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Probable conformations of the analgesically active basic anilide *N*-[(2-benzylmethylamino)propyl]-propionanilide

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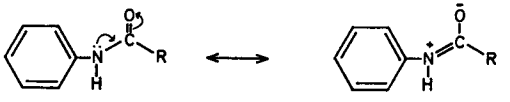
A spectroscopic (ultraviolet, infrared and nuclear magnetic resonance) study of *N*-[(2-benzylmethylamino)propyl]propionanilide hydrochloride is reported and probable conformations of this molecule (in which the phenyl group and amide function are non-planar, the protonated basic centre lies close to the amido-nitrogen atom, and the secondary methyl group is removed from the region above the aromatic plane) proposed on the basis of the spectroscopic results. Differences in analgesic stereospecificity and basic group structure between enantiomorphs of methadone and *N*-[(2-benzylmethylamino)propyl]propionanilide are discussed in terms of the probable conformations of the two analgesics.

RECENTLY attention was drawn to structural differences in the basic group of 3-amino-1,1-diphenylpropane analgesics such as methadone, and *N*-(2-aminopropyl)propionanilide analgesics such as diampromid, and to the different stereospecificity exhibited by the analgesic receptor towards enantiomorphs of the two classes (Casy & Hassan, 1967). Since both types of analgesic possess the system Ph–X–C–C–N< (where X is a non-hydrogen bearing atom), it seems likely (especially in view of differences in stereospecificity) that the relative orientation of the components of this system differ in the two classes of compound, with the probable result that their modes of binding to the analgesic receptor are dissimilar. The present spectroscopic examination was made to obtain evidence about the conformation of the molecules in question, and to ascertain whether any marked difference in the orientation of the system specified above does in fact exist in the two classes.

ULTRAVIOLET SPECTROSCOPY

Aniline has three absorption bands above 200 mμ; those at 208 and 280 mμ are associated with local excitation (L.E.) transitions of the aromatic π-electrons, and that at 230 mμ to the $\rho \rightarrow \pi$ electron transfer (E.T.) symbolized in (I) (Scott, 1964, and references there cited). Acetanilide and propionanilide also have three absorption bands above 200 mμ,

(I)



(II) (III)

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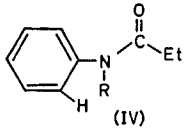
associated with transitions of a similar nature (Table 1). The intensity of the E.T. band of propionanilide is reduced as the solvent pH is lowered but is still relatively high even in N hydrochloric acid-ethanol [in contrast, the E.T. band of aniline is completely absent in 0·1N HCl (Forbes, Ralph & Gosine, 1958)]. In anilides the electron transfer may be represented by (II → III),* structure (III) being analogous to the styrene chromophore [λ_{max} 248 mμ ε 14,000 in ethanol (Scott, 1964)].

When hydrogen in the anilide (II; R = Et) is replaced by methyl,



(IV)

R = (a), Me; (b) Et; (c) iso C_3H_7; (d) CH_2·CH(Me)·N(CH_2·Ph)Me; (e) CH_2·CH(Me)·NMe_2

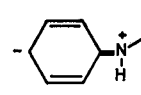
the E.T. band suffers a blue shift and an intensity decrease. These effects are larger in the *N*-ethyl anilide (IVb), while in the *N*-isopropyl anilide (IVc) the E.T. band is only just apparent (Table 1). The chromophore present in (III) is only effective when the phenyl and amide entities

TABLE 1. ULTRAVIOLET SPECTROSCOPIC CHARACTERISTICS OF SOME PROPIONANILIDE [PhN(COEt)R] DERIVATIVES

R	Solvent	λ_{max} mμ (ε) L.E. band	λ_{max} mμ (ε) E.T. band
Aniline	EtOH	208 (3860)[1]	236 (6050)
H[2]	EtOH	208 (11,600)[3]	244 (15,500)
H	0·01N HCl–EtOH–H_2O	209 (6300)	244 (13,000)
H	0·1N HCl–EtOH–H_2O	209 (5860)	244 (12,000)
H	N HCl–EtOH–H_2O	209 (6600)	244 (12,600)
Me	EtOH	211 (8000)	228 (6040)
Et	EtOH	211 (8700)	225[4] (6000)
iso Pr	EtOH	210 (8400)	225[4] (4200)
$CH_2CHMeN(CH_2Ph)Me$	EtOH	212 (17,400)[5]	225[6] (8700)
,,	H_2O[7]	205 (18,000)	225[6] (5200)
$CH_2CHMeNMe_2$	EtOH	210 (9400)	225[4] (5000)

[1] Also displays L.E. band at 287 mμ (ε 2200). [2] Acetanilide has λ_{max} 242 mμ (ε 14,400) (Ungnade, 1954). [3] Also displays L.E. band at 281 mμ (ε 500). [4] Inflection. [5] The higher intensity of this band is due to the additional phenyl group in the molecule. [6] Change of slope. [7] Hydrochloride.

are coplanar. Such conformations are progressively less favoured as the size of the *N*-substituent (R) increases because of non-bonded interactions between R and an *ortho*-hydrogen of the phenyl ring (evidence of models). Hence the changes in the E.T. band of the anilides, described above, are attributed to steric inhibition of resonance, an effect also demonstrated in *o*-alkylacetanilides (Ungnade, 1954). The E.T. bands of the basic anilides (IVd and e) are suppressed in a similar manner to that of the

* The alternative (II ⟶ ), proposed by Picard & McKay (1953), appears less likely because the amide carbonyl group is known to be highly polarized as in (III) (infrared evidence).

isopropyl derivative (IVc). The E.T. band is also suppressed in the hydrochloride salt of the anilide (IVd), examined in water.

It is concluded, therefore, that the more favoured conformations of the basic anilides (IVd and e) possess *N*-phenyl and amide moieties that do not lie in the same plane.

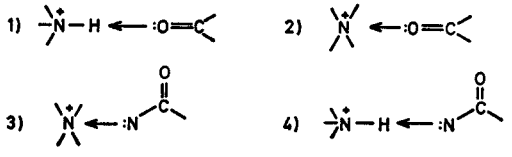
INFRARED SPECTROSCOPY

The carbonyl stretching frequency ($\nu_{C=O}$) of the *N*-ethyl propionanilide (IVb) falls in the normal range of 1670–1630 cm^{-1} quoted for tertiary amides (Rao, 1963) and is little altered when *N*-ethyl is substituted by a β-amino-group, as in the basic anilide (IVd) (Table 2, Nos 1 and 2).

TABLE 2. CARBONYL STRETCHING FREQUENCIES OF SOME PROPIONANILIDE [PhN(COEt)R] DERIVATIVES

No.	R	Form	Solvent (conc.)	$\nu_{C=O}$ cm^{-1}
1	Et	—	(film)	1661–2
	,,	—	CS_2 (10%)	1662
	,,	—	$CHCl_3$ (10%)	1649
2	$CH_3CHMeNMe(CH_2Ph)$	base	(film)	1663
	,,	,,	CS_2 (10%)	1666
	,,	,,	$CHCl_3$ (10%)	1649
3	,,	HCl	$CHCl_3$ (0·1)	1659
	,,	,,	,, (0·3)	1659·5
	,,	,,	,, (0·5, 1·0, 3·0, 5·0)	1658·5
	,,	,,	$CHCl_3$ (10%)	1665
	,,	,,	,, (20%)	1658–1668·5 (broad band)
	,,	,,	(Nujol mull)	1670
4	,,	MeI	$CHCl_3$ (10%)	1662
			(Nujol mull)	1658
5	$CH_3CHMeNMe_2$	base	(film)	1663
	,,	,,	$CHCl_3$ (10%)	1644·5
	,,	HNO_3	$CHCl_3$ (10%)	1661·5
	,,	,,	(Nujol mull)	1665

There is no infrared evidence, therefore, for an interaction between the amide and amino-functions of the basic anilide (IVd) in the non-protonated state. Solvent effects of similar degree are observed in both anilides, the $\nu_{C=O}$ shift of 13–17 cm^{-1} to lower wave numbers ($CS_2 \rightarrow CHCl_3$) being attributed to hydrogen bonding of the type $Cl_3CH \cdots O = C\lesssim$. $\nu_{C=O}$ for the anilide (IVd) hydrochloride is significantly *greater* (10–21 cm^{-1}) than that of the free base, the difference being a maximum when the salt is examined as a mull (Table 2, Nos 2 and 3). Elevation of $\nu_{C=O}$ is also seen in the methiodide of (IVd) and these results show that some interaction between the amide group and the positively charged basic centre occurs in protonated and quaternary salts of the basic anilide (IVd). Four types of interaction (intra and/or intermolecular) may be postulated, namely:



(the arrows denote the direction of electron flow)

Types 1 and 2 would weaken the C=O bond and hence lead to *lower* $\nu_{C=O}$ values. Interactions of types 3 and 4 reduce the availability of the nitrogen lone-pair of the amide function and would be expected to lead to a diminution of the ionic character ($\succ\overset{+}{N}=C\prec^{O}$) of the amide, with the result that the amide $\nu_{C=O}$ value is *raised.* This effect is analogous to the base-weakening influence of protonated nitrogen upon the second basic centre of a diamine.*

Operation of the interactions 1 and 4 require an acidic proton and hence would also be expected to influence the $\overset{+}{N}$—H stretching frequency. However, ν^{+}_{N-H} values for hydrochloride salts of the anilide (IVd) (2550 cm^{-1}, as mull) and benzylethylmethylamine (2500 cm^{-1}, as mull), an analogue of (IVd) lacking the amide function, show no significant difference and, on these grounds, it is considered that the acidic proton does not play an important role in these interactions. Types 2 and 3 do not require an acidic proton and may thus operate in the case of quaternary salts.

Since elevated, rather than reduced $\nu_{C=O}$ stretching frequencies are observed in both the hydrochloride and quaternary salts of (IVd), an interaction of type 3 is indicated. The data available suggest that the effect may be both inter- and intramolecular. The carbonyl stretching frequency is constant over the concentration range 5-0·1%. This behaviour is indicative of an intramolecular interaction, while higher values are observed in more concentrated solutions which is indicative of an intermolecular influence also operating (Table 2, No. 3). Both influences are liable to be optimum in the solid state, the highest $\nu_{C=O}$ value being seen when the anilide hydrochloride is examined as a mull. The $\nu_{C=O}$ infrared properties of the two anilides (IVd and e) are also alike, $\nu_{C=O}$ of the of the dimethylamino derivative (IVe) being elevated to a similar degree when the base is protonated [$\nu_{C=O}$ salt − $\nu_{C=O}$ base = 17 cm^{-1} for 10% solutions in chloroform (Table 2, No. 5)].

These results show that the preferred conformations of the anilide (IVd) hydrochloride in dilute solution (where intramolecular effects alone are assumed) are such that the protonated nitrogen centre lies in the vicinity of the amido-nitrogen atom (as in interaction 3).

NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

The nmr characteristics in $CDCl_3$ of *N*-[(2-benzylmethylamino)propyl]-propionanilide (IVd) as free base, hydrochloride and methiodide, and of the related compound (IVe), are given in Table 3. The following points of interest are to be noted:

(1) In the anilide hydrochloride (IVd), both the *N*-methyl and s-methyl signals are duplicated, each appearing as a doublet of doublets (Fig. 1). (The two *N*-methyl doublets overlap and a triplet is observed.) These results show that the hydrochloride exists as a mixture of *N*-epimers in

* In the monoprotonated salt of 1,2-ethanediamine, for example, charged nitrogen reduces the availability of the lone-pair electrons of the second basic centre, as seen from pK_a values [pK_a (H^+) 10·09; pK_a ($2H^+$) 7·00] (Albert & Serjeant, 1962).

TABLE 3. NUCLEAR MAGNETIC RESONANCE CHARACTERISTICS OF SOME *N*-(2-AMINOPROPYL) PROPIONANILIDES [PhN(COEt)R]

			nmr signals[1]					
R	Form	Solvent	Aromatic	N-Me	N-CH_2Ph	s-Me[4]	$COCH_2Me$[6]	Others
CH_2CHMe–$NMe(CH_2Ph)$	base	$CDCl_3$	437[2]	127[2]	216·5, 211[3]	59 (J7)	62 (J7)	230 (C–CH_2)[8]
		$CDCl_3$–CF_3CO_2H	450[7]	174[2]	266, 258[3]	81 (J6·5)	60·5 (J7)	124[9] (J7) ($COCH_2Me$)‖
,,	HCl	$CDCl_3$	463, 438[7]	171[4] (J6) 165[4] (J6)	very complex	92 (J7) 82·5 (J6)	62 (J7)	126[9] (broad) ($COCH_2Me$)
		$CDCl_3$–D_2O	462, 440[7]	171·5[2]	282, 269, 260, 247[3] (J_{AB}13)	85 (J7)	60·5 (J7)	127[9] (broad) ($COCH_2Me$)
,,	CH_3I	$CDCl_3$	447[2]	192[2]	247[3] (broad)	93[2]	59 (J7)	124[9] (broad) ($COCH_2Me$)
CH_2CHMe–NMe_2	base	$CDCl_3$	440[2]	129[2]	—	51 (J7)	59 (J7)	118[9] (J7) ($COCH_2Me$)
,,	HNO_3	$CDCl_3$	447, 445[5]	179[2]	—	80 (J6)	60 (J7)	127[9] (broad) ($COCH_2Me$)

[1] Chemical shifts in c/sec from TMS (operating frequency 60 Mc); coupling constants in c/sec. Concentrations approx. 10%. [2] Singlet or near-singlet. [3] Peaks of AB signal (outer peaks may be lost in noise). [4] Doublet. [5] Triplet. [6] Centre of multiplet. [7] Main peak(s) of multiplet. [8] Centre of deformed doublet. [9] Quartet.

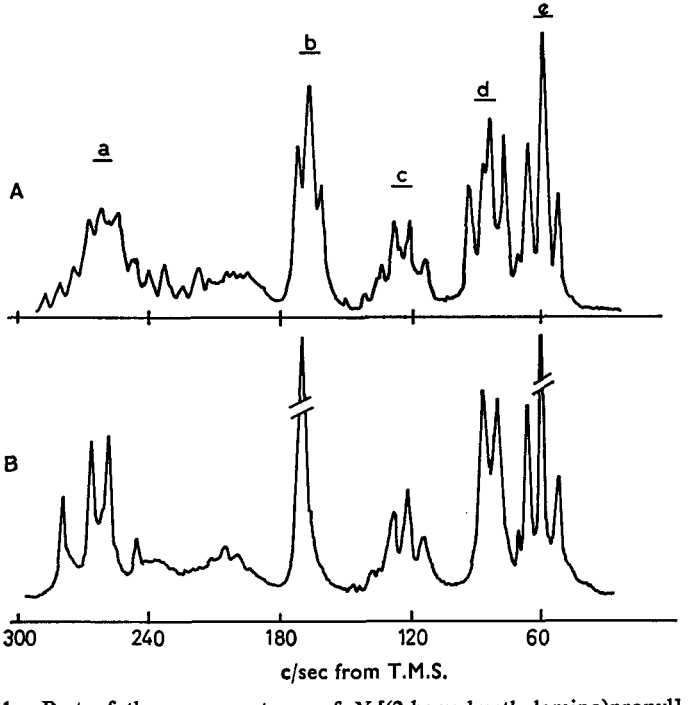
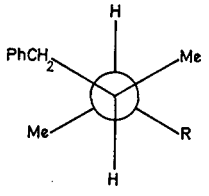
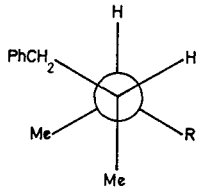


FIG. 1. Part of the nmr spectrum of *N*-[(2-benzylmethylamino)propyl] propionanilide hydrochloride: (A) in $CDCl_3$; (B) in $CDCl_3$–D_2O. Signals: a, NCH_2Ph; b, N·Me; c, $CO{\cdot}CH_2{\cdot}Me$; d, s-Me; e, $CO{\cdot}CH_2{\cdot}Me$.

$CDCl_3$, depicted in the Newman diagrams (V and VI), which arise as a result of the two possible modes of proton addition to the basic centre. (The assignment of configurations to these and related epimers will be discussed elsewhere.) In these conformations, the relative environments



(V)



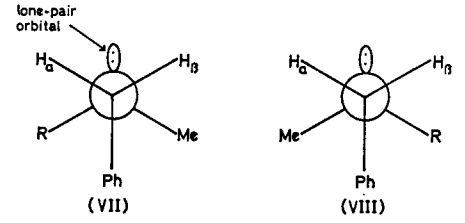
(VI)

R = CH_2·N(COEt)Ph
(Front atom is nitrogen)

of both the *N*-methyl and s-methyl groups differ, hence the two configurations of the salt exhibit different signals for these two groups. Additional multiplicity is observed in the *N*-methyl signal because of spin-spin coupling between *N*-methyl and the acidic proton on nitrogen. The nmr signal of the *N*-benzylmethylene (NCH_2Ph) protons, whose environments also differ in the two epimers, is discussed below. The sharp nature of the two *N*-methyl and s-methyl doublets indicates that the rate of proton exchange between epimers (resulting in their interconversion) must be relatively slow in $CDCl_3$. When proton exchange is accelerated by the addition of D_2O, the *N*-methyl signal becomes a singlet and the s-methyl, a doublet. Rapid proton exchange must also occur in the presence of trifluoroacetic acid and its anion since *N*- and s-methyl doublet of doublets were not observed when the anilide was examined in $CDCl_3$ — CF_3CO_2H (Table 3).

In the methiodide of (IVd), the *N*-methyl, N-CH_2Ph, and s-methyl signals were not duplicated, an expected result because the basic centre in this case is symmetrical.

(2) In the free base of the anilide (IVd), the *N*-benzylmethylene (NCH_2Ph) signal formed an AB pattern indicating the non-equivalence of the protons in this group. This pattern was most clearly visible when the anilide hydrochloride was examined in $CDCl_3$–D_2O (in the free base, the less intense, outer, peaks were obscured somewhat by the noise level)—the signal of the salt in dry $CDCl_3$ was more complex as a result of spin-spin coupling involving the acidic proton on nitrogen. Evidence for the non-equivalence of *N*-benzylmethylene protons was also obtained in the case of the compounds *N*-[2(benzylmethylamino)propyl]aniline and 1-benzylmethylamino-propan-2-ol (unpublished results). In acyclic tertiary amines, non-equivalence of the type depicted in (VII and VIII) may only arise if inversion of the nitrogen lone-pair (resulting in the interconversion of VII and VIII) is restricted, and has been demonstrated at low temperatures, when slow inversion rates obtain (Griffith & Roberts, 1965). No examples of a non-equivalent open-chain $-CH_2N<$ system have, to

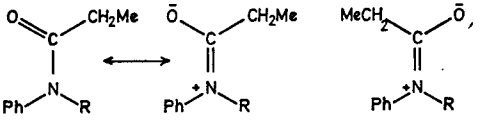


(VII) (VIII)

(Front atom is carbon, rear is nitrogen)

our knowledge, been previously reported at room temperature and the reasons for slow inversion rates in the present cases are being investigated.*

(3) The $COCH_2Me$ signal forms a broad, rather than a sharp quartet, a result probably due to the slow interconvertibility of the conformers (IX) and (X) through restricted rotation about the N–C bond which has



(IX) (X)

double bond character. The methylene protons environments differ in the two forms, while the methyl protons (which form a relatively sharp triplet) differ less in this respect because they are further removed from the *N*-substituents.

(4) The environment of s-methyl in the anilide (IVd) is similar to that of the same group in the diphenylpropane derivatives (XI; R = H and CN), as seen from the comparative chemical shift values.

$$Me_2N{\cdot}CH(Me){\cdot}CH_2{\cdot}CPh_2R$$

(XI)

secondary chemical shift c/sec from TMS (in $CDCl_3$)

R = H, 55 (base); 84 (HCl)
R = CN, 54 (base); 82 (HCl)
Anilide (IVd) 59 (base); 85 (HCl)

In the latter compounds there is evidence that the s-methyl groups are not especially shielded by the aromatic groups (Casy, 1967) [when aromatic shielding occurs the s-methyl signal shows a significant upfield shift, as in methadone (base, 29 c/sec; HCl, 42 c/sec)] and on these grounds it is concluded that the same holds true for s-methyl in the anilide (IVd).

A probable conformation of *N*-[(2-benzylmethylamino)propyl]propionanilide, based upon the described spectroscopic evidence, is shown in Fig. 2. It is consistent with the spectroscopic data in the following respects:

* A non-equivalent $-CF_2N<$ system has recently been described (Banks, Barlow, Haszeldine & McCreath, 1965).

(1) the phenyl group and amide function are non-planar (ultraviolet evidence);

(2) the protonated basic centre is close to the amido-nitrogen atom (infrared evidence) (the conformation in which carbonyl oxygen and ethyl are reversed is also probable);

(3) the s-methyl group does not lie above the plane of the aromatic ring (as it does in probable conformations of methadone—see later) and is judged to fall approximately on the boundary of the aromatic dia- and paramagnetic screening zones (nmr evidence shows that the s-methyl protons are not significantly shielded by the aromatic group).

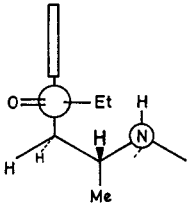


FIG. 2. Representation of a probable conformation of *N*-[(2-benzylmethylamino)-propyl]propionanilide hydrochloride. Note: 1. End-on view of aromatic ring is shown. 2. Amido-carbonyl carbon eclipses amido-nitrogen. 3. H and Me on C-2 may be interchanged. 4. For clarity, N·Me and ·CH_2·Ph substituents have been omitted.

The *N*-arylalkyl substituent of the basic anilide appears to have a minor influence upon the conformation of the molecule since the nmr spectral characteristics of the benzylmethyl- and dimethylamino-anilides (IVd and e) are similar with respect to common proton groups (Table 3).

A probable conformation of methadone hydrochloride, based upon crystallographic (Hanson & Ahmed, 1958) and spectroscopic evidence (Casy, 1967), is shown in Fig. 3. The major point of difference between

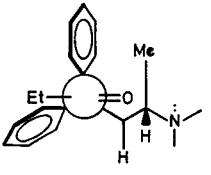


FIG. 3. Representation of a probable conformation of methadone hydrochloride (N·Me groups are omitted).

probable methadone and basic anilide conformations lies in the relative orientations of phenyl, s-methyl and basic nitrogen in the two molecules. In the methadone conformation (Fig. 3), the s-methyl group lies close to, and directly above, the plane of one of the aromatic rings (in consequence it falls well within the aromatic screening zone and has an abnormally high chemical shift on this account). In contrast, s-methyl in the basic anilide conformation (Fig. 2) is further removed from the aromatic ring

and is not situated above its plane. This difference arises from the fact that, while C-4 of methadone is tetrahedral, the equivalent atom of the anilide (the anilo-nitrogen) is trigonal, hence the relative orientations of the β-aminoethyl side-chain to the aromatic group must be dissimilar in the two compounds.

If it is assumed that the conformations shown in Figs 2 and 3 are likely to resemble those adopted by the analgesic at the receptor site, and further, that the phenyl-s-methyl-basic centre orientation of the methadone conformation (Fig. 3) is particularly conducive to drug-receptor association, a possible reason may be advanced for the differing stereochemical and basic group features of methadone and basic anilide analgesics. Although the spatial arrangement of the three groups specified above (as in Fig. 3) is not favoured in the basic anilide, this compound is nevertheless an active analgesic and it is therefore probable that its mode of binding to the receptor differs markedly from that of methadone. Hence, (1) the stereospecificity of the receptor towards enantiomorphic forms of the anilide is not necessarily the same as that which it exhibits towards methadone isomers, and (2) binding sites, additional to those operating in the case of the methadone-receptor association, may be required for the effective uptake of basic anilide molecules upon the receptor surface—such sites could possibly be provided by the arylalkyl *N*-substituent of basic anilides (absent in methadone and related compounds). It is significant, in this respect, that the dimethylamino anilide (IVe) has a low order of analgesic potency (Casy & Hassan, 1967).

In the *N*-arylalkylmethyl basic anilides, a second asymmetric centre is created when the basic nitrogen accepts a proton (nmr evidence) and it may well be that one particular configuration of the basic centre is preferred for drug-receptor association. Under conditions of rapid proton exchange the two epimers will be rapidly interconverting and that of the preferred configuration will readily be derived from the unfavoured epimer. However, if the interconversion rate in the vicinity of the receptor is slow [as would result if the physiological pH near the receptor was lower than the generally accepted figure of 7·2–7·4 (certain enzymes, for example, behave as though acting in environments some two pH units lower than the bulk (Weiss, 1963)], then the relative population of the two epimers may have an important influence upon the drug-receptor combination.

Experimental

N-*Methylpropionanilide.* Sodium hydride (1·44 g, 50% in oil) was added to a hot solution of propionanilide (4·5 g) in dry toluene (40 ml) and the mixture stirred and heated at 110–120° for 3 hr. Methyl iodide (4·29 g) in toluene (10 ml) was added to the resultant suspension of sodium propionanilide and the mixture stirred and heated for 6 hr. The cooled product was filtered and the filtrate evaporated under reduced pressure. The residue was distilled to give N-*methylpropionanilide* (4·5 g), b.p. 94–96°/0·1 mm, m.p. 57–59° (from light petroleum b.p. 60–80°). Found:

C, 73·4; H, 7·9; N, 8·2. $C_{10}H_{13}NO$ requires C, 73·6; H, 8·0; N, 8·5%. N-*Ethylpropionanilide*, b.p. 82–84°/0·6 mm (found: C, 74·5; H, 8·8; N, 8·0. $C_{11}H_{15}NO$ requires C, 74·5; H, 8·5; N, 7·9%) and N-*isopropylpropionanilide*, b.p. 90–91°/0·05 mm, m.p. 39–40° (from light petroleum b.p. 60–80°) (found: C, 75·3; H, 8·9; N, 7·3. $C_{12}H_{17}NO$ requires C, 75·3; H, 9·0; N, 7·3%) were similarly prepared using the appropriate alkyl halide.

The ultraviolet spectra were recorded on a Unicam S.P. 800, and the infrared spectra on a Unicam S.P. 100 spectrophotometer. In the infrared work, calibration was accurate to ± 1 cm^{-1} over the region 1630–1700 cm^{-1}, and cells of path length 0·05 mm (10 and 20%), 0·5 mm (0·5–3%) and 2 mm (0·1 and 0·3%) were used for the solution studies. The nmr spectra were recorded on a Varian A-60 spectrophotometer using deuterochloroform as solvent and TMS as internal standard.

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