Stereochemistry of Microbiological Hydroxylation. III. Hydroxylation of 3-Benzoyl-3-azabicyclo[3.3.1]nonane with *Rhizopus arrhizus*. Novel Chromic Acid Oxidations of Substrate and Product

ROY A. JOHNSON, HERBERT C. MURRAY, AND LESTER M. REINEKE

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

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Hydroxylation of 3-benzoyl-3-azabicyclo[3.3.1]nonane (1) by the microorganism *Rhizopus arrhizus* has been shown to give 3-benzoyl-*endo*-3-azabicyclo[3.3.1]nonan-6-ol (2) and (1*R*,5*R*)-3-benzoyl-3-azabicyclo[3.3.1]-nonan-1-ol (3). Chromic acid oxidation of 3 gave (3*R*)-3-(N-benzoyl-N-formyl)aminomethylcyclohexanone (5) and (3*R*)-3-(N-benzoyl)aminomethylcyclohexanone (6), whereas chromic acid oxidation of 1 gave 3-benzoyl-3-azabicyclo[3.3.1]nonan-3-one (8) and N-benzoyl-*cis*-3-aminomethylcyclohexanecarboxylic acid (9). Similarly, chromic acid oxidation of 1-benzoyl-3-methyl-3-piperidinol (10) gave N-benzoyl-N-formyl-5-aminopentan-2-one (11) and N-benzoyl-5-aminopentan-2-one (12). However, in contrast to the oxidation of 1, 1-benzoyl-3-methylpiperidine was not oxidized by chromic acid.

In our studies of the oxygenation of organic molecules by the microorganism *Sporotrichum sulfurescens*, the substrate 3-benzoyl-3-azabicyclo[3.3.1]nonane (1) was hydroxylated in excellent yield, giving 3-benzoyl-*endo*-3-azabicyclo[3.3.1]nonan-6-ol (2) as the sole major product.[1] With the hope of obtaining the 7-oxygenated derivative of 1, of possible interest for transannular reactions, the hydroxylation of 1 was attempted with *Rhizopus arrhizus*. A new hydroxy derivative (3, 25%), which had optical activity $[\alpha]D$ −40°, was obtained in addition to compound 2 (22%). While the observation of optical activity precluded a 7-oxygenated derivative, which has a plane of symmetry, the nature of this new product was of further interest since it might lead to needed stereochemical information about the course of these microbial reactions. The determination of the absolute stereochemistry of this optically active product and the observation of a novel chromic acid oxidation reaction provide the basis for the following discussion.

Only positions 1 and 2 remain as potential sites for the concurrent introduction of a hydroxyl group and asymmetry into substrate molecule 1. Examination of the nmr spectrum of 3 suggested that the hydroxyl group was on a tertiary carbon atom and this was confirmed by the absence of a carbinol proton signal in the much sharper nmr spectrum of the lithium aluminum hydride reduction product (4) of 3. Only C_1 (chemically, but not stereochemically, equivalent to C_5) can accommodate a tertiary hydroxyl group.

When oxidation of 3 with Jones reagent[2] was attempted, a reaction occurred but it was much slower than is ordinarily observed for the oxidation of an alcohol to a ketone by this procedure. The oxidation was followed by tlc and the formation of two products was observed. After separation of these two products by chromatography, it was found that the less polar (5, $[\alpha]D$ +20°) could be converted into the more polar (6, +20°) by contact with mineral acid. Elemental analysis indicated that 5 had gained an additional oxygen atom during the chromic acid oxidation and that conversion of 5 into 6 was accompanied by the loss of CO.

The structures of 5 and 6 were suggested by their spectral properties (see Experimental Section for ir and nmr spectra). From this data, it was postulated that oxidative cleavage of the C_1–C_2 bond of 3 had occurred, giving rise to a keto-imide structure for product 5 (see Chart I). Contact with acid during the oxidation or in subsequent treatment of 5 with acid could then lead to a keto-amide structure for compound 6. These structures are consistent with the spectral data of the compounds. The structure of 6 was confirmed by synthesis from 3-cyanophenol (7). Reduction of 7 over rhodium on carbon gave a product which was carried directly to racemic 6 *via* initial benzoylation of the amino group in the presence of excess hydroxide, followed by oxidation of the hydroxyl group to a ketone. The synthetic 6 (mp 90–92°) had an nmr spectrum identical with that of the optically active form of 6 (mp 115–117°).

Several pathways to cleavage product 5 may be suggested. These are (a) fragmentation[3] of an intermediate chromate ester, which is found to be stereochemically possible in Dreiding models of this molecule; (b) intramolecular attack of an intermediate chromate ester on the adjacent C_2 carbon, which is α to the amide nitrogen and thereby slightly activated toward oxidation;[4] (c) initial oxidation at the methylene carbon adjacent to nitrogen; or (d) dehydration followed by oxidation of the olefin. Although bridgehead reactivity has recently been demonstrated in bicyclo[3.3.1]nonane systems,[5] it may be expected that dehydration of 3 (pathway d) will still be a relatively unfavorable route because of the rigid bicyclic system. The possibility of initial oxidation at the α carbon (pathway c) has been tested. Treatment of 3-benzoyl-3-azabicyclo[3.3.1]-nonane (1) with Jones reagent does in fact lead to formation of the 2-carbonyl derivative 8, together with the ring-opened product 9, when a large excess of oxidant is added over a period of time. However, in an an-

(1) R. A. Johnson, M. E. Herr, H. C. Murray, L. M. Reineke, and G. S. Fonken, *J. Org. Chem.*, **33**, 3195 (1968).

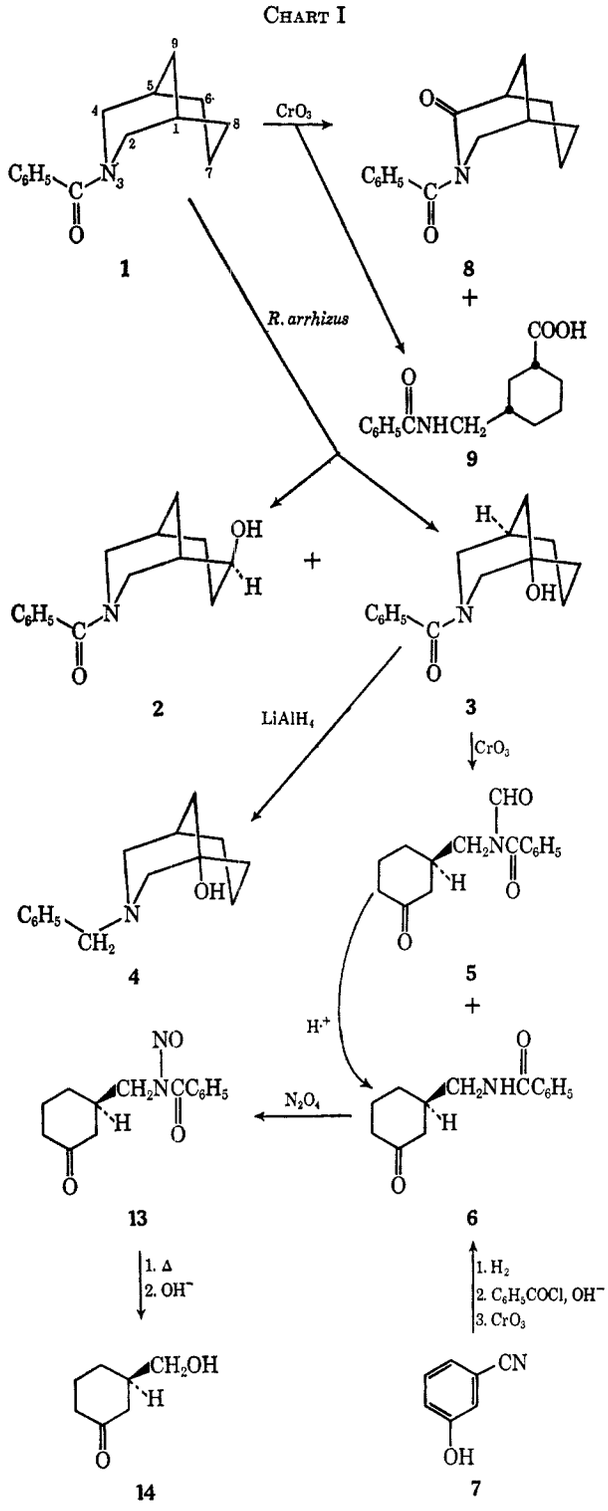
(2) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

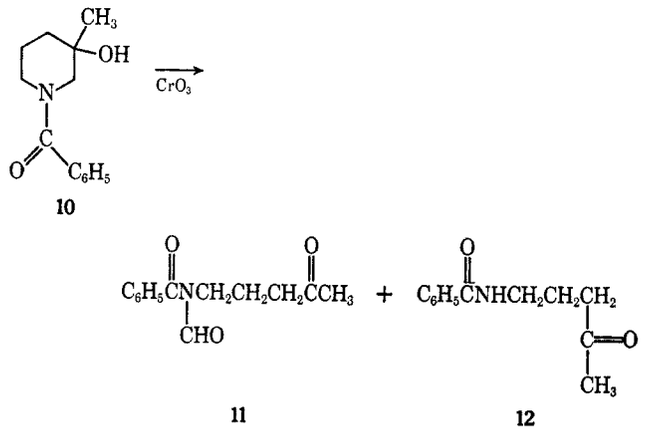
(3) *Cf.* C. A. Grob and P. W. Schiess, *Angew. Chem. Intern. Ed. Engl.*, **6**, 1 (1967).

(4) *Cf.* A. R. Doumaux, Jr., J. E. McKeon, and D. J. Trecker, *J. Amer. Chem. Soc.*, **91**, 3992 (1969), and references cited therein for examples of oxidation at carbon α to amide nitrogen, and R. I. Fryer, G. A. Archer, B. Brust, W. Zalley, and L. H. Sternbach, *J. Org. Chem.*, **30**, 1308 (1965), H. B. Henbest and M. J. W. Stratford, *J. Chem. Soc., C*, 995 (1966), and A. Cavé, C. Kan-Fan, P. Potier, J. LeMen, and M.-M. Janot, *Tetrahedron*, **23**, 4691 (1967), for example of oxidation by chromic acid, manganese dioxide, and chromic anhydride in pyridine, respectively, at carbon α to amine nitrogen.

(5) J. A. Marshall and H. Taubl, *J. Amer. Chem. Soc.*, **89**, 5965 (1967); J. R. Wiseman, *ibid.*, **89**, 5966 (1967); J. R. Wiseman, H-F. Chan, and C. J. Ahola, *ibid.*, **91**, 2812 (1969).

CHART I





alogous situation, oxidation of the tertiary alcohol 1-benzoyl-3-methyl-3-piperidinol (**10**) results in bond cleavage, giving **11** and **12**, but oxidation of 1-benzoyl-3-methylpiperidine does not occur. Therefore initial oxidation at the carbon α to nitrogen does not seem to be necessary for the oxidative cleavage of the tertiary alcohols. A choice between pathways a and b as well as other possibilities requires further mechanistic study.

The conversion of the bicyclic system of **3** into the cyclohexanone derivative **6** was fortuitous in that it made attractive the possibility of determining the absolute configuration of the optically active products. The absolute configuration of a number of 3-substituted cyclohexanones is known[6] or can be determined with the use of optical rotatory dispersion (ORD).[7] Removal of the benzoyl chromophore of **6** would give a 3-substituted cyclohexanone, which would be expected to have an anomalous Cotton curve in its ORD spectrum. We chose to remove the benzamide function of **6** by conversion into a benzoate *via* the nitrosoamide by the method of White.[8] Nitrosoamide **13** formed easily and, when pyrolyzed in refluxing carbon tetrachloride, the intermediate benzoate was obtained as the only major product (>97% of the reaction product) and was directly saponified to 3-hydroxymethylcyclohexanone (**14**). The ORD curve of **14** shows a positive Cotton effect and is closely analogous to the curve of (3*R*)-3-methylcyclohexanone.[9] From this correlation, **14** is assigned the configuration (3*R*)-3-hydroxymethylcyclohexanone as represented in Chart I. This leads to the assignment of the configuration (1*R*,5*R*)-3-benzoyl-3-azabicyclo[3.3.1]nonan-1-ol to microbial oxygenation product **3**.

Experimental Section[10]

Biotransformation Process.—The culture used in these experiments was *Rhizopus arrhizus* (ATCC 11145). A medium of commercial cerelose (10 g/l.) and cornsteep liquor (20 g/l.) was prepared with tap water and adjusted to pH 5.0 with sodium hydroxide. Flasks of the sterilized medium were inoculated with spores of *R. arrhizus*, which were grown on malt (wort) agar slants. The flasks were shaken for 24 hr (until heavy growth was apparent) and then used for seeding other flasks or tanks. The tanks used in this work were inoculated with 5 parts of the vegetative culture to 100 parts of fresh medium. On any scale, the culture is aerated with 5 vol. of air per min/100 vol. of culture in stirred vessels. The substance to be oxygenated was dissolved in dimethylformamide or acetone and was added after 24 hr of growth. The level of substrate used was 0.25 g/l. of culture. A conversion time of 24 hr at 28° was used. The mycelia were removed by filtration through Celite 545. The products and residual substrate were removed from the beer by extraction (four times) with methylene chloride, using a volume of solvent one-fourth that of the beer. The combined extract solvents were concentrated under reduced pressure.

(6) D. S. Noyce and D. B. Denney, *ibid.*, **74**, 5912 (1952); **76**, 768 (1954). D. S. Noyce and J. H. Canfield, *ibid.*, **76**, 3630 (1954).

(7) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965, pp 72–157.

(8) E. H. White, *J. Amer. Chem. Soc.*, **77**, 6008, 6011 (1955).

(9) C. Djerassi and G. W. Krakower, *ibid.*, **81**, 237 (1959).

(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. The ir 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. The ORD curve was obtained with a Cary Model 60 spectrophotometer. The mass spectrum was determined on an Atlas CH4 instrument. The high resolution mass spectrum was determined on a CEC-110 high resolution mass spectrometer.

3-Benzoyl-*endo*-3-azabicyclo[3.3.1]nonan-6-ol (2) and (1*R*,5*R*)-3-Benzoyl-3-azabicyclo[3.3.1]nonan-1-ol (3).—The residue from the concentrated methylene chloride extract from the bioconversion (125 l.) of 3-benzoyl-3-azabicyclo[3.3.1]nonane (**1**, 25.0 g, 0.109 mol) with *R. arrhizus* was dissolved in 50% ethyl acetate–benzene and placed on a silica gel chromatography column (2.5 kg, 10.5 × 50 cm), which was packed as a slurry in benzene. Elution with ethyl acetate (1-l. fractions) gave **3** in fractions 15–19 and **2** in fractions 24–35 with fractions 20–23 being a mixture of the two products. These latter fractions were combined and rechromatographed as above, using the appropriate quantities of adsorbent and solvent. In this way 6.87 g (0.0280 mol, 25%) of **3**, mp 138–140°, was obtained following recrystallization from acetone–Skellysolve B. Two additional recrystallizations from acetone–Skellysolve B gave colorless needles of **3**: mp 140–142°; $[\alpha]_D$ −40° (*c* 0.803, chloroform); ν_{OH} 3330, $\nu_{C=O,C=C}$ 1600, 1575, 1520, 1495, $\nu_{C_6H_5}$ 725, 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, 73.46; H, 7.76; N, 6.15.

In addition, 5.972 g (0.0244 mol, 22%) of **2**, mp 135–137° (lit.[1] mp 139–141°), $[\alpha]_D$ +4° (*c* 1.045, chloroform), was obtained following recrystallization from acetone–Skellysolve B. This product has an ir spectrum (in Nujol) which is identical with that of the 3-benzoyl-*endo*-3-azabicyclo[3.3.1]nonan-6-ol isolated from the bioconversion of **1** with *Sporotrichum sulfurescens*.[1]

(1*R*,5*R*)-3-Benzoyl-3-azabicyclo[3.3.1]nonan-1-ol (4).—A suspension of **3** (0.478 g, 0.00195 mol) in ether was reduced with lithium aluminum hydride (0.6 g). The resultant reduction product was crystallized from a cold pentane solution, giving 0.206 g (0.000892 mol, 45%) of crystals, mp 74–76°. Recrystallization, preceded by decolorization with activated charcoal, gave colorless crystals: mp 73–76°; $[\alpha]_D$ −24° (*c* 0.740, chloroform); ν_{OH} 3280, 3210, $\nu_{C=O}$ 1600, 1585, 1495, $\nu_{C_6H_5}$ 760, 745, 710, 700 cm^{-1} in Nujol; $\delta_{TMS}^{CDCl_3}$ 3.45 (–NCH$_2$C$_6$H$_5$, singlet, 2 H), 2.97, 2.78, 2.45, 2.10 (–CHCH$_2$N<, 4 H).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.84; H, 9.45; N, 6.13.

(3*R*)-3-(N-Benzoyl-N-formyl)aminomethylcyclohexanone (5) and (3*R*)-3-(N-Benzoyl)aminomethylcyclohexanone (6).—Jones reagent[2] (4 ml) was added to a solution of **3** (2.00 g, 0.00817 mol) in acetone (50 ml). The disappearance of the reddish brown color of chromic acid was slow. The solution was kept at room temperature overnight. More Jones reagent was added (total 7.8 ml over 3-day period) when tlc showed some starting material remaining. Water (100 ml) was added and the acetone was removed under reduced pressure. The aqueous phase was extracted with methylene chloride (4 × 25 ml). The organic extract was dried and concentrated to an oil. The oil was dissolved in benzene and placed on a chromatography column of silica gel (150 g) packed as a slurry in benzene. The following 100-ml fractions were collected: one of benzene, seven of 10% (v/v) ethyl acetate–benzene, nine of 20% ethyl acetate–benzene, eight of 50% ethyl acetate–benzene, and five of ethyl acetate. Fractions 11–15 were combined and crystallized from cold acetone–Skellysolve B, giving 0.777 g (0.0030 mol, 37%) of **5**, mp 73–76°. Two recrystallizations gave **5** as colorless crystals: mp 73–75°; $[\alpha]_D$ +20° (*c* 1.087, chloroform); $\nu_{C=O}$ 1715, 1705, 1660, $\nu_{C=C}$ 1600, 1575, 1490, $\nu_{C_6H_5}$ 715 cm^{-1} (in Nujol); $\delta_{TMS}^{CDCl_3}$ 9.00 (–NCHO, singlet, 1 H), 3.90 (–CHCH$_2$N<, doublet, J = 6.5 Hz, 2 H).

Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.78; H, 6.56; N, 5.33.

Fractions 25–28 were combined and crystallized from acetone–Skellysolve B, giving 0.174 g (0.00075 mol, 9%) of **6**, mp 115–117°. Recrystallization from acetone–Skellysolve B gave fine needles of **6**; mp 115–117°; $[\alpha]_D$ +20° (*c* 1.112, chloroform); $\delta_{TMS}^{CDCl_3}$ 3.40 (>CHCH$_2$NH–, triplet, J = 5.5 Hz, 2 H); *m/e* 231 (M$^+$), 208, 135, 134, 110, 105; ν_{NH} 3310, $\nu_{C=O}$ 1700, 1635, $\nu_{amide\ II}$ 1535, $\nu_{amide\ III}$ 1305, $\nu_{C=C}$ 1600, 1575, 1485, $\nu_{C_6H_5}$ 700 cm^{-1} (in Nujol). The ir spectrum was identical with that of the sample of **6** described below.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 73.20, 73.05; H, 7.87, 8.11; N, 6.02.

(3*R*)-3-(N-Benzoyl)aminomethylcyclohexanone (6) from Acid Treatment of 5.—Aqueous (70%) perchloric acid (22 drops) was added to a solution of **5** (0.095 g, 0.391 mmol) in methanol. The solution was kept at room temperature overnight. Tlc showed that reaction was complete after 1 hr. The solution was made alkaline with 1 *N* sodium hydroxide and was extracted with ether. The ether solution was dried and concentrated to an oil. Fine needles formed in ether–Skellysolve B and 0.037 g (0.160 mmol, 41%), mp 114–117°, was collected. The ir spectrum in Nujol was identical with that of the sample of **6** described above.

Synthesis of Racemic 6.—Oily amino alcohol (0.617 g) from the reduction of 3-cyanophenol (**7**) over rhodium on carbon in ethanol was benzoylated under Schotten–Baumann conditions. The isolated product was treated with aqueous 1 *N* sodium hydroxide in methanol to assure the absence of any benzoate group. The amido alcohol was purified by chromatography on Florisil (50 g). Elution with 25–50% acetone–Skellysolve B removed an oily product: $\nu_{OH,NH}$ 3430, 3330, $\nu_{C=O}$ 1640, $\nu_{amide\ II}$ 1540, $\nu_{C=C}$ 1570, 1495 cm^{-1} (neat). Since a mixture of *cis* and *trans* isomers is possible in this amido-alcohol product, it was oxidized directly to a keto amide with Jones reagent. Chromatography of the reaction product on silica gel (50 g) resulted in isolation of the desired ketone in 50% ethyl acetate–benzene eluates. Crystallization from acetone–Skellysolve B gave colorless crystals (0.048 g) of racemic **6**, mp 89–91°. Recrystallization from acetone–Skellysolve B gave crystals: mp 90–92°; ν_{NH} 3315, $\nu_{C=O}$ 1710, 1635, $\nu_{amide\ II}$ 1550, $\nu_{C=C}$ 1600, 1580, 1490, $\nu_{C_6H_5}$ 698 cm^{-1} (in Nujol); nmr spectrum in deuteriochloroform was identical with that of the optically active **6** described above.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.17; H, 7.20; N, 5.78.

(3*R*)-N-Benzoyl-N-nitroso-3-aminomethylcyclohexanone (13).—Following the procedure of White,[8] a solution of **6** ($[\alpha]_D$ +18°, 0.596 g, 0.00258 mol) in glacial acetic acid (17 ml) was cooled and stirred with anhydrous sodium acetate (0.7 g) until the acetic acid solidified. To this was added a cool (~15°) solution of dinitrogen tetroxide (1.0 ml) in glacial acetic acid (10 ml). The resulting mixture was stirred and allowed to warm to 20° over a period of 25 min. The mixture was then poured onto ice–water (150 ml) and the mixture was stirred. A flocculent, pale yellow solid precipitated. The solid was collected by filtration and washed with water. An ir spectrum of the dry solid (0.529 g, 0.00204 mol, 79%) showed complete conversion of the amide into nitrosoamide. Recrystallization of a portion of the solid from Skellysolve B gave pale yellow needles: mp 88–90° with gas evolution; $[\alpha]_D$ +31° (*c* 0.775, in chloroform); $\nu_{C=O}$ 1715, 1740 sh, $\nu_{C=C,N=O}$ 1600, 1580, 1480, $\nu_{C_6H_5}$ 715 cm^{-1} (in Nujol); *m/e* 260 (M$^+$), 230, 105, 77.

Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.69; H, 6.56; N, 10.88.

(3*R*)-3-Hydroxymethylcyclohexanone (14).—A solution of **13** (0.440 g, 0.00169 mol) in carbon tetrachloride (25 ml) over anhydrous sodium carbonate (0.1 g) was heated to reflux for 2 hr. The yellow color of the solution had disappeared after 1.5 hr. The insoluble solids were filtered off and the filtrate was concentrated under reduced pressure. A light yellow, oily product was obtained [$\nu_{C=O}$ 1720, $\nu_{C=C}$ 1600, 1580, 1490, $\nu_{C_6H_5}$ 715 cm^{-1} (neat)], which by vpc was composed of >97% a single component, assumed to be the benzoate of 3-hydroxymethylcyclohexanone. Without further purification, the oil was heated with 6 ml of 25% aqueous sodium hydroxide and 6 ml of methanol. The red-brown solution was heated to the boiling point of methanol for 30 min and the methanol was replaced as it was evaporated. Evaporation under reduced pressure removed excess methanol and also some water, leaving a brownish, moist solid. A saturated solution of sodium chloride (10 ml) and water (2 ml) was added to the residue and the resulting solution was extracted with ether (five 10-ml portions). The combined ether extracts were washed with water (8 ml), dried, and concentrated under reduced pressure, giving the product (0.100 g, 0.781 mmol, 46%) as a light yellow oil with the following RD (*c* 0.392, in methanol): $[\phi]_{580}$ +4°; $[\phi]_{500}$ +16°; $[\phi]_{400}$ +56.3°; $[\phi]_{360}$ +132°, $[\phi]_{340}$ +230°; $[\phi]_{320}$ +576°; $[\phi]_{310}$ +805°; $[\phi]_{307.5}$ +839°; $[\phi]_{305}$ +805°; $[\phi]_{300}$ +600°; $[\phi]_{295}$ +255°; $[\phi]_{290}$ −229°; $[\phi]_{280}$ −1050°; $[\phi]_{270}$ −1420°; $[\phi]_{265}$ −1450°; $[\phi]_{260}$ −1410°; $[\phi]_{250}$ −1240°. Calcd: mol wt, 128.0837. Found: mol wt, 128.0842 by high resolution mass spectrometry.

Chromic Acid Oxidation of 1-Benzoyl-3-methyl-3-piperidinol (10).—Jones reagent (1 ml) was added to a solution of **10** (0.237 g) in acetone (10 ml). Periodically over the course of several days, additional Jones reagent was added to the reaction mixture. The acetone solution was concentrated under reduced pressure, water (50 ml) was added, and the aqueous solution was extracted with methylene chloride (three 25-ml portions). The organic extract was dried and concentrated under reduced pressure.

The residue contained acetic acid as detected by the odor. The acetic acid was removed by appropriate extraction with bicarbonate. The oily product was chromatographed on a Florisil (10 g) column packed in benzene. Elution (50-ml fractions) with 10% acetone–Skellysolve B gave a viscous oil in fractions 2 and 3, which was identified as **N-benzoyl-N-formyl-5-aminopentan-2-one** (11) by its nmr spectrum: $\delta_{TMS}^{CDCl_3}$ 8.89 (–NCHO, singlet, 1 H), 3.72 (>NCH_2–, triplet, J = 6.5 Hz, 2 H), 2.53 (–$COCH_2$–, triplet, J = 6.5 Hz, 2 H), 2.13 (CH_3CO–, singlet, 3 H), 1.93 (–$CH_2CH_2CH_2$–, quintuplet, J = 6.5 Hz, 2 H). Fractions 5–11 contained a second product, which was identified as **N-benzoyl-5-aminopentan-2-one** (12) by its nmr spectrum [$\delta_{TMS}^{CDCl_3}$ 7.06 (–NH–, broad, 1 H), 3.35 (–NCH_2–, triplet, J = 6 Hz, 2 H), 2.53 (–$COCH_2$–, triplet, J = 6.5 Hz, 2 H), 2.10 (CH_3CO–, singlet, 3 H), 1.85 (–$CH_2CH_2CH_2$–, quintuplet, J = 6.5 Hz, 2 H)], and recovered starting material in a ratio of 2:1.

Chromic Acid Oxidation of 1. A. Isolation of 3-Benzoyl-3-azabicyclo[3.3.1]nonan-2-one (8).—Jones reagent (60 drops) was added to a solution of 1 (0.458 g) in acetone (10 ml) at room temperature over a period of 3 days. A thin layer chromatogram on silica gel (developed with 10% methanol–benzene and detected in iodine vapor) suggested that some 1 remained and a product less polar than 1. The organic material was isolated by removal of acetone, addition of water, and methylene chloride extraction. The organic material was chromatographed on Florisil (10 g) packed with Skellysolve B. Elution with 5% acetone–Skellysolve B gave the product in fractions 2–5. Recrystallization from acetone–Skellysolve B gave **8** as colorless crystals: mp 108–110°; $\nu_{C=O}$ 1695, 1670, $\nu_{C=C}$ 1625, 1600, 1575, 1490, $\nu_{C_6H_5}$ 735, 700 cm^{-1} in Nujol; $\delta_{CDCl_3}^{37°}$ 3.89 (–NCH_2–, doublet, J = 5 Hz, 2 H), 2.70 (–COCH–, broad singlet, half band width ~ 10 Hz, 1 H).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.35; H, 7.13; N, 5.82.

B. Isolation of N-Benzoyl-*cis*-3-aminomethylcyclohexanecarboxylic Acid (9).—In an experiment similar to the above, Jones reagent (45 ml) was added to 1 (6.97 g) over a period of 7 days. The organic material from the methylene chloride extract partially crystallized and from acetone–Skellysolve B, 1.15 g of crystalline solid, mp 178–182°, was obtained. The solid was insoluble in water but soluble in aqueous 5% sodium bicarbonate solution and was precipitated upon reacidification of the basic solution. Three recrystallizations of the solid from acetone–Skellysolve gave colorless crystals of **9**: mp 190–192°; ν_{NH} 3260, $\nu_{bonded\ OH}$ 3500–2300, $\nu_{C=O}$ 1700, 1650, 1635, $\nu_{amide\ II}$ 1550, $\nu_{C_6H_5}$ 700 cm^{-1} in Nujol; $\delta_{CDCl_3}^{37°}$ 8.76 (–NH–, triplet, J = 6 Hz, 1 H), 3.17 (–NCH_2–, triplet, J = 6 Hz).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.67; H, 7.28; N, 5.63.

Registry No.—1, 17037-72-8; 3, 21996-54-3; 4, 21996-55-4; 5, 21996-56-5; 6, 21996-57-6; racemic 6, 21996-58-7; 8, 22002-77-3; 9, 21996-59-8; 11, 21991-06-0; 12, 21991-07-1; 13, 21996-60-1; 14, 21996-61-2.

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Hydrolytic Rearrangements of 19-Methanesulfonoxyandrost-4-ene-3,17-dione and 19-Methanesulfonoxyandrosta-3,5-dien-17-one

JACK TADANIER, ROBERT HALLAS, AND JERRY R. MARTIN

Organic Chemistry Department, Research Division, Abbott Laboratories, North Chicago, Illinois 60064

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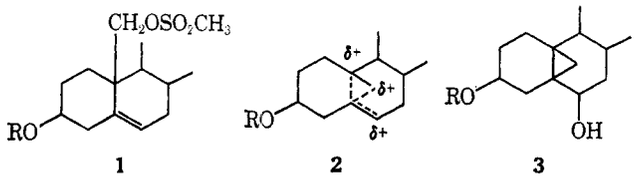
A study was made of the buffered hydrolyses of 19-methanesulfonoxyandrost-4-ene-3,17-dione (**4b**) and 19-methanesulfonoxyandrosta-3,5-dien-17-one (**5b**) for comparison with the results of hydrolysis of 19-substituted steroids with isolated Δ^5 double bonds. The acid-catalyzed rearrangements of 3β-methoxy-6β-hydroxy-5β,19-cycloandrostan-17-one (**28**) and 6β-hydroxy-5β,19-cycloandrostane-3,17-dione (**15**) are contrasted.

Participation of the isolated, homoallylic double bonds of Δ^5-19-substituted steroids **1** in kinetically controlled solvolyses has been found to lead to rearranged products **3** derived from 5β,19-cyclopropylcarbinyl cations **2**.[1] The present study of the buffered hydrolyses of 19-methanesulfonoxyandrost-4-ene-3,17-dione (**4b**) and 19-methanesulfonoxyandrosta-3,5-dien-17-one (**5b**) was undertaken to determine the effects of conjugation of the homoallylic double bonds on the nature of the products obtained.



1 2 3

19-Hydroxyandrost-4-ene-3,17-dione (**4a**) was prepared from 3β,19-dihydroxyandrost-5-en-17-one (**6**) by Oppenauer oxidation according to the procedure described in detail by Dauben and Ben-Efraim.[2] The methanesulfonate **4b** was prepared in essentially quantitative yield by treatment of **4a** with methanesulfonyl chloride in pyridine.

The preparation of 19-hydroxyandrosta-3,5-dien-17-one (**5a**) was based on a procedure which has been used to convert 10β-methyl-Δ^5-3β-hydroxy steroids into 10β-methyl-3,5-dienes.[3] 3β,19-Dihydroxy-17-ethylenedioxyandrost-5-ene (**7**) was prepared either directly from 6β,19-oxido-17-ethylenedioxy-3α,5α-cycloandrostane (**8**) by brief treatment with a small amount of water in dimethyl sulfoxide in the presence of a catalytic amount of sulfuric acid or by ketalization of 3β,19-dihydroxyandrost-5-en-17-one (**6**). Oppenauer oxidation of **7** gave 19-hydroxy-17-ethylenedioxyandrost-4-en-3-one (**9**) which was reduced with lithium tri-*t*-butoxyaluminum hydride in tetrahydrofuran to a mixture of the C_3-epimeric, allylic alcohols **10** according to the procedure of Klimstra and Colton.[4] The latter mixture was subjected to acid-catalyzed dehydration which occurred with concomitant hydrolysis of the

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