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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.

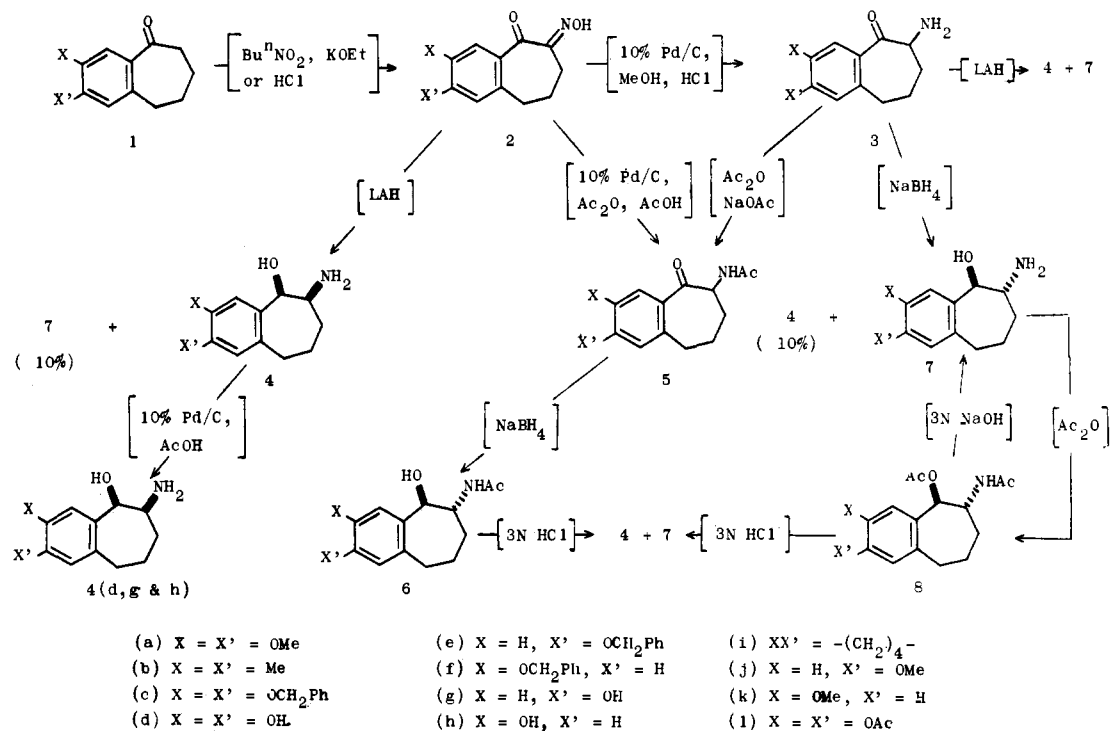
Rigid models of prototypes, having a limited number of permissible conformations, have been useful in receptor analysis. In continuing our study of compounds having the phenethylamine moiety in a rigid framework, 1-amino-methylisochromans¹ and *cis*- and *trans*-6-amino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ols² 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 corre-

sponding methoxy ketones using $\text{Py} \cdot \text{HCl}$ or $\text{AlCl}_3\text{-C}_6\text{H}_6$, and the corresponding benzyl ethers **1e** and **1c** were synthesized by treating the phenols with $\text{PhCH}_2\text{Cl-K}_2\text{CO}_3$ 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.

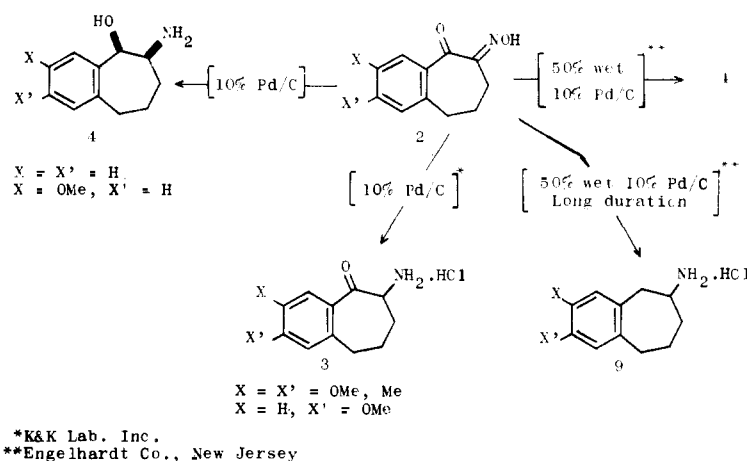
The catalytic reduction of oximino ketones, **2**, was found to depend on the activity of the catalyst and the nature of the substituents in the benzene ring (Scheme II). The catalytic reduction of 2-methoxy and 2,3-dimethoxy oximino ketones **2a** and **2j** in MeOH-HCl using dry 10% Pd/C stopped at 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



†Communication No. 1624 from Central Drug Research Institute, Lucknow, India.

Scheme II



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-ols (**3a** and **3b**) on reduction with NaBH₄ 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-dibenzoyloxy-6-oximino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one, (iii) catalytic reduction of 2,3-dibenzoyloxy-6-oximino-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ol, and (iv) nitrosation of 2,3-diacetoxy ketone **11** gave intractable products; **4d** was ultimately obtained by LAH reduc-

tion of 2,3-dibenzoyloxy-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 Ac₂O-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 NaBH₄ gave *trans*-acetamidoheptenols **6a** and **6b**, respectively, whereas reduction of 6-acetamido-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one² with NaBH₄ gave a 1:1 mixture of *cis* and *trans* isomers; *trans*-**7b** on treatment with Ac₂O-MeOH gave *trans*-**8b** and treatment with Ac₂O 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 $\delta 5.2$ ($J \approx 1$ 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 $\delta 3.7$ 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-CH₂'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-CH₂'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 ($\delta 4.52$) of the axial H-5 in a *trans* isomer relative to the equatorial H-5 ($\delta 4.85$). 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.

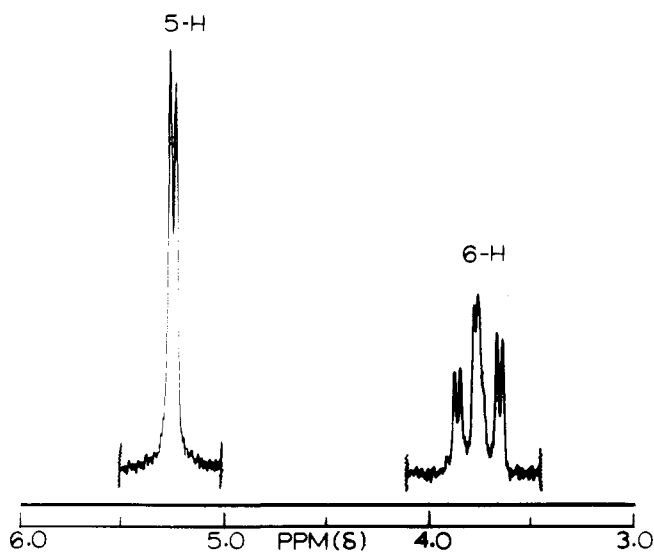


Figure 1.

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[‡] 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 LD₅₀ 150 mg/kg, ip, in mice. It reduced locomotor activity in mice at 15 mg/kg ip, gave protection against amphetamine toxicity (ED₅₀, 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 transaminase 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 (LD₅₀, 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 μ g/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-dichloroisoproterenol (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.

Experimental Section

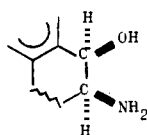
Melting points were taken in a bath. Ir spectra were measured with a Perkin-Elmer Model 137 spectrometer and nmr spectra with a Varian A-60D spectrometer (Me₄Si). The nmr spectra were taken in CDCl₃, unless otherwise stated, and the values are given in parts per million. All compds were routinely checked 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 $\pm 0.4\%$ of the theoretical values.

γ -(3,4-Dimethylbenzoyl)butyric Acid. AlCl₃ (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 PhNO₂ (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 PhNO₂ layer was sepd, washed (H₂O), and extd with Na₂CO₃ soln, the combined ext was made acidic, and the solid product was filtered, washed (H₂O), and crystd from C₆H₆-petr ether or aq EtOH, mp 115–116° (lit.³ mp 117–118°), yield 11.0 g (50%).

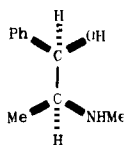
δ -(3,4-Dimethylphenyl)valeric Acid. γ -(3,4-Dimethylbenzoyl)butyric acid (44.0 g) was added gradually to mixt of Zn-Hg (100.0 g), H₂O (75 ml), concd HCl (176 ml), and PhMe (100 ml), and the mixt was refluxed for 36 hr. An addl quantity of concd HCl (50 ml) was added 3 times after every 6-hr interval. The soln was cooled, the org layer sepd, and the aq portion dild (H₂O) and extd (Et₂O). The combined PhMe and Et₂O 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 (H₂O), and extd (Et₂O). The ext was dried (Na₂SO₄) and concd and the residue crystd from EtOAc-petr ether, mp 163–164°, yield 1.2 g (62%). Anal. (C₁₁H₁₂O₃) C, H.

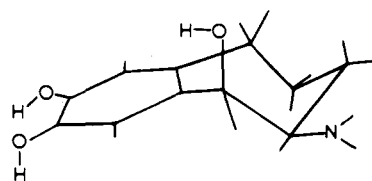
(b) The dimethoxy ketone 1a (5.0 g) and AlCl₃ (15.0 g) in dry C₆H₆ (100 ml) were refluxed for 4 hr, and the complex was decompd by ice-HCl mixt. The soln, on work-up, gave 1d, yield 3.0 g (70%).



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



(-)-Ephedrine



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

Figure 2.

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-5H-benzocyclohepten-5-one (1c). PhCH₂Cl (2.53 g, 0.02 mole) was added to a soln of 1d (1.9 g, 0.01 mole) and dry K₂CO₃ (15.0 g) in dry Me₂CO (50 ml) and the mixt was refluxed for 12 hr, cooled, filtered, and concd. The residue was taken up in Et₂O, washed (10% NaHCO₃ and H₂O), dried (Na₂SO₄), and concd, and the residue crystd from PhH-petr ether, colorless leaflets, mp 110–113°, yield 2.9 g (80%). *Anal.* (C₂₅H₂₄O₂) C, H.

δ-(*m*-Methoxyphenyl)valeric Acid. 5-(*m*-Methoxyphenyl)penta-2,4-dienoic acid⁴ (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 H₂SO₄, and extd into C₆H₆–EtOAc. The ext was washed (H₂O), dried (Na₂SO₄), 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-5H-benzocyclohepten-5-one (1g) was prepd by demethylation of 1j using AlCl₃ in place of AlBr₃ as described by Khan, *et al.*,⁴ mp 164°, yield 80%.

2-Benzyloxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (1e). A mixt of 1g (3.52 g, 0.02 mole), PhCH₂Cl (3.79 g, 0.03 mole), and dry K₂CO₃ (5.0 g) in dry Me₂CO (60 ml) was refluxed for 72 hr, and worked up to give the product as a viscous syrup, yield 4.0 g (80%). *Anal.* (C₁₈H₁₆O₂) C, H.

3-Benzyloxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (1f) was obtained from 1h⁶ by treatment with PhCH₂Cl as described above, viscous syrup, yield 1.8 g (72%). *Anal.* (C₁₈H₁₆O₂) C, H.

2,3-Diacetoxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (1i). Compd 1d (1.92 g, 0.01 mole) and Ac₂O (5 ml) were heated on a steam bath for 2 hr, excess reagent was removed under reduced pressure, and the residue was crystd from C₆H₆–petr ether, mp 132–133°, yield 2.4 g (89%). *Anal.* (C₁₅H₁₄O₅) C, H.

trans-2,3-Dimethoxy-6-amino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol (7a). Compd 3a⁸ (5.43 g, 0.02 mole) was dissolved in EtOH (100 ml) and reduced by slow addn of NaBH₄ (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 C₆H₆ as colorless needles, mp 135°, yield 4.0 g (75%), *R_f* 0.692 (C₆H₆–MeOH, 1:1), nmr, H-5, 4.5 (d, *J* = 9 Hz). *Anal.* (C₁₃H₁₉NO₃) C, H, N. The hydrochloride was obtained as colorless leaflets from EtOH–Et₂O, mp 186–187°. *Anal.* (C₁₃H₁₉NO₃·HCl) C, H, N.

2,3-Dimethoxy-6-acetamido-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (5a) was obtd by hydrogenation of 2a (2.49 g, 0.01 mole) in AcOH (60 ml) and Ac₂O (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 C₆H₆–petr ether as colorless needles, mp 145–147° (lit.⁵ mp 153), yield 2.2 g (80%). *Anal.* (C₁₅H₁₉NO₄) C, H, N.

trans-2,3-Dimethoxy-6-acetamido-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol (6a). Compd 5a (5.54 g, 0.02 mole) in MeOH (100 ml) was reduced with NaBH₄ (3.8 g, 0.1 mole) under ice cooling, and the product obtd on work-up was crystd from C₆H₆–petr ether as colorless needles, mp 163–165°, yield 3.9 g (70%). *Anal.* (C₁₅H₂₁NO₄) C, H, N.

cis-2,3-Dimethoxy-6-amino-6,7,8,9-tetrahydro-5H-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–Et₂O the pure cis isomer was obtained as colorless leaflets, mp 230°, yield 0.6 g (45%). *Anal.* (C₁₃H₁₉NO₃·HCl) C, H, N.

6-Oximino-2,3-dimethyl-6,7,8,9-tetrahydro-5H-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 Et₂O (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 (H₂O), the aq phase was sep'd and made acidic, and the product was obt'd as pale yellow needles, filtered, and crystd from C₆H₆, mp 192°, yield 1.5 g (70%). *Anal.* (C₁₃H₁₅NO₂) C, H, N.

2,3-Dimethyl-6-amino-6,7,8,9-tetrahydro-5H-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 H₂ ceased, and the soln was worked up in the usual way; the hydrochloride crystd from EtOH–Et₂O, mp 205–207°, yield 2.0 g (85%). *Anal.* (C₁₃H₁₇NO·HCl) C, H, N.

trans-2,3-Dimethyl-6-amino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol (7b) was obt'd by reduction of 3b with NaBH₄ as described for 7a, colorless cryst product from C₆H₆, mp 178–180°, yield 75%, *R_f* 0.266 (C₆H₆–MeOH, 1:1), nmr, H-5, 4.5 (d, *J* = 10 Hz). *Anal.* (C₁₃H₁₉NO) C, H, N.

2,3-Dimethyl-6-acetamido-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (5b). Compd 2b on hydrogenation in AcOH–Ac₂O soln using 10% Pd/C catalyst at room temp and atm pressure gave 5b as viscous syrup, yield 82%. *Anal.* (C₁₅H₁₉NO₂) C, H, N.

trans-2,3-Dimethyl-6-acetamido-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol (6b) was prep'd from 5b by reduction with NaBH₄ or by heating 7b (1.0 g) with Ac₂O (2 ml) in MeOH (20 ml) on a steam bath for 4 hr, the product crystd from C₆H₆–petr ether, mp 165–166°, yield 60%; nmr (CF₃COOH), H-5, 6.5 (d, *J* = 10 Hz). *Anal.* (C₁₅H₂₁NO₂) C, H, N. Base hydrolysis of 6b regenerated 7b.

Acid Hydrolysis of trans-2,3-Dimethyl-6-acetamido-6,7,8,9-tetrahydro-5H-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 sep'd was filtered, mp 140–162°. Tlc (C₆H₆–MeOH, 1:1) showed it to be a mixt of 2 products, which were sep'd by fractional crystn from C₆H₆–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.* (C₁₃H₁₉NO) 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-5H-benzocyclohepten-5-one Hydrochloride (3b). Compd 3b (0.6 g) was added to a suspension of LAH (1.0 g) in Et₂O (50 ml) and the mixt was stirred for 24 hr at room temp, decomp'd, extd (CHCl₃), dried (Na₂SO₄), 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-5H-benzocycloheptene (8b). A soln of 7b (2.05 g, 0.01 mole) in Ac₂O (10 ml) was heated on a steam bath for 1 hr. It was conc'd and the residue crystd from C₆H₆–petr ether, mp 175–177°, yield 2.5 g (84%), *R_f* 0.8 (C₆H₆–MeOH, 30:1). *Anal.* (C₁₅H₂₃NO₃) 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-5H-benzocyclohepten-5-ol. Compd 4b (2.08 g, 0.01 mole), on heating with Ac₂O (5 ml) and MeOH (40 ml) for 4 hr, gave the required product, crystd from C₆H₆–petr ether, mp 176–178°, yield 2.2 g (87%). *Anal.* (C₁₅H₂₁NO₂) C, H, N.

2,3-Dibenzyloxy-6-oximino-6,7,8,9-tetrahydro-5H-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 Et₂O (25 ml), as described above, gave 2c as pale yellow leaflets from C₆H₆–petr ether, mp 150°, yield 3.2 g (80%). *Anal.* (C₂₅H₂₃NO₄) C, H, N.

(b) *n*-BuONO (2.06 g, 0.02 mole) in dry Et₂O (25 ml) was added dropwise to a suspension of 1c (3.72 g, 0.01 mole) in dry Et₂O (40 ml), while a stream of HCl gas was passed through the soln. After 1 hr, the soln was conc'd and the product crystd from EtOH, mp 148°, yield 3.5 g (87%).

2,3-Dibenzyloxy-6-oximino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol was obt'd from 2c by reduction with NaBH₄ as described above. After completion of the reduction, the soln was acidified and the product crystd from C₆H₆–petr ether as pale yellow crystals, mp 140°, yield 85%. *Anal.* (C₂₅H₂₅NO₄) C, H, N.

cis-2,3-Dibenzyloxy-6-amino-6,7,8,9-tetrahydro-5H-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 obt'd 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 C₆H₆–hexane gave pure cis isomer, mp 135°, yield 1.60 g (84%), nmr, H-5, 4.8 (d, *J* = 1 Hz). *Anal.* (C₂₅H₂₇NO₃) C, H, N. Similarly 2b on reduction with LAH gave *cis*-4b.

cis-2,3-Dihydroxy-6-amino-6,7,8,9-tetrahydro-5H-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–CHCl₃–Et₂O, 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 hygroscopic. *Anal.* (C₁₁H₁₅NO₂) C, H, N.

2-Methoxy-6-amino-6,7,8,9-tetrahydro-5H-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–Et₂O, mp 192–196°, yield 70%. *Anal.* (C₁₂H₁₇NO·HCl) C, H, N.

3-Methoxy-6-oximino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (2k) was prep'd as described for 2b; crystd from aq EtOH, mp 153–155°, yield 40%. *Anal.* (C₁₂H₁₃NO₃) C, H, N.

cis-**3-Methoxy-6-amino-6,7,8,9-tetrahydro-5H-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–Et₂O, mp 245° dec, yield 48%; nmr, H-5, 5.04 (d, *J* = 1.5 Hz). *Anal.* (C₁₂H₁₇NO₂ · HCl) C, H, N.

3-Benzoyloxy-6-oximino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (2f) was prep'd as described for 2b, crystd from EtOH, mp 156–161°, yield 87%. *Anal.* (C₁₈H₁₇NO₃) C, H, N.

cis-**3-Benzoyloxy-6-amino-6,7,8,9-tetrahydro-5H-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.* (C₁₈H₂₁NO₂) C, H, N.

cis-**3-Hydroxy-6-amino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol (4h)**. Compd 4f, on catalytic reduction as described for 4d, gave 4h as colorless product, crystd from MeOH–Et₂O, mp 172–174°; nmr, H-5, 5.2 (d, *J* = 1 Hz). *Anal.* (C₁₁H₁₅NO₂ · H₂O) N.

2-Benzoyloxy-6-oximino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (2e) was obt'd in 62% yield, when 1e was treated with KOEt and *n*-BuONO in dry Et₂O as described for 2b, crystd from EtOH, mp 188°. *Anal.* (C₁₈H₁₇NO₃) C, H, N.

cis-**2-Benzoyloxy-6-amino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol (4e)**. Compd 2e was reduced with LAH by following the procedure described for 4c, crystd from C₆H₆–petr ether, mp 129°, yield 70%, nmr, H-5, 4.9 (d, *J* = 1 Hz). *Anal.* (C₁₈H₂₁NO₂) C, H, N.

cis-**2-Hydroxy-6-amino-6,7,8,9-tetrahydro-5H-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.* (C₁₁H₁₅NO₂ · H₂O) C, H, N.

7-Oximino-6-oxo-1,2,3,4,7,8,9,10-octahydro-6H-cyclohepta[b]-naphthalene (2i) was obt'd on treatment of 1i⁷ with *n*-BuONO and KOEt in Et₂O at 0° as pale yellow cryst substance, crystd from C₆H₆–petr ether, mp 202° dec, yield 65%. *Anal.* (C₁₅H₁₇NO₂) C, H, N.

7-Amino-6-oxo-1,2,3,4,7,8,9,10-octahydro-6H-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–Et₂O, mp 210° dec, yield 88%. *Anal.* (C₁₅H₁₉NO · HCl · 0.5H₂O) C, H, N.

cis- and *trans*-**7-Amino-6-hydroxy-1,2,3,4,7,8,9,10-tetrahydro-6H-cyclohepta[b]naphthalene (4i and 7i)**. NaBH₄ (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, conc'd, dild (H₂O), and ext'd (EtOAc). The EtOAc layer was washed (H₂O), dried (Na₂SO₄), and conc'd, and the residue was crystd from CHCl₃–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.* (C₁₅H₂₁NO) 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 obt'd 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-7H-cyclohepta[b]naphthalene.

trans-**7-Acetamido-5-acetoxy-1,2,3,4,7,8,9,10-octahydro-6H-cyclohepta[b]naphthalene (8i)**. A mixt of 4i and 7i (140 mg) in Ac₂O (16 ml) was heated on a steam bath for 2.5 hr and conc'd, and the residue passed through a silica gel column. The product on tlc (C₆H₆–EtOH, 9:1) was found to be a mixt of 2 products, which were sepd by column chromatog using 80 mesh silica gel and CHCl₃–EtOH (99:1) as the eluent. The product obt'd from the earlier fractions (92 mg), mp 190°, was the *trans* isomer, nmr, H-5, 5.75 (d, *J* = 9 Hz). *Anal.* (C₁₉H₂₅NO₃) C, H, N.

7-Acetamido-6-oxo-1,2,3,4,7,8,9,10-octahydro-6H-cyclohepta[b]naphthalene (5i). A mixt of 3i (600 mg), NaOAc (572 mg), Ac₂O (700 mg), and H₂O (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.* (C₁₇H₂₁NO₂) C, H, N.

cis- and *trans*-**7-Acetamido-6-hydroxy-1,2,3,4,7,8,9,10-octahydro-6H-cyclohepta[b]naphthalene**. Compd 5i on reduction with NaBH₄ in MeOH gave a mixt of *cis* and *trans* isomers, crystd from C₆H₆–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.* (C₁₇H₂₃NO₂) C, H, N.

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