Benzomorphan-related Compounds. Part 21.[1] Synthesis of 7,8-Benzomorphans *via* 2-Aryl-4-piperidones†

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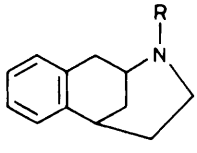
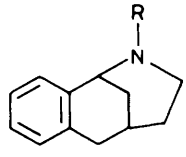
A new synthesis of 1,2,3,4,5,6-hexahydro-1,5-methano-2-benzazocines (7,8-benzomorphans) based on the acid-catalysed cyclization of 2-arylpiperidine-4-carboxylic acids is reported. The required carboxylic acids were prepared from 2-aryl-4-piperidones, by reaction with tosylmethyl isocyanide followed by hydrolysis of the resulting 4-cyanopiperidines.

The 7,8-benzomorphans are bridgehead polycyclic systems related to the well known analgesics[2] 6,7-benzomorphans,[3] in which the aromatic ring is fused to the C(7)–C(8) side of the morphan (2-azabicyclo[3.3.1]nonane)[4] system.

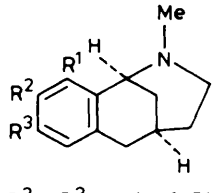
The synthesis of these compounds has been accomplished by two different approaches which differ in the bond formed in the last synthetic step: (i) closure of the piperidine ring by lactamization of 4-amino-1,2,3,4-tetrahydronaphthalene-2-acetic acid derivatives[5,6] and (ii) elaboration of the B-ring by formation of the C(1)–C(10a) bond by cyclization of 4-benzoyl-(or 4-benzyl)-2,3,4,5-tetrahydropyridinium salts.[7,8] Formation of a 7,8-benzomorphan system as a by-product in the Stevens rearrangement of 1,3,4-trimethyl-1-(3,4,5-trimethoxybenzyl)-1,2,5,6-tetrahydropyridinium chloride has also been reported[9] (see Figure).



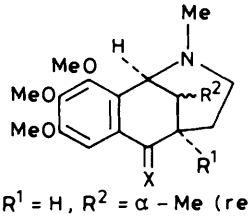
6,7 - BENZOMORPHAN



7,8 - BENZOMORPHAN



$R^1 = R^2 = R^3 = H$ (ref. 5)
$R^1 = R^3 = H, R^2 = OH$ (ref. 6)
$R^1 = R^3 = H, R^2 = OMe$ (ref. 6)
$R^1 = OMe, R^2 = R^3 = H$ (ref. 8)
$R^1 = R^2 = H, R^3 = OMe$ (ref. 8)
$R^1 = R^2 = R^3 = OMe$ (ref. 8)



X = O, $R^1 = H$, $R^2 = \alpha$-Me (ref. 7)
X = H_2, R^1 = Me, $R^2 = \beta$-Me (ref. 9)

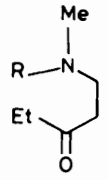
Figure. 7,8-Benzomorphans reported in the literature

In the context of our studies on the synthesis of 6,7-benzomorphan analogues[1,7-10] and continuing our interest in the use of 2-aryl-4-piperidones as synthetic intermediates,[1,11] in this paper we report a new synthetic route to 7,8-benzomorphans *via* 2-aryl-4-piperidones, which are easily accessible by Mannich reaction between an aromatic aldehyde and a β-amino ketone[12] or by cyclization of appropriate imino acetals.[13] The synthesis implies the introduction of a functionalized one-carbon unit on the piperidone carbonyl group and further closure of ring B in the last synthetic step by formation of the C(6)–C(6a) bond through acid-catalysed cyclization of 2-arylpiperidine-4-carboxylic acids.

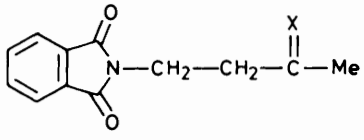
2-Aryl-4-piperidones (**9**), (**10**), and (**11**) were chosen as starting materials for our synthesis. Although preparation of ketones (**9**) and (**10**) by Mannich cyclization of the corresponding imino acetals, (**6**) and (**7**) respectively, had been previously reported,[13b] the piperidone (**9**) was also obtained by an alternative Mannich cyclization involving condensation between amino ketone (**2**) hydrochloride and 2,3,4-trimethoxybenzaldehyde in the presence of an equimolecular amount of toluene-*p*-sulphonic acid (PTSA). Under these conditions a 4:1 diastereoisomeric mixture of the piperidone (**9**) and the corresponding *cis*-isomer (**12**) was obtained. The relative configurations were easily assigned (by n.m.r. spectroscopy) from the chemical-shift value of the doublet due to the methyl group in the 3-position of the piperidine ring. This signal appears at lower field (δ 1.0) in the *cis*-isomer (**12**) (axial methyl

† A preliminary communication of part of this work was presented at the 'XIX Reunión Bienal de la Real Sociedad Española de Química,' Santander, 1982, by J. Bosch, M. Rubiralta, and M. Moral.

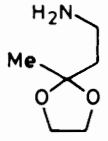
group) than in the major, *trans*-isomer (**9**) (δ 0.75;[13b] equatorial methyl group) owing to the deshielding effect of the nitrogen lone pair.[14] The required amino ketone (**2**) was prepared from 1-chloropentan-3-one[15] by reaction with *N*-methylbenzylamine and subsequent hydrogenolysis.



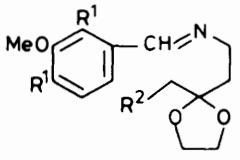
(**1**) R = $CH_2C_6H_5$
(**2**) R = H



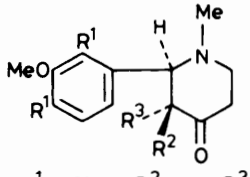
(**3**) X = O
(**4**) X = OCH_2CH_2O



(**5**)



(**6**) R^1 = OMe, R^2 = Me
(**7**) R^1 = H, R^2 = Me
(**8**) R^1 = R^2 = H



(**9**) R^1 = OMe, R^2 = H, R^3 = Me
(**10**) R^1 = R^2 = H, R^3 = Me
(**11**) R^1 = R^2 = R^3 = H
(**12**) R^1 = OMe, R^2 = Me, R^3 = H

On the other hand, 2-aryl-4-piperidone (**11**) was conveniently obtained in 63% yield in a three-step 'one-pot' synthesis from imino acetal (**8**), by methylation with methyl fluorosulphonate and further hydrolysis, according to our previously developed procedure.[13] Imino acetal (**8**) was prepared in good yield in a four-step sequence by reaction of 4-chlorobutan-2-one[16] with potassium phthalimide, followed by acetalation of the resulting phthalimido ketone (**3**), hydrazinolysis of the phthalimido acetal (**4**), and further condensation of amino acetal (**5**) with 3-methoxybenzaldehyde.

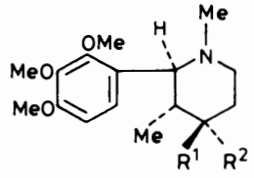
The transformation of 2-aryl-4-piperidones (**9**)—(**11**) into the corresponding 4-cyanopiperidines was effected, in one step, by reaction with tosylmethylisocyanide (TosMIC).[17] This reagent provides an efficient method for the direct conversion of ketones into their homologous nitriles through the addition of one carbon unit.[18] Thus, reaction of the piperidone (**9**) with TosMIC in 1,2-dimethoxyethane (DME), using potassium t-butoxide as the base in t-butyl alcohol, afforded a good yield a 2:1 epimeric mixture of 4-cyanopiperidines (**13**) and (**14**), which were separated by column chromatography. The i.r. spectra of nitriles (**13**) and (**14**) exhibited a characteristic absorption at 2 240 cm^{-1}, whereas the most significant signals in the n.m.r. spectra were those corresponding to the axial C-2 methine protons since they allowed us to assign the stereochemistry. This signal appeared at lower field (δ 3.35) in the C(2)—C(4) *trans*-isomer (**14**) than in the *cis*-isomer (**13**) owing to the anisotropic deshielding effect exerted by the axial cyano group upon the axial C-2 proton.[19]

Similarly, reaction of piperidones (**10**) and (**11**) with TosMIC led to epimeric mixtures of the corresponding 4-cyanopiperidines, from which the major, C(2)–C(4) *cis*-isomers, (**15**) and (**17**) respectively, were isolated in pure form and characterized. In the last case, the carboxamide (**19**) resulting from partial hydrolysis of the cyano group of (**17**) was isolated as a by-product. The relative configurations were assigned, as above, by n.m.r. spectroscopy, from the chemical shifts of the axial C-2 protons.

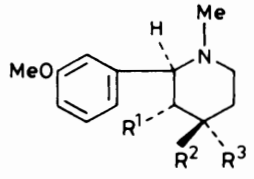
Although *a priori* only the diastereoisomers in which the piperidine C-2 and C-4 substituents are *cis* can undergo cyclization to a 7,8-benzomorphan system, epimerization at the C-4 piperidine position occur during the subsequent hydrolytic step,[10c] so the separation of isomers is unnecessary from a synthetic standpoint.

The Hoeben–Hoesch cyclization of 4-cyanopiperidines (**13**) and (**15**) under a variety of conditions [zinc chloride, boron trifluoride–ether, or polyphosphoric acid (PPA)] failed; therefore we turned our attention to the Friedel–Crafts cyclization of the corresponding carboxylic acids.

The direct alkaline hydrolysis of the epimeric mixtures of 4-cyanopiperidines (**13**) and (**14**), or (**15**) and (**16**), into the amino acids required for cyclization presented some difficulties, and the intermediate carboxamides, (**20**) and (**21**) respectively, were obtained after refluxing for 48 hours in 20% aqueous potassium hydroxide. Their stereochemistries were assigned on the basis of their n.m.r. data. The chemical shift (δ < 0.7) of the doublet due to the methyl group at the piperidine 3-position indicated that this group was positioned equatorially.[14] This



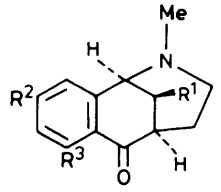
(**13**) R^1 = CN, R^2 = H
(**14**) R^1 = H, R^2 = CN
(**20**) R^1 = $CONH_2$, R^2 = H
(**22**) R^1 = CO_2H, R^2 = H
(**25**) R^1 = CO_2Et, R^2 = H



(**15**) R^1 = Me, R^2 = CN, R^3 = H
(**16**) R^1 = Me, R^2 = H, R^3 = CN
(**17**) R^1 = H, R^2 = CN, R^3 = H
(**18**) R^1 = H, R^2 = H, R^3 = CN
(**19**) R^1 = H, R^2 = $CONH_2$, R^3 = H
(**21**) R^1 = Me, R^2 = $CONH_2$, R^3 = H
(**23**) R^1 = Me, R^2 = CO_2H, R^3 = H
(**24**) R^1 = H, R^2 = CO_2H, R^3 = H
(**26**) R^1 = Me, R^2 = CO_2Et, R^3 = H

fact was confirmed from the observed coupling constant of the doublet corresponding to the axial C-2 methine proton in compound (**21**), J 10 Hz, a value indicative of a *trans*-diaxial coupling. However, amino acid (**23**) was obtained after prolonged reflux (two weeks) of the mixture of nitriles (**15**) and (**16**) in aqueous potassium hydroxide, whereas amino acid (**22**) was more conveniently obtained by treatment of amide (**20**) with 'isoamyl' nitrite* and acid. These acids, (**22**) and (**23**), were characterized as the corresponding ethyl esters, (**25**) and (**26**) respectively. In contrast, 4-cyanopiperidines (**17**) and (**18**) were easily converted into the amino acid (**24**) by hydrolysis with aqueous barium hydroxide. This result probably means that the cyano group is less hindered due to the absence of the methyl substituent at the piperidine 3-position.

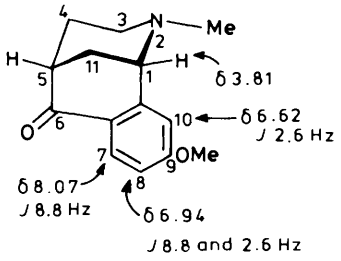
The last step of the synthesis was the cyclization of the 2-arylpiperidine-4-carboxylic acids (**22**)—(**24**). The Friedel–Crafts cyclization of carboxylic acids upon benzene rings has been successfully used in the synthesis of 6,7-benzomorphans,[20] B-homobenzomorphans,[10c,21] C-homobenzomorphans,[22] and 3-benzazocines.[23] While this reaction was satisfactorily accomplished by heating acids (**23**) and (**24**) in the presence of PPA, similar treatment of amino acid (**22**) failed to give any cyclized product. Thus, cyclization of compound (**24**) afforded in 12% yield a mixture of 7,8-benzomorphans (**27**) and (**28**), the latter as a minor product coming from electrophilic attack at the *ortho*-position to the benzene substituent. In this case the observed demethylation can be accounted for in the light of the reported lability of methoxy groups *peri* to a carbonyl group.[24]



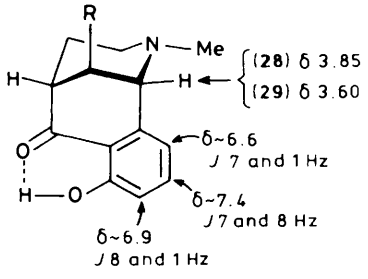
(**27**) $R^1 = R^3 = H$, $R^2 = OMe$
(**28**) $R^1 = R^2 = H$, $R^3 = OH$
(**29**) $R^1 = Me$, $R^2 = H$, $R^3 = OH$

The structural assignment of 7,8-benzomorphans (**27**) and (**28**) was effected from their i.r. and n.m.r. data. Thus, in the i.r. spectrum of (**27**) a characteristic absorption at 1 670 cm^{-1}, due to the carbonyl group conjugated with the aromatic ring, was observed. In contrast, in (**28**) this signal appeared at 1 640 cm^{-1} as a consequence of the hydrogen bond with the hydroxy group, which diminishes the double-bond character of the carbonyl group. The splitting pattern and coupling constants of the signals in the aromatic region of the n.m.r. spectra of 7,8-benzomorphans (**27**) and (**28**) clearly established that cyclization had occurred at the *para* and *ortho* positions, respectively, to the activating substituent. Thus, two doublets (J 8.8 and 2.6 Hz) and a doublet of doublets were observed for the aromatic protons of the major 7,8-benzomorphan (**27**) whereas three doublets of doublets (J 8, 7, and 1 Hz) corresponding to three protons in a vicinal relationship were observed in the n.m.r. spectrum of compound (**28**). Other characteristic signals were a singlet due to the methoxy group of (**27**) and the triplets corresponding to the C-1 ($\delta \sim 3.8$) and C-5 ($\delta \sim 2.7$) methine protons of both compounds.

* 'Isoamyl' nitrite refers to the commercial product, a mixture of (mainly) isopentyl nitrite together with 1-methylbutyl nitrite and other contaminants.



(**27**)



(**28**) R = H
(**29**) R = Me

The molecular peaks at m/z 231 for (**27**) and at m/z 217 for (**28**) in the mass spectra, the base peaks at m/z 96 (*N*-methyldihydropyridinium ion), as well as the major fragments at m/z 44 ($MeNH{=}CH_2^+$), and m/z 174 for (**27**) and 160 for (**28**) (naphthalene type), confirm the 6-oxo-7,8-benzomorphan nucleus and are in agreement with those reported for the basic skeleton.[8,25]

Finally, treatment of amino acid (**23**) with PPA furnished the 7,8-benzomorphan (**29**) in 13% yield as the only isolable product, in which cleavage of the methoxy substituent had also occurred. On the basis of the multiplicity and coupling constants of signals corresponding to the aromatic protons, which were similar to those of compound (**28**), we established that the *ortho* position to the hydroxy group was the site of cyclization. The axial orientation of the 11-methyl group with respect to the piperidine ring follows from the *trans*-relationship between substituents at positions 2 and 3 in the starting piperidinecarboxylic acid, and was confirmed (by n.m.r. spectroscopy) from the chemical shift (δ 1.37) of the 11-methyl signal, which appeared deshielded owing to the anisotropic effect of the piperidine nitrogen lone pair.[14]

As we have already indicated, amino acid (**22**) failed to give any cyclized product when it was treated with PPA or trifluoroacetic anhydride–acid mixtures. This failure can be attributed to the deactivating effect exerted by the two methoxy groups *meta* to the site of cyclization.[26]

The synthesis here reported establishes a new synthetic route to 7,8-benzomorphans and further illustrates the utility of 2-aryl-4-piperidones as intermediates in the synthesis of polycyclic compounds having the 2-arylpiperidine moiety.

Experimental

M.p.s were determined on a Büchi capillary melting-point apparatus and are uncorrected. ^1H N.m.r. spectra were taken on a Perkin-Elmer R-24B or, when indicated, on a Varian XL-200 spectrometer. ^{13}C N.m.r. spectra were recorded with a Varian XL-200 spectrometer. The chemical shifts are reported in p.p.m. downfield from tetramethylsilane (TMS). I.r. spectra were taken

with a Perkin-Elmer 577 spectrophotometer. Mass spectra were recorded on a Hewlett-Packard 5930A mass spectrometer. Column and thin-layer chromatographs were carried out on silica gel (Merck, 63—200 μm), and the spots were located with u.v. light or iodoplatinate reagent. Preparative thin-layer chromatography (p.l.c.) was run on silica gel plates $60F_{254}$ (Merck), layer thickness 2 mm, using ether–acetone as developing solvent. All distillations were effected using a Büchi GKR-50 Kugelrohr apparatus. The temperatures cited are the maximum temperature of the oven during the distillation. Microanalyses were carried out at the 'Instituto de Química Bio-Orgánica,' Barcelona. Ether refers to diethyl ether.

1-*Benzyl(methyl)aminopentan*-3-*one* (**1**).—A solution of 1-chloropentan-3-one[15] (54 g, 0.45 mol) in anhydrous ether (200 cm^3) was gradually added to a solution of *N*-methylbenzylamine (103 g, 0.85 mol) in anhydrous ether (200 cm^3). The reaction mixture was stirred at 30 °C for 7 h. The precipitate formed was filtered off and washed with ether. The combined ethereal solutions were washed twice with 2M-aqueous sodium hydroxide and dried over anhydrous potassium carbonate. After evaporation of the solvent, the amino ketone (**1**) (77 g, 83%) was obtained; $\nu_{max.}$ ($CHCl_3$) 1 705 cm^{-1} (CO); δ_H($CDCl_3$) 1.00 (3 H, t, CH_2Me), 2.1 (3 H, s, NMe), 2.35 (2 H, q, $MeCH_2$), 3.45 (2 H, s, $ArCH_2$), 2.6 (4 H, br t, CH_2CH_2), and 7.26 (5 H, s, ArH). A sample of compound (**1**) was recrystallized as the *hydrochloride*, m.p. 122—123 °C (from acetone) (Found: C, 64.25; H, 8.15; Cl, 14.6; N, 5.65. $C_{13}H_{20}ClNO$ requires C, 64.6; H, 8.3; Cl, 14.7; N, 5.8%); $\nu_{max.}$ (KBr) 1 710 cm^{-1} (CO); δ_H($CDCl_3$) 1.05 (3 H, t, CH_2Me), 2.5 (2 H, q, $MeCH_2$), 2.65 (3 H, s, $\overset{+}{N}Me$), 3.25 (4 H, br t, CH_2CH_2), 4.25 (2 H, s, $ArCH_2$), and 7.60 (5 H, m, ArH).

1-*Methylaminopentan*-3-*one Hydrochloride* (**2**)·*HCl*.—A suspension of (**1**) hydrochloride (34.4 g, 0.14 mol) in absolute ethanol (150 cm^3) was hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium–charcoal (3.4 g). When the absorption ceased, the catalyst was filtered off and the clear solution was evaporated to give (**2**) hydrochloride (17.9 g, 83%) as a hygroscopic gum; $\nu_{max.}$(NaCl) 1 710 cm^{-1} (CO); δ_H($CDCl_3$) 1.1 (3 H, t, CH_2Me), 2.55 (2 H, q, $MeCH_2$), 2.7 (3 H, s, $\overset{+}{N}Me$), and 3.2 (4 H, m, CH_2CH_2).

4-*Phthalimidobutan*-2-*one* (**3**).—To a solution of 4-chlorobutan-2-one[16] (119 g, 1.1 mol) in *N*,*N*-dimethylformamide (500 cm^3) was added potassium phthalimide (174 g, 0.98 mol) in small portions. The resulting suspension was refluxed for 32 h. The reaction mixture was poured into water–ice, and extracted with chloroform. The organic extract was washed successively with aqueous sodium carbonate and water, dried, and evaporated to give the phthalimide (**3**) (179 g, 90%), m.p. 107—109 °C (from hexane–acetone) (Found: C, 66.6; H, 5.05; N, 6.3. $C_{12}H_{11}NO_3$ requires C, 66.35; H, 5.1; N, 6.45%); $\nu_{max.}$(KBr) 1 710 and 1 770 cm^{-1} (CO); δ_H($CDCl_3$) 2.15 (3 H, s, Me), 2.8 (2 H, t, $COCH_2$), 3.85 (2 H, t, NCH_2), and 7.5—7.9 (4 H, m, ArH).

4-*Phthalimidobutan*-2-*one Ethylene Acetal* (**4**).—A stirred solution of the phthalimido ketone (**3**) (179 g, 0.82 mol), PTSA (73 g, 0.38 mol), ethylene glycol (130 cm^3), and anhydrous benzene (1 l) was refluxed for 48 h with removal of water by a Dean–Stark trap. The reaction mixture was poured into water–ice and extracted with benzene. The extracts were washed successively with aqueous potassium carbonate and water, dried, and evaporated to give the *phthalimido acetal* (**4**) (177 g, 72%), m.p. 119—120 °C (from hexane–acetone) (Found: C, 64.35; H, 5.7; N, 5.25. $C_{14}H_{15}NO_4$ requires C, 64.35; H, 5.75; N, 5.35%); $\nu_{max.}$(KBr) 1 705 and 1 770 cm^{-1} (CO); δ_H(CCl_4) 1.3 (3 H, s, Me), 1.95 (2 H, t, $OCCH_2$), 3.65 (2 H, t, NCH_2), 3.85 (4 H, s, 2 × OCH_2), and 7.4—7.7 (4 H, m, ArH).

4-*Aminobutan*-2-*one Ethylene Acetal* (**5**).—A solution of the phthalimide (**4**) (177 g, 0.76 mol), 80% hydrazine hydrate (200 cm^3), and methanol (1 l) was refluxed for 15 h, and then the solvent was removed under reduced pressure at room temperature. The residue was cooled, and 20% aqueous sodium hydroxide (400 cm^3) was added. After being stirred for 30 min, the solution was extracted with chloroform. The extract was washed with water, dried, and evaporated to yield the *amino acetal* (**5**) (71 g, 70%); b.p. 190—200 °C/0.3 mmHg (Found: C, 48.4; H, 9.8; N, 9.05. $C_6H_{13}NO_2 \cdot H_2O$ requires C, 48.3; H, 10.05; N, 9.4%); $\nu_{max.}$(NaCl) 3 380 cm^{-1} (NH); δ_H($CDCl_3$) 1.3 (3 H, s, Me), 1.8 (2 H, t, $OCCH_2$), 2.1 (2 H, br s, NH_2), 2.75 (2 H, t, NCH_2), and 3.9 (4 H, s, 2 × OCH_2).

4-(3-*Methoxybenzylideneamino*)*butan*-2-*one Ethylene Acetal* (**8**).—A solution of the amino acetal (**5**) (22 g, 0.16 mol) and 3-methoxybenzaldehyde (19 g, 0.14 mol) in anhydrous benzene (350 cm^3) was stirred at 0 °C for 30 min, at room temperature for 1 h, and under reflux for 4 h. After additional reflux with removal of water by a Dean–Stark trap (16 h), the solvent was evaporated off to give the *imine* (**8**) (37 g, 88%), b.p. 250 °C/0.5 mmHg (Found: C, 67.25; H, 7.8; N, 5.4. $C_{14}H_{19}NO_3$ requires C, 67.45; H, 7.7; N, 5.6%); $\nu_{max.}$(NaCl) 1 640 cm^{-1} (C=N); δ_H(CCl_4) 1.3 (3 H, s, CMe), 1.9 (2 H, t, $OCCH_2$), 3.55 (2 H, t, NCH_2), 3.7 (3 H, s, OMe), 3.8 (4 H, s, OCH_2), 6.6—7.3 (4 H, m, ArH), and 8.0 (1 H, s, N=CH).

cis- *and* trans-1,3-*Dimethyl*-2-(3′-4′-5′-*trimethoxyphenyl*)-4-*piperidone* (**12**) *and* (**9**).—PTSA monohydrate (22.6 g, 0.12 mol) was added to a solution of 2,3,4-trimethoxybenzaldehyde (23.1 g, 0.12 mol) in an anhydrous mixture of benzene (100 cm^3) and toluene (100 cm^3). Then, a suspension of (**2**) hydrochloride (17.9 g, 0.12 mol) in anhydrous toluene (75 cm^3) was added and the mixture was stirred at reflux under nitrogen atmosphere overnight with removal of water by a Dean–Stark trap. The solvent was evaporated off to give an oil which was dissolved in 10% hydrochloric acid (100 cm^3). The aqueous solution was extracted with benzene, basified with solid potassium carbonate, and extracted with ether. The ethereal extract was dried and evaporated to give a 4:1 mixture of the piperidones (**9**) and (**12**) (18 g, 52%). The *cis*-isomer (**12**) was isolated as an oil by column chromatography on elution with benzene–chloroform (9:1); $\nu_{max.}$ ($CHCl_3$) 1 710 cm^{-1} (CO); δ_H(CCl_4) 1.0 (3 H, d, *J* 6 Hz, 3-Me), 2.05 (3 H, s, NMe), 3.0—3.6 (2 H, m, 2-H_{ax} and 6-H_{eq}), 3.75 (6 H, s, 2 × OMe), 3.8 (3 H, s, OMe), 6.55 (1 H, d, *J* 9 Hz, ArH), and 7.05 (1 H, d, *J* 9 Hz, ArH); δ_C($CDCl_3$) 11.33 (q, CMe), 42.53 (q, NMe), 44.62 (d, C-3), 49.04 (t, C-5), 55.99 (q, 4′-OMe), 60.77 and 61.12 (2 q, 2′- and 3′-OMe), 62.65 (d, C-2), 63.84 (t, C-6), 108.05 (d, C-5′), 122.12 (d, C-6′), 127.79 (s, C-1′), 141.90 (s, C-3′), and 151.22 and 152.51 p.p.m. (2 s, C-2′ and -4′). A sample of this isomer was recrystallized as the *hydrochloride*, m.p. 172—174 °C (from acetone–ether) (Found: C, 57.9; H, 7.4; Cl, 11.1; N, 4.15. $C_{16}H_{24}ClNO_4$ requires C, 58.25; H, 7.35; Cl, 10.75; N, 4.25%); $\nu_{max.}$(KBr) 1 725 cm^{-1} (CO); δ_H($CDCl_3$) 1.15 (3 H, d, *J* 6 Hz, 3-Me), 2.6 (3 H, d, *J* 4 Hz, $\overset{+}{N}Me$), 3.8 (3 H, s, OMe), 3.85 (3 H, s, OMe), 3.9 (3 H, s, OMe), 4.6—5.0 (2 H, m, 2-H_{ax} and 6-H_{eq}), 6.85 (1 H, d, *J* 9 Hz, ArH), and 7.9 (1 H, d, *J* 9 Hz, ArH).

Elution with benzene–chloroform (4:6) afforded the *trans*-isomer (**9**), identical with that obtained by Mannich cyclization of the corresponding imino acetal.[13b]

2-(3-*Methoxyphenyl*)-1-*methyl*-4-*piperidone* (**11**).—A solution of methyl fluorosulphonate (2.7 cm^3, 34 mmol) in anhydrous methylene dichloride (10 cm^3) was slowly added at −30 °C under nitrogen to a stirred solution of the imine (**8**) (6 g, 24

mmol) in anhydrous methylene dichloride (30 cm^3). The mixture was stirred at −30 °C for 3 h, and at room temperature for 16 h. After addition of a solution of anhydrous PTSA (5 g, 26 mmol) in anhydrous benzene (10 cm^3), the mixture was refluxed for 4 h and the solvent was evaporated off to give an oil which was dissolved in 20% hydrochloric acid (100 cm^3). The aqueous solution was refluxed for 1 h, extracted with benzene, basified with solid potassium carbonate, and extracted with chloroform. The chloroform solution was dried and evaporated to give the piperidone (**11**) (3.3 g, 63%); $\nu_{max.}$(NaCl) 1 710 cm^{-1} (CO); $\delta_H(CDCl_3)$ 2.05 (3 H, s, NMe), 2.9 (1 H, br d, *J* 12 Hz, 2-H_{ax}), 3.15 (1 H, m, 6-H_{eq}), 3.7 (3 H, s, OMe), and 6.5—7.2 (4 H, m, ArH); $\delta_C(CDCl_3)$ 41.58 (t, C-5), 42.95 (q, NMe), 49.68 (t, C-3), 55.24 (t, C-6), 55.64 (q, OMe), 69.87 (d, C-2), 112.61 and 113.22 (2 d, C-2′ and -4′), 119.55 (d, C-6′), 129.81 (d, C-5′), 143.84 (s, C-1′), 159.98 (s, C-3′), and 208.12 p.p.m. (s, CO); *m/z* 219 (M^+), 218, 176, 162, 148, 112 (100), and 69. Crystallization as the *hydrochloride* gave a solid, m.p. 107—109 °C (from acetone) (Found: C, 57.0; H, 7.75; N, 5.2. $C_{13}H_{18}ClNO_2 \cdot H_2O$ requires C, 57.05; H, 7.35; N, 5.1%); $\nu_{max.}$($CHCl_3$) 1 725 cm^{-1} (CO); $\delta_H(CD_3OD)$ 2.0—2.5 (4 H, m, 3- and 5-H_2), 2.5 (3 H, s, $\overset{+}{N}$Me), 3.0—3.6 (2 H, m, 2-H_{ax} and 6-H_{ax}), 3.7 (3 H, s, OMe), 4.0—4.4 (1 H, m, 6-H_{eq}), and 6.7—7.4 (4 H, m, ArH).

(2r,3t,4c)- *and* (2r,3t,4t)-1,3-*Dimethyl*-2-(2,3,4-*trimethoxyphenyl*)*piperidine*-4-*carbonitrile* (**13**) *and* (**14**).—To a solution of the piperidone (**9**) (2 g, 6.8 mmol) in anhydrous DME (15 cm^3) was added under nitrogen a solution of freshly sublimed potassium t-butoxide (8.3 g, 74 mmol) in t-butyl alcohol (70 cm^3) and then, dropwise, a solution of TosMIC[17] (2.6 g, 13.5 mmol) in anhydrous DME (30 cm^3). The resulting mixture was stirred at 60 °C for 1 h, and at room temperature for 18 h, poured into ice–water, and extracted with ether. The extract was dried and evaporated to yield a 2:1 epimeric mixture of the nitriles (**13**) and (**14**) (2.88 g, 72%). The two epimers were separated by column chromatography. Elution with chloroform gave compound (**13**); $\nu_{max.}$(NaCl) 2 240 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.8 (3 H, br d, *J* 6 Hz, 3-Me), 1.9 (3 H, s, NMe), 2.8—3.2 (2 H, m, 2-H_{ax} and 6-H_{eq}), 3.85 (9 H, s, 3 × OMe), 6.6 (1 H, d, *J* 10 Hz, ArH), and 6.95 (1 H, br d, *J* 10 Hz, ArH). A sample of this isomer was recrystallized as the *hydrochloride*, m.p. 182—185 °C (from acetone–ether) (Found: C, 60.15; H, 7.55; Cl, 10.35; N, 8.1. $C_{17}H_{25}ClN_2O_3$ requires C, 59.9; H, 7.3; Cl, 10.15; N, 8.2%); $\nu_{max.}$ 2 240 cm^{-1} (CN); $\delta_H(CDCl_3)$ 1.0 (3 H, d, *J* 6 Hz, 3-Me), 2.5 (3 H, d, *J* 5 Hz, $\overset{+}{N}$Me), 3.85 (3 H, s, OMe), 3.9 (3 H, s, OMe), 3.97 (3 H, s, OMe), 6.85 (1 H, d, *J* 10 Hz, ArH), and 7.8 (1 H, d, *J* 10 Hz, ArH). The nitrile (**14**) was eluted with chloroform–methanol (98:2); $\nu_{max.}$(NaCl) 2 240 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.8 (3 H, d, *J* 6 Hz, 3-Me), 2.0 (3 H, s, NMe), 2.9—3.2 (1 H, m, 6-H_{eq}), 3.35 (1 H, d, *J* 10 Hz, 2-H_{ax}), 3.85 (9 H, s, 3 × OMe), 6.6 (1 H, d, *J* 10 Hz, ArH), and 6.97 (1 H, d, *J* 10 Hz, ArH). A sample of compound (**14**) was recrystallized as the *hydrochloride*, m.p. 200—205 °C (from acetone-ether) (Found: C, 60.25; H, 7.55; Cl, 10.4; N, 8.1%); $\nu_{max.}$(KBr) 2 245 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.9 (3 H, d, *J* 6 Hz, 3-Me), 2,45 (3 H, d, *J* 4 Hz, $\overset{+}{N}$Me), 3.85 (6 H, s, OMe), 3.95 (3 H, s, OMe), 4.0—4.3 (1 H, m, 6-H_{eq}), 6.85 (1 H, d, *J* 10 Hz, ArH), and 7.85 (1 H, d, *J* 10 Hz, ArH).

r-2-(3-*Methoxyphenyl*)-1,t-3-*dimethylpiperidine*-c-4-*carbonitrile* (**15**).—In a similar manner as above, from the piperidone (**10**)[13b] (2.97 g, 12.6 mmol), potassium t-butoxide (15 g, 0.13 mol), and TosMIC (4.9 g, 25.1 mmol), a 2:1 epimeric mixture of the nitriles (**15**) and (**16**) (2.8 g, 93%) was obtained. The isomer (**15**) was isolated as an oil by column chromatography on elution with benzene–chloroform (3:7); $\nu_{max.}$(NaCl) 2 240 cm^{-1} (CN); $\delta_H(CDCl_3)$ 0.75 (3 H, d, *J* 6 Hz, 3-Me), 1.8 (3 H, s, NMe), 2.35 (1 H, d, *J* 11 Hz, 2-H_{ax}), 2.9—3.0 (1 H, m, 6-H_{eq}), 3.6 (3 H, s, OMe), and 6.5—7.3 (4 H, m, ArH). An analytically pure sample was obtained by recrystallization of the *picrate*, m.p. 219—220 °C (from ethanol) (Found: C, 53.0; H, 4.85; N, 14.45. $C_{21}H_{23}N_5O_8$ requires C, 53.3; H, 4.9; N, 14.8%); $\nu_{max.}$(KBr) 2 260 cm^{-1} (CN); $\delta_H(CDCl_3$–[$^2H_6$]dimethyl sulphoxide) 0.9 (3 H, d, *J* 6 Hz, 3-Me), 2.55 (3 H, s, $\overset{+}{N}$Me), 3.75 (3 H, s, OMe), 4.1 (1 H, m, 6-H_{eq}), and 6.7—7.5 (4 H, m, ArH).

cis-2-(3-*Methoxyphenyl*)-1-*methylpiperidine*-4-*carbonitrile* (**17**).—In a similar manner as above, from the piperidone (**11**) (1.5 g, 6.8 mmol), potassium t-butoxide (8.3 g, 74 mmol), and TosMIC (2.25 g, 11.5 mmol), a 2:1 epimeric mixture of the nitriles (**17**) and (**18**) (0.56 g, 36%) was obtained. The isomer (**17**) was isolated by p.l.c.; $\nu_{max.}$(NaCl) 2 220 cm^{-1} (CN); δ_H (200 MHz; $CDCl_3$) 2.0 (3 H, s, NMe), 2.8 (1 H, dd, *J* 11 and 3 Hz, 6-H_{eq}), 3.1 (1 H, br d, *J* 11 Hz, 2-H_{ax}), 3.8 (3 H, 3, OMe), and 6.8—7.3 (4 H, m, ArH). An analytically pure sample was obtained by recrystallization of the *picrate*, m.p. 178—179 °C (from ethanol) (Found: C, 52.6; H, 4.8; N, 14.95. $C_{20}H_{21}N_5O_8$ requires C, 52.3; H, 4.6; N, 15.25%).

The aqueous phase was extracted with chloroform. The chloroform solution was dried and evaporated to give cis-2-(3-*methoxyphenyl*)-1-*methylpiperidine*-4-*carboxamide* (**19**) (0.42 g, 25%). An analytical sample was obtained by p.l.c., m.p. 134—136 °C (from acetone–ether) (Found: C, 67.2; H, 8.3; N, 11.6. $C_{14}H_{20}N_2O_2$ requires C, 67.4; H, 8.6; N, 11.9%); $\nu_{max.}$(NaCl) 3 320, 3 190 (NH_2), and 1 660 cm^{-1} (CO); δ_H (200 MHz; $CDCl_3$) 2.05 (3 H, s, NMe), 2.85 (1 H, dd, *J* 11 and 3 Hz, 2-H_{ax}), 3.15 (1 H, dt, *J* 11 and 3 Hz, 6-H_{eq}), 3.8 (3 H, s, OMe), 5.8 (2 H, br, NH_2), and 6.9—7.2 (4 H, m, ArH).

1,t-3-*Dimethyl*-r-2-(2,3,4-*trimethoxyphenyl*)*piperidine*-c-4-*carboxamide* (**20**).—A solution of the nitriles (**13**) and (**14**) (0.5 g, 1.64 mmol) in a mixture of ethanol (5 cm^3) and 20% aqueous potassium hydroxide (40 cm^3) was refluxed for 5 h. The resulting mixture was extracted with chloroform, and the extract was dried, and evaporated to give the *carboxamide* (**20**) (0.37 g, 70%); m.p. 118—120 °C (from acetone–ether) (Found: C, 59.75; H, 8.15; N, 7.9. $C_{17}H_{26}N_2O_4 \cdot H_2O$ requires C, 60.0; H, 8.2; N, 8.2%); $\nu_{max.}$($CHCl_3$) 3 530, 3 410 (NH_2), and 1 680 cm^{-1} (CO); δ_H (200 MHz; $CDCl_3$–CD_3OD) 0.67 (3 H, d, *J*6 Hz, 3-Me), 2.13 (3 H, s, NMe), 3.24 (1 H, br d, *J* 12 Hz, 6-H_{eq}), 3.87 (6 H, s, 2 × OMe), 3.89 (3 H, s, OMe), 5.55 (2 H, br, NH_2), 6.68 (1 H, d, *J* 9 Hz, ArH), and 7.15 (1 H, d, *J* 9 Hz, ArH); *m/z* 322 (M^+), 307, 291, 278, 236, 208, 179, 69, 55, and 44 (100).

A solution of carboxamide (**20**) (2.0 g, 6.5 mmol) in glacial acetic acid (15 cm^3) was saturated with hydrogen chloride for 15 min. Then, freshly distilled 'isoamyl' nitrite (1 cm^3, 65 mmol) was slowly added. The mixture was stirred at room temperature for 30 min and then refluxed for 15 min. After evaporation of the solvent, the residue was washed with ether and dissolved in water. The aqueous solution was basified with potassium carbonate, washed with chloroform, and evaporated to dryness. The resulting solid was dried over phosphorus pentaoxide and digested several times with boiling absolute ethanol. The ethanolic extracts were evaporated to give the crude amino acid (**22**) (1.6 g) slightly contaminated with inorganic salts. Esterification of acid (**22**) with ethanol saturated with hydrogen chloride afforded, after the usual work-up, the ester (**25**); $\nu_{max.}$($CHCl_3$) 1 725 cm^{-1} (CO); δ_H (200 MHz; $CDCl_3$) 0.58 (3 H, d, *J* 6 Hz, 3-Me), 1.26 (3 H, t, CH_2*Me*), 2.0 (3 H, s, NMe), 2.48 (1 H, d, *J* 10 Hz, 2-H_{ax}), 3.14 (1 H, dt, *J* 11.2 and 4.8 Hz, 6-H_{eq}), 3.81 (3 H, s, OMe), 3.82 (6 H, s, 2 × OMe), 4.15 (2 H, q, *CH*$_2$Me), 6.65 (1 H, d, *J* 10 Hz, ArH), and 7.1 (1 H, d, *J* 10 Hz, ArH).

r-2-(3-*Methoxyphenyl*)-1,t-3-*dimethylpiperidine*-c-4-*carboxamide* (**21**).—In a similar manner as above, from an epimeric mixture of nitriles (**15**) and (**16**) (0.62 g, 4 mmol), ethanol (5

cm^3), and 20% aqueous potassium hydroxide (10 cm^3) was obtained the *carboxamide* (**21**) (0.53 g, 81%); m.p. 168—170 °C (from ether–acetone) (Found: C, 68.7; H, 8.55; N, 10.5. $C_{15}H_{22}N_2O_2$ requires C, 68.7; H, 8.5; N, 10.65%); $\nu_{max.}$(KBr) 3 320 (NH) and 1 675 cm^{-1} (CO); δ_H (200 MHz; $CDCl_3$–CD_3OD) 0.61 (3 H, d, *J* 6 Hz, 3-Me), 1.98 (3 H, s, NMe), 2.46 (1 H, d, *J* 10 Hz, 2-H_{ax}), 3.07 (1 H, dt, *J* 11 and 3 Hz, 6-H_{eq}), 3.82 (3 H, s, OMe), 6.8—6.9 (2 H, br, NH_2), and 6.6—7.3 (4 H, m, ArH); *m/z* 262 (M^+), 247, 218, 176, 162, 148 (100), 114, and 97.

r-2-(3-*Methoxyphenyl*)-1,t-3-*dimethylpiperidine*-c-4-*carboxylic Acid* (**23**) *and Ethyl* r-2-(3-*Methoxyphenyl*)-1,t-3-*dimethylpiperidine*-c-4-*carboxylate* (**26**).—A solution of the epimeric mixture of the nitriles (**15**) and (**16**) (3.43 g, 13 mmol) in a mixture of ethanol (25 cm^3) and 30% aqueous potassium hydroxide (40 cm^3) was refluxed for 2 weeks. After evaporation of the ethanol, the aqueous solution was neutralized with 1M-hydrochloric acid and evaporated to dryness. The residue was dried over phosphorus pentaoxide and digested several times with boiling absolute ethanol. The ethanolic extracts were evaporated to give the acid (**23**) (2.7 g, 74%).

A sample of compound (**23**) (0.5 g, 1.9 mmol) was dissolved in ethanol saturated with hydrogen chloride (30 cm^3) and the solution was refluxed for 3 h. The residue after evaporation was dissolved in water, and the solution was basified with 20% aqueous potassium carbonate, and extracted with chloroform. The extracts were dried and evaporated to give the ester (**26**) (0.3 g, 53%); $\nu_{max.}$(NaCl) 1 730 cm^{-1} (CO); δ_H(CCl_4) 0.5 (3 H, br d, 3-Me), 1.2 (3 H, t, CH_2Me), 1.85 (3 H, s, NMe), 2.8—3.0 (1 H, m, 6-H_{eq}), 3.7 (3 H, s, OMe), 4.0 (2 H, q, $MeCH_2$), and 6.5—7.5 (4 H, m, ArH); *m/z* 291 (M^+), 273, 246, 218, 184 (100), and 121. A sample of ester (**26**) was recrystallized as the *picrate*, m.p. 145—147 °C (from ethanol) (Found: C, 54.7; H, 5.75; N, 11.0. $C_{23}H_{28}N_4O_9$ requires C, 54.75, H, 5.4; N, 11.1%).

9-*Methoxy*-2-*methyl*-2,3,4,5-*tetrahydro*-1H-1,5-*methano*-2-*benzazocin*-6-*one* (**27**) *and* 7-*Hydroxy*-2-*methyl*-2,3,4,5-*tetrahydro*-1H-1,5-*methano*-2-*benzazocin*-6-*one* (**28**).—A solution of the nitriles (**17**) and (**18**) (1.1 g, 4.7 mmol) in a mixture of dioxane (50 cm^3) and saturated aqueous barium hyroxide (50 cm^3) was refluxed for 6 h. The resulting mixture was saturated with carbon dioxide, filtered, and evaporated to dryness. The crude amino acid (**24**) thus obtained (1.5 g) was stirred with PPA (80 g) under nitrogen at 135 °C for 5 h. The resulting mixture was poured into an excess of conc. ammonium hydroxide–ice and extracted with ether. The evaporation of the dried extract gave the 7,8-*benzomorphan* (**27**) (0.1 g, 10%). An analytically pure sample was obtained by p.l.c. (Found: C, 69.8; H, 7.25; N, 5.85. $C_{14}H_{17}NO_2 \cdot \frac{1}{2}H_2O$ requires C, 70.0; H, 7.5; N, 5.85%); $\nu_{max.}$($CHCl_3$) 1 670 cm^{-1} (CO); δ_H (200 MHz; $CDCl_3$) 2.25 (3 H, s, NMe), 2.27 (1 H, dt, *J* 13 and 3 Hz, 11-H_β), 2.73 (1 H, br t, *J* 3 Hz, 5-H), 3.81 (1 H, t, *J* 3.3 Hz, 1-H), 3.90 (3 H, s, OMe), 6.62 (1 H, d, *J* 2.6 Hz, 10-H), 6.94 (1 H, dd, *J* 8.8 and 2.6 Hz, 8-H), and 8.07 (1 H, d, *J* 8.8 Hz, 7-H); *m/z* 231 (M^+), 188, 174, 96 (100), and 44.

The aqueous solution was extracted with chloroform. The extract was dried and evaporated to give the 7,8-*benzomorphan* (**28**) (22 mg). An analytically pure sample was isolated by p.l.c. (Found: C, 70.35; H, 6.95; N, 6.3. $C_{13}H_{15}NO_2 \cdot \frac{1}{4}H_2O$ requires C, 70.4; H, 7.0; N, 6.3%); $\nu_{max.}$($CHCl_3$) 3 100—3 500 (OH) and 1 640 cm^{-1} (CO); δ_H(200 MHz; $CDCl_3$) 1.90 (1 H, m, 4-H_{eq}), 1.9—2.2 (2 H, m, 3- and 4-H_{ax}), 2.24 (3 H, s, NMe), 2.3—2.5 (2 H, m, 11-H_2), 2.61 (1 H, dd, *J* 12.6 and 3.6 Hz, 3-H_{eq}), 2.79 (1 H, br t, *J* 3 Hz, 5-H_{eq}), 3.85 (1 H, t, *J* 3 Hz, 1-H_{eq}), 6.62 (1 H, dd, *J* 7 and 1 Hz, 10-H), 6.97 (1 H, dd, *J* 8 and 1 Hz, 8-H), and 7.47 (1 H, dd, *J* 8 and 7 Hz, 9-H); *m/z* 217 (M^+), 174, 160, 96 (100), and 44.

7-*Hydroxy*-2,11-*dimethyl*-2,3,4,5-*tetrahydro*-1H-1,5-*methano*-2-*benzazocin*-6-*one* (**29**).—A mixture of the acid (**23**) (1.26 g, 4.7 mmol) and PPA (100 g) was vigorously stirred under nitrogen at 140 °C for 16 h. The mixture was cooled, poured into an excess of conc. ammonium hydroxide–ice, and extracted with chloroform. Evaporation of the dried extract gave the product (**29**) (0.14 g, 13%) as an oil which was purified by column chromatography through silica gel (98:2 chloroform–methanol as eluant); $\nu_{max.}$($CHCl_3$) 3 100—3 500 (OH) and 1 635 cm^{-1} (CO); δ_H (200 MHz; $CDCl_3$) 1.37 (3 H, d, *J* 6.8 Hz, 11-Me), 1.66 (1 H, br d, *J* 12 Hz, 4-H_{eq}), 1.95 (1 H, br t, *J* 12 Hz, 4-H_{ax}), 2.21 (3 H, s, NMe), 3.60 (1 H, br s, 1-H), 6.60 (1 H, dd, *J* 7 and 1 Hz, 10-H), 6.92 (1 H, dd, *J* 8 and 1 Hz, 8-H), and 7.45 (1 H, dd, *J* 8 and 7 Hz, 9-H); *m/z* 231 (M^+), 216, 188, 110 (100), and 44. A sample of compound (**29**) was recrystallized as the *hydrochloride*, m.p. 265—267 °C (from acetone) (Found: C, 62.65; H, 6.75; 5.2. $C_{14}H_{18}ClNO_2$ requires C, 62.8; H, 6.75; N, 5.25%); $\nu_{max.}$($CHCl_3$) 3 250—3 500 (OH) and 1 640 cm^{-1} (CO); δ_H (200 MHz; $CDCl_3$) 1.71 (3 H, d, *J* 7 Hz, 11-Me), 2.65 (3 H, br s, NMe), 3.33 (1 H, br d, *J* 10 Hz, 3-H_{eq}), 4.22 (1 H, br s, 1-H), 6.83 (1 H, br d, 10-H), 7.10 (1 H, d, *J* 8.6 Hz, 8-H), and 7.53 (1 H, t, 8.6 Hz, 9-H).

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