oxy)ethyl bromide,[19] mp 45–46° (petr ether, bp 100–120°). *Anal.* ($C_{11}H_{12}BrNO$) C, H.

1-(*p*-Cyanophenoxy)-2-(toluene-*p*-sulfonyloxy)propane.—*p*-Cyanophenol (23.8 g) was treated with propylene oxide (15.5 ml) under the described conditions[18] and an Et_2O soln of the crude 1-(*p*-cyanophenoxy)-2-propanol was washed (1 *N* NaOH, H_2O), dried ($MgSO_4$), and evapd. An ice-cooled soln of the residue in pyridine (100 ml) was treated with TsCl (40 g) and after 2 hr was dild with H_2O (1 l.) and extd with Et_2O which was washed (1 *N* HCl, H_2O), dried ($MgSO_4$), and evapd. The oil was chromatogd on silica with Et_2O to obtain, as the first component, an oil, which was crystd from MeOH to give the tosylate (12.8 g), mp 107–109°. *Anal.* ($C_{17}H_{17}NO_4S$) C, H, N.

(19) J. N. Ashley, H. J. Barber, A. J. Ewins, G. Newbery, and A. D. H. Self, *J. Chem. Soc.*, 103 (1942).

3-(*p*-Nitrophenyl)propyl Chloride.—Nitration of 3-phenylpropyl chloride[20] gave a product which was shown to contain 2 major components in approx equal amts by glpc (apiezon celite at 150°). The prod (59.6 g) distd at 0.5 mm through a spinning-band column (108 × 2 cm) giving fractions of bp 129–130° (16.3 g) and 148–149° (19.8 g). Chromatog of the 2-fractions on alumina using petr ether (60–80°) gave homogeneous products. The lower boiling isomer absorbed (ir) at 1530, 1350, and 790 cm^{-1} (ortho) and the higher boiling isomer at 1505, 1335, and 840 cm^{-1} (para).[21]

(20) J. Buchi, J. Enezian, G. Enezian, G. Valette, and C. Pattani, *Helv. Chim. Acta*, **43**, 1971 (1960).

(21) *Cf.* C. P. Conduit, *J. Chem. Soc.*, 3273 (1959).

Microbiological and Chemical Modification of *N*-Benzoyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (*N*-Benzoylmecamylamine)

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Received December 8, 1970

The metabolic transformation of the *N*-Bz derivative of the ganglionic blocking agent mecamylamine [*N*-benzoyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (**1**)] by *Sporotrichum sulfurescens* results in oxygenation at positions 6 and 7 to give the hydroxylamides **2** and **3**. Several mecamylamine analogs (**4–7** and **10–21**) were prepared from the microbial metabolites.

The chemical preparations and structure–activity relationships of *N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (mecamylamine) and analogs as ganglionic blocking agents have been well documented.[1] Our interest in the microbial oxygenation of the title compound (**1**) was 2-fold; *viz.*, to compare the stereochemistry and relationship of the enzymic hydroxylation site of the products with related biotransformations,[2] and to observe the effects of the products and their analogs on hypertension.

Fermentation of *N*-benzoyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine with *Sporotrichum sulfurescens* produced a complex mixture of hydroxylated products from which it was possible to isolate a major component in 21% yield; if the mixture was oxidized before undertaking isolations, 2 major ketonic products could be obtained, one of mp 82°, in 24% yield and the other, of mp 136–138°, in 29% yield. It was further determined that oxidation of the originally isolated OH compd led to the ketone melting at 82°. Examination of the nmr spectrum of the ketoamides cast some light on their structures. There are only 3 possibilities for ketone attachment to the substrate (**1**), *i.e.*, at C_5, C_6, or C_7. The spectrum of *N*-benzoylmecamylamine (**1**) showed a sharp signal, 3 H, at δ 2.92 ppm for the NCH_3 protons. A medium broad signal, 1 H, with no discernable splitting pattern, at δ 2.48 ppm, was assigned to the tertiary proton at C_1. The remainder of the spectrum, aside from the Ph protons, was in the range between δ 0.80 and 2.10 ppm with sharp signals at δ 1.20, 1.24, and 1.53 ppm for the 3 CCH_3 groups. The spectrum of both ketones showed the signal for the tertiary proton at C_1 downfield, as a shoulder at the base of the NCH_3 signals; the NCH_3 plus the shoulders now integrated for 4 protons. This downfield shift of protons at C_1 is very likely caused by the C=O attachments being α to the C_1H, *i.e.*, at C_6 and at C_7. The ketones of mp 82° and mp 136–138° were reduced with $NaBH_4$ to give two hydroxyamides, both of which were not present in the original biotransformation mixture.

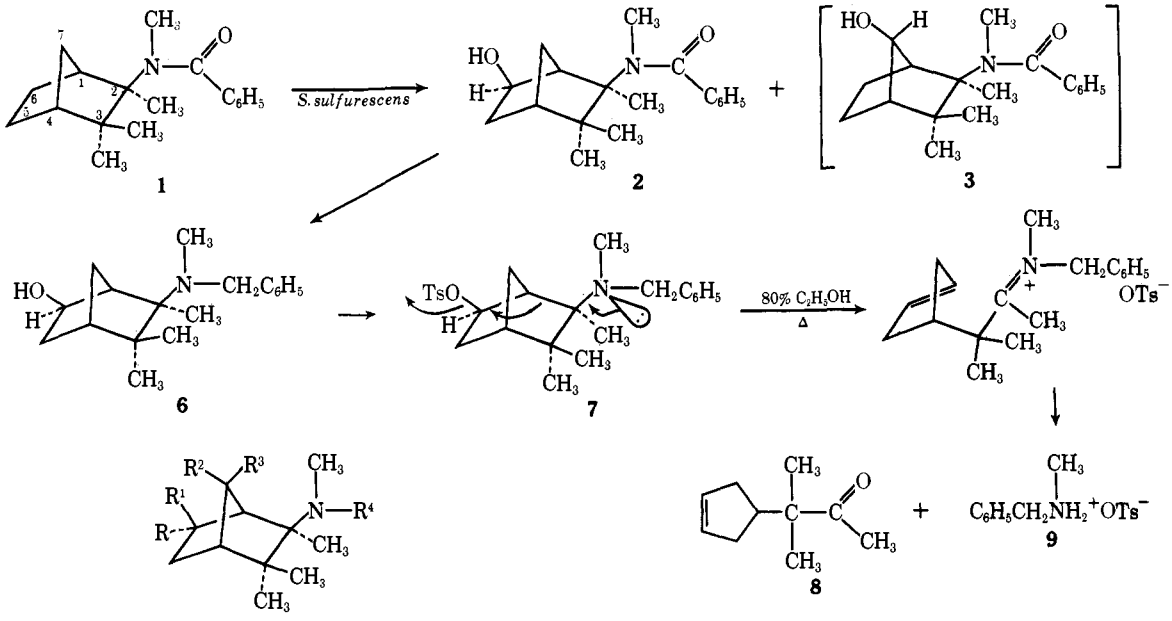
The structure of the alcohol isolated directly from the fermentation was shown to be *exo*-6-hydroxy-*N*-benzoyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (**2**) by solvolytic fragmentation. Grob and coworkers[3] have shown in their studies on 1-methyl-4-, -5-, and -7-decahydroquinolyl tosylates that if a C–OTs bond and the free electron pair on N are in an antiperiplanar position with respect to the intermediate transfer bond, these compds undergo quantitative stereospecific fragmentation. Compound **2** was reduced with LAH to a hydroxybenzylamine (**6**) and then converted to its tosyl ester (**7**). This compd, upon heating in 80% aq EtOH, was converted exclusively to its fragmentation products, *N*-methylbenzylamine salt (**9**) and 3-methyl-3-(3-cyclopentenyl)-2-butanone (**8**). The ketone **8** was identified by its nmr and ir spectra and by analysis as a 2,4-dinitrophenylhydrazone. The nmr spectrum showed 2 equivalent olefinic protons, with a coupling constant approaching zero, as a singlet at δ 5.67 ppm. It should

(1) C. A. Stone, M. L. Torchiana, K. L. Meckelnherd, J. Stavorski, M. Sletzinger, G. A. Stein, W. V. Rugle, D. F. Reinhold, W. A. Gaines, H. Arnold, and K. Pfister, III, *J. Med. Pharm. Chem.*, **5**, 665 (1962); (b) K. Pfister, III, and G. A. Stein, U. S. Patent 2,831,027 (April 15, 1958); (c) G. A. Stein, M. Sletzinger, H. Arnold, D. Reinhold, W. Gaines, K. Pfister, III, *J. Amer. Chem. Soc.*, **78**, 1514 (1956); (d) Z. J. Vejlelek and M. Provita, *Collect. Czech. Chem. Commun.*, **24**, 2614 (1959); (e) N. D. Edge, S. J. Corne, G. E. Lee, and W. R. Wragg, *Brit. J. Pharmacol. Chemother.*, **15**, 207 (1950).

(2) (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, and G. S. Fonken, *J. Org. Chem.*, **35**, 622 (1970), and ref cited therein.

(3) (a) C. A. Grob, H. R. Kiefer, H. J. Lutz, and H. J. Wilkins, *Helv. Chim. Acta*, **50**, 416 (1967); (b) R. A. Johnson, H. C. Murray, L. M. Reineke, and G. S. Fonken, *J. Org. Chem.*, **33**, 3207 (1968), have applied this principle in their structure studies of benzoyl-*trans*-decahydroquinolinol; one of them (R. A. Johnson) suggested the applicability to this work.

SCHEME I



4, R + R¹ = O; R² = R³ = H; R⁴ = COC_6H_5
5, R = R¹ = H; R² + R³ = O; R⁴ = COC_6H_5
10, R = OH; R¹ = R² = R³ = H; R⁴ = COC_6H_5
11, R = R¹ = R² = H; R³ = OH; R⁴ = COC_6H_5
12, R = OH; R¹ = R² = R³ = H; R⁴ = $CH_2C_6H_5$
13, R = R¹ = R² = H; R³ = OH; R⁴ = $CH_2C_6H_5$
14, R = OTs; R¹ = R² = R³ = H; R⁴ = $CH_2C_6H_5$
15, R = R¹ = R² = H; R³ = OTs; R⁴ = $CH_2C_6H_5$

be noted in passing that the coupling constant for the olefinic protons of cyclopentene also approaches zero and the signal appears as a singlet at δ 5.80 ppm. The CH_3 attachment on the ketone was a sharp signal at δ 2.10 ppm and the $C(CH_3)_2$ protons appeared as a sharp signal at δ 1.03 ppm. The remaining 5 protons were distributed in the region between δ 0.70 and 2.80 ppm. The C=O in the ir spectrum produced a strong maximum at 1700 cm^{-1} and CH=CH produced a weak maximum at 1620 cm^{-1}. This is the fragmentation ketone one would obtain *exclusively* from the *exo*-6-hydroxyamide (**2**). This therefore establishes the ketone of mp 82° obtained from the oxidation of **2** as the C_6-ketone (**4**) and the hydroxyamide obtained from the $NaBH_4$ reduction of **4** as *endo*-6-hydroxy-*N*-benzoyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (**10**). This is also the OH isomer one would expect from steric considerations of hydride reduction of this ketone. The hydroxyamide **10** was reduced with LAH to hydroxybenzylamine **12** and then converted to the tosyl ester **14**. Upon heating **14** in 80% aq EtOH for 23 hr, tlc disclosed that some starting material remained, and there was a slight conversion to ketone **8** and amine salt **9**, along with a less polar material which has not been identified.

We concluded therefore, that the ketone, mp 136–138°, was the C_7-ketone **5** and, from steric consideration, the $NaBH_4$ reduction product gave the alcohol isomer **11** with OH syn with respect to the N attachment to the 5-membered ring. Further verification for this was obtained by reducing **11** with LAH to the hydroxybenzylamine **13** and converting it in turn to its tosyl ester **15**. If the OH group had the anti configuration, Grob fragmentation of **15** would give 3-methyl-3-(2-cyclopentenyl)-2-butanone. However, heating the tosyl ester **15** for 23 hr did not give this ketone. This leaves the structure *anti*-7-hydroxy-*N*-benzoyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (**3**) for the hydroxylated product that we were unable to isolate directly from the fermentation.

The products obtained from this biotransformation are thus seen to conform with the pattern observed previously for other biological hydroxylations with *S. sulfurescens*,[2] *i.e.*, the alcohol group introduced into the substrate by the microorganism has been oriented trans equatorial with respect to the C_2 C–N bond and the open-face general plane of the hydroxylated ring. Because of the rotational flexibility of the amide carbonyl, there is a preferred conformation at which both C atoms 6 and 7 are at equal distances and 5.5 Å from the C=O center of high negative density, thus fitting the pattern previously described for hydroxylations with *S. sulfurescens*.[2]

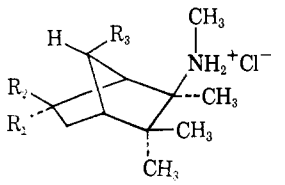
Each of the hydroxylbenzylamines, **6**, **12**, and **13**, was cleaved by reduction with H_2 and Pd/C catalyst, and the products were isolated as the HCl salts to obtain the hydroxylated products analogous to the ganglionic blocking agent *N*,2,3,3-tetramethyl-*exo*-2-norbornanamine. Compounds **16**, **17**, and **18** (Table I) were thus obtained.

The reaction of the hydroxyamides **2**, **10**, and **11** with CH_2N_2 plus $Al(i\text{-}PrO)_3$ as a catalyst according to the method of Popelak and Letterbauer,[4] converted the OH groups to Me ethers. In each case, the Me ether of **2**, **10**, and **11** was reduced with LAH to the corresponding benzylamine and then the benzyl moiety was reductively cleaved with H_2 to produce **19**, **20**, and **21**, resp (Table I). In each case, the crude Me ether of the

(4) A. Popelak and G. Lettenbauer, *Arch. Pharm. (Weinheim)*, **295**, 427 (1962).

TABLE I

ANALOGS OF MECAMYLAMINE



Compd	R_1	R_2	R_3	Overall yield, %	Mp, °C dec	Formula	*Anal.*[5]
16	H	OH	H	86	282	$C_{11}H_{21}NO \cdot HCl$	C, H, Cl
17	OH	H	H	80	244–247	$C_{11}H_{21}NO \cdot HCl$	C, H, Cl
18	H	H	OH	72	270–275	$C_{11}H_{21}NO \cdot HCl$	N, Cl
19	H	OCH_3	H	34	253	$C_{12}H_{23}NO \cdot HCl$	C, H, N, Cl
20	OCH_3	H	H	49	282	$C_{12}H_{23}NO \cdot HCl$	C, H, N, Cl
21	H	H	OCH_3	48	285	$C_{12}H_{23}NO \cdot HCl$	C, H, N, Cl

benzamide and the benzylamine was carried through to the final products.

Biological Activity.—Preliminary testing has shown that **19**, **20**, and **21** were about equal to mecamylamine. HCl in their ability to lower the blood pressure of renal hypertensive (Goldblatt) rats for periods of 4 hr. The corresponding OH compounds **16**, **17**, and **18** were less active, which may be due to decreased lipophilicity of the OH isomers over the corresponding Me ethers.

In order to determine that the hypotensive activity was due to ganglionic blockade and not some other mechanism, **20** was selected for study. Vasoconstrictor responses evoked in the perfused hind limb of the anesthetized dog[5] by electrical stimulation of preganglionic sympathetic nerves were consistently reduced, while those evoked by postganglionic sympathetic nerve stimulation and intraarterially administered norepinephrine were not. Furthermore, the agent reduced the systemic blood pressure without a concomitant reduction in the resistance of the sympathetically denervated perfused extremities.

Experimental Section[6]

Biotransformation.—The culture used in these experiments was *S. sulfurescens* v. Beyma (ATCC 7159). The fermentation and extn process has been described previously.[2a] The substrate level is given below in the description of the isolations.

***N*-Benzoyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (1).**—A mixt of 78.0 g of *N*,2,3,3-tetramethyl-*exo*-2-norbornanamine·HCl,[1a] 600 ml of 10% NaOH soln, and 48 ml of BzCl was stirred in an ice bath for 1 hr and at room temp for 1 hr. After adding 36 ml more of BzCl, the mixt was stirred for 24 hr and extd with Et_2O, and the ext was washed with H_2O and dried (Na_2SO_4). The solvent was removed, and the residue was crystd by dissolving in MeOH and adding H_2O. The solid was recovered, dried, and recrystd from hexane: yield 98.0 g; mp 64–65°. *Anal.* ($C_{18}H_{25}NO$) C, H, N.

Isolation of *exo*-6-Hydroxy-*N*-benzoyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (2).—The residue extd from the fermentation of 12.0 g of *N*-benzoyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (**1**) in 100 l. of medium was chromatogd over a column (4 cm diam) of 600 g of Florisil.[7a] The material was placed on the column with 300 ml of CH_2Cl_2 and eluted by the linear gradient method with 18 l. of solvent—SSB[7b] containing increasing proportions of Me_2CO from 0 to 18%. Cuts of 325 ml each were collected, and the residues therefrom were examined by tlc.[8a] Fractions 38–43 were essentially a single entity; these were pooled and crystd from EtO_2: yield, 3.05 g (21%); mp 178–180°. The anal. sample was recrystd from CH_2Cl_2–EtO_2, mp 180–182°. *Anal.* ($C_{18}H_{25}NO_2$) C, H, N.

Isolation of 6- and 7-Keto-*N*-benzoyl-*N*,2,3,3,-tetramethyl-*exo*-2-norbornanamine (4 and 5) from the Oxidized Fermentation Extract.—The residue extd from the fermentation of 30.0 g of **1** in 120 l. of medium was dissolved in 500 ml of Me_2CO and oxidized with 35.0 ml of CrO_3 soln by the Jones method.[9] The neutral residue from this oxidation was 30 g of dark oil. This material was placed on a column (5.8 cm diam) of 1500 g of Florisil[6a] with 200 ml of CH_2Cl_2. The column was eluted in cuts of 1 l. each with 4 l. each of SSB containing 5, 8, 11, 14, and 17% Me_2CO. Fractions were pooled as indicated in Table II on the basis of tlc[8b] examination of the residues.

TABLE II

CHROMATOGRAPHY

Pool	Fractions	Wt, g
A	4–6	7.62
B	7	4.83
C	8–10	9.32
D	11	1.50

6-Keto-*N*-benzoyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (4).—Pool A contd the low mp isomer (**4**), 24% yield. The anal. sample was recrystd from Et_2O–SSB: mp 82°. *Anal.* ($C_{18}H_{23}NO_2$) C, H, N.

7-Keto-*N*-benzoyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (5).—Pool B was a mixt of **4** and **5**. Pool C contd the high mp isomer (**5**), 29% yield. The anal. sample was obtained by crystn from Me_2CO–SSB, mp 136–138°. *Anal.* ($C_{18}H_{23}NO_2$) C, H, N.

***exo*-6-Hydroxy-*N*-benzyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (6).**—Five g of **2** in 100 ml of anhyd THF was added during 10 min with stirring to a mixt of 5.0 g of LAH and 100 ml of EtO_2. The mixt was refluxed for 70 min, chilled in a cold bath at −10°, and cautiously treated with 25 ml of H_2O while stirring vigorously. When the mixt was completely white, the inorg solid was removed by filtration and washed well with Et_2O. The combined filtrate and wash were dried ($MgSO_4$), and the solvent was evapd to yield 4.76 g of product as a colorless syrup—one material by tlc.[8c] For testing purposes and for anal., this free base dissolved in EtO_2 was converted to its HCl salt (**6**) by addition of a slight excess of ethereal HCl. Recrystn was from MeOH–EtO_2, mp 164–165° dec. *Anal.* ($C_{18}H_{28}NOCl$) C, H, Cl.

***exo*-6-Hydroxy-*N*-benzyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine Tosylate (7).**—Three g of **6** was dissolved in 15 ml of

(5) L. Beck, *Amer. J. Physiol.*, **201**, 123 (1961).

(6) Nmr spectra were detd in $CDCl_3$ at 60 mcps on a Varian Model A-60 spectrometer with ref to Me_4Si. Pertinent nmr and ir assignment data are contd in the discussion and are not repeated in the Experimental Section. Melting points were taken in capillaries and are cor. Anal. results are represented by the symbols of the elements and the values obtained were within ±0.4% of the calcd values.

(7) (a) A synthetic magnesium silicate product, The Floridin Company, Warren, Pa.; (b) SSB = Skellysolve B, a petroleum hydrocarbon fraction, bp 60–70°, Skelly Oil Company, Kansas City, Mo.

(8) Silica gel Uniplate (9 × 2.5 cm), Analtech, Inc., Wilmington, Del.; (a) development repeated three times with 20% Me_2CO in SSB (v/v); (b) developed with 20% Me_2CO in $CHCl_3$ (v/v); (c) developed with 20% MeOH in C_6H_6 (v/v).

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

C_6H_5N and treated with 4.0 g of TsCl at room temp for 22 hr. The mixt was poured onto 50 g of ice and stirred. The aq phase was decanted from the oily product which was washed twice with H_2O by stirring and decantn. Finally, about 2.0 ml of MeOH was added to the oil which finally crystd upon rubbing with a glass rod. The product was recovered by filtration and washed with a little cold MeOH: yield 3.40 g; mp 62–66°. The anal. sample was obtd by recrystn from MeOH, mp 67–69°. *Anal.* ($C_{25}H_{33}NO_3S$) C, H, N, S.

Fragmentation of 7 and Isolation of 3-Methyl-3-(3-cyclopentenyl)-2-butanone (8) as Its 2,4-Dinitrophenylhydrazone (8′).—**7** (1 g) and 25 ml of 80% aq EtOH were heated on a steam bath under a reflux condenser. The mixt was examined by tlc[7c] at intervals, and the heating was terminated after 23 hr. The starting material, R_f 0.42, had almost completely reacted after 110 min and at 23 hr the conversion to **8**, R_f 0.58, and **9**, R_f 0.00, was complete. The mixt was diluted with 25 ml of H_2O and extd with 100 ml of Et_2O. The ext was washed once with H_2O and dried (Na_2SO_4). The solvent was evapd on a steam bath and the liquid **8** quickly dried in a desiccator.[10] A portion of the oil was used to determine its ir, neat, in an aluminum foil pocket between salt plates and its nmr in $CDCl_3$. The remainder of the oil was converted to a 2,4-DNP (**8′**), mp 154–155°, recrystd from EtOH. *Anal.* ($C_{16}H_{10}N_4O_1$) C, H, N.

Isolation of N-Methylbenzylamine·HOTs (9).—The above reaction was repeated. The reaction mixt was concd to dryness *in vacuo;* the residue was triturated with Et_2O, and the resulting solid was recrystd from MeOH–Et_2O, mp 154–155°. *Anal.* ($C_{15}H_{19}NO_3S$) C, H, N, S.

***endo*-6-Hydroxy-*N*-benzoyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (10).**—Compd **4** (15 g), dissolved in 250 ml of MeOH, was stirred with 10.0 g of $NaBH_4$ in 50 ml of H_2O for 16 hr. The mixt was chilled and carefully treated with 50% aq AcOH until pH 6. Most of the MeOH was allowed to evap in a hood, the mixt was dild with 100 ml of H_2O and chilled, and the solid product was recovered by filtration, washed with H_2O, and dried; yield, 14.84 g; mp 223–227°. Recrystd from MeOH–H_2O, mp 230–231°. *Anal.* ($C_{18}H_{25}NO_2$) C, H, N.

***endo*-6-Hydroxy-*N*-benzyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (12)** was prepd in almost quant yield from **10** as described for the prepn of **6** from **2**. The HCl salt (**12′**) was recrystd from MeOH–Me_2O, mp 89–90° dec. *Anal.* ($C_{14}H_{24}ClNO$) N, Cl.

***endo*-6-Hydroxy-*N*-benzyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine tosylate (14)** was prepd from 1.17 g of **12** as described for the prepn of **7** from **6**: yield, 1.40 g; mp 116–117° from MeOH. *Anal.* ($C_{24}H_{33}NO_3S$) C, H, N, S.

***syn*-7-Hydroxy-*N*-benzoyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (11)** was prepd from 6.0 g of **5** as described for the prepn of **10** from **4**: yield, 4.34 g; mp 186–188°; recrystd from Me_2O–H_2O, mp 186–187°. *Anal.* ($C_{18}H_{25}NO_2$) C, H, N.

***syn*-7-Hydroxy-*N*-benzyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine (13)** was prepd in nearly quant yield from 4.34 g of **11**. The HCl salt (**13′**) was recrystd from MeO_2–Et_2O, mp 151–153°. *Anal.* ($C_{18}H_{28}ClNO$) N, Cl.

***syn*-7-Hydroxy-*N*-benzyl-*N*,2,3,3-tetramethyl-*exo*-2-norbornanamine tosylate (15)** was prepd from 3.67 g of **13** as described for the prep of **7** from **6**: yield, 3.34 g; mp 124–126° from MeOH. *Anal.* ($C_{24}H_{33}NO_3S$) C, H, N, S.

General Procedure for 16, 17, and 18.—The hydroxybenzylamine (**6**, **12**, or **13**) (4.0 g) was dissolved in 30 ml of EtOH, 0.75 g of 10% Pd/C was added, and the mixt was shaken with H_2 (3.16 kg/cm²) for 16 hr or until the uptake of H_2 was complete. The catalyst was removed by filtration, and the filtrate was concd *in vacuo* to a solid, free base. This was dissolved in Et_2O and treated with a slight excess of ethereal HCl to ppt the HCl salt. This was recovered by filtration, washed with Et_2O, and dried.

General Procedure for 19, 20, and 21.—A soln of 5.46 g (0.02 mole) of hydroxyamide, *e.g.*, **11**, in 150 ml of CH_2Cl_2 was treated with 2.5 g of $Al(i\text{-}PrO)_3$ and then with 100 ml of a CH_2Cl_2 soln of CH_2N_2.[11] After standing at room temperature for 3.5 hr, 100 ml more of CH_2Cl_2 soln of CH_2N_2 was added. The mixt was allowed to stand for 22 hr. The soln was washed with 100 ml of H_2O, 100 ml of 10% H_2SO_4, and twice with 50 ml of H_2O, and dried ($NaSO_4$). The CH_2Cl_2 soln was chromatogd over 273 g of Florisil[6a] eluting by the linear gradient method with 6 l. of solvent, SSB[6b] containing increasing proportions of Me_2CO from 0 to 15%. Cuts of 200 ml each were taken, and the residues were examined by tlc[7c] and ir. Cuts 10–15 contd the crude product, Me ether of the hydroxyamide. This, dissolved in 50 ml of Et_2O was reduced with a soln of 4.0 g of LAH in 100 ml of Et_2O and the mixt worked up as described for the prepn of **6**. The crude Me ether of the benzylamine was obtd as a white solid. It was dissolved in 100 ml of warm EtOH. The soln was reduced with H_2 and 0.5 g of 10% Pd/C catalyst, and the product was converted to the HCl salt and recrystd from MeOH–Et_2O as described for the prepn of **16**, **17**, and **18**. See Table I for yields (overall for three steps) and mp's.

Acknowledgments.—We thank L. M. Reineke and assistants for some of the chromatographic assays; J. R. Heald, I. N. Pratt, and M. J. Sutton for technical assistance. The biological activity data were provided by J. R. Weeks, R. G. Montgomery, and D. W. DuCharme of the Upjohn Laboratories.

(10) This compd has a fairly high vapor pressure and soon evaporates at room temp, as noted by its rapid disappearance from salt plates after ir detd.

(11) The CH_2N_2 soln was prepd from 265 ml of CH_2Cl_2, 22.0 g of *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine, and 70 ml of 45% KOH soln.