

## Benzomorphan Related Compounds. Part 20.<sup>1</sup> Synthesis of $\beta$ -Norbenzomorphans via 2-Aryl-4-piperidones †

Joan Bosch,\* Mario Rubiralta, Montserrat Moral, and Jordi Bolós

Department of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, Barcelona-28, Spain

A short and efficient synthesis of 2,3,4,5-tetrahydro-1*H*-1,5-methano-2-benzazepines ( $\beta$ -norbenzomorphans) carrying hydroxy, alkoxy, and acyloxy groups at the C-5 position, based on the acid-catalysed cyclization of 2-aryl-1-formyl-4-piperidones, is described.

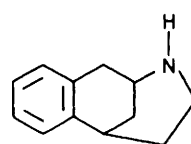
Structural modifications of the benzomorphan ring system<sup>2</sup> have produced interesting new morphine-like analgesics. Thus,  $\beta$ -nor-,<sup>3,4</sup> *C*-nor-,<sup>5</sup>  $\beta$ -homo-,<sup>6</sup> *C*-homo-,<sup>7</sup>  $\beta$ -nor-*C*-homo-,<sup>8</sup> and  $\beta$ -homo-*C*-nor-benzomorphans<sup>9</sup> have been synthesized. In spite of their significant analgesic activity, only one synthetic route to  $\beta$ -norbenzomorphans with a 1,5-methano-2-benzazepine skeleton has been described; the ring C of the tricyclic system was formed by lactamization of a 1-aminoindan-3-ylacetic acid.<sup>3</sup>

In connection with our studies on benzomorphan-related compounds,<sup>10</sup> we wish to report a new and short synthetic route to  $\beta$ -norbenzomorphans carrying a hydroxy, alkoxy, or acyloxy group at the C-5 position. Such compounds can be considered as analogues of prodines which are conformationally restricted by the connection of the aryl and piperidine rings. The synthesis implies the closure of ring B in the last synthetic step by formation of the C(5)–C(5a) bond through the acid-catalysed cyclization of 2-aryl-4-piperidones, which are easily accessible by Mannich-type cyclization of the appropriate imino ketones<sup>11</sup> or imino acetals.<sup>12</sup>

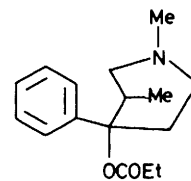
There are precedents for acid-catalysed intramolecular cyclizations by the electrophilic attack of a ketone carbonyl group on an activated aromatic ring,<sup>13,14</sup> and some of those reported afford bridged polycyclic systems.<sup>14</sup> However, 2-aryl-4-piperidone (**1**)<sup>12</sup> was recovered unchanged after being refluxed in boron trifluoride–ether, and when it was heated in the presence of 48% hydrobromic acid, it gave the phenol (**2**) in 54% yield. Similar treatment with hydrobromic acid of the 2-aryl-4-piperidone (**5**), prepared by reaction of the ketone (**1**) with methylmagnesium iodide, afforded the phenol (**6**) in 63% yield.

Similarly, in previous work we found that 2-indol-3-yl- and 2-phenyl-1,4-dimethyl-1,2,3,6-tetrahydropyridines failed to give the corresponding *C*-norindolo-<sup>15</sup> or  $\beta$ -norbenzomorphans<sup>16</sup> under acidic conditions. In view of the successful acid-catalysed cyclization of 2-arylmethyl-4-piperidones,<sup>14a</sup> 2-arylmethylpiperidin-4-ols,<sup>17</sup> and 2-arylmethyl-1,2,5,6-tetrahydropyridines to 6,7-benzomorphan systems<sup>2</sup> or heteroaromatic analogues,<sup>18</sup> the reluctance of the above 2-arylpiperidines to cyclize could be interpreted by assuming that, in the acidic reaction medium, the protonated aminoalkyl substituent deactivates the benzene ring on electrophilic attack.<sup>19</sup>

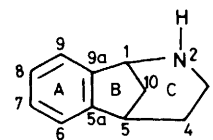
In order to try and circumvent the above difficulties we turned our attention to the piperidone (**4**), in which the *N*-formyl substituent<sup>19,20</sup> was also expected to exert a favourable conformational effect since it is known that the  $\alpha$ -substituents in *N*-acylpiperidines are axially oriented to relieve steric crowding with the amide carbonyl group.<sup>21</sup> In this preferred piperidine



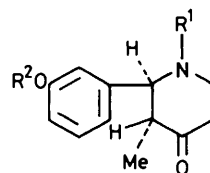
6,7-Benzomorphan



Prodine



B-Norbenzomorphan

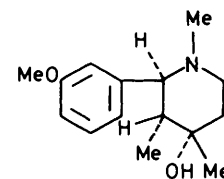


(1)  $R^1 = R^2 = \text{Me}$

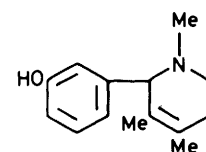
(2)  $R^1 = \text{Me}, R^2 = \text{H}$

(3)  $R^1 = \text{H}, R^2 = \text{Me}$

(4)  $R^1 = \text{CHO}, R^2 = \text{Me}$



(5)



(6)

conformation, electrophilic attack of the ketone carbonyl group upon the axial benzene ring should take place more easily than in the above piperidone (**1**) which has two equatorial piperidine substituents.

The *N*-formylpiperidone (**4**) was obtained as a mixture of rotamers (Figure 1) from the piperidone (**3**)<sup>12</sup> by reaction with acetic formic anhydride. These rotamers, resulting from hindered rotation of the formyl group, were easily distinguishable in the <sup>1</sup>H n.m.r. spectrum<sup>22</sup> which showed two doublets for the axial methyl group, two doublets for the equatorial C-2 methine proton, and two singlets for the formyl hydrogen. The assignments were made on the basis of the chemical shift of the C-2 methine proton, which in the major *cis* rotamer is deshielded by the amide carbonyl group.<sup>23</sup> The piperidone (**4**) easily epimerizes to the most stable *cis*-isomer (**7**), having an

† A preliminary communication of part of this work was presented at the 2nd Congreso Nacional de la Real Sociedad Española de Química Terapéutica, Madrid, 1982, by J. Bosch, M. Rubiralta, M. Moral, and J. Bolós.

equatorial methyl group. The  $^1\text{H}$  n.m.r. spectrum of (7) also revealed the presence of two rotamers (Table 1, Figure 1).

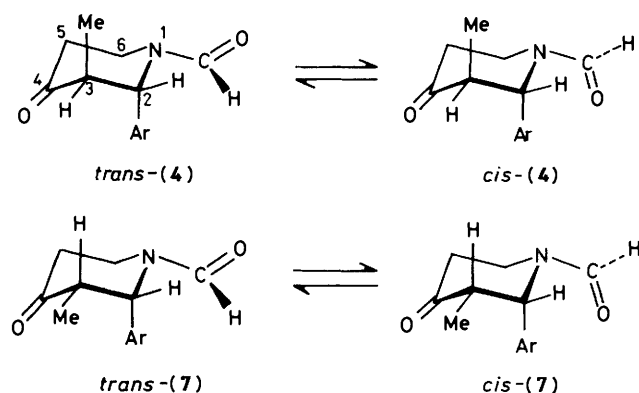


Figure 1. Conformations of the rotamers of the *N*-formylpiperidones (4) and (7)

The variable temperature spectral data of the *N*-formylpiperidones (4) and (7) are reported in Table 1. Increasing the temperature gave rise to line-shape phenomena which are typical for hindered exchange processes. The coalescence temperature of the 2-H and CHO signals and the estimated value<sup>24</sup> for the activation free energy of rotamer interconversion are given in Table 2.

Treatment of compound (4) with boron trifluoride-ether at 110 °C (lower temperatures were ineffective) gave the  $\beta$ -norbenzomorphan (8) as a mixture of the C-10 epimers, from which the major  $\beta$ -isomer (axial 10-methyl group) was isolated by column chromatography. The formation of a cyclized product was evident from the disappearance of the i.r. absorption at 1715  $\text{cm}^{-1}$  corresponding to the ketone carbonyl group of (4), and by the relative intensities of the aromatic protons in the  $^1\text{H}$  n.m.r. spectrum. Other characteristic signals of compound (8 $\beta$ ) are a triplet at  $\delta$  1.20 and a quartet at  $\delta$  3.40, due to the 5-ethoxy group which results from alkylation due to the presence of boron trifluoride-ether at reflux temperature. The  $^1\text{H}$  n.m.r. spectrum of (8 $\beta$ ), in particular the doublets at  $\delta$  4.50 and 5.45 due to the equatorial C-1 methine proton, also indicated the presence of two rotamers (1:1 ratio). The base peak at  $m/z$  275 as well as the major fragments in the mass spectrum confirm the structure of compound (8 $\beta$ ) and are in agreement with those reported for the basic  $\beta$ -norbenzomorphan skeleton.<sup>3b</sup>

The formation of minor amounts of the  $\alpha$ -isomer (8 $\alpha$ ) is attributed to the partial isomerization, under the acidic cyclization conditions, of the axial 3-methyl substituent, located  $\alpha$  to the ketone group in the starting piperidone (4), to the more stable, equatorial position.

Acid hydrolysis of the *N*-formyl group of compounds (8) gave the epimeric secondary amines (9), which could allow the further introduction of radicals of greater pharmacological use on the nitrogen atom of the piperidine ring. On the other hand, lithium aluminium hydride reduction of the epimeric mixture of (8) afforded a mixture of the *N*-methyl derivatives (10) which were separated by column chromatography. Their stereochemistries were assigned on the basis of the chemical shift of the doublet corresponding to the 10-methyl group in the  $^1\text{H}$  n.m.r. spectrum. In the case of the major  $\beta$ -isomer, this signal appears at lower field ( $\delta$  1.21) than in the minor  $\alpha$ -isomer ( $\delta$  0.76) owing to the deshielding effect of the piperidine nitrogen lone pair.<sup>25</sup> This criterion has been used in the stereochemical assignment of similar diastereoisomeric mixtures in the benzo-,<sup>26</sup> thieno-,<sup>27</sup> and benzo[*b*]thieno-morphan<sup>28</sup> series. The

Table 1.  $^1\text{H}$  N.m.r. (200 MHz) data of the *N*-formyl-4-piperidones (4) and (7) in  $(\text{CD}_3)_2\text{SO}$

Temp. (°C)	2-H			
	<i>trans</i> -(4) <sup>a</sup>	<i>cis</i> -(4)	<i>trans</i> -(7)	<i>cis</i> -(7)
19.5 <sup>b</sup>	4.56d ( <i>J</i> 7 Hz)	5.54d ( <i>J</i> 7 Hz)	5.08d ( <i>J</i> 7 Hz)	6.06d ( <i>J</i> 7 Hz)
19.5	4.76d ( <i>J</i> 7 Hz)	5.01d ( <i>J</i> 7 Hz)	5.29d ( <i>J</i> 7 Hz)	5.76d ( <i>J</i> 7 Hz)
49.6	4.78d ( <i>J</i> 7 Hz)	5.08d ( <i>J</i> 7 Hz)	5.30d ( <i>J</i> 7 Hz)	5.79d ( <i>J</i> 7 Hz)
74.5	4.77br s	5.12br s	5.29d ( <i>J</i> 7 Hz)	5.80d ( <i>J</i> 7 Hz)
99.5	4.7—4.9br	5.0—5.2br	5.29br s	5.80br s
119.5	4.6—5.2br		5.2—5.4br	5.7—5.9br
139.6	4.7—5.1br		5.2—5.4br	5.7—5.9br
159.3	4.97br s		5.2—5.4br	5.7—5.9br

Temp. (°C)	CHO			
	<i>trans</i> -(4)	<i>cis</i> -(4)	<i>trans</i> -(7)	<i>cis</i> -(7)
19.5 <sup>b</sup>	8.25s	8.33s	8.15s	8.43s
19.5	8.19s	8.24s	8.15s	8.43s
69.3	8.19br s	8.24br s	8.15s	8.43s
74.1	8.19br	8.24br	8.15s	8.43s
79.3	8.1—8.3br		8.15br s	8.43br s
84.0	8.22br s		8.15br s	8.43br s
99.2	8.22s		8.0—8.2br	8.3—8.5br
139.2	8.22s		8.0—8.2br	8.3—8.5br
159.9	8.22s		8.0—8.4br	

<sup>a</sup> The rotamer containing the C(2)-N and the formyl C=O bonds in a relative transoid conformation is called *trans*. <sup>b</sup> N.m.r. spectrum in  $\text{CDCl}_3$ .

Table 2. Dynamic n.m.r. data of the *N*-formylpiperidones (4) and (7)

Compound	Proton observed	$\Delta\delta$ (Hz) <sup>a</sup>	$T_c$ (°C)	$K_c$ ( $\text{s}^{-1}$ )	$\Delta G^\ddagger$ ( $\text{kJ mol}^{-1}$ )
(4)	2-H	49.6	119.5	110.6	78.5
(4)	CHO	9.6	79.3	21.4	77.6
(7)	2-H	93.6	> 159.0		
(7)	CHO	56.8	159.9	126.6	89.3

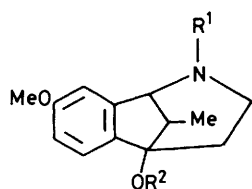
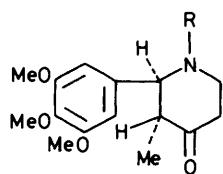
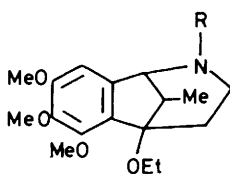
<sup>a</sup> At 19.5 °C.

bridgehead C-1 proton of compound (10 $\beta$ ) appears as a doublet at  $\delta$  3.64 ( $\delta$  3.77 in the fundamental  $\beta$ -norbenzomorphan system<sup>3b</sup>), with a coupling constant (4 Hz) in agreement with that predicted from the Karplus equation.<sup>29</sup>

In a similar way, 2-trimethoxyphenyl-4-piperidone (16),<sup>30</sup> prepared by the general procedure described in our previous papers,<sup>11,12</sup> was converted into the *N*-formyl derivative (17); this was then cyclized with boron trifluoride-ether to give the  $\beta$ -norbenzomorphan (18), which was reduced with lithium aluminium hydride to give the *N*-methyl derivative (19).

As expected, when the *N*-formyl-4-piperidone (4) was heated in the presence of aluminium chloride in nitromethane solution, cyclization occurred to give a  $\beta$ -norbenzomorphan structure (11) carrying a 5-hydroxy substituent. Again, a mixture of the C-10 epimers was obtained, both as a mixture of rotamers. The i.r. spectrum of the isomers (11) showed a strong absorption at 1650  $\text{cm}^{-1}$  and a broad absorption at 3100—3500  $\text{cm}^{-1}$ , due to the formyl and hydroxy groups, respectively.

As in the 5-ethoxy series, the acid hydrolysis of compound (11) gave the *N*-unsubstituted  $\beta$ -norbenzomorphan (12), whereas lithium aluminium hydride reduction furnished the corresponding *N*-methyl derivative (13). The stereochemistries of the  $\alpha$ - and  $\beta$ -epimers were assigned as above from the chemical

(8)  $R^1 = \text{CHO}$ ,  $R^2 = \text{Et}$ (9)  $R^1 = \text{H}$ ,  $R^2 = \text{Et}$ (10)  $R^1 = \text{Me}$ ,  $R^2 = \text{Et}$ (11)  $R^1 = \text{CHO}$ ,  $R^2 = \text{H}$ (12)  $R^1 = R^2 = \text{H}$ (13)  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ (14)  $R^1 = \text{Me}$ ,  $R^2 = \text{COMe}$ (15)  $R^1 = \text{Me}$ ,  $R^2 = \text{COEt}$ (16)  $R = \text{H}$ (17)  $R = \text{CHO}$ (18)  $R = \text{CHO}$ (19)  $R = \text{Me}$ 

shift of the 10-methyl signal in the  $^1\text{H}$  n.m.r. spectrum. The assignment of structures (13 $\alpha$ ) and (13 $\beta$ ), as well as (10 $\beta$ ) and (12 $\beta$ ), was confirmed from the  $^{13}\text{C}$  n.m.r. data (Figure 2). Thus, the 10-methyl and C-4 signals of the  $\beta$ -epimers appear at higher field than those of the  $\alpha$ -epimers owing to a ' $\gamma$ -gauche' effect. Similar chemical shift differences have been observed in the 6,7-benzomorphan series.<sup>31</sup>

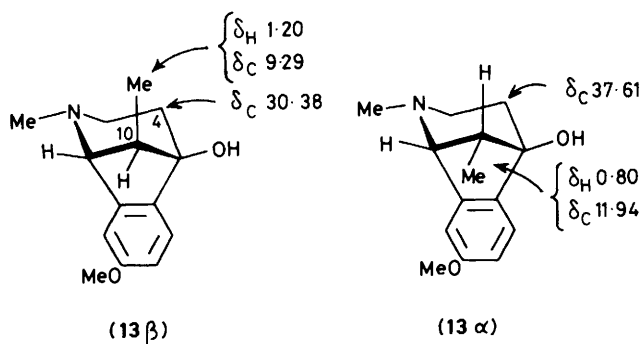


Figure 2.  $^{13}\text{C}$  N.m.r. data of the *N*-methyl- $\beta$ -norbenzomorphan (13)

Finally, treatment of the major isomer (13 $\beta$ ) with acetic or propionic anhydride gave the corresponding 5-acyloxy derivatives (14 $\beta$ ) and (15 $\beta$ ), respectively, which can be considered to be hybrids of prodines and  $\beta$ -norbenzomorphanes.

The accessibility of the 2-aryl-4-piperidones<sup>11,12</sup> and the good yield in the cyclization step make the described procedure a valuable route for the synthesis of  $\beta$ -norbenzomorphanes carrying 5-oxy substituents.

## Experimental

M.p.s were determined on a Büchi capillary melting point apparatus and are uncorrected.  $^1\text{H}$  N.m.r. spectra were taken on

a Perkin-Elmer R-24B or, when indicated, on a Varian XL-200 spectrometer.  $^{13}\text{C}$  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). Variable temperature measurements were determined before recording a spectrum by using a standard glycol sample. 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 chromatography were carried out on silica gel (Merck, 63–200  $\mu\text{m}$ ), and the spots were located with u.v. light of iodoplatinate reagent. Preparative thin-layer chromatographs were run on silica gel plates 60F<sub>254</sub> (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.

*trans*-2-(3-Hydroxyphenyl)-1,3-dimethyl-4-piperidone (2).—A solution of piperidone (1)<sup>12</sup> (0.3 g, 1.29 mmol) in 48% hydrobromic acid (10 cm<sup>3</sup>) was heated at 110 °C for 5 h. The reaction mixture was concentrated under reduced pressure, basified with aqueous potassium carbonate, and extracted with chloroform. The organic layer was dried and evaporated to give the phenol (2) (0.15 g, 54%), m.p. 142–143 °C (from acetone) (Found: C, 71.3; H, 7.95; N, 6.4. C<sub>13</sub>H<sub>17</sub>NO<sub>2</sub> requires C, 71.2; H, 7.8; N, 6.4%);  $\nu_{\text{max}}$ (KBr) 2 300–3 300 (OH) and 1 710 cm<sup>-1</sup> (C=O);  $\delta_{\text{H}}$ (CDCl<sub>3</sub>–DMSO) 0.70 (3 H, br, 3-Me), 2.00 (3 H, s, NMe), and 6.6–7.2 (4 H, m, ArH);  $m/z$  219 ( $M^+$ ), 162, 148, 134 (ArCH=N<sup>+</sup>CH<sub>2</sub>), and 126.

*t*-2-(3-Methoxyphenyl)-1,3,4-trimethylpiperidin-4-ol (5).—To a mixture of magnesium (0.2 g, 8.6 mmol) in anhydrous ether (20 cm<sup>3</sup>), a solution of methyl iodide (1.2 g, 8.45 mmol) in anhydrous ether (10 cm<sup>3</sup>) was added dropwise. The resulting mixture was stirred for 15 min at room temperature under nitrogen. Then, a solution of piperidone (1)<sup>12</sup> (0.99 g, 4.24 mmol) in anhydrous ether (15 cm<sup>3</sup>) was added, and the mixture was refluxed for 1 h, poured into water–ice, and acidified with 20% hydrochloric acid. The aqueous solution was basified with sodium carbonate solution and extracted with chloroform. The extract was dried (MgSO<sub>4</sub>) and evaporated to give the piperidinol (5) (0.93 g, 88%) as an oil, b.p. 240 °C/0.1 mmHg (Found: C, 71.8; H, 9.25; N, 5.9. C<sub>15</sub>H<sub>23</sub>NO<sub>2</sub> requires C, 72.2; H, 9.3; N, 5.6%);  $\nu_{\text{max}}$ (NaCl) 3 100–3 650 cm<sup>-1</sup> (OH);  $\delta_{\text{H}}$ (CDCl<sub>3</sub>) 0.60 (3 H, d,  $J$  7 Hz, 3-Me), 1.22 (3 H, s, 4-Me), 1.91 (3 H, s, NMe), 3.71 (3 H, s, OMe), and 6.6–7.3 (4 H, m, ArH);  $m/z$  249 ( $M^+$ ), 176, 148, 142, 84, and 42.

2-(3-Hydroxyphenyl)-1,3,4-trimethyl-1,2,5,6-tetrahydropyridine (6).—A solution of the piperidinol (5) (0.66 g, 2.65 mmol) in 48% hydrobromic acid (10 cm<sup>3</sup>) was refluxed for 5 h. The reaction mixture was basified with aqueous sodium carbonate solution and extracted with chloroform. The extract was dried (MgSO<sub>4</sub>) and evaporated to give the tetrahydropyridine (6) (0.36 g, 63%), m.p. 137–138 °C (from acetone) (Found: C, 77.1; H, 8.6; N, 6.3. C<sub>15</sub>H<sub>21</sub>NO requires C, 77.4; H, 8.8; N, 6.45%);  $\nu_{\text{max}}$ (KBr) 2 100–3 500 cm<sup>-1</sup> (OH);  $\delta_{\text{H}}$ (CDCl<sub>3</sub>) 1.32 (3 H, s, 3-Me), 1.65 (3 H, s, 4-Me), 2.11 (3 H, s, NMe), 3.52 (1 H, s, 2-H), 6.5–7.2 (4 H, m, ArH), and 7.60 (1 H, s, OH);  $m/z$  217 ( $M^+$ ), 202, and 124.

*trans*-1-Formyl-2-(3-methoxyphenyl)-3-methyl-4-piperidone (4).—A mixture of anhydrous formic acid (6.27 g, 0.13 mol) and acetic anhydride (13.9 g, 0.13 mol) was stirred at 60 °C for 1 h. Then a solution of piperidone (3)<sup>12</sup> (6.67 g, 0.026 mol) in tetrahydrofuran (10 cm<sup>3</sup>) was added, and the resulting mixture

was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, basified with sodium carbonate solution, and extracted with chloroform. The extract was dried ( $\text{MgSO}_4$ ) and evaporated to give the *formylpiperidone* (**4**) (6.6 g, 87%), b.p. 240 °C/0.1 mmHg (Found: C, 67.9; H, 7.35; N, 5.6.  $\text{C}_{14}\text{H}_{17}\text{NO}_3$  requires C, 68.0; H, 6.95; N, 5.7%;  $v_{\text{max.}}$ (NaCl) 1 715 (ketone C=O) and 1 670  $\text{cm}^{-1}$  (amide C=O);  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) 1.22 and 1.27 (3 H, 2 d,  $J$  7 Hz, 3-Me), 3.79 and 3.81 (3 H, 2 s, OMe), 4.50 and 5.54 (1 H, 2 d,  $J$  5 Hz, 2-H), 6.6—7.4 (4 H, m, ArH), and 8.25 and 8.33 (1 H, 2 s, CHO);  $m/z$  247 ( $M^+$ ), 218 ( $M^+ - \text{CHO}$ ), 162 (ArCH=NHCH=CH<sub>2</sub>), and 148 (100%, ArCH=N=CH<sub>2</sub>). The *trans*-piperidone (**4**) slowly epimerized to give the *cis*-isomer (**7**), easily distinguishable from the n.m.r. of the mixture;  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) 1.07 and 1.09 (3 H, 2 d,  $J$  7 Hz, 3-CH<sub>3</sub>), 3.77 and 3.81 (3 H, 2 s, OCH<sub>3</sub>), 5.08 and 6.06 (1 H, 2 d,  $J$  7 Hz, 2-H), and 8.15 and 8.43 (1 H, 2 s, CHO).

*trans*-1-Formyl-3-methyl-2-(3,4,5-trimethoxyphenyl)-4-piperidone (**17**).—Operating as above, from the piperidone (**16**)<sup>30</sup> (9.3 g, 33 mmol), anhydrous formic acid (14.7 g, 0.32 mol), and acetic anhydride (29.5 g, 0.29 mol), the *formylpiperidone* (**17**) (8.6 g, 85%) was obtained, m.p. 117—119 °C (from ether-acetone) (Found: C, 62.2; H, 6.85; N, 4.54.  $\text{C}_{16}\text{H}_{21}\text{NO}_5$  requires C, 62.5; H, 6.9; N, 4.55%;  $v_{\text{max.}}$ (KBr) 1 720 (ketone C=O), 1 660 (amide C=O), and 1 130  $\text{cm}^{-1}$  (OMe);  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 1.25 and 1.30 (3 H, 2 d,  $J$  7 Hz, 3-Me), 3.75 (9 H, s, OMe), 4.50 and 5.50 (1 H, 2 d,  $J$  5 Hz, 2-H), 6.38 and 6.42 (2 H, 2 s, ArH), and 8.15 and 8.20 (1 H, 2 s, CHO).

5-Ethoxy-2-formyl-8-methoxy-10-methyl-2,3,4,5-tetrahydro-1H-1,5-methano-2-benzazepine (**8**).—A solution of the piperidone (**4**) (1.5 g, 6 mmol) in boron trifluoride-ether (15  $\text{cm}^3$ ) was stirred under nitrogen at 105—110 °C for 5 h. The resulting mixture was poured into a saturated solution of ammonium chloride and basified with sodium carbonate. Extraction with chloroform afforded an oil which by <sup>1</sup>H n.m.r. was found to be a 1:3 mixture of the benzazepines (**8 $\alpha$** ) and (**8 $\beta$** ). The major  $\beta$ -isomer (1.09 g, 65%) was isolated as an oil by column chromatography on elution with benzene-chloroform (3:7) (Found: C, 67.1; H, 7.65; N, 5.0.  $\text{C}_{16}\text{H}_{21}\text{NO}_3 \cdot 0.5\text{H}_2\text{O}$  requires C, 67.6; H, 7.8; N, 4.9%;  $v_{\text{max.}}$ (NaCl) 1 660  $\text{cm}^{-1}$  (NCO);  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 1.00 (3 H, d,  $J$  7 Hz, 10-Me), 1.20 (3 H, t,  $J$  7 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.40 (2 H, q,  $J$  7 Hz, OCH<sub>2</sub>), 3.70 (3 H, s, OMe), 4.50 and 5.45 (1 H, 2 d,  $J$  5 Hz, 1-H), 6.7—7.2 (3 H, m, ArH), and 7.97 and 8.00 (1 H, 2 s, CHO);  $m/z$  275 ( $M^+$ ), 246 ( $M^+ - \text{CHO}$ ), 218, 204, and 175. The  $\alpha$ -isomer could be detected from the n.m.r. of the reaction mixture;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 0.80 (3 H, d,  $J$  7 Hz, 10-Me), 4.45 and 5.30 (1 H, 2 s, 1-H), and 7.87 and 8.10 (1 H, 2 s, CHO).

5-Ethoxy-2-formyl-6,7,8-trimethoxy-10-methyl-2,3,4,5-tetrahydro-1H-1,5-methano-2-benzazepine (**18**).—Operating as above, from the piperidone (**17**) (750 mg, 2.44 mmol) and boron trifluoride-ether (15  $\text{cm}^3$ ), the benzazepines (**18 $\alpha$** ) and (**18 $\beta$** ) (1:3) were obtained. The major  $\beta$ -isomer (0.43 g, 53%) was isolated as an oil by column chromatography on elution with benzene-chloroform (2:8) (Found: C, 64.2; H, 7.65; N, 4.05.  $\text{C}_{18}\text{H}_{25}\text{NO}_5$  requires C, 64.45; H, 7.5; N, 4.2%;  $v_{\text{max.}}$ (NaCl) 1 650  $\text{cm}^{-1}$  (NCO);  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) 1.05 and 1.06 (3 H, 2 d,  $J$  7 Hz, 10-Me), 1.39 (3 H, t,  $J$  7 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.40 (2 H, q,  $J$  7 Hz, OCH<sub>2</sub>), 3.83 and 3.86 (3 H, 2 s, OMe), 3.85 and 3.87 (3 H, 2 s, OMe), 4.02 and 4.03 (3 H, 2 s, OMe), 4.50 and 5.50 (1 H, 2 d,  $J$  5 Hz, 1-H), 6.59 and 6.66 (1 H, 2 s, ArH), and 8.11 and 8.12 (1 H, 2 s, CHO);  $m/z$  335 ( $M^+$ ), 321, 307, 278, 264, 250, 236, 219, 206, and 43 (100%).

2-Formyl-5-hydroxy-8-methoxy-10-methyl-2,3,4,5-tetrahydro-1H-1,5-methano-2-benzazepine (**11**).—Freshly sublimed anhydrous aluminium chloride (2 g, 15 mmol) was added to a solution of the piperidone (**4**) (2 g, 8.1 mmol) in nitromethane (15  $\text{cm}^3$ ), and the resulting mixture was heated at 90 °C for 3 h under nitrogen. The solvent was distilled off, the residue was dissolved in 2M-hydrochloric acid and extracted with 3:1 chloroform-methanol. The aqueous solution was basified with sodium carbonate and extracted with chloroform. The combined organic extracts were washed with aqueous sodium carbonate, dried ( $\text{MgSO}_4$ ), and evaporated to give the benzazepines (**11 $\alpha$** ) and (**11 $\beta$** ) (1:3; 1.3 g, 68%), b.p. 240 °C/0.2 mmHg (Found: C, 67.8; H, 7.05; N, 5.45.  $\text{C}_{14}\text{H}_{17}\text{NO}_3$  requires C, 68.0; H, 6.95; N, 5.75%;  $v_{\text{max.}}$ ( $\text{CHCl}_3$ ) 3 100—3 500 (OH) and 1 650  $\text{cm}^{-1}$  (NCO);  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 0.85 and 1.00 (3 H, 2 d,  $J$  7 Hz,  $\alpha$  and  $\beta$  10-Me), 3.70 (3 H, s, OMe), 4.40 and 5.25 (2 br, 1-H  $\alpha$ -isomer), 4.45 and 5.35 (2 d,  $J$  5 Hz, 1-H  $\beta$ -isomer), 6.6—7.3 (3 H, m, ArH), 7.80 and 8.00 (2 s, CHO  $\alpha$ -isomer), and 7.90 and 7.95 (2 s, CHO  $\beta$ -isomer);  $m/z$  247 ( $M^+$ ), 218 ( $M^+ - \text{CHO}$ ), 190, 176, 175, and 174 (100%).

5-Ethoxy-8-methoxy-10-methyl-2,3,4,5-tetrahydro-1H-1,5-methano-2-benzazepine (**9**).—A solution of the benzazepines (**8**) (0.1 g, 0.36 mmol) in 20% hydrochloric acid (15  $\text{cm}^3$ ) and methanol (10  $\text{cm}^3$ ) was refluxed for 2 h. After evaporation of the methanol, the aqueous solution was basified with sodium carbonate solution and extracted with chloroform. The organic layer was dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to give a 1:4 mixture of  $\alpha$ - and  $\beta$ -isomers as a yellow oil (80 mg, 89%). After recrystallization of the hydrochloride from acetone, the major isomer (**9 $\beta$** ) was obtained, m.p. 242—244 °C (Found: C, 61.6; H, 7.7; N, 4.45.  $\text{C}_{15}\text{H}_{22}\text{ClNO}_2 \cdot 0.5\text{H}_2\text{O}$  requires C, 61.5; H, 7.9; N, 4.8%;  $v_{\text{max.}}$ (KBr) 1 270 and 1 140  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$ ( $\text{CDCl}_3$ ) 1.20 (3 H, d,  $J$  7 Hz, 10-Me), 1.35 (3 H, t,  $J$  7 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.38 (2 H, q,  $J$  7 Hz, OCH<sub>2</sub>), 3.80 (3 H, s, OMe), 4.60 (1 H, br, 1-H), and 6.8—7.3 (3 H, m, ArH);  $m/z$  247 ( $M^+$ ), 218 (100%,  $M^+ - \text{Et}$ ), 202, 190, and 173.

5-Hydroxy-8-methoxy-10-methyl-2,3,4,5-tetrahydro-1H-1,5-methano-2-benzazepine (**12**).—Operating as above, from a mixture of the benzazepines (**11**) (1.3 g, 5.26 mmol), an oil (**12**) (0.76 g, 66%) was obtained. After recrystallization of the hydrochloride, the major isomer (**12 $\beta$** ) was separated, m.p. 269—270 °C (from acetone-ether) (Found: C, 61.2; H, 7.25; Cl, 14.15; N, 5.7.  $\text{C}_{13}\text{H}_{18}\text{ClNO}_2$  requires C, 61.05; H, 7.1; Cl, 13.85; N, 5.5%;  $v_{\text{max.}}$ (KBr) 3 340 (OH), 2 800 (NH), and 1 140  $\text{cm}^{-1}$ . From a sample of (**12 $\beta$** )-hydrochloride, the free base was obtained;  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) 1.20 (3 H, d,  $J$  7 Hz, 10-Me), 3.80 (3 H, s, OMe), 4.03 (1 H, d,  $J$  4 Hz, 1-H), and 6.8—7.2 (3 H, m, ArH);  $\delta_{\text{C}}$ ( $\text{CDCl}_3$ ) 159.48 (s, C-8), 141.74 (s, C-9a), 141.00 (s, C-5a), 121.01 (d, C-6), 113.41 (d, C-7), 109.54 (d, C-9), 79.02 (s, C-5), 60.65 (d, C-1), 55.43 (q, OMe), 51.74 (d, C-10), 39.49 (t, C-3), 31.13 (t, C-4), and 9.21 p.p.m. (q, 10-Me);  $m/z$  219 ( $M^+$ ), 190, 176 (100%), 175, and 161.

5-Ethoxy-8-methoxy-2,10-dimethyl-2,3,4,5-tetrahydro-1H-1,5-methano-2-benzazepine (**10**).—Lithium aluminium hydride (1 g, 26 mmol) was slowly added to a solution of the benzazepines (**8**) (1.36 g, 4.9 mmol) in anhydrous dimethoxyethane (15  $\text{cm}^3$ ). The mixture was stirred at room temperature for 2 h, and then methanol (15  $\text{cm}^3$ ) and water (50  $\text{cm}^3$ ) were added dropwise. The mixture was stirred for 15 min and filtered. The precipitate was washed with chloroform and the filtered solution was extracted with chloroform. The combined chloroform solutions were dried ( $\text{MgSO}_4$ ) and evaporated to give an oil which by <sup>1</sup>H n.m.r. was found to be a 1:3 mixture of  $\alpha$ - and  $\beta$ -benzazepines (**10**) (0.96 g, 75%). Column chrom-

atography with benzene–chloroform (1:9) as eluant afforded the *major isomer* (**10 $\beta$** ) as an oil;  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) 1.21 (3 H, d,  $J$  7 Hz, 10-Me), 1.24 (3 H, t,  $J$  7 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.17 (3 H, s, NMe), 3.41 (2 H, q,  $J$  7 Hz,  $\text{OCH}_2$ ), 3.64 (1 H, d,  $J$  4 Hz, 1-H), 3.83 (3 H, s, OMe), 6.74 (1 H, d,  $J$  2.4 Hz, 9-H), 6.84 (1 H, dd,  $J$  2.4 and 8 Hz, 7-H), and 7.14 (1 H, d,  $J$  8 Hz, 6-H);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 158.75 (s, C-8), 139.23 (s, C-9a), 137.89 (s, C-5a), 121.63 (d, C-6), 112.20 (d, C-7), 111.21 (d, C-9), 84.24 (s, C-5), 67.42 (d, C-1), 57.46 (t,  $\text{OCH}_2$ ), 55.44 (q, OMe), 48.78 (t, C-3), 45.56 (d, C-10), 43.13 (q, NMe), 30.39 (t, C-4), 15.93 (q,  $\text{OCH}_2\text{CH}_3$ ), and 9.33 p.p.m. (q, 10-Me);  $m/z$  261 ( $M^+$ ), 232 ( $M^+ - \text{Et}$ ), 216 ( $M^+ - \text{OEt}$ ), 204, 203, 174, and 173 (100%). Crystallization as the *picrate* gave a solid, m.p. 161–162 °C (from ethanol) (Found: C, 54.15; H, 5.4; N, 11.25.  $\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_9$  requires C, 53.9; H, 5.35; N, 11.45%);  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) 1.19 (3 H, d,  $J$  7 Hz, 10-Me), 1.19 (3 H, t,  $J$  7 Hz,  $\text{OCH}_2\text{CH}_3$ ), 1.61 (1 H, dd,  $J$  5 and 13 Hz, 4- $H_{\text{eq}}$ ), 1.8–2.0 (1 H, m, 3- $H_{\text{ax}}$ ), 2.3–2.5 (1 H, ddd,  $J$  6, 13.5 and 13.5 Hz, 4- $H_{\text{ax}}$ ), 2.66 (3 H, d,  $J$  4 Hz, NMe), 2.7–2.8 (1 H, m, 10- $H_{\text{eq}}$ ), 3.32 (2 H, q,  $J$  7 Hz,  $\text{OCH}_2$ ), 3.5–3.6 (1 H, m, 3- $H_{\text{eq}}$ ), 3.81 (3 H, s, OMe), 4.50 (1 H, d,  $J$  3.5 Hz, 1-H), 6.93 (1 H, d,  $J$  2.3 Hz, 9-H), 7.01 (1 H, dd,  $J$  2.3 and 8.2 Hz, 7-H), and 7.23 (1 H, d,  $J$  8.2 Hz, 6-H).

The  $\alpha$ -*isomer* (**10 $\alpha$** ) was obtained on elution with chloroform–methanol (99:1) and was recrystallized as the *picrate*, m.p. 191–192 °C (from ethanol) (Found: C, 54.2; H, 5.35; N, 11.1.  $\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_6$  requires C, 53.9; H, 5.35; N, 11.1%);  $\delta_{\text{H}}$  (200 MHz;  $\text{CDCl}_3$ ) 0.76 (3 H, d,  $J$  7 Hz, 10-Me), 1.21 (3 H, t,  $J$  7 Hz,  $\text{OCH}_2\text{CH}_3$ ), 1.66 (1 H, dd,  $J$  5 and 13 Hz, 4- $H_{\text{eq}}$ ), 1.9–2.1 (1 H, m, 3- $H_{\text{ax}}$ ), 2.67 (3 H, d,  $J$  4.8 Hz, NMe), 2.7–2.9 (1 H, ddd,  $J$  6, 12.6 and 12.6 Hz, 4- $H_{\text{ax}}$ ), 3.11 (1 H, q,  $J$  7 Hz, 10- $H_{\text{ax}}$ ), 3.3–3.5 (1 H, m, 3- $H_{\text{eq}}$ ), 3.6–3.7 (2 H, m,  $\text{OCH}_2$ ), 3.80 (3 H, s, OMe), 4.28 (1 H, s, 1-H), 6.86 (1 H, d,  $J$  2.3 Hz, 9-H), 6.99 (1 H, dd,  $J$  2.3 and 8.2 Hz, 7-H), and 7.23 (1 H, d,  $J$  8.2 Hz, 6-H).

*5-Hydroxy-8-methoxy-2,10-dimethyl-2,3,4,5-tetrahydro-1H-1,5-methano-2-benzazepine* (**13**).—Operating as above, from the benzazepines (**11**) (1.13 g, 4.57 mmol) the product (0.8 g, 75%) was obtained as a mixture of  $\alpha$ - and  $\beta$ -isomers, which were separated by column chromatography. Elution with chloroform gave the  $\beta$ -*isomer*, m.p. 114–115 °C (from ether);  $\nu_{\text{max}}$  (KBr) 3 100–3 500  $\text{cm}^{-1}$  (OH);  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.20 (3 H, d,  $J$  6 Hz, 10-Me), 2.10 (3 H, s, NMe), 3.48 (1 H, d,  $J$  4 Hz, 1-H), 3.70 (3 H, s, OMe), and 6.5–7.2 (3 H, m, ArH);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 158.70 (s, C-8), 140.83 (s, C-5a), 138.62 (s, C-9a), 120.91 (d, C-6), 112.19 (d, C-7), 110.98 (d, C-9), 79.37 (s, C-5), 67.75 (d, C-1), 55.43 (q, OMe), 52.31 (d, C-10), 48.87 (t, C-3), 43.06 (q, NMe), 30.38 (t, C-4), and 9.29 p.p.m. (q, 10-Me);  $m/z$  233 ( $M^+$ ), 190 (100%), 175, 172, 161, and 115. A sample of this *isomer* was recrystallized as the *hydrochloride*, m.p. 238–239 °C (from ethanol) (Found: C, 62.05; H, 7.55; N, 5.05.  $\text{C}_{14}\text{H}_{20}\text{ClNO}_2$  requires C, 62.3; H, 7.5; N, 5.2%).

Elution with chloroform–methanol (95:5) afforded the  $\alpha$ -*isomer*, m.p. 140–142 °C (from benzene–hexane);  $\nu_{\text{max}}$  (KBr) 3 300–3 400  $\text{cm}^{-1}$  (OH);  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 0.80 (3 H, d,  $J$  7 Hz, 10-Me), 2.15 (3 H, s, NMe), 3.50 (1 H, br s, 1-H), 3.73 (3 H, s, OMe), and 6.5–7.2 (3 H, m, ArH);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 159.27 (s, C-8), 137.18 (s, C-5a), 136.85 (s, C-9a), 122.32 (d, C-6), 112.94 (d, C-7 or C-9), 112.33 (d, C-9 or C-7), 81.48 (s, C-5), 71.05 (d, C-1), 55.47 (q, OMe), 54.94 (d, C-10), 49.90 (t, C-3), 42.61 (q, NMe), 37.61 (t, C-4), and 11.85 p.p.m. (q, 10-Me).

*5-Ethoxy-6,7,8-trimethoxy-2,10-dimethyl-2,3,4,5-tetrahydro-1H-1,5-methano-2-benzazepine* (**19**).—Operating as above from the benzazepines (**18**) (0.69 g, 2.06 mmol) in anhydrous tetrahydrofuran (15  $\text{cm}^3$ ) and lithium aluminium hydride (0.25 g, 6.59 mmol), the benzazepine (**19**) was obtained (0.57 g, 86%) as a mixture of  $\alpha$ - and  $\beta$ -isomers. After column chromatography

with chloroform as eluant, the major  $\beta$ -*isomer* (**19 $\beta$** ) was obtained and recrystallized as the *hydrochloride*, m.p. 176–178 °C (from acetone) (Found: C, 59.15; H, 8.3; N, 3.9.  $\text{C}_{18}\text{H}_{28}\text{ClNO}_4 \cdot 0.5\text{H}_2\text{O}$  requires C, 58.9; H, 8.0; N, 3.8%);  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.30 (3 H, d,  $J$  7 Hz, 10-Me), 1.35 (3 H, t,  $J$  7 Hz,  $\text{OCH}_2\text{CH}_3$ ), 2.15 (3 H, s, NMe), 3.45 (2 H, q,  $J$  7 Hz,  $\text{OCH}_2$ ), 3.50 (1 H, d,  $J$  4 Hz, 1-H), 3.80 (6 H, s, OMe), 3.85 (3 H, s, OMe), and 6.35 (1 H, s, ArH).

*5-Acetoxy-8-methoxy-2,10-dimethyl-2,3,4,5-tetrahydro-1H-1,5-methano-2-benzazepine* (**14**).—A mixture of the benzazepine (**13 $\beta$** ) (0.95 g, 4.0 mmol), triethylamine (2  $\text{cm}^3$ ), and acetic anhydride (15  $\text{cm}^3$ ) was heated at 80 °C for 4 h under nitrogen. The reaction mixture was poured into ice–water, basified with aqueous sodium carbonate, and extracted with chloroform. The organic layer was washed with water, dried ( $\text{MgSO}_4$ ), and evaporated to give the *product* (**14 $\beta$** ) (0.64 g, 57%) as an oil which was purified by preparative t.l.c. (Found: C, 69.55; H, 7.75; N, 4.9.  $\text{C}_{16}\text{H}_{21}\text{NO}_3$  requires C, 69.8; H, 7.7; N, 5.1%);  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 1 720  $\text{cm}^{-1}$  (C=O);  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.12 (3 H, d,  $J$  7 Hz, 10-Me), 1.98 (3 H, s, COMe), 2.03 (3 H, s, NMe), 3.40 (1 H, d,  $J$  5 Hz, 1-H), 3.70 (3 H, s, OMe), and 6.5–7.1 (3 H, m, ArH);  $m/z$  275 ( $M^+$ ), 216, 200, 173 (100%), 159, and 158.

*8-Methoxy-2,10-dimethyl-5-propionyloxy-2,3,4,5-tetrahydro-1H-1,5-methano-2-benzazepine* (**15**).—Operating as above, from the benzazepine (**13 $\beta$** ) (0.92 g, 3.9 mmol), triethylamine (2  $\text{cm}^3$ ), and propionic anhydride (15  $\text{cm}^3$ ), the *product* (**15**) (0.76 g, 66%) was obtained. An analytically pure sample of the propionyloxy derivative (**15 $\beta$** ) was obtained by column chromatography through aluminium oxide (Fluka 507 C), eluting with benzene–chloroform (9:1), followed by preparative t.l.c. (Found: C, 70.9; H, 7.95; N, 5.2.  $\text{C}_{17}\text{H}_{23}\text{NO}_3$  requires C, 70.6; H, 8.0; N, 4.85%);  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 1 730  $\text{cm}^{-1}$  (C=O);  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.10 (3 H, t,  $J$  7 Hz,  $\text{OCH}_2\text{CH}_3$ ), 1.20 (3 H, d,  $J$  7 Hz, 10-Me), 2.10 (3 H, s, NMe), 2.35 (2 H, q,  $J$  7 Hz,  $\text{COCH}_2$ ), 3.55 (1 H, d,  $J$  5 Hz, 1-H), 3.70 (3 H, s, OMe), and 6.6–7.2 (3 H, m, ArH);  $m/z$  289 ( $M^+$ ), 216, 200, 173 (100%), and 158.

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## References

- Part 19, J. Bosch, M. Rubiralta, N. Valls, M. Moral, and G. Cao, *An. Quim.*, 1984, **80**C.
- D. C. Palmer and M. J. Strauss, *Chem. Rev.*, 1977, **77**, 1.
- (a) A. E. Jacobson and M. Mokotoff, *J. Med. Chem.*, 1970, **13**, 7; (b) M. Mokotoff and A. E. Jacobson, *J. Heterocycl. Chem.*, 1970, **7**, 773.
- P. H. Mazzocchi and B. C. Stahly, *J. Med. Chem.*, 1979, **22**, 455.
- (a) K. Mitsuhashi, S. Shiotani, R. Oh-Uchi, and K. Shiraki, *Chem. Pharm. Bull.*, 1969, **17**, 434; (b) G. N. Walker and D. Alkalay, *J. Org. Chem.*, 1971, **36**, 491; (c) T. Kometani and S. Shiotani, *J. Med. Chem.*, 1978, **21**, 1105; (d) H. Finch, *Tetrahedron Lett.*, 1982, **23**, 4393.
- (a) F. J. Smith and G. R. Proctor, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2141; (b) G. R. Proctor and F. J. Smith, *ibid.*, 1981, 1754.
- (a) M. Takeda and H. Kugita, *J. Med. Chem.*, 1970, **13**, 630; (b) S. Shiotani, T. Kometani, and K. Mitsuhashi, *Chem. Pharm. Bull.*, 1972, **20**, 277; (c) M. Takeda, H. Inone, M. Konda, S. Saito, and H. Kugita, *J. Org. Chem.*, 1972, **37**, 2677; (d) S. Shiotani and T. Kometani, *Chem. Pharm. Bull.*, 1973, **21**, 1053; (e) S. Shiotani, T. Kometani, and K. Mitsuhashi, *J. Med. Chem.*, 1975, **18**, 1266; (f) S. Shiotani, T. Kometani, K. Mitsuhashi, T. Nozawa, A. Kurobe, and O. Futsukaichi, *ibid.*, 1976, **19**, 803; (g) T. Kometani and S. Shiotani, ref. 5c.
- (a) P. H. Mazzocchi and A. M. Harrison, *J. Med. Chem.*, 1978, **21**, 238; (b) P. H. Mazzocchi and B. C. Stahly, *ibid.*, 1981, **24**, 457; (c) P. H. Mazzocchi, E. W. Kordoski, and R. Rosenthal, *J. Heterocycl. Chem.*, 1982, **19**, 941.

- 9 (a) G. R. Proctor and F. J. Smith, *J. Chem. Res.*, 1980; (S), 286; (b) R. Achini, *Helv. Chim. Acta*, 1981, **64**, 2203; (c) S. J. Miller, G. R. Proctor, and D. I. C. Scoper, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2927.
- 10 (a) J. Bosch, D. Mauleón, and R. Granados, *An. Quim.*, 1982, **78C**, 236; (b) J. Bosch, A. Domingo, and R. Granados, *J. Heterocycl. Chem.*, 1983, **20**, 887; and previous papers of this series.
- 11 (a) J. Bosch, M. Rubiralta, A. Domingo, and J. Sistaré, *J. Heterocycl. Chem.*, 1981, **18**, 47; (b) J. Bosch and M. Rubiralta, *An. Quim.*, 1983, **79C**, 27.
- 12 (a) J. Bosch, M. Rubiralta, and M. Moral, *Heterocycles*, 1982, **19**, 473; (b) J. Bosch, M. Rubiralta, M. Moral, and M. Valls, *J. Heterocycl. Chem.*, 1983, **20**, 595.
- 13 (a) R. E. Ireland, D. A. Evans, D. Glover, G. M. Rubottom, and H. Young, *J. Org. Chem.*, 1969, **34**, 3717; (b) G. Neff, U. Eder, G. Haffer, G. Sauer, and R. Wiechert, *Chem. Ber.*, 1976, **109**, 3025; (c) G. Laus and G. Van Binst, *Tetrahedron*, 1979, **35**, 849; (d) S. Ghosh, R. Dasgupta, J. Chakravarty, and U. R. Ghatak, *J. Chem. Soc., Perkin Trans. 1*, 1980, 804; (e) F. Hahne, and F. Zymalkowski, *Arch. Pharm. (Weinheim, Ger.)*, 1979, **312**, 472.
- 14 (a) M. Takeda and E. L. May, *J. Med. Chem.*, 1970, **13**, 1223; (b) G. Büchi, S. J. Gould, and F. Näf, *J. Am. Chem. Soc.*, 1971, **93**, 2492; (c) R. D. Gless and H. Rapoport, *J. Org. Chem.*, 1979, **44**, 1324.
- 15 J. Bosch and M. Feliz, *An. Quim.*, 1982, **78C**, 240.
- 16 J. Bosch and M. Rubiralta, unpublished data.
- 17 (a) M. Takeda, A. E. Jacobson, K. Kanematsu, and E. L. May, *J. Org. Chem.*, 1969, **34**, 4154; (b) T. Kametani, K. Kigasawa, K. Wakisaka, F. Satoh, T. Aoyama, and H. Ishimaru, *J. Heterocycl. Chem.*, 1971, **8**, 769; (c) T. Kametani, K. Kigasawa, H. Hiiragi, N. Wagatsuma, S. Saitoh, and H. Sugi, *ibid.*, 1973, **10**, 313.
- 18 J. Bosch, D. Mauleón, F. Boncompte, and R. Granados, *J. Heterocycl. Chem.*, 1981, **18**, 263.
- 19 K. C. Rice, W. C. Ripka, J. Reden, and A. Brossi, *J. Org. Chem.*, 1980, **45**, 601.
- 20 K. C. Rice and A. Brossi, *J. Org. Chem.*, 1980, **45**, 592.
- 21 (a) F. Johnson, *Chem. Rev.*, 1968, **68**, 375; (b) R. A. Johnson, *J. Org. Chem.*, 1968, **33**, 3627.
- 22 W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, 1970, **70**, 517.
- 23 (a) H. Paulsen and K. Todt, *Angew. Chem., Int. Ed. Engl.*, 1966, **5**, 899; (b) G. Büchi, S. J. Gould, and F. Näf, ref. 14b; (c) C. Szántay, G. Blaskó, M. Bárczai-Beke, G. Dörnyei, and L. Radics, *Heterocycles*, 1980, **14**, 1127.
- 24 (a) H. Kessler, *Angew. Chem., Int. Ed. Engl.*, 1970, **9**, 219; (b) F. P. Gasparro and N. H. Kolodny, *J. Chem. Educ.*, 1977, **54**, 258.
- 25 T. M. Moyenehan, K. Schofield, R. A. Y. Jones, and R. A. Katritzky, *J. Chem. Soc.*, 1962, 2637.
- 26 (a) S. E. Fullerton, E. L. May, and E. D. Becker, *J. Org. Chem.*, 1962, **27**, 2144; (b) A. F. Casy and A. P. Parulkar, *Can. J. Chem.*, 1969, **47**, 3623.
- 27 M. Alvarez, J. Bosch, R. Granados, and F. López, *J. Heterocycl. Chem.*, 1978, **15**, 193.
- 28 M. Alvarez, J. Bosch, and M. Feliz, *J. Heterocycl. Chem.*, 1978, **15**, 1089.
- 29 M. Karplus, *J. Chem. Phys.*, 1959, **30**, 11.
- 30 J. Bosch, M. Moral, M. Rubiralta, and J. Bolós, presented at the 2nd Congreso Internacional de Ciencias Farmacéticas, Barcelona, Spain, 1983.
- 31 A. F. Casy, A. O. Ogundaini, and R. T. Parfitt, *Org. Magn. Reson.*, 1982, **20**, 254.

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