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Phenethylamine in a Rigid Framework. 2,3-Substituted *cis*- and *trans*-6-Amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols†

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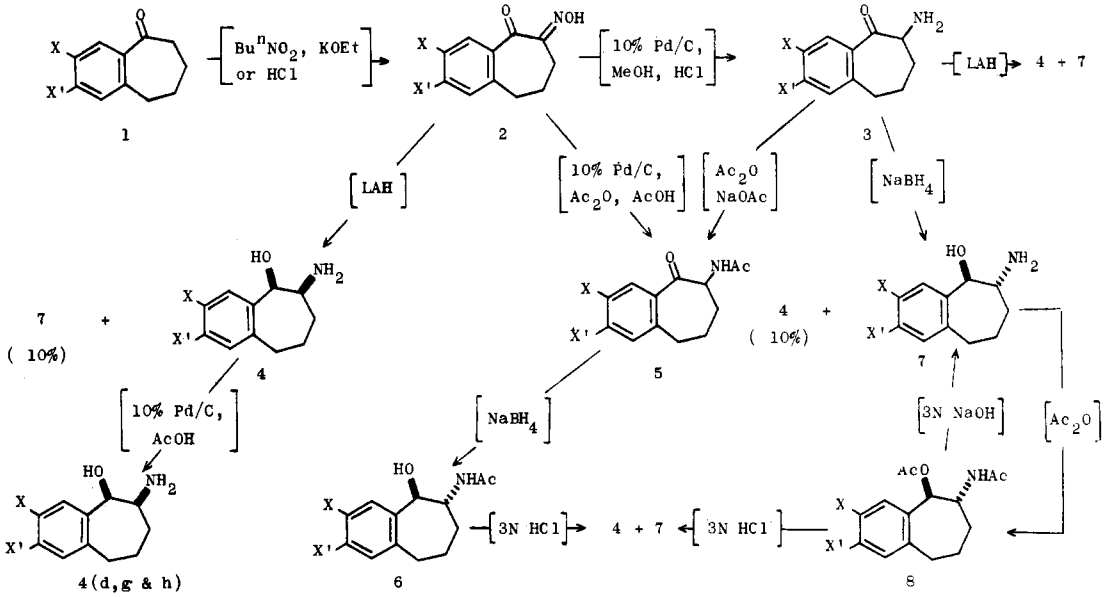
The synthesis and biological activity of 2,3-substituted *cis*- and *trans*-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols are described; *cis*-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol exhibited significant tranquilizing activity, while *cis*-2,3-dihydroxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol showed marked sympathomimetic activity.

Rigid models of prototypes, having a limited number of permissible conformations, have been useful in receptor analysis. In continuing our study of compounds having the phenethylamine moiety in a rigid framework, 1-aminomethylisochromans[1] and *cis*- and *trans*-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols[2] were reported earlier. In this paper we report the synthesis and biological evaluation of *cis*-2-hydroxy-, -3-hydroxy- and -2,3-dihydroxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols and some related 2,3-disubstituted analogs.

The scheme of synthesis is described in Scheme I. Most of the 6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones (**1**) required as starting materials were known compounds and were prepared by literature methods.[3-7] 2-Hydroxy- and 2,3-dihydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones (**1g, 1d**) were prepared by demethylation of the corresponding methoxy ketones using Py · HCl or $AlCl_3$–C_6H_6, and the corresponding benzyl ethers **1e** and **1c** were synthesized by treating the phenols with $PhCH_2Cl$-K_2CO_3 in Me_2CO. 2,3-Diacetoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (**1l**) was prepared by heating **1d** with Ac_2O. The oximino ketones **2** were obtained by treating the ketones **1** with *n*-BuONO in the presence of dry HCl, NaOEt, or KOEt.

The catalytic reduction of oximino ketones, **2**, was found to depend on the activity of the catalyst and the nature of the substituents in the benzene ring (Scheme II). The catalytic reduction of 2-methoxy and 2,3-dimethoxy oximino ketones **2a** and **2j** in MeOH–HCl using dry 10% Pd/C stopped at the stage of the amino ketone **3**, while 3-methoxy and the unsubstituted oximino ketones gave the corresponding aminoheptenols **4** under the same conditions. The same re-

Scheme I



(a) X = X' = OMe
(b) X = X' = Me
(c) X = X' = OCH_2Ph
(d) X = X' = OH
(e) X = H, X' = OCH_2Ph
(f) X = OCH_2Ph, X' = H
(g) X = H, X' = OH
(h) X = OH, X' = H
(i) XX' = $-(CH_2)_4-$
(j) X = H, X' = OMe
(k) X = OMe, X' = H
(l) X = X' = OAc

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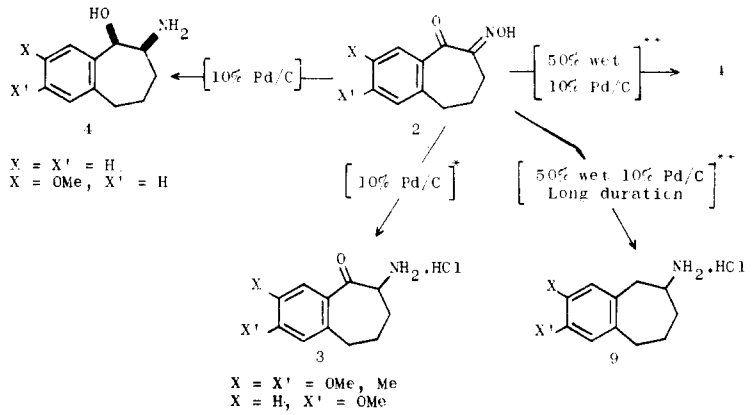
Scheme II



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duction using 50% wet 10% Pd/C gave *cis*-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols (**4**) in every case, and on prolonging the time of hydrogenation the corresponding 6-amino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (**9**) was obtained. As expected, the rate of hydrogenation of the 2-methoxy oximino ketone **2j** was faster than that of the corresponding unsubstituted or the 3-methoxy oximino ketone **2k**. The 2,3-disubstituted 6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones (**3a** and **3b**) on reduction with $NaBH_4$ gave the corresponding *trans*-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols (**7a** and **7b**) as the major products, along with small quantities (~10%) of cis isomers, while LAH reduction gave 1:1 mixtures of cis and trans isomers.

Attempted synthesis of *cis*-2,3-dihydroxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (**4d**) by (i) demethylation of 2,3-dimethoxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol, (ii) catalytic reduction of 2,3-dibenzyloxy-6-oximino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one, (iii) catalytic reduction of 2,3-dibenzyloxy-6-oximino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol, and (iv) nitrosation of 2,3-diacetoxy ketone **1l** gave intractable products; **4d** was ultimately obtained by LAH reduction of 2,3-dibenzyloxy-6-oximino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (**2c**) which gave **4c**, followed by catalytic hydrogenation in AcOH. Similarly, other 2- and 3-substituted 6-oximino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones (**2**) on reduction with LAH gave the corresponding 2- and 3-substituted *cis*-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols (**4**) as major products.

The hydrogenation of **2a** and **2b** in the presence of Ac_2O-AcOH using 10% Pd/C gave 6-acetamido-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones (**5a** and **5b**) which on reduction with $NaBH_4$ gave *trans*-acetamidoheptenols **6a** and **6b**, respectively, whereas reduction of 6-acetamido-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one[2] with $NaBH_4$ gave a 1:1 mixture of cis and trans isomers; *trans*-**7b** on treatment with Ac_2O-MeOH gave *trans*-**6b** and treatment with Ac_2O only gave *trans*-**8b**. Hydrolysis of *trans*-**6b** and -**8b** with 3 *N* NaOH regenerated the original isomer while treatment with 3 *N* HCl caused epimerization and a mixture of cis and trans isomers (**4b** and **7b**) was obtained. The isomers could be separated by fractional crystallization.

Stereochemical Assignments. The nmr spectrum of **4** (X = X' = H) is given in Figure 1. The doublet at δ5.2 ($J \approx 1$ Hz) is assigned to H-5. This order of 5,6 coupling could arise with the cycloheptene ring in a boat conformation with 5,6-trans stereochemistry (H-5 e and H-6 a) or in a twist chair conformation with 5,6-cis stereochemistry (H-5 e and H-6 a). The sextet for H-6 at δ3.7 with 2 couplings of about 6.0 and 6.5 Hz, respectively, and a small coupling of *ca.* 1.5 Hz is strongly in favor of this isomer having a twist chair conformation, in which case the dihedral angle between H-6 and the two 7-CH_2's would be 20° and 135°, respectively, and the 3 couplings involved would thus be *ca.* 7.0, 7.5, and 1.0 Hz. By contrast, in the boat conformation with 5,6-trans isomer H-6 and the two 7-CH_2's, the dihedral angles would be *ca.* 90 and 170°, respectively, and the 3 couplings involved would thus be about 1, 1, and 9 Hz. This isomer thus is assigned a 5,6-cis stereochemistry, and the isomer of mp 147-148° with $J_{5,6} = 9$ Hz, a 5,6-trans stereochemistry. This is further supported by the deshielding of peri H-4 in the trans isomer whose 5-OH is equatorial; it is not so in the cis isomer. This would also be consistent with the normal upfield position (δ4.52) of the axial H-5 in a trans isomer relative to the equatorial H-5 (δ4.85). In all the other cases also the isomer having $J_{5,6} \approx 1$ Hz have been assigned the cis and the other with $J_{5,6} \approx 8$ Hz a trans conformation.

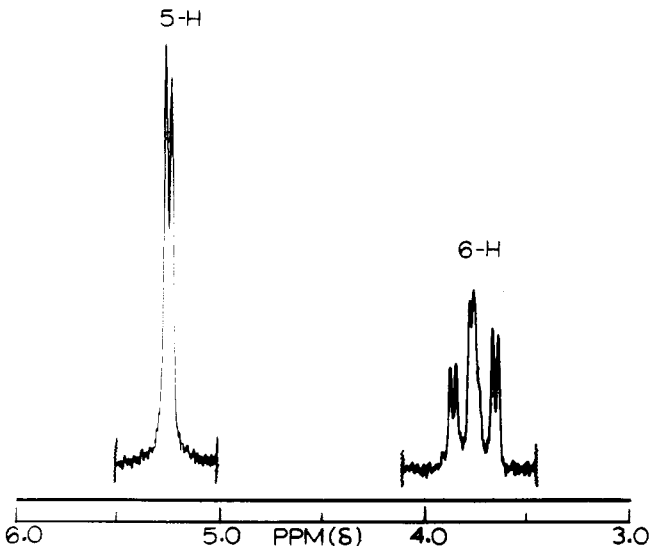


Figure 1.

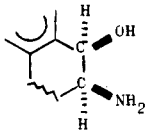
Biological Evaluation and Discussion. The compounds were evaluated for their pharmacological activity by standard methods. The only noteworthy activities found were the tranquilizing activity of *cis*-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol[2] and the sympathomimetic activity of *cis*-2,3-dihydroxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (**4d**).

cis-6-Amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol‡ has LD_{50} 150 mg/kg, ip, in mice. It reduced locomotor activity in mice at 15 mg/kg ip, gave protection against amphetamine toxicity (ED_{50}, 73 mg/kg, po), potentiated barbiturate effects, showed typical effects of a tranquilizer in the EEG in rabbits, and in rats caused selective block of conditioned avoidance response. It was a weak antiemetic against apomorphine-induced emesis in dogs. In evaluations for cardiovascular effects it showed weak sympathomimetic activity. The corresponding trans isomer did not reduce locomotor activity, gave only partial protection against amphetamine toxicity, and had no effect on conditioned avoidance response. The cis isomer has the same configuration as ephedrine (*R*, *S*) (Figure 2). The fact that the cis isomer is much more active than the trans isomer would indicate that the ephedrine configuration is necessary for the activity of these compounds. The corresponding 2,3-dimethyl- and 2,3-dimethoxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols were much less active.

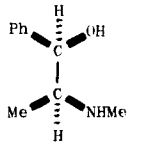
In view of the promising tranquilizing activity shown by *cis*-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol, its subacute toxicity in rats and dogs was studied. The compound, when administered to rats at a dose of 100-200 mg/kg per day, caused no adverse effects on body weight, hematology findings, blood chemistry values, and organ weight. No lesions attributable to the drug were found in gross necropsy examination. However, when administered to dogs at a dose of 50 mg/kg twice a day for 13 days it caused a marked increase in body temp and loss of body weight. Blood analysis showed elevated alk phosphatase and transminase activities. Gross necropsy examination showed hemorrhages in the heart, lung, and stomach, microscopic findings confirmed this. The testes contained very few spermatozoa. All these lesions were typical of heat prostration. In view of these adverse toxic effects this compound has not been studied further.

Compd **4d** in gross observation studies in mice (LD_{50}, 150 mg/kg, ip) showed only slight depression, and no other noteworthy effects.§ It exhibited vasopressor response in a normal anesthetized cat at a dose of 1 mg/kg iv (51 mm for 13 min); the effect was dose dependent. The responses to epinephrine, norepinephrine, and tyramine were potentiated by pretreatment with the compd. In higher doses, it produced contraction of the nictitating membrane. The effects were much more pronounced in reserpinized cats, but greatly reduced after pretreatment with α-adrenergic blocking agents such as tolazoline hydrochloride (5 mg/kg) and yohimbine (1 mg/kg).

Compd **4d** produced relaxation of the rabbit intestine at 1-2 μg/ml, and this effect was blocked by the α-adrenergic blocking agents tolazoline hydrochloride and yohimbine, but not by a β-blocking agent like 3,4-dichloroisoprotrenol (DCI). It showed stimulant effect on rabbit heart *in vitro* which could be blocked by a β blocker (DCI); **4d** thus appears to have a direct sympathomimetic effect, stimulating the α-adrenergic receptors. Nmr data indicate that the most likely conformation of **4d** is the one shown below (Figure 3). Thus, the α-adrenergic receptor structure would be one that can accommodate this molecule.



cis-6-Amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol



(−)-Ephedrine

Figure 2.

Experimental Section

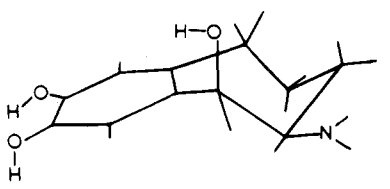
Melting points were taken in a bath. Ir spectra were measured with a Perkin-Elmer Model 137 spectrometer and nmr spectra with a Varian A-60D spectrometer (Me_4Si). The nmr spectra were taken in $CDCl_3$, unless otherwise stated, and the values are given in parts per million. All compds were routinely checked for their structure by ir and nmr spectrometry, described only for compds with some special features. Where analyses are indicated by symbols of the elements, anal. results obtained for those elements were within ±0.4% of the theoretical values.

γ-(3,4-Dimethylbenzoyl)butyric Acid. $AlCl_3$ (20.0 g) was gradually added to a cooled soln of *o*-xylene (10.6 g, 0.1 mole) and glutaric anhydride (11.4 g, 0.1 mole) in $PhNO_2$ (100 ml) kept below 5°; the mixt was stirred for 3 hr, and the complex reaction mixt was decompd by pouring it onto crushed ice and dil HCl. The $PhNO_2$ layer was sepd, washed (H_2O), and extd with Na_2CO_3 soln, the combined ext was made acidic, and the solid product was filtered, washed (H_2O), and crystd from C_6H_6–petr ether or aq EtOH, mp 115-116° (lit.[3] mp 117-118°), yield 11.0 g (50%).

δ-(3,4-Dimethylphenyl)valeric Acid. γ-(3,4-Dimethylbenzoyl)-butyric acid (44.0 g) was added gradually to mixt of Zn-Hg (100.0 g), H_2O (75 ml), concd HCl (176 ml), and PhMe (100 ml), and the mixt was refluxed for 36 hr. An addl quantity of concd HCl (50 ml) was added 3 times after every 6-hr interval. The soln was cooled, the org layer sepd, and the aq portion dild (H_2O) and extd (Et_2O). The combined PhMe and Et_2O ext were concd, and the residue was crystd from petr ether as colorless needles, mp 64-65° (lit.[3] mp 65-66°), yield 30.3 g (75%).

2,3-Dihydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (1d). (a) A mixt of **1a** (2.20 g, 0.01 mole) and Py · HCl (11.55 g, 0.1 mole) was heated at 210-220° for 30 min, cooled, dild (H_2O), and extd (Et_2O). The ext was dried (Na_2SO_4) and concd and the residue crystd from EtOAc–petr ether, mp 163-164°, yield 1.2 g (62%). *Anal.* ($C_{11}H_{12}O_3$) C, H.

(b) The dimethoxy ketone **1a** (5.0 g) and $AlCl_3$ (15.0 g) in dry C_6H_6 (100 ml) were refluxed for 4 hr, and the complex was decompd by ice–HCl mixt. The soln, on work-up, gave **1d**, yield 3.0 g (70%).



cis-2,3-Dihydroxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol

Figure 3.

‡Biological data obtained from Riker Laboratory, Northridge, Calif. (unpublished results).

§R. C. Srimal and G. B. Singh, Department of Pharmacology (unpublished work).

2,3-Dibenzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (1c). $PhCH_2Cl$ (2.53 g, 0.02 mole) was added to a soln of **1d** (1.9 g, 0.01 mole) and dry K_2CO_3 (15.0 g) in dry Me_2CO (50 ml) and the mixt was refluxed for 12 hr, cooled, filtered, and concd. The residue was taken up in Et_2O, washed (10% $NaHCO_3$ and H_2O), dried (Na_2SO_4), and concd, and the residue crystd from PhH–petr ether, colorless leaflets, mp 110–113°, yield 2.9 g (80%). *Anal.* ($C_{25}H_{24}O_3$) C, H.

δ-(*m*-Methoxyphenyl)valeric Acid. 5-(*m*-Methoxyphenyl)penta-2,4-dienoic acid[4] (27.0 g) was dissolved in 20% NaOH (400 ml) and was reduced by adding Ni–Al alloy (41.0 g) to the boiling soln. After completed addn, the soln was stirred for 2 hr, filtered, and poured onto dil H_2SO_4, and extd into C_6H_6–EtOAc. The ext was washed (H_2O), dried (Na_2SO_4), and concd to give the product as a colorless liq, yield 20.0 g, bp 142 (10^{-2} mm) [lit.[4] bp 135–145 (0.2 mm)].

2-Hydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (1g) was prepd by demethylation of **1j** using $AlCl_3$ in place of $AlBr_3$ as described by Khan, *et al.*,[4] mp 164°, yield 80%.

2-Benzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (1e). A mixt of **1g** (3.52 g, 0.02 mole), $PhCH_2Cl$ (3.79 g, 0.03 mole), and dry K_2CO_3 (5.0 g) in dry Me_2CO (60 ml) was refluxed for 72 hr, and worked up to give the product as a viscous syrup, yield 4.0 g (80%). *Anal.* ($C_{18}H_{18}O_2$) C, H.

3-Benzyloxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (1f) was obtained from **1h**[6] by treatment with $PhCH_2Cl$ as described above, viscous syrup, yield 1.8 g (72%). *Anal.* ($C_{18}H_{18}O_2$) C, H.

2,3-Diacetoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (1l). Compd **1d** (1.92 g, 0.01 mole) and Ac_2O (5 ml) were heated on a steam bath for 2 hr, excess reagent was removed under reduced pressure, and the residue was crystd from C_6H_6–petr ether, mp 132–133°, yield 2.4 g (89%). *Anal.* ($C_{15}H_{16}O_5$) C, H.

***trans*-2,3-Dimethoxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (7a).** Compd **3a**[8] (5.43 g, 0.02 mole) was dissolved in EtOH (100 ml) and reduced by slow addn of $NaBH_4$ (3.8 g, 0.1 mole) with ice cooling and stirring. After 12 hr, the reaction mixt was worked up and the product crystd from C_6H_6 as colorless needles, mp 135°, yield 4.0 g (75%), R_f 0.692 (C_6H_6–MeOH, 1:1), nmr, H-5, 4.5 (d, J = 9 Hz). *Anal.* ($C_{13}H_{19}NO_3$) C, H, N. The hydrochloride was obtained as colorless leaflets from EtOH–Et_2O, mp 186–187°. *Anal.* ($C_{13}H_{19}NO_3 \cdot HCl$) C, H, N.

2,3-Dimethoxy-6-acetamido-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (5a) was obtd by hydrogenation of **2a** (2.49 g, 0.01 mole) in AcOH (60 ml) and Ac_2O (20 ml) using 10% Pd/C catalyst. After 8 hr, the catalyst was filtered off, the filtrate was concd, and the residue was crystd from C_6H_6–petr ether as colorless needles, mp 145–147° (lit.[5] mp 153), yield 2.2 g (80%). *Anal.* ($C_{15}H_{19}NO_4$) C, H, N.

***trans*-2,3-Dimethoxy-6-acetamido-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (6a).** Compd **5a** (5.54 g, 0.02 mole) in MeOH (100 ml) was reduced with $NaBH_4$ (3.8 g, 0.1 mole) under ice cooling, and the product obtd on work-up was crystd from C_6H_6–petr ether as colorless needles, mp 163–165°, yield 3.9 g (70%). *Anal.* ($C_{15}H_{21}NO_4$) C, H, N.

***cis*-2,3-Dimethoxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol Hydrochloride (4a).** Compd **6a** (1.39 g, 0.005 mole) on hydrolysis with 3 *N* HCl (50 ml) gave a mixt of cis and trans isomers. On fractional crystn of the hydrochloride from EtOH–Et_2O the pure cis isomer was obtained as colorless leaflets, mp 230°, yield 0.6 g (45%). *Anal.* ($C_{13}H_{19}NO_3 \cdot HCl$) C, H, N.

6-Oximino-2,3-dimethyl-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (2b). A mixt of **1b** (1.88 g, 0.01 mole) and *n*-BuONO (1.03 g, 0.01 mole) in dry Et_2O (25 ml) was added dropwise to an ice-cooled soln of KOEt (1.68 g, 0.02 mole) in abs EtOH (25 ml). The reaction mixt was left overnight in a refrigerator and dild (H_2O), the aq phase was sepd and made acidic, and the product was obtd as pale yellow needles, filtered, and crystd from C_6H_6, mp 192°, yield 1.5 g (70%). *Anal.* ($C_{13}H_{15}NO_2$) C, H, N.

2,3-Dimethyl-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one Hydrochloride (3b). Compd **2b** (2.17 g, 0.01 mole), 10% Pd/C (0.5 g), and concd HCl (4 ml) in EtOAc–MeOH (50 ml, 1:1) was hydrogenated at room temp and atm pressure until the absorption of H_2 ceased, and the soln was worked up in the usual way; the hydrochloride crystd from EtOH–Et_2O, mp 205–207°, yield 2.0 g (85%). *Anal.* ($C_{13}H_{17}NO \cdot HCl$) C, H, N.

***trans*-2,3-Dimethyl-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (7b)** was obtd by reduction of **3b** with $NaBH_4$ as described for **7a**, colorless cryst product from C_6H_6, mp 178–180°, yield 75%, R_f 0.266 (C_6H_6–MeOH, 1:1), nmr, H-5, 4.5 (d, J = 10 Hz). *Anal.* ($C_{13}H_{19}NO$) C, H, N.

2,3-Dimethyl-6-acetamido-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (5b). Compd **2b** on hydrogenation in AcOH–Ac_2O soln using 10% Pd/C catalyst at room temp and atm pressure gave **5b** as viscous syrup, yield 82%. *Anal.* ($C_{15}H_{19}NO_2$) C, H, N.

***trans*-2,3-Dimethyl-6-acetamido-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (6b)** was prepd from **5b** by reduction with $NaBH_4$ or by heating **7b** (1.0 g) with Ac_2O (2 ml) in MeOH (20 ml) on a steam bath for 4 hr, the product crystd from C_6H_6–petr ether, mp 165–166°, yield 60%; nmr (CF_3COOH), H-5, 6.5 (d, J = 10 Hz). *Anal.* ($C_{15}H_{21}NO_2$) C, H, N. Base hydrolysis of **6b** regenerated **7b.**

Acid Hydrolysis of *trans*-2,3-Dimethyl-6-acetamido-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol. A suspension of **6b** (2.47 g, 0.01 mole) in 3 *N* HCl (70 ml) was refluxed gently for 4 hr, cooled, and made alk, and the colorless cryst product which sepd was filtered, mp 140–162°. Tlc (C_6H_6–MeOH, 1:1) showed it to be a mixt of 2 products, which were sepd by fractional crystn from C_6H_6–petr ether to give the cis isomer, more sol, colorless crystals, mp 141°, R_f 0.80; nmr H-5, 4.8 (d, J = 1 Hz) [*Anal.* ($C_{13}H_{19}NO$) C, H, N], and the trans isomer, from the less sol fraction, colorless crystals, mp and mmp with **7b**, 178°, R_f 0.226.

LAH Reduction of 2,3-Dimethyl-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one Hydrochloride (3b). Compd **3b** (0.6 g) was added to a suspension of LAH (1.0 g) in Et_2O (50 ml) and the mixt was stirred for 24 hr at room temp, decompd, extd ($CHCl_3$), dried (Na_2SO_4), and concd, mp 140–158° (crude product), yield 0.4 g. The nmr spectrum of the crude product showed it to be a mixt of cis and trans isomers (1:1).

***trans*-2,3-Dimethyl-5-acetoxy-6-acetamido-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (8b).** A soln of **7b** (2.05 g, 0.01 mole) in Ac_2O (10 ml) was heated on a steam bath for 1 hr. It was concd and the residue crystd from C_6H_6–petr ether, mp 175–177°, yield 2.5 g (84%), R_f 0.8 (C_6H_6–MeOH, 30:1). *Anal.* ($C_{17}H_{23}NO_3$) C, H, N.

Compd **8b**, on base hydrolysis, regenerated **7b**, while hydrolysis with 3 *N* HCl gave a mixt of cis and trans isomers.

***cis*-2,3-Dimethyl-6-acetamido-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol.** Compd **4b** (2.08 g, 0.01 mole), on heating with Ac_2O (5 ml) and MeOH (40 ml) for 4 hr, gave the required product, crystd from C_6H_6–petr ether, mp 176–178°, yield 2.2 g (87%). *Anal.* ($C_{15}H_{21}NO_2$) C, H, N.

2,3-Dibenzyloxy-6-oximino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (2c). (a) **1c** (3.72 g, 0.01 mole) on treatment with KOEt (1.68 g, 0.02 mole) and *n*-BuONO (2.06 g, 0.2 mole) in dry Et_2O (25 ml), as described above, gave **2c** as pale yellow leaflets from C_6H_6–petr ether, mp 150°, yield 3.2 g (80%). *Anal.* ($C_{25}H_{23}NO_4$) C, H, N.

(b) *n*-BuONO (2.06 g, 0.02 mole) in dry Et_2O (25 ml) was added dropwise to a suspension of **1c** (3.72 g, 0.01 mole) in dry Et_2O (40 ml), while a stream of HCl gas was passed through the soln. After 1 hr, the soln was concd and the product crystd from EtOH, mp 148°, yield 3.5 g (87%).

2,3-Dibenzyloxy-6-oximino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol was obtd from **2c** by reduction with $NaBH_4$ as described above. After completion of the reduction, the soln was acidified and the product crystd from C_6H_6–petr ether as pale yellow crystals, mp 140°, yield 85%. *Anal.* ($C_{25}H_{25}NO_4$) C, H, N.

***cis*-2,3-Dibenzyloxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (4c).** To a stirred suspension of LAH (1.9 g, 0.05 mole) in dry THF (30 ml), a soln of **2c** (2.05 g, 0.005 mole) in dry THF (45 ml) was added dropwise. The reaction mixt was refluxed and stirred for 12 hr. The nmr spectrum of the crude product obtd after usual work-up showed it to be a mixt of cis and trans isomers (90:10), which on purification by chromatog on silica gel followed by crystn from C_6H_6–hexane gave pure cis isomer, mp 135°, yield 1.60 g (84%), nmr, H-5, 4.8 (d, J = 1 Hz). *Anal.* ($C_{25}H_{27}NO_3$) C, H, N. Similarly **2b** on reduction with LAH gave *cis*-**4b.**

***cis*-2,3-Dihydroxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (4d).** A soln of **4c** (6.0 g) in glacial AcOH (150 ml) was hydrogenated at room temp and atm pressure by using 10% Pd/C (2.5 g) (K & K Laboratories). After 4 hr, the soln was worked up, and the free base crystd from MeOH–$CHCl_3$–Et_2O, mp 182° dec, developed a red color at 120°, yield 4.0 g, nmr, H-5, 4.9 (d, J = 1.5 Hz). The free base was unstable at room temp and on keeping in air at room temp it developed a red color; the hydrochloride is very hydroscopic. *Anal.* ($C_{11}H_{15}NO_3$) C, H, N.

2-Methoxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene Hydrochloride (9j). A soln of **2j** in MeOH–HCl was hydrogenated at atm pressure and room temp using 10% Pd/C (50% wet, Engelhardt Co., N. J.); after 20 hr the soln was worked up; the hydrochloride crystd from EtOH–Et_2O, mp 192–196°, yield 70%. *Anal.* ($C_{12}H_{17}NO \cdot HCl$) C, H, N.

3-Methoxy-6-oximino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (2k) was prepd as described for **2b**; crystd from aq EtOH, mp 153–155°, yield 40%. *Anal.* ($C_{12}H_{13}NO_3$) C, H, N.

***cis*-3-Methoxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol Hydrochloride (4k).** A soln contg **2k** in MeOH–HCl was hydrogenated at atm pressure and room temp by using 10% Pd/C (K & K Laboratories). After 19 hr, the soln was worked up, crystd from EtOH–Et_2O, mp 245° dec, yield 48%; nmr, H-5, 5.04 (d, J = 1.5 Hz). *Anal.* ($C_{12}H_{17}NO_2 \cdot HCl$) C, H, N.

3-Benzyloxy-6-oximino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (2f) was prepd as described for **2b**, crystd from EtOH, mp 156–161°, yield 87%. *Anal.* ($C_{18}H_{17}NO_3$) C, H, N.

***cis*-3-Benzyloxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (4f).** Compd **2f**, on reduction with LAH in THF as described for **4c**, gave a pale yellow syrup, yield 75%, nmr, H-5, 5.0 (broad singlet, J half-bandwidth = 4 Hz). *Anal.* ($C_{18}H_{21}NO_2$) C, H, N.

***cis*-3-Hydroxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (4h).** Compd **4f**, on catalytic reduction as described for **4d**, gave **4h** as colorless product, crystd from MeOH–Et_2O, mp 172–174°; nmr, H-5, 5.2 (d, J = 1 Hz). *Anal.* ($C_{11}H_{15}NO_2 \cdot H_2O$) N.

2-Benzyloxy-6-oximino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one (2e) was obtd in 62% yield, when **1e** was treated with KOEt and *n*-BuONO in dry Et_2O as described for **2b**, crystd from EtOH, mp 188°. *Anal.* ($C_{18}H_{17}NO_3$) C, H, N.

***cis*-2-Benzyloxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (4e).** Compd **2e** was reduced with LAH by following the procedure described for **4c**, crystd from C_6H_6–petr ether, mp 129°, yield 70%, nmr, H-5, 4.9 (d, J = 1 Hz). *Anal.* ($C_{18}H_{21}NO_2$) C, H, N.

***cis*-2-Hydroxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol (4g).** Compd **4e** on catalytic hydrogenation (10% Pd/C) in AcOH at room temp and atm pressure gave **4g** in 75% yield, free base crystd from MeOH, mp 210° dec, nmr, H-5, 5.2 (d, J = 1 Hz). *Anal.* ($C_{11}H_{15}NO_2 \cdot H_2O$) C, H, N.

7-Oximino-6-oxo-1,2,3,4,7,8,9,10-octahydro-6*H*-cyclohepta[*b*]-napthalene (2i) was obtd on treatment of **1i**[7] with *n*-BuONO and KOEt in Et_2O at 0° as pale yellow cryst substance, crystd from C_6H_6–petr ether, mp 202° dec, yield 65%. *Anal.* ($C_{15}H_{17}NO_2$) C, H, N.

7-Amino-6-oxo-1,2,3,4,7,8,9,10-octahydro-6*H*-cyclohepta[*b*]-naphthalene (3i). The oximino ketone **2i** on catalytic reduction (10% Pd/C) in MeOH–HCl at room temp and atm pressure, gave **3i**, crystd from EtOH–Et_2O, mp 210° dec, yield 88%. *Anal.* ($C_{15}H_{19}NO \cdot HCl \cdot 0.5H_2O$) C, H, N.

***cis*- and *trans*-7-Amino-6-hydroxy-1,2,3,4,7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]naphthalene (4i and 7i).** $NaBH_4$ (1.5 g) was added in portions to a stirred soln of the amino ketone hydrochloride **3i** (2.65 g, 0.01 mole) in MeOH (100 ml) at 0° and the mixt was stirred for 5 hr, concd, dild (H_2O), and extd (EtOAc). The EtOAc layer was washed (H_2O), dried (Na_2SO_4), and concd, and the residue was crystd from $CHCl_3$–petr ether (60–80°), mp 155–159°, yield 1.86 g. Nmr showed a mixt of cis and trans isomers; H-5 at 4.5 and 4.8 (d, J = 9 Hz and J = 1 Hz). *Anal.* ($C_{15}H_{21}NO$) C, H, N.

On fractional crystn of the mixt (300 mg) from EtOH (30 ml), the fraction which sepd first (110 mg) was homogeneous by tlc and nmr, mp 178–180°, nmr, H-5, 4.5 (d, J = 9 Hz), and was assigned the trans configuration. The second isomer could not be obtd pure from the filtrate. The treatment of *trans*-hydroxyamino compd **7i** with 3 *N* HCl at 90° for 1 hr gave a mixt of cis and trans isomers along with an oily nonbasic compd, most likely 7-oxo-1,2,3,4,6,8,9,-10-octahydro-7*H*-cyclohepta[*b*]naphthalene.

***trans*-7-Acetamido-5-acetoxy-1,2,3,4,7,8,9,10-octahydro-6*H*-cyclohepta[*b*]naphthalene (8i).** A mixt of **4i** and **7i** (140 mg) in Ac_2O (16 ml) was heated on a steam bath for 2.5 hr and concd, and the residue passed through a silica gel column. The product on tlc (C_6H_6–EtOH, 9:1) was found to be a mixt of 2 products, which were sepd by column chromatog using 80 mesh silica gel and $CHCl_3$–EtOH (99:1) as the eluent. The product obtd from the earlier fractions (92 mg), mp 190°, was the trans isomer, nmr, H-5, 5.75 (d, J = 9 Hz). *Anal.* ($C_{19}H_{25}NO_3$) C, H, N.

7-Acetamido-6-oxo-1,2,3,4,7,8,9,10-octahydro-6*H*-cyclohepta[*b*]naphthalene (5i). A mixt of **3i** (600 mg), NaOAc (572 mg), Ac_2O (700 mg), and H_2O (60 ml) was stirred for 1.5 hr. A colorless crystn solid sepd, which was filtered and crystd from EtOH, mp 132°, yield 500 mg. *Anal.* ($C_{17}H_{21}NO_2$) C, H, N.

***cis*- and *trans*-7-Acetamido-6-hydroxy-1,2,3,4,7,8,9,10-octahydro-6*H*-cyclohepta[*b*]naphthalene.** Compd **5i** on reduction with $NaBH_4$ in MeOH gave a mixt of cis and trans isomers, crystd from C_6H_6–hexane, mp 148–149°, yield 75%, nmr, H-5, 4.65 and 4.9 (d, J = 6.5 Hz, and s, J half-bandwidth = 2.5 Hz). *Anal.* ($C_{17}H_{23}NO_2$) C, H, N.

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