Stetter, J. Gartner, and P. Tacke, *Angew. Chem.*, **4**, 153 (1965).