Synthesis and Stereochemical Analysis of 2-Amino-1,2,3,4-tetrahydro-1,4-methanonaphthalene-2-carboxylic Acid, A Conformationally Rigid Phenylalanine Derivative

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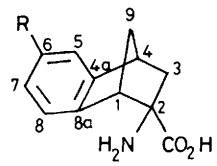
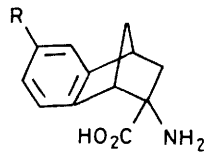
A rigid phenylalanine analogue, 2-amino-1,2,3,4-tetrahydro-1,4-methanonaphthalene-2-carboxylic acid (**3**) of unknown stereochemistry was obtained as the sole amino acid product from a Strecker reaction with 1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-one (**4**). Compound (**4**) was initially treated with benzylamine and potassium cyanide to give 2-benzylamino-2-cyano-1,2,3,4-tetrahydro-1,4-methanonaphthalene (**5**), which was then converted into 2-benzylamino-2-carboxamido-1,2,3,4-tetrahydro-1,4-methanonaphthalene (**6**) by treatment with 70% sulphuric acid. *N*-Debenzylation of (**6**) by hydrogenolysis with 5% palladium-on-charcoal catalyst afforded 2-amino-2-carboxamido-1,2,3,4-tetrahydro-1,4-methanonaphthalene (**7**) which gave the acid (**3**) on heating in 10% sulphuric acid. A stereochemical analysis of (**3**) by ^{1}H n.m.r., ^{13}C n.m.r., and auto-correlated two-dimensional n.m.r. spectroscopy, determined the structure to be 2-*endo*-amino-1,2,3,4-tetrahydro-1,4-methanonaphthalene-2-*exo*-carboxylic acid (**1a**). Treatment of 1,2,3,4-tetrahydro-1,4-methanonaphthalene-2-spiro-5′-hydantoin (**9**) [obtained from a Bucherer reaction with (**4**)] with aqueous barium hydroxide also afforded (**1a**) as the only amino acid product.

Structure–activity studies recently carried out in this laboratory have focused on the biological properties of rigid phenylethylamine systems in order to examine the importance of molecular conformation on the biological activity. We have shown that 2-amino substituted 1,2,3,4-tetrahydro-1,4-methanonaphthalenes represent rigid, pharmacologically interesting analogues of more conformationally flexible phenylethylamine compounds such as amphetamine,[1] dopamine,[2] and noradrenaline,[3] which may provide useful information about the nature of agonist–receptor interactions in these phenylethylamine systems. Recently, our interest has been directed towards the synthesis of enkephalin derivatives containing a conformationally restrained *N*-terminal tyrosine residue, and we have shown[4] that replacing the 1-tyrosyl moiety in Leu-enkephalin methyl ester with a (2-amino-6-hydroxy-1,2,3,4-tetrahydronaphthalenyl)-2-carbonyl grouping, leads to a 7 to 8 times higher agonist activity at the analgesic μ-receptor subtype in guinea pig ileum, when compared to Leu-enkephalin, and an almost 30-fold decrease in potency, *versus* Leu-enkephalin, on mouse vas deferens preparation, a tissue in which the δ-receptor predominates. The completely rigid aromatic amino acids (**1a**) and (**2a**), and (**1b**) and (**2b**), thus represent conformationally defined analogues of phenylalanine and tyrosine, respectively, which should be of potential value in determining the effect of completely restricting the conformational flexibility of the tyrosyl moiety in the enkephalins on receptor recognition.

This present report describes the synthesis and stereochemical analysis of 2-amino-1,2,3,4-tetrahydro-1,4-methanonaphthalene-2-carboxylic acid (**3**); this was obtained from a Strecker synthesis, starting from the previously reported ketone (**4**), and afforded only one of the two expected stereoisomers of (**3**) from this reaction sequence.



(**1**)
a; R = H
b; R = OH

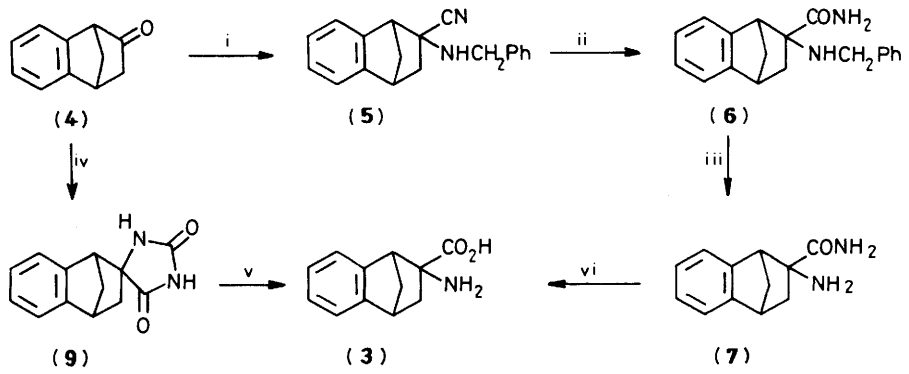


(**2**)
a; R = H
b; R = OH

Results and Discussion

Treatment of 1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-one (**4**) with benzylamine and KCN in aqueous ethanolic HCl gave a pure stereoisomer (**5**) in 86% yield. No other isomeric product could be detected in the reaction mixture. This product could be hydrolysed to the carboxamido derivative (**6**) in 70% H_2SO_4 solution. Hydrogenolytic *N*-debenzylation of compound (**6**) was carried out in ethanolic glacial acetic acid, using palladium–charcoal (5%) as catalyst, and afforded the product (**7**) in 45% yield. Hydrolysis of compound (**7**) in 10% H_2SO_4 solution, heated at reflux for 5 h, afforded 2-amino-1,2,3,4-tetrahydro-1,4-methanonaphthalene-2-carboxylic acid (**3**) in 79% yield (Scheme).

In a rigid molecule such as (**3**) the Karplus relationship[5] can be applied to interpret the n.m.r. spectra and elucidate the stereochemistry at C-2. It is clear from Dreiding models of the two possible isomers of the acid (**3**) that the largest $^3J_{CH}$ vicinal coupling of the carbonyl carbon should be to the 3-H which is *cis* to it. If the carboxy group has the *exo* geometry as in compound (**1a**) this coupling would be to the *exo* 3-H, while if it is *endo* as in (**2a**), then coupling would be to the *endo* 3-H; 1-H is not at a favourable angle for coupling to the carbonyl carbon in either configuration of the carboxy group. Selective decoupling of the doublet of doublets centred at 3.04 p.p.m. in the ^{1}H n.m.r. spectrum of compound (**3**) causes the carbonyl doublet in the proton coupled ^{13}C n.m.r. spectrum to collapse to a singlet (see Figure 1). Hence, the problem of assigning the configuration of the carboxy and amino groups in the acid (**3**) is narrowed down to being able to unequivocally assign the *exo* and *endo* 3-H.



Scheme. *Reagents:* $PhCH_2NH_2$, KCN; ii, H_2SO_4; iii, Pd-C 5%, EtOH; iv, NH_4CO_3, KCN; v, $Ba(OH)_2$; vi, 10% H_2SO_4

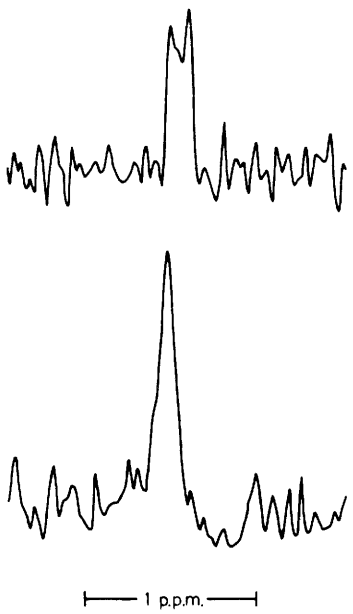


Figure 1. ^{13}C N.m.r. spectrum of compound (**3**) in $(CD_3)_2SO$–DCl with the scale expanded in the region of 173 p.p.m., (*a*) showing the $^3J(CH)$ vicinal coupling of the carbonyl carbon, and (*b*) showing collapse of the $^3J(CH)$ coupling after selective decoupling of the doublet of doublets centred at 3.04 p.p.m. in the ^1H n.m.r. spectrum of (**3**)

The aliphatic region of the ^1H n.m.r. spectrum of (**3**) in deuteriotrifluoroacetic acid ([$^2H_2$]-TFA) shows resonances in six regions, each of these signals integrating for one proton. These regions consist of a doublet of doublets (*J* 2.78, 13.9 Hz) with a central chemical shift of 3.04 p.p.m., a broad doublet centred at 2.67 p.p.m. (*J* 10.31 Hz), a doublet with unresolved fine structure centred at 2.18 p.p.m. (*J* 10.31 Hz), and a doublet of doublets centred at 1.79 p.p.m. (*J* 3.96 Hz, 13.9 Hz), and two broad singlets at 3.95 and 3.70 p.p.m. The methylenes at C-3 and C-9 should each have large geminal coupling and give rise to AB patterns. Only vicinal couplings are possible at the bridgeheads, and of these the coupling from 4-H to the *exo* 3-H should be the largest because of the small dihedral angle between these hydrogens.

An auto-correlated two-dimensional (2-D) n.m.r. experiment[6] was run and a contour plot of the results is shown in Figure 2. Two AB patterns are readily identifiable from the off-diagonal peaks. One consists of the resonances at 3.04 and 1.79 p.p.m.; the other shows the resonances at 2.67 and 2.18 p.p.m. There is a coupling of 3.79 Hz from the bridgehead signal at 3.70 p.p.m. to the doublet at 3.04 p.p.m. This is the largest coupling of the bridgehead hydrogens and the doublet at 3.04 p.p.m. is therefore assigned to the *exo* 3-H. The resonance at 1.79 p.p.m. is assigned to the *endo* 3-H leaving the remaining pair of resonances attributable to the 9-H's. These can be distinguished by further analysis of the 2-D experiment which shows a coupling between the *endo* 3-H at 1.79 p.p.m. and the resonance at 2.18 p.p.m. of 3.96 Hz. This would be the expected long range W-coupling from the *endo* 3-H to the *syn* 9-H, leaving the remaining resonance at 2.67 p.p.m. to be assigned to the *anti* 9-H. Because the *syn* 9-H is juxtaposed over the aromatic ring, whereas the *anti* 9-H is not, the ring anisotropy would tend to push the chemical shift of the *syn* 9-H more upfield than the *anti* 9-H.

Since the carbonyl carbon resonance collapses to a singlet on irradiation of the 3.04 p.p.m. resonance in the ^1H n.m.r. spectrum, and is unaffected upon irradiation of the 1.79 p.p.m. resonance, the carboxy group must be in the *exo*-configuration, and the stereochemistry of compound (**3**) is as indicated in structure (**1a**). The large downfield shift of the *exo* 3-H is probably due to a preference for the conformation in which it lies in the plane of the carbonyl group. The shift assignments and couplings described above and additional confirmation from 2-D *J* spectra[6] are summarized in the Table.

The assignment of *exo*-stereochemistry to the 2-carboxy group in (**3**) indicates that in the initial reaction of (**4**) with benzylamine, attack of cyanide ion on the resulting imino intermediate (**8**) occurs at the *exo*-face of the molecule to give the kinetically more favourable 2-*endo*-benzylamino-2-*exo*-cyano stereoisomer of (**5**). From similar reactions with other cyclic ketones,[7–10] including norbornanone[9] and the related ketone, 1,4-dihydro-1,4-ethanonaphthalen-2(3*H*)-one[11] (**10**), mixtures of both *exo*- and *endo*-amino acids are obtained. The present results obtained with compound (**4**) are interesting in that, to our knowledge, they represent the first example of stereochemical specificity in a Strecker reaction involving a cyclic ketone.

We have also observed that the acid (**1a**) is the only isomeric product obtained from the Bucherer reaction of compound (**4**) with ammonium carbonate and KCN followed by barium hydroxide hydrolysis of the intermediate spirohydantoin (**9**). Again, these results are somewhat surprising in view of a report on the formation of nearly equal mixtures of isomeric hydantoins from the reaction of (**10**)[11] with ammonium carbonate and KCN under similar conditions. So far, we have been unable to detect the presence of the isomeric amino acid (**2a**) in the reaction products from either of the above synthetic routes.

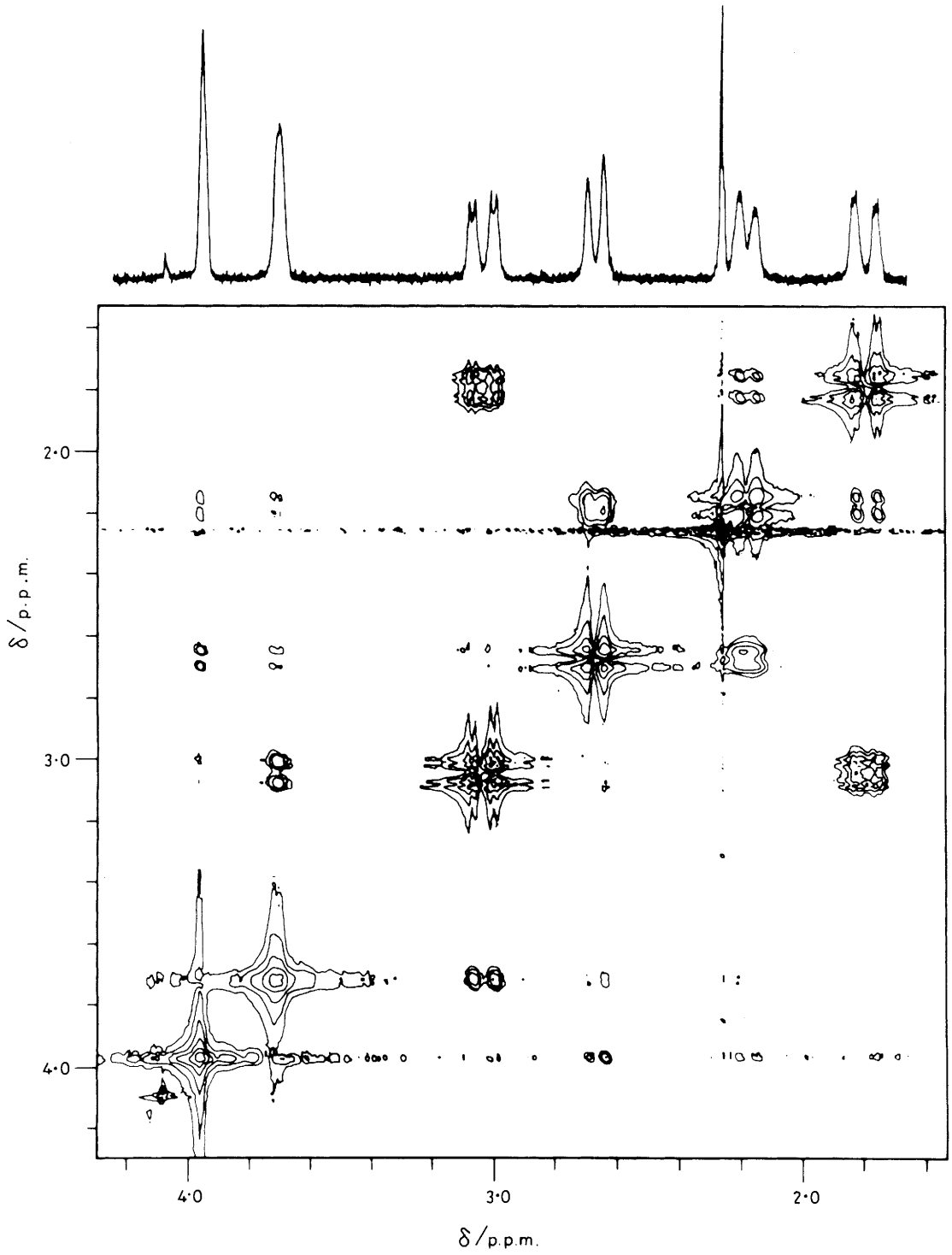
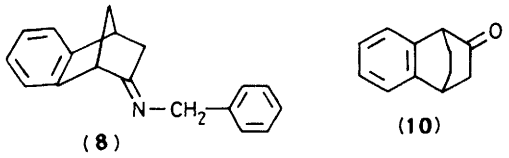


Figure 2. 200 MHz Auto-correlated two-dimensional ^{1}H n.m.r. spectrum of compound (**3**) in TFA



(**8**)

(**10**)

Experimental

M.p.s were measured on a Reichert hot-stage microscope. Recrystallization solvents are shown in parentheses. Yields of solids refer to products obtained prior to recrystallization. I.r. spectra were recorded on a Perkin-Elmer model 237 grating spectrophotometer.

^{1}H N.m.r. spectra were recorded on Perkin-Elmer R24 (60 MHz) or Varian XL-200 (200 MHz) spectrometers; ^{13}C n.m.r. spectra (50.3 MHz) and two dimensional n.m.r. spectra were recorded on a Varian XL-200 spectrometer. As expected, the n.m.r. parameters are solvent and pH dependent. Microanalyses were conducted by Mr. M. Hart, Department of Chemistry, Manchester.

Table. N.m.r. parameters for the acid (**3**)

δ_H ([$^2H_1$]-TFA)		J_{1H}/Hz ([$^2H_1$]-TFA)		δ_C/p.p.m. [$(CD_3)_2SO$–DCl]	
1-H	3.15	$^2J_{2\text{-}exo,3\text{-}endo}$	13.9(3)	C-1	52.4
3-*exo*-H	3.04	$^2J_{9\text{-}anti,9\text{-}syn}$	10.30	C-2	63.8
3-*endo*-H	1.79	$^3J_{3\text{-}exo,4}$	3.78	C-3	49.4
4-H	3.15	$^4J_{3\text{-}endo,9\text{-}syn}$	3.96	C-4	43.5
9-*anti*-H	2.67	$^3J_{3\text{-}endo,4}$	(0.48)	C-4a	141.0
9-*syn*-H	2.18	$^3J_{1,9\text{-}syn}$	1.26	C-5[a]	127.0
		$^3J_{1,9\text{-}anti}$	1.76	C-6[b]	122.3
		$^3J_{4,9\text{-}anti}$	1.76	C-7[b]	124.8
				C-8[a]	128.5
				C-8a	148.5
				C-9	67.0
				C=O	172.9

[a,b] Signals may be interchanged.

2-*Benzylamino*-2-*cyano*-1,2,3,4-*tetrahydro*-1,4-*methanonaphthalene* (**5**).—1,2,3,4-Tetrahydro-1,4-methanonaphthalen-2-one (**4**)[12] (1 g, 6.0 mmol) in ethanol (20 ml) was added to a solution of benzylamine (0.75 g, 7.0 mmol) in water (20 ml), made just acid with dilute HCl. The solution was cooled to 0 °C in an ice–sodium chloride bath, and KCN (0.49 g, 8.0 mmol) in water (20 ml) was added dropwise, during 5 min, with vigorous stirring. The cooling bath was removed and the solution stirred at room temperature for 24 h, during which time the oily precipitate, formed after addition of the KCN, had crystallized. The crystals were collected by filtration affording 2-*benzylamino*-2-*cyano*-1,2,3,4-*tetrahydro*-1,4-*methanonaphthalene* (**5**) (1.49 g, 86%), m.p. 93—100 °C, $\nu_{max.}$ (KCl) 2 210 cm^{-1} (C≡N); $\delta(CDCl_3)$ 1.12 (1 H, s, exchangeable with D_2O, NH), 1.21 (1 H, d of d, *J* 3 and 12 Hz, *exo* 3-H), 2.09 (2 H, m, 9-H), 2.63 (1 H, d of d, *J* 4 and 12 Hz, *endo* 3-H), 3.36 (1 H, m, 1-H), 3.77 (1 H, m, 4-H), 3.83 (2 H, s, benzyl CH_2), and 6.96—7.50 (9 H, m, aromatic H) (Found: C, 83.2; H, 6.5; N, 10.2. $C_{19}H_{18}N_2$ requires C, 83.2; H, 6.6; N, 10.2%).

2-*Benzylamino*-2-*carboxamido*-1,2,3,4-*tetrahydro*-1,4-*methanonaphthalene* (**6**).—Compound (**5**) (1.3 g) was stirred with 70% H_2SO_4 (20 ml) at room temperature for 1 h and the mixture poured onto crushed ice (100 g). When all the ice had melted the resulting mixture was filtered and the filtrate adjusted to pH 3 with 5M-NaOH solution. A white precipitate was formed, which was collected by filtration at the pump and crystallized from diethyl ether to afford 2-*benzylamino*-2-*carboxamido*-1,2,3,4-*tetrahydro*-1,4-*methanonaphthalene* (**6**) (950 mg, 69%), m.p. 145—148 °C, $\nu_{max.}$(KCl) 1 655 and 5 858 cm^{-1}, $\delta(CDCl_3)$ 1.20 (1 H, d of d, *endo* 3-H), 2.22 (2 H, m, 9-H), 2.70 (1 H, d of d, *exo* 3-H), 3.31 (1 H, m, 1-H), 3.57 (2 H, d of d, benzyl CH_2), 3.69 (1 H, m, 4-H), 6.08 (3 H, br s, NH), 6.84—7.55 (4 H, m, ArH), and 7.14 (5 H, s, aromatic H of benzyl group) (Found: C, 77.6; H, 6.9; N, 9.2. $C_{19}H_{20}N_2O\cdot 1/8H_2O$ requires C, 77.5; H, 6.9; N, 9.5%). (This trace of water was not removable on prolonged drying.)

2-*Amino*-2-*carboxamido*-1,2,3,4-*tetrahydro*-1,4-*methanonaphthalene* (**7**).—Compound (**6**) (8.9 g) was dissolved in absolute ethanol (100 ml), and palladium–charcoal catalyst (5%, 2 g) was added. Glacial acetic acid (20 ml) was added to the reaction mixture, and the mixture was hydrogenated with stirring at room temperature and atmospheric pressure overnight, until no further uptake of hydrogen was observed. The catalyst was removed by filtration and washed with hot 96% ethanol. The combined filtrate and washings were evaporated to dryness and the residue partitioned between 5M-HCl (200 ml) and ethyl acetate (100 ml). The acidic aqueous layer was separated, basified with 4M-NaOH solution to pH 9 and extracted with ethyl acetate (2 × 100 ml). There remained some insoluble material in the aqueous layer which was collected by filtration. The combined ethyl acetate extracts were dried, filtered, evaporated to dryness, and the residue crystallized from diethyl ether. Both the insoluble material and the crystallized material from the extract were identified as 2-*amino*-2-*carboxamido*-1,2,3,4-*tetrahydro*-1,4-*methanonaphthalene* (**7**) (2.79 g, 45%), m.p. 174—177 °C, $\nu_{max.}$(KCl) 3 350 (NH_2), 1 665, 1 653, 1 575, 1 560, and 1 540 cm^{-1}; $\delta(CDCl_3)$ 0.93 (1 H, d of d, *endo* 3-H), 2.20 (2 H, m, 9-H), 2.96 (1 H, d of d, *exo* 3-H), 3.37 (1 H, m, 1-H), 4.63 (1 H, m, 4-H), 5.75 (4 H, br s, NH), and 6.55—7.90 (4 H, m, aromatic H) (Found: C, 67.8; H, 6.8; N, 12.9. $C_{12}H_{14}N_2O$ requires C, 68.2; H, 7.1; N, 13.2%).

1,2,3,4-*Tetrahydro*-1,4-*methanonaphthalene*-2-*spiro*-5′-*hydantoin* (**9**).—A solution of ammonium carbonate (28.6 g, 0.18 mol) in 50% aqueous ethanol (200 ml) was added to a solution of (**4**) (11.1 g, 0.07 mol) in 50% aqueous ethanol (40 ml), in a two-necked flask fitted with a reflux condenser and a dropping funnel. The flask was warmed to 50 °C in an oil-bath and a solution of KCN (4.6 g, 0.072 mol) in water (40 ml) was added in small portions during 1 h. The reaction mixture was stirred magnetically and the temperature held at 58—60 °C for 5 h. The ethanol was then removed by evaporation and the aqueous mixture was allowed to cool and extracted with ethyl acetate (3 × 200 ml). The combined organic extracts were dried, filtered, and evaporated to dryness and the residue was triturated with diethyl ether to afford white crystals of 1,2,3,4-*tetrahydro*-1,4-*methanonaphthalene*-2-*spiro*-5′-*hydantoin* (**9**), m.p. 225—229 °C (methanol–diethyl ether); $\nu_{max.}$(KCl) 1 785, 1 775, and 1 725 cm^{-1}; $\delta[(CD_3)_2SO]$ 1.28 (1 H, d of d, *J* 5 and 14 Hz, *endo* 3-H), 1.63 (1 H, m, *syn* 9-H), 2.22—2.80 (2 H, m, *anti* 9-H and *exo* 3-H), 3.38—3.57 (2 H, m, 1-H and 4-H), 6.77 (1 H, br s, exchangeable with D_2O, 1′-NH), 7.18 (4 H, m, aromatic H), and 10.60 (1 H, br s, exchangeable with D_2O, 3′-NH) (Found: C, 68.3; H, 5.4; N, 11.8. $C_{13}H_{12}N_2O_2$ requires C, 68.4; H, 5.2; N, 12.3%). The aqueous layer was carefully acidified to pH 2 with concentrated H_2SO_4 to afford a further crop of the above product (total yield 12.07 g, 76%).

2-endo-*Amino*-1,2,3,4-*tetrahydro*-1,4-*methanonaphthalene*-2-exo-*carboxylic Acid* (**1a**).—*Method a.* A solution of (**7**) (2.5 g) in 10% H_2SO_4 (100 ml) was heated at reflux, for 5 h. The reaction mixture was then filtered while still hot and the filtrate was cooled in an ice-bath, basified to pH 6 with 4M-NaOH solution, evaporated under reduced pressure to a low volume (*ca.* 20 ml), and allowed to cool to afford white crystals of 2-endo-*amino*-1,2,3,4-*tetrahydro*-1,4-*methanonaphthalene*-2-exo-*carboxylic acid* (**1a**) (1.98 g, 79%) m.p. 227.5—229.5 °C, $\nu_{max.}$(KCl) 1 660, 1 645, 1 625, and 1 540 cm^{-1}; $\delta(D_2O$; 60 MHz) 1.48 (1 H, d of d, *J* 4 and 14 Hz, *endo* 3-H), 2.25 (2 H, m, 9-H), 2.95 (1 H, d of d, *J* 4 and 14 Hz, *exo* 3-H), 3.58 (1 H, m, 1-H), 3.76 (1 H, m, 4-H), and 7.37 (4 H, m, aromatic H). The *hydrochloride salt* was prepared from a portion of the product and had m.p. 228—231 °C (decomp.) (Found: C, 67.8; H, 6.8; N, 12.9. $C_{12}H_{13}NO_2\cdot HCl\cdot 1/2H_2O$ requires C, 68.2; H, 7.1; N, 13.2%).

Method b. Compound (**9**) (6.63 g, 0.029 mol), barium hydroxide [$Ba(OH)_2\cdot 8H_2O$] (17.6 g, 0.056 mol), and water (100 ml) were placed in a two-necked flask fitted with a nitrogen inlet and a reflux condenser, and the mixture was heated under reflux under nitrogen for 70 h. The mixture was then filtered while hot, and the collected solid washed with an equal volume of water. The combined filtrate and washings were saturated with carbon dioxide, heated to the boiling point, and refiltered. The filtrate on cooling afforded white crystals of (**9**) (140 mg, 2% returned). The mother-liquors were evaporated to *ca.* 50 ml to afford white crystals (4.69 g, 80%), which had identical spectral properties

(i.r., ^{1}H n.m.r., and ^{13}C n.m.r. spectra) with (**1a**) prepared *via* method a above.

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