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# STRUCTURE AND SPECTROSCOPY OF PRODUCTS DERIVED FROM SOME 3-AMINO-1,1-DIPHENYLPROPANES AND CYANOGEN BROMIDE

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**Abstract** Reaction between cyanogen bromide and some 3-amino-1,1-diphenylpropanes, variously substituted at C-1, leads either to N-cyano derivatives or to tetrahydrofurans The spectroscopy of these products is reported and discussed, and the configurations of *cis* and *trans* 2-ethyl-5-methyl-3,3-diphenyltetrahydrofuran assigned on the basis of differences in their PMR spectra

CONVERSION of the readily available 3-t-amino-1,1-diphenylpropyl cyanides Ia and IIa and derived compounds to corresponding 3-sec-amino derivatives by the von Braun cyanogen bromide procedure offers a potential route to intermediates required for the synthesis of N-alkyl and aralkyl analogues of methadone and related analgesics. Reaction of the cyanides Ia and IIa and the ketones Ib, IIIb and IVb has previously been reported[1, 2] and, in this paper, the effect of cyanogen bromide upon other t-amino-1,1-diphenylpropane derivatives is studied and some spectroscopic properties of the products discussed.

The dimethylamino cyanides Ia and IIa react with cyanogen bromide to give cyanomethyl derivatives;[1] the morpholino (IIIa) and piperidino (IIa, $NMe_2$ replaced by 1-piperidino) analogues reacted similarly (after a more prolonged reaction period), with opening of the heterocyclic rings, giving the N-bromo-oxyalkyl and N-bromoalkyl-cyano derivatives Vb and VId respectively. Hydrolysis of Vb and VId proceeded in the same way as that of the cyanomethyl cyanides Va and VIa,[1] 2-iminopyrrolidines rather than sec-amines being formed. The terminal OH group of the cyclic product VIIIe, derived from VId, was unaffected by ethanolic hydrogen chloride, while that of the pyrrolidine from Vb was displaced by chloride to yield the derivative VIIf (mass spectrometry evidence†). It has been shown that the amino-ketones Ib, IIIb and IVb lose their basic group and cyclize to form the tetrahydrofuran IXa or X when treated with cyanogen bromide[1,2] and it is now

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† Molecular, stable and metastable ion peaks were in accord with assigned structures. A stable ion was formed from VIIf by cleavage of $(CH_2)_2Cl$, and from VIIIe by cleavage of $(CH_2)_4OH$ from the N-1 side chain

[1] N J Harper, D Jones and A B. Simmonds; *J. Chem. Soc.* (C), 438 (1966).

[2] A F Casy and M M A Hassan; *J. Chem. Soc* (C), 683 (1966).

reported that the 3-amino-1,1-diphenylpropanes Ic–f behave similarly in this reaction. Thus, α-methadol (Ic) was converted to the 2-ethyltetrahydrofuran IXb β-methadol giving the corresponding diastereoisomer (these cyclic ethers are also obtained by the pyrolysis of the methiodides of α- and β-methadol);[3] [4] the amino amide Id gave the 2-iminotetrahydrofuran IXc, while both the amino acid Ie and the amino-ester If were converted to the 2-ketotetrahydrofuran IXd. In most of the above experiments, substrate hydrobromides were isolated in addition to cyclic products, the yield of the tetrahydrofuran being improved, with methadone as substrate, by including potassium carbonate as acid-absorbent in the reaction mixture. α-Acetylmethadol (Ig) and cyanogen bromide gave the substrate hydrobromide and a non-basic product consisting of approximately equal parts of the cyanomethyl derivative XI and the α-tetrahydrofuran IXb (proportions assessed from PMR integral data). The cyanogen bromide-induced conversion of the amino ketones IIb and IVb (derivatives with a Me substituent α- to the quaternary carbon atom) to a tetrahydrofuran occurred less readily than that of the β-methyl analogues Ib and IIIb. The tetrahydrofuran X was isolated in low yield from the morpholino ketone-derived reaction product[2] while PMR evidence indicated the non-basic product from isomethadone (IIb) to consist chiefly of the cyclic ether X and the cyanomethyl ketone IIb ($NMe_2$ replaced by NMeCN). The amino ketimines IIh and IVh and cyanogen bromide gave the cyano derivatives XIIa and b respectively (isolated as hydrobromides), spectroscopic evidence (below) showing the cyano group to be attached to the imino, rather than the 3-amino, nitrogen atom.

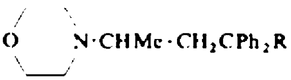
These reactions show that 3-amino-3-methyl-1,1-diphenylpropanes only yield 3-N-cyano derivatives with cyanogen bromide when an oxygen function on carbon δ- to the amino group is either absent (as in the cyanides I–IVa) or substituted (as in α-acetylmethadol Ig); since methiodides of 3-amino-1,1-diphenylpropanes undergo analogous cyclizations on pyrolysis,[3] those induced by cyanogen bromide probably proceed by the rearward approach of oxygen upon nitrogen in the quaternary state $[R_2\overset{+}{N}(CN)\quad]$.

$NMe_2 \cdot CHMe \cdot CH_2 \cdot CPh_2R$

I

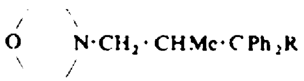
$NMe_2 \cdot CH_2CHMe \cdot CPh_2R$

II



$O(CH_2CH_2)_2N \cdot CHMe \cdot CH_2CPh_2R$

III



$O(CH_2CH_2)_2N \cdot CH_2 \cdot CHMe \cdot CPh_2R$

IV

In I–IV, R = (a) CN, (b) COEt, (c) CH(OH)Et, (d) $CONH_2$, (e) $CO_2H$, (f) $CO_2Et$, (g) CH(OCOMe)Et, (h) C=NH·Et

$RN(CN) \cdot CHMe \cdot CH_2 \cdot CPh_2CN$

V

$RN(CN) \cdot CH_2 \cdot CHMe \cdot CPh_2CN$

VI

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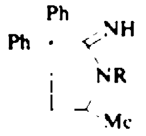
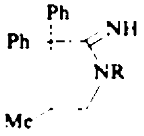
[3] N. R. Easton, S. J. Nelson and V. B. Fish; *J. Am. Chem. Soc.* 77, 2547 (1955).

[4] P. S. Portoghese and D. A. Williams; *J. Pharm. Sci.* 55, 990 (1966).

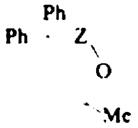


VII

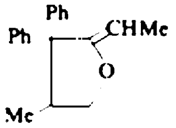


VIII

In V VIII, R = (a) Me, (b) $(CH_2)_2O(CH_2)_2Br$, (c) $(CH_2)_2O(CH_2)_2N(CH_2)_5$,
(d) $(CH_2)_5$ Br, (e) $(CH_2)_5OH$, (f) $(CH_2)_2O(CH_2)_2Cl$



IX



X

Z = (a) C:CHMe, (b) CHEt,
(c) C:NH, (d) C:O

$MeN(CN)\cdot CHMe\cdot CH_2\cdot CPh_2\cdot CH(OCOMe)Et$

XI

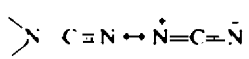
$R\cdot CH_2\cdot CHMe\cdot CPh_2\cdot C{:}(NCN)Et$

XII

R = (a) $NMe_2$, (b) 1-morpholino

*IR spectroscopy*

The IR spectra of the N-cyanopropyl cyanides Va and b, VIa and d show intense absorption bands at 2200 cm$^{-1}$, the C—CN bands of the precursor t-amino cyanides (also near 2200 cm$^{-1}$) being very weak. Similarly placed bands occur in the spectra of the N-cyano-ester XI (m) and the ketimines XIIa and b (s). The high intensity of $\nu_{C\equiv N}$ in the N-cyano function is probably due to the cyanide triple bond being more polar when linked to nitrogen than when joined to a saturated carbon atom as a result of contributions from the resonance form XIII. The iminopyrrolidines VIIa



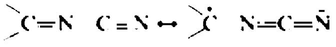
XIII

and f and VIIIc have $\nu_{C=N}$ frequencies near 1630 cm$^{-1}$ (s), moved to near 1685 cm$^{-1}$ in corresponding hydrochlorides (displacement of these bands to higher frequencies in salts is in accord with the C=N bond being less polar when the adjacent pyrrolidino nitrogen atom is positively charged). In contrast with the related acyclic ketimines IIh and IVh, the pyrrolidines have well defined $\nu_{N-H}$ bands near 3300 cm$^{-1}$ (m), but no clear N–H deformation bands (the ketimines have bands of this nature near 1720 cm$^{-1}$);[2] in corresponding hydrochlorides, bands in the region 2750–2300 cm$^{-1}$, characteristic of $\nu_{\overset{+}{N}-H}$ in t-amine salts,[5] are absent, hence imino nitrogen is the protonation site (double bond shifts to endocyclic $C_2$—NR position).

[5] C N R Rao, *Chemical Applications of Infrared Spectroscopy* Academic Press, New York (1963)

All the tetrahydrofurans, except the α- and β-2-ethyl derivatives IXb, have IR spectra which show strong absorption bands in the 1650–1760 $cm^{-1}$ region. The relative positions of the $\nu_{C=N}$ bands in the iminotetrahydrofuran IXc (1678 $cm^{-1}$) and the iminopyrrolidines VII and VIII (near 1630 $cm^{-1}$) reflects the greater electronegative influence of oxygen upon the C=N bond. The $\nu_{C=O}$ band in the 2-ketotetrahydrofuran IXd occurs at 1757 $cm^{-1}$ (s), a value characteristic of saturated γ-lactones.[5] Both 2-ethylidene derivatives IXa and X show $\nu_{C=C}$ bands near 1685 $cm^{-1}$ (s), the high intensity of these bands being attributed to the polarizing influence of the oxygen atom adjacent to the carbon carbon double bond (cf. the relative intensities of $\nu_{C\equiv N}$ in the C–CN and N–CN functions discussed above).[*]

In the spectra of the cyano-ketimines XIIa and b, the strong intensity of the $\nu_{C\equiv N}$ bands near 2200 $cm^{-1}$ is considered the result of resonance interaction between the cyano group and the adjacent imino nitrogen atom (XIV). The same interaction



XIV

should also render the imine C=N bond more polar and, in accord with this interpretation, the $\nu_{C=N}$ band in the cyano-ketimines is near 1600 $cm^{-1}$ (s), its position in the precursor ketimines being approximately 1630 $cm^{-1}$ (m).[2] The N-cyano derivatives XIIa and b show significant UV absorption ($\lambda_{max}$ 244 mμ ε 6000 approx in ethanol) as anticipated from the conjugated nature of the cyano-ketimine function (the acyclic ketimine IIh exhibits benzenoid absorption only).

*PMR spectroscopy*

The PMR spectral characteristics of the acyclic and cyclic products derived from 3-amino-1,1-diphenylpropanes and cyanogen bromide are given in Tables 1 and 2 respectively. Comparison of N-methyl and sec-methyl chemical shifts in the N-cyano derivatives (Table 1, 1–5) with those of the precursor t-amines (Table 3) demonstrates the deshielding influence of the N-cyano group upon these proton groups. In the case of sec-methyl, this influence is much greater in derivatives with Me groups α- to cyanomethyl (Table 1.1, 3 and 5) than in those with β-substituents (2 and 4) and is unusually high in the case of the α-acetylmethadol-derived product (5). The similar chemical shift values for N-methyl in the cyano-ketimine XIIa and its precursor IIh show the dimethylamino group to be intact in the former compound (as does also the nature and integral of the signal in the corresponding hydrobromide), in support of its formulation as XIIa.

In the cyclic derivatives (Table 2) the sec-methyl chemical shifts fall in the range 81·5–85 c/s when Me is α- to protonated nitrogen (Table 2.1 and 3 hydrochlorides) or to oxygen (Table 2.5–7 and 11) except in the case of the α-tetrahydrofuran (Table 2.8); when sec-Me is β- to the heteroatom its chemical shift is near 50 c/s (Table 2.2, 4 and 10), the higher field values being attributed to aromatic screening as follows. A favoured conformation for 4-methyltetrahydrofurans will be one in which the

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[*] The significantly lower wave-numbers of $\nu_{C=C}$ bands in related acyclic vinyl ethers (near 1611 and 1634 $cm^{-1}$)[6] may be related to greater *p*-orbital interaction in the cyclic ethers as a result of restricted rotation about the O–C vinylic bond.

[6] W. H. T. Davison and G. R. Bates, *J. Chem. Soc.* 2607 (1953)

TABLE 1. PMR CHARACTERISTICS OF SOME N-CYANO-3-AMINO-1,1-DIPHENYLPROPANES

| No. | Compound | PMR signals[a] Aryl | N-Me | sec-Me | Others |
|---|---|---|---|---|---|
| 1 | Va | 444[b] | 157·5[b] | 75[c] (6·5) | |
| 2 | VIa | 447[d] ($W_H$ 15) | 169[b] | 72[e] ($J$ 6·5) | |
| 3 | Vb[f] | 444[d] | | 76[c] (6) | |
| 4 | VId | 448, 446[d] ($W_H$ 16) | | 73[e] ($J$ 6·5) | |
| 5 | XI | 442, 437[d] | 146[b] | 63[c] (6) | 122[b] $\mathrm{O\underline{Me}}$<br>50[g] (5) $\mathrm{OCH_2\underline{Me}}$ |
| 6 | XIIa HBr | 446[d] | 183, 169[o] ($W_H$ 8) | 77[e] ($J$ 7) | 223[p] ($J$ 7) $\mathrm{\underline{C}H_2Me}$<br>26[q] ($J$ 7) $\mathrm{CH_2Me}$ |
| | XIIa base | 438[d] | 131[b] | 51[e] ($J$ 6·5) | 154[p] ($J$ 7) $\mathrm{CH_2Me}$<br>26[q] ($J$ 7) $\mathrm{CH_2\underline{Me}}$ |
| 7 | XIIb base | 441, 437[d] | | 52[e] ($J$ 6·5) | 154[p] ($J$ 7) $\mathrm{CH_2Me}$<br>27[q] ($J$ 7) $\mathrm{CH_2\underline{Me}}$ |

*Footnotes for Tables* 1, 2 and 3.

[a] Chemical shifts in c/s from TMS ($CDCl_3$ as solvent unless otherwise stated) spectra being measured at a frequency of 60 Mc (in one case, *viz.*, Table 2, No. 11, a spectrum was also recorded at 100 Mc); coupling constants and widths at half height ($W_H$) in c/s.

[b] Singlet.

[c] Doublet showing virtual coupling, outer peak separation in parenthesis.

[d] Main peak (s) of multiplet.

[e] Doublet.

[f] In $CCl_4$.

[g] Deformed triplet, outer peak separation in parenthesis.

[h] Centre of multiplet.

[i] Absent in presence of $D_2O$.

[j] Analysed as the AM portion of an AMX system in most cases; $J_g$ and $J_v$ refer to gem and vic coupling respectively.

[k] Centre of unsymmetrical quartet.

[l] Broad singlet (integral 5 protons), minor peak at 62 in $CDCl_3$.

[m] Main peak of poorly resolved triplet (integral 5 protons).

[n] Quartet superimposed upon multiplet due to 2- or 3-methine proton.

[o] Broad bands forming sharp singlet at 176 in presence of $D_2O$.

[p] 1:2:2:1 quartet.

[q] 1:3:1 triplet.

[r] Total product of catalytic reduction of IXa, integrals (int) in parenthesis.

[s] Main peaks of signal, see Fig. 3 for $CDCl_3$ spectrum.

[t] Becomes singlet when sample irradiated at 165 c/s.

[u] Becomes singlet when sample irradiated at 389 c/s.

[v] Ref. 14 and unpublished results.

TABLE 2. PMR CHARACTERISTICS OF SOME 3,3-DIPHENYLPYRROLIDINES AND TETRAHYDROFURANS

| No. | Compound | PMR Signals[a]<br>Aryl | Methine protons | 4 (or 5) methylene protons[j] | *sec*-Me | Others |
|---|---|---|---|---|---|---|
| 1 | VIIa HCl | 444, 442[d] | 233[h] | 188[h] $J_g$ 13·5 $J_v$ 6<br>155·5[h] $J_g$ 13·5 $J_v$ 9 | 83[e] ($J$ 6·5) | 212[b] NMe<br>405[h,i] NH |
| 2 | VIIIa HCl | 443[d] | Not resolvable | Not resolvable | 52[c] (6) | 222[b] NMe<br>387[h,i] NH |
| 3 | VIIf HCl | 446[d] | Not resolvable | 191[h] $J_g$ 13 $J_v$ 6<br>153[h] $J_g$ 13 $J_v$ 9 | 82·5[e] ($J$ 7) | — |
|  | VIIf base | 442, 437[d] | 246[h] | 168[h] $J_g$ 12·5 $J_v$ 5·5<br>139[h] $J_g$ 12·5 $J_v$ 9 | 75[e] ($J$ 6) | 282[h,i] NH |
| 4 | VIIIe HCl | 444, 440[d] | Not resolvable | Not resolvable | 53[c] (6) | 384[h,i], 212[h,i]<br>$\dot{N}$H and OH |
|  | VIIIe base | 438[d] | Not resolvable | Not resolvable | 51[e] ($J$ 6) | 294[h,i] NH and OH |
| 5 | IXc | 442, 436[d] | 258[h] ($W_H$ 23) | 174[h] $J_g$ 12·5 $J_v$ 5<br>158[h] $J_g$ 12·5 $J_v$ 10 | 84[e] ($J$ 6) | 406[b,i] NH |
| 6 | IXd | 441, 439[d] | 269[h] ($W_H$ 28) | 186[h] $J_g$ 12·5 $J_v$ 5<br>153[h] $J_g$ 12·5 $J_v$ 10·5 | 85[e] ($J$ 6) |  |
| 7 | α-IXb | 438, 434[d] | 275[h] ($W_H$ 14) 2-H<br>241[h] ($W_H$ 22) 5-H | 151[k] $J_g$ 12 $J_v$ 9·4<br>134[h] $J_g$ 12 $J_v$ 6·8 | 82[e] ($J$ 6) | 58[f] ($W_H$ 3·5) 2-$CH_2Me$ |
|  | In benzene | — | 268[h] ($W_H$ 8) 2-H<br>235[h] ($W_H$ 22) 5-H | 139[h] $J_g$ 12 $J_v$ 9·5<br>119[h] $J_g$ 12 $J_v$ 6 | 73[e] ($J$ 6) | 60[f] ($W_H$ 3·5) 2-$CH_2Me$ |
|  | In pyridine | — | 272[h] ($W_H$ 9) 2-H<br>235[h] ($W_H$ 22) 5-H | 149[h] $J_g$ 12 $J_v$ 9·5<br>131[h] $J_g$ 12 $J_v$ 6·5 | 77[e] ($J$ 6) | 59[f] ($W_H$ 3·5) 2-$CH_2Me$ |

TABLE 2. PMR CHARACTERISTICS OF SOME 3,3-DIPHENYLPYRROLIDINES AND TETRAHYDROFURANS *continued*

| | | PMR Signals[a] | | | | |
|---|---|---|---|---|---|---|
| No. | Compound | Aryl | Methine protons | 4 (or 5)-methylene protons[j] | *sec*-Me | Others |
| 8 | β-IXb | 437[d] | 272[h] ($W_H$ 10)<br>2- and 5-H | 187[h] $J_g$ 13 $J_v$ 8<br>125[h] $J_g$ 13 $J_v$ 6 | 70·5[e] ($J$ 6) | 60·5[m] 2-$CH_2Me$ |
| 9 | α-β IXb mixture[c] | 431, 426[d]<br>(int 92) | 241[h] α-5-H<br>(int 6)<br>273, 266[d]<br>α, β-2-H, β-5-H<br>(int 12) | 151, 131[h] α- (int 10)<br>184, 123[h] β- (int 9) | 80[e] α- (int 22)<br>69·5[e] β- (int 18) | 60, 58[d], α, β-$CH_2Me$ |
| 10 | X | 438[d] | 242[e] ($J$ 7)<br>vinyl proton | 222, 212·5, 207<br>204, 197[d] | 97·5[e] ($J$ 7) vinyl Me<br>49·5[f] (6·5) 4-Me | |
| 11 | IXa | 441, 432[d] | 237[e] ($J$ 7)<br>vinyl proton | 159, 153, 149·5[i] | 99·5[e] ($J$ 7) vinyl Me<br>81·5[e] ($J$ 6) 5-Me | — |
| | In benzene | — | 241[h] vinyl<br>and 5-H | 144, 136[i] | 108·5[e] ($J$ 7) vinyl Me<br>69·5[e] ($J$ 6) 5-Me | — |
| | In pyridine | | 245[h] vinyl<br>and 5-H | 158·5, 151·1, 150·5[i] | 105[e] ($J$ 7) vinyl Me<br>77[e] ($J$ 6) 5-Me | |
| | 100 Mc spectrum | 710[d] | 389[m] ($J$ 7)<br>vinyl proton | 261[h] $J_g$ 12 $J_v$ 5<br>245·5[h] $J_g$ 12 $J_v$ 9 | 164[m] ($J$ 7) vinyl Me<br>131[e] ($J$ 6) 5-Me | — |

(Footnotes, see Table 1.)

plane of the aromatic ring *cis* to 4-Me is approximately at right angles to that of the heterocyclic ring, whereby *cis* Ph Me interactions are a minimum; in such conformations the Me group lies above the aromatic plane (within the aryl diamagnetic screening zone) and its resonance position will therefore be moved upfield.[7]

The two C-4 methylene and the C-5 methine protons of the 5-methyl cyclic derivatives IX form spin spin coupled systems ranging from the AMX to ABX type. Analysis of the AM (or AB) signal is possible in most cases, but resolution of the C-5 proton signal (X) is hampered by its additional coupling to the 5-Me protons. When the three protons approach an AMX system, the high field methylene signal is near 150 c s and the low field, 180 c s (Table 2.1, 3, 5, 6 and 8), both being four line signals with $J_{gem}$ 12 13 c s. The former signal probably arises from the proton ($H_\beta$) *trans* to the methine proton ($H_x$) and the latter from the *cis* proton ($H_\alpha$), because $J_{vic}$ (high field) is consistently larger than $J_{vic}$ (low field). This argument is based on the reasonable assumption that the C-4 and C-5 substituents are staggered[8] with the $H_\alpha H_x$ and the $H_\beta H_x$ dihedral angles intermediate between 0° and 60°, and 120° and 180° respectively (see diagram), leading (by application of the dihedral angle dependence of coupling constants[9]) to the conclusion that $J_{\beta x}$ should exceed $J_{\alpha x}$. The two methylene signals are most widely separated and show the greatest uniformity in line height in the case of the β-tetrahydrofuran IXb. In the α-isomer, however, the two signals overlap, the inner being much more intense than the outer lines

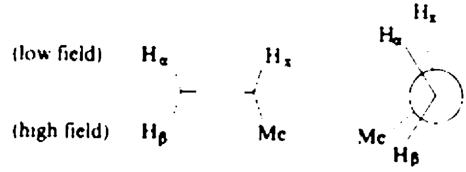

TABLE 3. PMR CHARACTERISTICS OF SOME 1-AMINO-3,3-DIPHENYLPROPANES[c]

| Compound | PMR Signal[a] N–Me[b] | *sec*-Me[c] |
|---|---|---|
| Ia | 128 | 54 |
| IIa | 132 | 69 |
| IIIa | | 56 5 |
| IIa (NMe$_2$ replaced by piperidino | | 67 |
| Ig | 131 | 26 |
| IIh | 134 | 55 |
| IVh | | 53 |

(Footnotes, see Table 1).

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[7] C. E. Johnson and F. A. Bovey, *J. Chem. Phys.* **29**, 1012 (1958)

[8] E. L. Eliel, N. L. Alinger, J. J. Angyal and G. A. Morrison, *Conformational Analysis* p. 200. Wiley, New York (1965)

[9] M. Karplus, *J. Chem. Phys.* **30**, 11 (1959); K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.* **83**, 4623 (1961)

(Fig. 1), and signal resolution (aided by spectral studies in benzene and pyridine, Table 2.7) shows that the $H_\beta$ proton (154 c/s $J_{vic}$ 9 in $CDCl_3$) has a normal, while the $H_\alpha$ proton (137 c/s $J_{vic}$ 6 in $CDCl_3$) has an abnormally high field position. The difference between the C-4 methylene signals of the α- and β-tetrahydrofurans IXb provides evidence of configuration, since it may be interpreted in terms of the α-isomer having a *cis* and the β-, a *trans* 2-Et 5-Me configuration. In the *cis* isomer, the conformation of phenyl *cis* to 2-ethyl will be influenced largely by the bulky flanking substituent, while that of *trans* Ph (not adjacent to a bulky group) will be determined by the gem-Ph group. Dreiding models indicate that a preferred anti-planar *cis* Ph-heterocyclic ring orientation (in which *cis* Ph 2-Et interactions are a minimum) makes the same orientation for *trans* phenyl unfavourable because of *o*-hydrogen interactions. A favoured conformation for the latter group (in which non-bonded interactions involving the *trans* *o*-hydrogen protons and both the *gem*-Ph and 2-Et groups are a minimum) is shown in Fig. 2; this places the α-C-4 methylene proton within the screening zone of the adjacent Ph group and, in consequence, its resonance position is moved up-field and the chemical shift difference between $H_\alpha$ and $H_\beta$ decreases. In the β-isomer (*trans* 2-Et 5-Me) interactions between 2-Et and a flanking Ph group will likewise be an important factor in determining the preferred configuration of Ph *trans* to the Et group. Here, however, the methylene proton *cis* to 5-Me ($H_\beta$) will be screened and, as a result, the $H_\alpha$–$H_\beta$ chemical shift difference will increase because $H_\beta$ has the higher field position in normal examples. These arguments account for the well-separated $H_\alpha$ and $H_\beta$ signals and the unusually

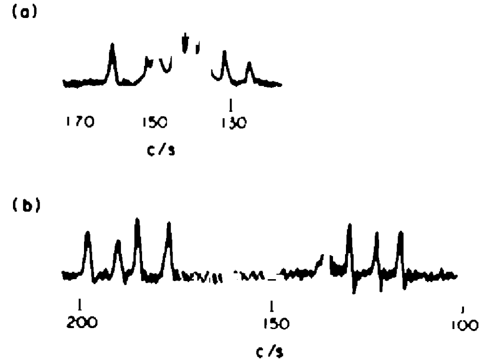

FIG. 1. C-4 Methylene protons PMR signal of (a) α-IXb and (b) β-IXb in $CDCl_3$.

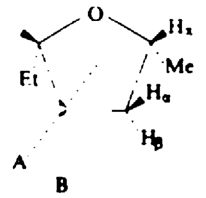

FIG. 2. Diagram of Dreiding model of *cis* (2-Et 5-Me) IXb viewed from above. Heavy lines lie above, and dotted lines below, the plane of the tetrahydrofuran ring; A and B denote the planes of the aromatic rings *cis* and *trans* to 2-Et respectively

high field position (125 c/s) of $H_\beta$ in the β-isomer IXb. Models of *cis* and *trans* IXb with preferred Ph conformations as in Fig. 2 show the methylene protons of the 2-Et group of both isomers and the 5-Me group of the β-isomer to lie in an aromatic screening zone, while the 5-methine proton (β-isomer) falls approximately in the plane of the *cis* aromatic ring. These observations are in accord with the nature (α- a broad singlet, β- a deformed triplet) and similar high-field resonance positions of the two 5-Et signals, the higher field position of the β-5-Me and the lower position of the β-5-methine proton, further supporting the configurational assignments.

Portoghese and Williams[4] based the same configurational assignments upon the fact that the catalytic hydrogenation of IXa gave an isomeric mixture composed of 2 parts of α- and one part of β- IXb. From a study of molecular models they concluded the top face of IXa to be more accessible to the hydrogenation catalyst than the side which is *cis* to the C-5 Me group and hence concluded that the major isomer should have the *cis*-2-Et 5-Me configuration. In our hands, the catalytic reduction of IXa went to completion (a 60% yield of IXb was previously reported), as shown by the complete absence of the vinylic methyl doublet in the PMR spectrum of the total product, and the α:β ratio (approx 1·1:0·9) showed that the reduction was not significantly stereospecific under our conditons.

In the 2-ethylidene derivative IXa the 4-methylene signal is AB in type, having only three prominent lines in $CDCl_3$ (Fig. 3) while in benzene and pyridine the signal

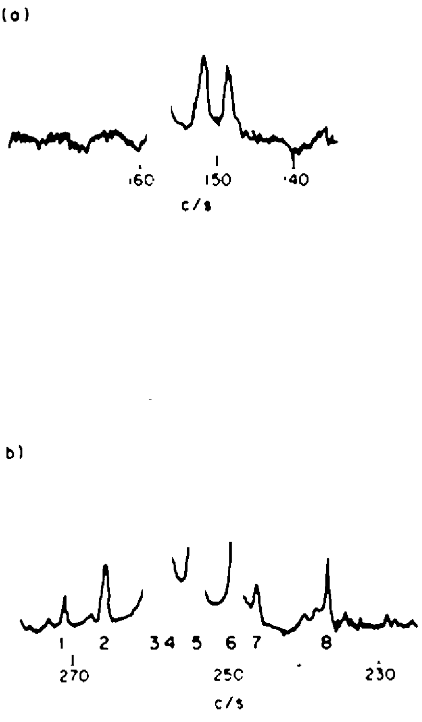

Fig. 3 C-4 Methylene protons PMR signal of IXa in $CDCl_3$ recorded at (a) 60 Mc and (b) 100 Mc/s

reduces to a broad doublet. It is seen from the eight-line signal obtained at 100 Mc (Fig. 3) that the intense singlet at 159 c/s (60 Mc spectrum) is produced by overlap of lines 3 and 4, while the "doublet" upfield of the 159 c/s singlet represents lines 5 and 6, of the 100 Mc signal. From the relative $J_{vic}$ values associated with the two methylene proton signals, it follows again that the $H_a$ proton (*cis* to $H_x$) of IXa has an unusually high field position and this result may also be attributed to differential aromatic screening. The 2-ethylidene group constitutes a steric factor deflecting the Ph groups into planes at right angles to that of the heterocyclic ring. Phenyl *trans* to the 5-Me group may approach this plane more closely than may the *cis* Ph substituent because Ph/Me interactions are generated in anti-planar ring orientations involving this aromatic group. Models reveal that the net result of these interactions is to make $H_a$ the more screened of the two methylene protons, whence its resonance position is moved up-field.

## EXPERIMENTAL

*General method for the reaction of 3-amino-1,1-diphenylpropanes with cyanogen bromide*

The 3-amino-1,1-diphenylpropane (0·01 mole)[10] and CNBr (0·01 mole) in $CHCl_3$ were stirred at room temp or heated under reflux and then diluted with ether. Any ppt which separated (hydrobromide or methobromide of substrate in most cases) was collected and the filtrate concentrated and extracted with dil HCl to remove water soluble and basic material. Non-basic products in the organic phase were then examined. In the following specific cases, weight of substrate, reaction period and temp are given in parenthesis after each example.

(a) *The 3-morpholino cyanide* IIIa (19·9 g, 4 days, reflux) and CNBr (6·4 g) in $CHCl_3$ (200 ml) gave the N-cyano deriv Vb as an oil (23 g). This oil (4·3 g), piperidine (3·3 g) and EtOH (25 ml) were heated under reflux for 4 hr, concentrated and diluted with ether, the piperidine hydrobromide which separated removed by filtration and the filtrate washed with water, dried ($Na_2SO_4$) and evaporated. The residue (4·9 g), with EtOH–HCl gave the *hydrochloride* of Vc, m.p. 122–124°. (Found: C, 68·9; H, 7·7; N, 11·6; equiv wt 465. $C_{27}H_{35}ClN_4O$ requires: C, 69·5; H, 7·9; N, 12·0%; equiv wt 467.)

(b) 2-*Methyl-3-piperidino*-1,1-*diphenylpropyl cyanide* (19·1 g, 6 days, reflux) and CNBr (6·4 g) in $CHCl_3$ (250 ml) gave the N-*cyano deriv* VId (22 g), m.p. 56–58° from EtOH. (Found: C, 64·8; H, 6·2; N, 10·05. $C_{23}N_{26}N_3Br$ requires: C, 65·1; H, 6·2; N, 9·9%.) The N-cyanomethylamino derivs V and VIa were prepared by the reported method[1]

(c) *Methadone* (Ib, 3·1 g, 6 hr reflux), CNBr (1·06 g) and $K_2CO_3$ (4·1 g) in acetone (100 ml) gave IXa (2·4 g, 92%), m.p. 79–80° from EtOH–$H_2O$ (reported[1] m.p. 80·5°).

(d) α-*Methadol* (Ic, 3·1 g, 2 hr room) and CNBr (1·06 g) in $CHCl_3$ (50 ml) gave Ic *hydrobromide* (2·5 g), m.p. 203–205°. (Found: C, 64·2; H, 7·6; N, 3·5. $C_{21}H_{30}BrNO$ requires: C, 64·3; H, 7·7; N, 3·6%) and the α-2-ethyltetrahydrofuran IXb (1·2 g), m.p. 89–91° from EtOH (Found: C, 84·8; H, 8·5. Calc for $C_{19}H_{22}O$: C, 85·65; H, 8·3%), reported[3] m.p. 88–90° for material prepared by pyrolysis of the α-methiodide Ic. Pyrolysis of the α-hydrobromide Ic (3·7 g) also gave IXb, m.p. and mixed m.p. 89–91° (1·2 g)

(e) β-*Methadol* (Ic, 6·2 g, 2 hr room) and CNBr (2·12 g) in $CHCl_3$ (50 ml) gave the β-*hydrobromide* Ic (4·9 g), m.p. 208–209° from AcOEt–MeOH (Found: C, 64·8; H, 7·85; N, 3·6%), and the β-2-*ethyltetrahydrofuran* IXb (4 g), m.p. 61–62° from EtOH–$H_2O$. (Found: C, 85·5; H, 8·45. $C_{19}H_{22}O$ requires: C, 85·65; H, 8·3%.)

(f) The *amino amide* Id (3·2 g, 2·5 hr room) and CNBr (1·06 g) in $CHCl_3$ (50 ml) gave the substrate (1·5 g, recovered via the hydrobromide) and IXc (1·5 g), m.p. 113–115° from benzene-n-hexane (reported[11] m.p. 115–116°).

(g) The *amino acid* Ie (5·94 g, 2 hr room) and CNBr (2·12 g) in $CHCl_3$ (50 ml) gave Ie *hydrobromide* (3 g), m.p. 200–202° from EtOH–ether. (Found: C, 58·1; H, 6·7. $C_{19}H_{24}BrNO_2 \cdot H_2O$ requires: C, 57·6; H, 6·6%) and the lactone IXd (1 g), m.p. 111–113° from n-hexane (reported[11] m.p. 111–112°).

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[10] P. A. J. Janssen, *Synthetic Analgesics, Part I. Diphenylpropylamines* and Refs there cited. Pergamon Press, Oxford (1960)

[11] N. R. Easton, J. H. Gardner and J. R. Stevens, *J. Am. Chem. Soc.* 69, 2941 (1947)

(h) The *amino ester* If (3·25 g, 3h, room) and CNBr (1·06 g) in $CHCl_3$ (40 ml) gave IXd (2·4 g), m.p. and mixed m.p. 111–113°.

(i) β-*Acetyl methadol* (Ig, 7·05 g, 3 hr room) and CNBr (2·12 g) in $CHCl_3$ (100 ml) gave Ig *hydrobromide* (2·5 g), m.p. 230–232° from EtOH–ether. (Found: C, 63·8; H, 7·5. $C_{23}H_{32}BrNO_2$ requires: C, 63·6; H, 7·5%.) $\nu_{\overset{+}{N}-H}$ 2640 cm$^{-1}$, and a mixture (4·2 g), m.p. 84° from EtOH, of IXb and the cyanomethyl deriv XI. PMR characteristics in $CDCl_3$: IXb, 5-Me doublet 82 c/s (integral 12), 2-Et singlet (broad) 59 c/s; XI, N-Me singlet 146 c/s, COMe singlet 122 c/s (integral 15), $CH_2\underline{Me}$ signal 50 c/s. The mixture was recrystallized from pet. ether b.p. 60–80° to give the *cyanomethyl deriv* XI (2·1 g), m.p. 134–135°. (Found: C, 75·5; H, 7·7; N, 7·5. $C_{23}H_{28}N_2O_2$ requires: C, 75·8; H, 7·7; N, 7·7%.) $\nu_{C=O}$ 1725 cm$^{-1}$. Ig *methobromide*, m.p. 214–216° from EtOH–ether. (Found: C, 60·9; H, 7·95. $C_{24}H_{34}BrNO_2 \cdot H_2O$ requires: C, 61·8; H, 7·8%.) $\nu_{\overset{+}{N}-H}$ band absent, was prepared as a reference compound.

(j) *Isomethadone* (IIb, 4·5 g, 3 hr room) and CNBr (1·7 g) in $CHCl_3$ (50 ml) gave a non-basic oil (3·5 g) which distilled at 180°/0·4 mm. $\nu_{max}$ 2200 (CN), 1700 cm$^{-1}$ (CO). Its PMR spectrum in $CDCl_3$ had signals which indicated the presence of X [quartet 236 c/s (vinyl H), doublets 99 c/s (vinyl Me) and 57 c/s (5-Me)] and the cyanomethyl analogue of IIb [singlet 173 c/s (N-Me), doublet 81 c/s (sec-Me), triplet 44 ($CH_2\underline{Me}$)]. Pure X, m.p. 166–168°, was obtained from reaction of the morpholino ketone IVb with CNBr.[2]

(k) The *dimethylamino-ketimine* IIh (3·08 g, 2 hr room) and CNBr (1·06 g) in $CHCl_3$ (50 ml) gave the *cyano-ketimine* (XIIa) *hydrobromide* (2·6 g), m.p. 257–259° from EtOH–acetone. (Found: C, 62·4; H, 7·5; N, 9·8. $C_{22}H_{28}BrN_3 \cdot 0{\cdot}5\ H_2O$ requires: C, 62·3; H, 7·0; N, 9·9%.) $\nu_{H_2O}$ 3370 cm$^{-1}$.

(l) The *morpholino-ketimine* IVh (5 g, 12 hr room) and CNBr (2 g) in $CHCl_3$ (50 ml) gave the *cyano-ketimine* (XIIb) *hydrobromide* (4·5 g), m.p. 260–261° (dec) from EtOH–$CHCl_3$. (Found: C, 60·5; H, 6·6. $C_{24}H_{30}BrN_3O \cdot H_2O$ requires: C, 60·75; H, 6·8%.) $\nu_{H_2O}$ 3400 cm$^{-1}$.

### *Hydrolysis of the* N-*cyanopropyl cyanides* V *and* VIa, Vb *and* VId

A mixture of Vb (4·32 g) and 6% HCl in water (100 ml) was heated under reflux for 12 hr, cooled and extracted with ether (to remove non-bases). The basic product (3·1 g), recovered from the aqueous phase as usual, with EtOH–HCl gave the *2-iminopyrrolidine* (VIIf) *hydrochloride*, m.p. 181–183° from EtOH–ether. (Found: C, 64·05; H, 6·6; N, 7·05. $C_{21}H_{26}Cl_2N_2O$ requires: C, 64·1; H, 6·7; N, 7·1%.) Mass spectrum main-peaks: 356 (molecular ion, VIIf requires 356·5), 355, 293 (stable ions), 242 (metastable ion, calc 241). The same treatment of VId (4·3 g) gave the *2-iminopyrrolidine* VIIIe (2·3 g), m.p. 115–117° from pet. ether b.p. 60–80°. (Found: C, 78·7; H, 8·0; N, 8·7. $C_{22}H_{28}N_2O$ requires: C, 78·8; H, 8·1; N, 8·35%.) It gave a *hydrochloride*, m.p. 222–224° from EtOH–ether (Found: C, 70·3; H, 8·0; N, 7·2. $C_{22}H_{29}ClN_2O$ requires: C, 70·9; H, 7·8; N, 7·5%.) Mass spectrum main-peaks: 336 (molecular ion, VIIIe requires 336), 335, 264 (stable ions), 208 (metastable ion, calc 206). Hydrolysis of Va gave VIIa hydrochloride, m.p. 274–276° (reported[13] m.p. 277°) while that of VIa gave VIIIa hydrochloride, m.p. 265–267°, reported[13] m.p. 239°. (Found: C, 71·8; H, 7·3; N, 9·2. Calc for $C_{18}H_{21}ClN_2$: C, 71·9; H, 7·6; N, 9·3%.)

### *Reduction of the tetrahydrofuran* IXa

Compound IXa (1·5 g) in 95% EtOH (100 ml) and 10% Pd-C (0·2 g) were shaken with $H_2$ at room temp and press for 5 hr (theoretical amount of $H_2$ absorbed). The mixture was filtered and the filtrate evaporated to give a mixture of α- and β- IXb (1·5 g), m.p. 68–70° (PMR, Table 2·9), which was fractionally crystallized from EtOH to give α-IXb (0·5 g), m.p. and mixed m.p. 89–91° and β-IXb (60 mg), m.p. and mixed m.p. 60–62°.

The IR spectra were recorded with an S.P. 100 spectrophotometer (solids as Nujol mulls, liquids as films) and the PMR spectra with Varian A-60, HA-100 and Perkin-Elmer R-10 instruments; the mass spectra were obtained with an M.S.9 double focusing mass spectrometer (resolving power about 12,000).

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