Proton Magnetic Resonance Spectra of Some Amphetamines and Related Compounds and Observations on Rotamer Populations

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Data from the p.m.r. spectra of β-amino-, β-aminohydrochloride-, β-hydroxy-, and β-nitro-α-phenylpropanes having methyl or methoxy substituents on the phenyl ring (37 compounds in all) are presented. The α and β protons of the side-chain give a pattern usually analyzable as ABX. The data are discussed in terms of correlations of coupling constants and chemical shifts with electronegativity of the substituent groups, steric and electronic effects, and apparent changes in rotamer populations. Hydrogen-bonding between the amino group of amphetamines and a methoxyl function at the ortho position in the phenyl ring is indicated for the salts but not the free bases.

On présente les données relatives aux spectres r.m.p. de β-amine, chlorhydrate de β-amino, β-hydroxy, et β-nitro α-phénylpropanes, ayant des substituants méthyles ou méthoxy sur le noyau phényle (37 composés en tout). Les protons α et β sur la chaîne latérale donnent un spectre analysable habituellement selon un ABX. Les données sont discutées en fonction des relations des constantes de couplage et des déplacements chimiques avec l'électronégativité des groupes substituants, les effets stériques et électroniques et les modifications apparentes dans les populations des rotamères. La liaison hydrogène entre le groupe amine des amphétamines et le groupe méthoxy en position ortho sur le noyau phényle est établie dans les sels mais non dans les bases libres.

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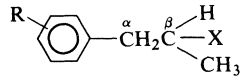
The analysis of the p.m.r. spectra of organic molecules is an established technique in conformational analysis (1). 1,2-Disubstituted ethanes have received considerable attention (2) and the conformations of acetylcholine (3) and its seleno (4) and thio (4, 5) isologues and very recently its α- and β-methyl derivatives (6) have been investigated by these methods.

Some predictions have been made about the conformation of amphetamines (7). A model accounting for the psychotomimetic activity of methoxyamphetamines and phenethylamines was proposed (8) in which the conformational behavior of these compounds was suggested to be modified by intramolecular hydrogen bonding. Such models have been strongly criticized (7, 9). We were therefore interested in the possibility of analyzing the p.m.r. spectra of amphetamines having methoxy or methyl groups on the phenyl ring, and their salts (since amphetamines are virtually completely ionized at physiological p*H*), for rotamer populations. The methylene (benzylic, α) and methine (β) protons of the side-chain give rise to a spectral pattern ($\alpha_1\alpha_2\beta$) approximating the ABX type for fast rotation with unequal populations (1). To the end of investigating factors affecting the stability of the various rotameric forms, we also prepared and examined corresponding compounds **I** in which the amino function is replaced by hydroxyl and by nitro groups. Preliminary work on dimethoxyamphetamines has been presented (10).



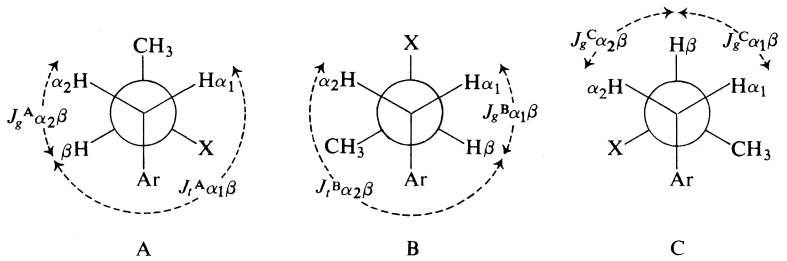
I

Discussion

We will assume at first that compounds $ArCH_2CH(CH_3)X$ exist in a dynamic equilibrium between the three classically staggered rotamers A, B, and C shown in Fig. 1 having mole fractions *a*, *b*, and *c* respectively.[1] The correspondence of protons α_1 and α_2 *as depicted* with the upfield (α′) or downfield (α) observed benzylic signals is discussed later in terms of the compound type. Vicinal coupling between protons is indicated in the figure, superscripts A, B, or C denoting the rotamer and subscripts *t* or *g* the coupling type (*trans* or *gauche*).

If $J\alpha_1\beta$ and $J\alpha_2\beta$ are the two observed (mean) vicinal couplings, then

[1]An approximate analysis of such a three-spin system for determining conformational equilibria has been presented by Snyder (11).



A B C

FIG. 1. Staggered rotamers of $ArCH_2CH(CH_3)X$; coupling constants indicated.

[1] $$J\alpha_1\beta = aJ_t^{A}\alpha_1\beta + bJ_g^{B}\alpha_1\beta + cJ_g^{C}\alpha_1\beta$$

[2] $$J\alpha_2\beta = aJ_g^{A}\alpha_2\beta + bJ_t^{B}\alpha_2\beta + cJ_g^{C}\alpha_2\beta$$

To simplify the present analysis for any one compound or series (X constant) the following approximations are made:

$$(i)\ J_t^{A}\alpha_1\beta = J_t^{B}\alpha_2\beta = J_t$$

$$(ii)\ J_g^{C}\alpha_1\beta \simeq J_g^{A}\alpha_2\beta = J_g$$

$$(iii)\ J_g^{C}\alpha_2\beta \simeq J_g^{B}\alpha_1\beta = J_{g'}$$

Equations 1 and 2 then reduce to the approximate form

[3] $$J\alpha_1\beta = aJ_t + bJ_{g'} + cJ_g$$

[4] $$J\alpha_2\beta = aJ_g + bJ_t + cJ_{g'}$$

also

[5] $$1 = a + b + c$$

The chief factors affecting these couplings in our series for constant dihedral angles depend on the electronegativities of the α and β substituents indicating that when X is more electronegative than CH_3, $J_{g'} > J_g$ (2, 12, 13). If the signals from the diastereotopic protons observed as α and α′ can be unambiguously assigned to the protons depicted as α_1 and α_2 in Fig. 1, and values of J_t, J_g, and $J_{g'}$, are available, then a, b, and c are easily obtained. If $J_g = J_{g'}$, simple algebra gives

$$a = \frac{J\alpha_1\beta - J_g}{J_t - J_g}$$

$$b = \frac{J\alpha_2\beta - J_g}{J_t - J_g}$$

and $$c = \frac{J_t + J_g - (J\alpha_1\beta + J\alpha_2\beta)}{J_t - J_g}$$

which are useful for preliminary estimates of rotamer stability.

The selection of suitable values for J_t, J_g, and $J_{g'}$ is hampered by the paucity of information on model compounds.

Other workers (14) have used $J_t = 12.0$ Hz as a starting point. This figure with the J_g and $J_{g'}$ values chosen below gives reasonable, greater than zero results for a, b, and c using our observed coupling constants. We therefore adopted $J_t = 12.0$ Hz as a suitable round number for the amphetamines. Abraham and Gatti (2) have recently devized precise equations for estimating vicinal coupling constants in 1,2-disubstituted ethanes, and it is reasonable that *changes* of the same order would be followed by our compounds. Averaging their coefficients and using Huggins' electronegativities (15) suggests that J_t decreases by about 0.7 Hz when X is changed from NH_2 to OH. The unchanged J_{vic} in triethylamine and tetraethylammonium salts (16) and work on *cis*-3-methyl-2-phenylmorpholine (17) indicates that J_t will be scarcely changed on protonation of the amphetamine amino group. 4-Nitro groups exert a negative increment on the (negative) geminal coupling of benzylic protons compared with NH_2 (18) and comparing compounds **1–6** with **19–24** (Table 1) shows a similar trend, the NO_2 seeming therefore to be less electronegative than NH_2 (10). Accordingly, J_t may increase (more positive) slightly when NO_2 is substituted for NH_2 in **I**.

The most important difference affecting the relative magnitudes of J_g and $J_{g'}$ seems to be the changing disposition of the CH_3 and X groups. Extrapolation of the coefficients for 1,2-disubstituted propanes (2) suggests the maximum difference (when X = N) to be about 1 Hz, and in the absence of definitive data $J_{g'} = 3.0$, $J_g = 2.0$, or $J_{g'} = J_g = 2.0$ are chosen as reasonable values for our compounds (19).

Table 2 shows how a, b, and c change with choice of J_t, J_g, and $J_{g'}$, for typical observed couplings. The calculated ratio of the two minor contributors is most affected by this choice, but

TABLE 1. Data from the p.m.r. spectra* of amphetamines and derivatives of structure I

Compound	Substitut on	X	ArR	β-H†	β-CH_3‡	$\overline{\alpha_1\alpha_2}$	$-J\alpha_1\alpha_2$ (Hz)	$\alpha_1 - \alpha_2$ (p.p.m.)	α′	(Jα′β)	α	(Jαβ)
1	2-CH_3	NH_2	7.69	6.87	8.86	7.36	13.1	9.05	7.43	(8.75)	7.28	(4.35)
2	3-		7.67	6.90	8.88	7.41	13.0	11.3	7.50	(8.5)	7.32	(4.3)
3	4-		7.70	6.90	8.90	7.45	13.2	11.2	7.54	(8.75)	7.36	(4.4)
4	2-CH_3O		6.20	6.80	8.88	7.37	12.9	10.8	7.45	(8.4)	7.28	(4.4)
5	3-		6.21	6.83	8.88	7.41	12.8	11.0	7.51	(8.3)	7.32	(4.5)
6	4-		6.23	6.88	8.92	7.45	13.0	9.5	7.55	(8.4)	7.39	(4.4)
7	2,3-$(CH_3)_2$		7.74, 7.80	6.88	8.89	7.37	13.2	11.1	7.46	(8.6)	7.28	(4.4)
8	2,4-		7.73, 7.73	6.87	8.90	7.42	13.3	9.7	7.50	(8.8)	7.34	(4.4)
9	2,5		7.73, 7.73	6.83	8.88	7.42	13.2	10.5	7.51	(8.8)	7.34	(4.4)
10	2,3-$(CH_3O)_2$		6.15, 6.18	6.81	8.88	7.37	12.7	8.1	7.44	(8.7)	7.30	(4.1)
11	2,4-		6.22, 6.22	6.84	8.92	7.45	13.0	10.9	7.54	(8.2)	7.36	(4.2)
12	2,5-		6.28, 6.28	6.83	8.91	7.43	12.5	10.3	7.51	(8.4)	7.35	(4.4)
13	3,4-		6.14, 6.14	6.85	8.88	7.44	13.0	10.1	7.53	(8.4)	7.35	(4.5)
14	3,5-		6.25, 6.25	6.83	8.89	7.47	13.0	12.0	7.57	(8.5)	7.37	(4.3)
15	2,3,4-$(CH_3O)_3$		6.07, 6.08, 6.18	6.82	8.90	7.44	13.0	10.8	7.53	(8.4)	7.35	(4.4)
16	2,4,5-		6.12, 6.17, 6.20	6.88	8.88	7.42	12.8	10.4	7.51	(8.4)	7.34	(4.5)
17	2,4,6-		6.20, 6.22, 6.22	6.90	8.91	7.40						
18	3,4,5-		6.10, 6.10, 6.12	6.83	8.81	7.42	13.0	13.9	7.55	(8.5)	7.32	(4.4)
19	2-CH_3	NO_2	7.70	5.25	8.48	6.84	14.0	21.95	7.01	(7.3)	6.67	(6.9)
20	3-		7.70	5.25	8.49	6.90	14.0	19.5	7.07	(7.05)	6.73	(6.95)
21	4-		7.70	5.26	8.50	6.90	14.0	18.5	7.05	(6.85)	6.75	(7.15)
22	2-CH_3O		6.20	5.10	8.51	6.86	13.6	13.1	6.97	(6.8)	6.75	(7.35)
23	3-		6.24	5.25	8.48	6.88	13.8	19.5	7.05	(6.9)	6.72	(7.1)
24	4-		6.25	5.29	8.50	6.90	14.0	17.0	7.04	(7.1)	6.76	(7.2)
25	2,5-$(CH_3O)_2$		6.24, 6.29	5.11	8.50	6.89	13.6	12.95	6.99	(6.5)	6.78	(7.1)
26	2-CH_3O	OH	6.22	5.95	8.81	7.24						
27	3-		6.23	6.00	8.80	7.32						
28	4-		6.23	6.05	8.81	7.35						
29	2,3-$(CH_3O)_2$	$NH_3^+Cl^-$	6.11, 6.16	6.35	8.61	6.95	13.0	15.9	7.09	(8.8)	6.82	(5.2)
30	2,4-		6.19, 6.23	6.40	8.64	7.01	13.1	16.0	7.14	(8.65)	6.87	(5.35)
31	2,5-		6.20, 6.27	6.40	8.61	6.99	13.1	13.6	7.10	(8.5)	6.88	(5.5)
32	3,4-(H_2O)		6.17, 6.19	?	8.64	7.00	13.0	27.7	7.23	(9.6)	6.77	(4.3)
33	3,5-		6.23, 6.23	6.45	8.60	7.00	13.1	25.2	7.20	(9.5)	6.79	(4.5)
34	2,3,4-$(CH_3O)_3$		6.06, 6.13, 6.18	?	8.61	7.00	13.2	17.1	7.15	(8.5)	6.86	(5.5)
35§	2,4,5-		6.13, 6.16, 6.16	?	8.61	7.01	13.0	14.0	7.13	(8.1)	6.90	(4.4)
36	2,4,6-		6.17, 6.17, 6.17	?	8.59	7.02						
37	3,4,5-		6.14, 6.14, 6.18	?	8.59	7.02	13.0	21.7	7.20	(9.2)	6.83	(4.8)

*τ-Values, measured with a Varian A-60A spectrometer using solutions at 40°, 10–15% in $CDCl_3$ containing TMS as internal standard. Signals (two recordings) were reproducible ± 0.01 p.p.m. Signals from the α and β protons were recorded at 100 Hz sweep width. Data from **10–14** have been presented before (10). Appropriate aromatic proton signals and integration ratios were observed.

†These signals were multiplets. Those from **34–37** were obscure: these salts are only moderately soluble in $CDCl_3$. Compound **32** crystallizes as a monohydrate, and the H_2O obscures the signal

‡Doublets: *J ca.* 6.5 Hz.

§Spectrum poor, lines 4 and 5 of ABX system not resolved, could lead to errors in $J_{\alpha_1\beta}$ and $J_{\alpha_2\beta}$.

TABLE 2. The effect of choice of J_t, $J_{g'}$, and J_g on apparent rotamer populations*

			Observed $J\alpha_1\beta = 5$, $J\alpha_2\beta = 8$			Observed $J\alpha_2\beta = 5$, $J\alpha_1\beta = 8$ Hz		
J_t	$J_{g'}$	J_g	*a*	*b*	*c*	*a*	*b*	*c*
11	2	2	33	67	0	67	33	0
13	2	2	27	55	18	55	27	18
12	2	2	30	60	10	60	30	10
12	3	2	24	58	18	57	29	14
12	2	1	31	63	6	60	36	4
12	3	1	25	61	14	57	35	8
12	4	1	21	58	21	55	33	12
			Observed $J\alpha_1\beta = 4$, $J\alpha_2\beta = 9$			Observed $J\alpha_2\beta = 4$, $J\alpha_1\beta = 9$ Hz		
			a	*b*	*c*	*a*	*b*	*c*
11	2	2	22	78	0	78	22	0
13	2	2	18	64	18	64	18	18
12	2	2	20	70	10	70	20	10
12	3	2	13	68	19	68	19	13
12	2	1	21	72	7	70	27	3
12	3	1	15	70	15	68	26	6
12	1	3	26	68	6	70	15	15

*a, b, and c expressed as mole fractions % to the nearest integer.

whatever the chosen constants, it is seen that the *direction* in which a and b change for various observed couplings is determined by the *observed* coupling constants. It is obviously unwise to make dogmatic statements from our results about the stability of the sterically disfavored rotamer C relative to that of the other minor rotamer, and small (*i.e.*, less than 10%) differences in apparent rotamer populations comparing *series* (X changing) should be viewed cautiously.

Results

Table 1 presents p.m.r. data for solutions of our compounds in deuterochloroform at 40 °C. The benzylic protons and the β proton give signals $\alpha_1\alpha_2\beta$ which were analyzed in the second order as ABX, assuming that $J\alpha_1\alpha_2$ is negative and $J\alpha_1\beta$ and $J\alpha_2\beta$ are positive. At first it is not possible to say which of α_1 and α_2 (Fig. 1) is at higher field, and Table 1 merely describes them as α and α′. Because the β-H is coupled to the α-CH_3, only the AB part was used to find $J\alpha_2\beta$ (1). In general these eight lines (numbered 1–8 from high to low field) were plainly visible, but for compounds **1–3** and **7–9** line 1 was obscured by the aromatic methyl signal and was calculated from $J\alpha_1\alpha_2$ revealed by lines 2–4, 5–7, and 6–8. Further, it happened that the broad NH_2 signal of compounds **1–3** came in the $\alpha_1\alpha_2$ region, although the AB lines projected from the envelope. Changing the concentration somewhat shifted the NH_2 signal and addition of D_2O caused its disappearance, but did not cause any detectable shift in any of the other lines, and the values recorded for **1–3** are for $CDCl_3$ solutions with D_2O added. We also noted that the presence of impurities, even to the extent of some 50–60% of crude reaction mixture in some cases, had no effect on the spectral analysis on comparison with purified material. These observations lend confidence in the spectra.

Table 1 shows that at 60 MHz, the coupling between α_1 and α_2 is about the same as their chemical shift difference. Indeed for compounds **17** and **36** (2,4,6-trimethoxy-substitution pattern) the signals are degenerate, resemble the A_2B case, and were not calculable as ABX. The methoxyphenyl propanols **26** and **28** also present an A_2B-like pattern at 60 MHz: lines 4 and 6 are superimposed, 3 and 5 partially overlap, and 1, 2, 7, and 8 are extremely weak.

Chemical Shifts

There is a trend for the band center of the α-protons ($\overline{\alpha_1\alpha_2}$) to shift slightly upfield in the monosubstituted series **1–3**, **4–6**, **19–21**, **22–24**, and **26–28** as the substituent shifts further from the benzylic carbon. The coupling constant data discussed below show that this is not due to consistent changes in the relative rotamer populations. The center $\overline{\alpha_1\alpha_2}$ of the other compounds remains approximately constant except that for

2,3-disubstituted compounds it appears at rather lower field. Steric hindrance to rotation of the phenyl ring and through-space effects from substituents seem unlikely explanations for this and we suggest that the effect results from the changing magnitude of inductive effects on the benzylic carbon (20). These influences should change $J\alpha_1\alpha_2$ very slightly (18) but no consistent pattern emerges from our results for these series.

The chemical shifts of the β-H and the β-CH_3 in the series **1–3**, **4–6**, **19–21**, and **26–28** are generally shifted to slightly higher fields as the substituent changes from the ortho to meta to the para position. Decreasing the population of rotamer C with this change (increasing the shielding of the β-H by the *gauche* aryl group) is unlikely on steric grounds and not supported by rotamer population changes derived from coupling constant data. For the nitro compounds **22–25** the effect on β-H is very marked and is discussed further below.

The downfield shifts observed in the β-CH_3, the β-H (and the $\overline{\alpha_1\alpha_2}$ signals), when the NH_2 group is protonated are considerably smaller than when the NH_2 is replaced by NO_2. Accordingly the J_t and J_g changes are probably greater on conversion of the NH_2 into NO_2 than on hydrochloride formation, which is in line with our earlier discussion and the calculations presented below.

Coupling Constants and Rotamer Populations

These are best discussed in terms of the compound type.

Amphetamines

Rotamer populations calculated from the appropriate expressions using $J_t = 12.0$, $J_{g'} = 3.0$ and $J_g = 2.0$ and using $J_t = 12.0$, $J_{g'} = J_g = 2.0$ (10) are in the Depository of Unpublished Data. The range of values found shows that there is almost no change in the conformational equilibria of the amphetamines as a result of changing the aromatic substitution pattern for methyl and methoxy substituents (a or $b \simeq 65$, b or $a \simeq 20$, $c \simeq 15\%$). This is readily seen in the coupling constants of Table 2. Reasons for supposing that α_1 will be at lower field than α_2 have been given (10) and if this is so, then rotamer B is predominant, in agreement with calculations (7). The amino group exerts greater steric demands than a nitro group (21). Our results for nitro compounds (below) show that A and B are roughly equally populated, hence an increase in b and a decrease in a on going from the nitro, series to the amino series appears reasonable. We conclude that for aryl-substituted amphetamines, the rotamer in which the amino and aryl functions are *trans* is the most stable and that at 40 °C it is present as some 55–70% of the equilibrium mixture in $CDCl_3$ solution.

The proposition (8) that hydrogen-bonding between the amino group and an oxygen atom at the ortho position to the side chain could seriously affect the conformational equilibria is not confirmed by our work on these free bases. An investigation of intra-molecular NH....O bonding in compound **4** by the i.r. sequential dilution technique showed only free NH absorption at 3635 and 3605 cm^{-1} at a concentration below 0.4% in carbon tetrachloride.[2]

Amphetamine Hydrochlorides

For the reasons given above, we consider that J_t, $J_{g'}$, and J_g, will be little changed from their values in the free bases. Table 3 presents results for methoxylated compounds in $CDCl_3$. There is obviously a significant difference between salts with an ortho oxygen and those without. The population of rotamer C is very low and considered to be zero in the following discussion of the four possibilities (average % given).

Case 1. Compounds with *o*-CH_3O have 65% A, others have 25% A.

Case 2. Compounds with *o*-CH_3O have 65% A, others have 75% A.

Case 3. Compounds with *o*-CH_3O have 35% A, others have 75% A.

Case 4. Compounds with *o*-CH_3O have 35% A, others have 25% A.

The shielding effects of a *gauche* or *trans* $NH_3^{(+)}Cl^{(-)}$ moiety have not been defined, although what follows confirms an earlier inference (22) that a *gauche* $NH_3^+....Cl^-$ has a shielding effect. Therefore the definition of which observed α signal corresponds with α_1 or α_2 and hence which of the calculated rotamer percentages applies to A and which to B is not at first possible. The following points are pertinent:

(i) Chemical Shifts of the Benzylic Protons

Assuming that the chemical shift changes between α_1 and α_2 of the salts are primarily due to effects from the β groups, then a linear rela-

[2]We thank Mr. J. C. Ethier for this result.

TABLE 3. Calculated rotamer populations of amphetamine hydrochlorides*

Compound	$J\alpha_1\beta > J\alpha_2\beta$			$J\alpha_1\beta < J\alpha_2\beta$		
	a	*b*	*c*	*a*	*b*	*c*
29	68	32	0	32	68	0
30	66.5	33.5	0	33.5	66.5	0
31	65	35	0	35	65	0
32	76	23	1	23	76	1
33	75	25	0	25	75	0
34	65	35	0	35	65	0
35†	61	24	15	24	61	15
37	72	28	0	28	72	0

*a, b, and c expressed as mole fractions %, using $J_t = 12, J_{g'} = J_g = 2$ Hz. For conditions of measurement see Table 1.
†Possible errors in $J\alpha\beta$ and $J\alpha'\beta$ (footnote §, Table 1) may be responsible for this apparently anomalous result.

tionship is expected between the chemical shift of α_1 with a rotamer percentage in one form A or B (C ≃ O) and similarly for α_2. There are fair fits with linearity when appropriate graphs are plotted for any of cases 1–4, and no conclusion can be drawn.

Case 1. For *o*-methoxylated salts, the H with larger coupling is α_1 which is observed upfield. Proton α_2 is shielded by a *gauche* CH_3 in both A and B, but when A dominates, α_1 has the greater *gauche* NH_3^+ effect which is therefore shielding. When A drops from 65 to 25%, α_2 shifts upfield (6.85 to 7.21 τ) because there is more *gauche* NH_3^+ influence. However, a deshielding effect of about 0.33 p.p.m. on α_1 (7.11 to 6.78 τ) for only a 40% decrease in *gauche* CH_3 influence (see A) seems to be somewhat excessive; *cis* and *trans* 3-methyl-2-phenylmorpholine hydrochlorides exist some 98% in the forms having *anti* and *gauche* 2-H/3-CH_3 conformations respectively in $CDCl_3$ solution and the 2-H signals are at 4.56 and 5.19 respectively (17).

Case 2. Similarly, shielding by *gauche* NH_3^+ is indicated, and as A increases, α_2 would shift downfield (6.85 to 6.78 τ) because (see rotamer B) there is a 10% decrease in the *gauche* NH_3^+ interaction. An upfield shift of about 0.1 p.p.m. (7.11 to 7.21 τ) for α_1 seems excessive for a 10% increase in the *gauche* CH_3 shielding.

Case 3. The relative magnitudes of the *gauche* CH_3 and NH_3^+ shielding or deshielding are important here and in case 4. The downfield shift for α_2 from 7.11 to 6.78 τ with decrease in B indicates that the *gauche* NH_3^+ has a shielding effect. Proton α_1 shifts from 6.85 to 7.21 τ which seems large for a 40% increase in the *gauche* CH_3 interaction.

Case 4. As in case 3, α_1 is at lower field because there is less shielding by the *gauche* CH_3 or because of *gauche* NH_3^+ effects. The shifts of α_2 (7.11 to 7.21 τ with increase in B) demonstrate that the *gauche* NH_3^+ has a shielding effect. The downfield shift in α_1 of about 0.07 p.p.m. (6.85 to 6.78 τ) for a 10% decrease in *gauche* CH_3 interaction is in fair agreement with the morpholine salts cited above.

Our initial assumptions and the small changes observed in the mean position of the benzylic signal with different substitution pattern do not allow a decision, although case 4 seems the most supportable. An important conclusion is that the NH_3^+ moiety *shields gauche* protons.

(ii) Chemical Shifts of the β-CH_3

If *a* is larger in the meta OCH_3 series, the β-CH_3 would be less shielded by the aryl group. Inspection of Tables 1 and 4 shows differences of β-CH_3 no greater than in the case of the free bases, where there is little change in rotamer populations, strongly suggesting that there is no major change in rotamer populations in the salts, *i.e.*, the "cross over" cases 1 and 3 are improbable. Table 4 shows that the downfield shifts of the β-CH_3 signal on going from the free amphetamines to their salts ($\Delta\tau$ CH_3) are generally greater for compounds with an *o*-CH_3O than for those without, *i.e.*, the increase of A in the ortho series on salt formation appears to be greater than for the meta series. The correlation is not good, but the results are best compatible with case 4.

From points *i* and *ii*, case 4 appears the most likely. Rotamer B is dominant, as for the free bases, but H-bonding or electrostatic interaction of some kind allows extra A in the ortho methoxyl series. Intramolecular hydrogen bonding between

TABLE 4. Changes in the chemical shift of the β-CH_3 group on protonation of amphetamines*

CH_3O-Substitution type	2,3-Di	2,4-Di	2,5-Di	2,3,4-Tri	2,4,5-Tri	3,4-Di	3,5-Di	3,4,5-Tri
τ β-CH_3 base (*i*)	8.88	8.92	8.91	8.90	8.88	8.88	8.89	8.81
τ β-CH_3 salt (*ii*)	8.61	8.64	8.61	8.61	8.61	8.64	8.60	8.59
Δτ CH_3 (= *i* − *ii*)	0.27	0.28	0.30	0.29	0.27	0.24	0.29	0.22
% A increase in salts†								
Case 1	47	40.5	41	41	36‡	−2	2	4
Case 2	47	40.5	41	41	36‡	51	52	48
Case 3	11	7.5	11	11	−1‡	51	52	48
Case 4	11	7.5	11	11	−1‡	−2	2	4

*For di- and trimethoxyamphetamines of Table 1 under the conditions described there, see footnote *.
†From difference in *a* values using $J_t = 12, J_{g'}$ (Table 3) $= J_g = 2$ Hz (*a* of bases ≃25%).
‡This value probably in error, see footnote †.

the protonated amino group and an ortho methoxyl is suggested by Snyder's model (7), and a similar interaction was inferred (22) for 1-(4-methoxyphenyl)-1-methoxy-2-aminopropane hydrochloride. An interaction with the aromatic bonds has been suggested as stabilizing the corresponding conformation for β-phenylethanols (21). Even if our estimate of *c* is somewhat inaccurate, it certainly seems that C is a small contributor. Rotamers A and C both have *gauche* aryl and NH_3^+ groups, so this agrees with the sterically favored B being dominant. Other amphetamine hydrochlorides were insufficiently soluble in $CDCl_3$ for spectral measurement. Amphetamines are protonated at physiological p*H*. Unfortunately, investigation of conformational behavior in water (using D_2O) was frustrated by the resultant chemical shift and/or coupling constant (rotamer population) changes: lines 4 and 6 were superimposed and 3 and 5 barely resolved. Results for other systems (23) suggest that the gross conformational features of the salts would be the same in different solvents. Our results (Table 5) provide evidence that amphetamine salts indeed exhibit conformational behavior of the type postulated by Snyder (8) but this does not correlate well with the degree of psychotomimetic activity.

1-Aryl-2-nitropropanes

The rotamer populations in Table 6 were calculated using $J_t = 13, J_{g'} = 3$, and $J_g = 2$ Hz. The increase in the chosen coupling constant values from that in amphetamines is in accord with the earlier discussion, and receives some experimental justification in that within this *J* *gauche* range, J_t must be increased if $a + b \not> 1$. Table 6 shows that for any one compound, *c* is little affected by the choice of which of α_1 and α_2 is at higher field. Because steric effects probably determine populations trends, it might be supposed that the greatest difference in *a* and *b* should be observed for the compounds with the substituent CH_3 or OCH_3 ortho to the side-chain. This seems to be the case if α_1 is at low field for the methyl compounds, but at high field for the methoxy compounds. However, the chemical shifts of the benzylic protons are about the same in both series and rotamer populations are little changed, so it seems more reasonable to expect that the same proton depicted as α_1 or α_2 (Fig. 1) appears at higher field in *both* series (and for the 2,5-dimethoxy compound **25**). Preliminary evidence suggested that the NO_2 group strongly shields *gauche* protons of a similar type (22), but a *gauche* CH_3 also shields and population changes (Table 6) are too small to allow an estimate of the relative magnitude of the shielding by these two groups, critical in deciding which of α_1 and α_2 is which. Rotamer A places the β-CH_3 *trans* to the aryl ring, and on steric grounds (CH_3 > NO_2) A would be the more stable. Our data for meta and para substituted compounds suggest that B is slightly more stable whether α_1 or α_2 is at high field, but the calculated *a*, *b*, and *c* depend on the chosen coupling constants and small errors in their values could reverse the order of apparent stability, since *a* and *b* are nearly equal.

TABLE 5. Data from the p.m.r. spectra* of dimethoxyamphetamine hydrochlorides

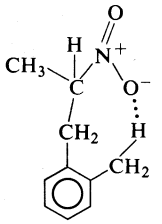
Compound†	$(CH_3O)_2Ar$	β-H‡	β-CH_3§	$\overline{\alpha_1\alpha_2}$
29	6.17, 6.26	6.40	8.77	7.10
30	6.25, 6.25	6.44	8.80	7.23
31	6.25, 6.28	6.4	8.78	7.18
32	6.23, 6.25	6.4	8.77	7.20
33	6.28, 6.28	6.4	8.77	7.20

*τ-Values, measured in D_2O solution (external TMS); otherwise see Table 1.
†See Table 1 for substitution pattern.
‡Multiplets, band-center not well defined.
§Doublets, *J ca.* 6.5 Hz.

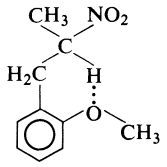
TABLE 6. Calculated rotamer populations of 1-aryl-2-nitropropanes*

Compound	Substitution	% if α_1 at low field			% if α_1 at high field		
		a	*b*	*c*	*a*	*b*	*c*
19	2-CH_3	40.3	47.0	12.7	44.2	43.4	12.4
20	3-CH_3	40.9	44.6	14.5	41.9	43.7	14.4
21	4-CH_3	42.9	42.8	14.3	40.0	45.5	14.5
22	2-CH_3O	44.4	42.5	13.1	39.3	47.4	13.3
23	3-CH_3O	42.4	43.2	14.4	40.4	45.0	14.6
24	4-CH_3O	43.1	45.3	11.6	42.2	46.2	11.6
25	2,5-$(CH_3O)_2$	42.8	39.3	17.9	36.8	44.7	18.5

*a, b, and c expressed as mole fractions %, using $J_t = 13$, $J_{g'} = 3$, and $J_g = 2$ Hz. For conditions of measurement see Table 1.



II



III

Extrapolation to the ortho compounds could be complicated by interactions of the type **II** and **III**. Although **II** is in our opinion unlikely, **III** is worth consideration: the β-H is rendered quite acidic by the nitro group. Type **III** may occur for rotamers A or B, probably with some distortion and lower symmetry imparted to the rotating phenyl ring. Evidence that this interaction occurs is found in the unusually low field resonance of the β-H in the ortho-methoxy compounds **22** and **25**. An increase in *c* might have such an affect (aryl group and β-H *trans*) but this does not seem to be the case for **22**. Further, the *o*-OCH_3 signal is at about 0.04 p.p.m. to lower field for **22** compared with **23** and **24**, whereas in the alcohols **26–28** and amphetamines **4–6** the differences are about 0.00 and 0.02 p.p.m. respectively. We conclude that for simple 1-aryl-2-nitropropanes the populations of rotamers A and B are roughly equal.

1-Aryl-2-propanols

A hydroxyl group is considerably less bulky than an amino group, and hence the ratio *b*:*a* is predicted to be less than in the case of amphetamines described earlier. In $CDCl_3$ solution at 40 °C the spectra of 1-aryl-2-propanols resemble the A_2B case. Since positive increments in J_{gem} result from the presence of more electronegative substituents (18) (*e.g.* O *cf.* N) the observation suggests that the chemical shift difference between the benzylic protons is now quite small. The same type of chemical shift *changes* occur as in the amino and nitro series. The low field position of $\overline{\alpha_1\alpha_2}$ in ortho methoxylated compounds is more marked; both it and the β-CH_3 signal are shifted by about 0.1 p.p.m. to lower field on changing the β substituent from NH_2 to OH, and the β-H is deshielded by about 0.8 p.p.m. Nibbering *et al.* (24) found that the corresponding vicinal couplings for solutions of 3,3,3-trideutero-1-phenylpropan-2-ol were not affected by concentration changes within the range 0.2–0.5 mol fraction in CCl_4. The benzylic protons were separated by about 6 Hz at 60 MHz. Their observed couplings (average 5.6 and 7.1 Hz) suggest populations of A (or B) about 36, B (or A) about 51, and C about 13%. Whatever assignment of signal to α_1 or α_2 is correct, the ratio *b*:*a* is lower than for the amphetamines, as predicted above.

Experimental

The compounds described here were prepared by standard methods, all were obtained as racemates.

Amphetamines

The appropriately substituted β-methyl-β-nitrostyrene was reduced using lithium aluminum hydride in ether or tetrahydrofuran. When a very impure amphetamine was obtained, it was generally isolated by regeneration from its hydrochloride. The common by-products of reaction seemed (p.m.r., i.r.) to be the corresponding oximes; their presence had no detectable effect on the p.m.r. spectrum of the amphetamine on the evidence from pure and impure materials. All 18 compounds were characterized as their hydrochlorides.

Amphetamine Hydrochlorides

These compounds were precipitated from ethereal solutions of the amphetamines on addition of a solution of hydrogen chloride in dry ether. All were recrystallized from isopropanol/hexane and gave satisfactory analyses (C, H, and N ±0.3%) except that 2,3- and 2,5-dimethylamphetamine hydrochloride were very hygroscopic:

Anal. Calcd. for $C_{11}H_{18}ClN$: C, 66.16; H, 9.09; N, 7.02; and Calcd. for $C_{11}H_{18}ClN \cdot \frac{1}{2}H_2O$: C, 63.28; H, 9.17; N, 6.71. Found: C, 63.18; H, 8.75; N, 6.76; and C, 63.94; H, 8.76; N, 6.70 respectively.

2,3,4-, 2,4,5-, and 2,4,6-Trimethoxyamphetamine appeared to be similarly hygroscopic.

Anal. Calcd. for $C_{12}H_{20}ClNO_3$: C, 55.09; H, 7.70; N, 5.35; and Calcd. for $C_{12}H_{20}ClNO_3 \cdot \frac{1}{2}H_2O$: C, 53.29; H, 7.82; N, 5.17. Found: C, 53.93; H, 7.41; N, 5.26; C, 53.87; H, 7.57; N, 5.27; and C, 53.71; H, 7.55; N, 5.37 respectively.

Satisfactory analyses were obtained after rigorous drying immediately before analysis. 3,4-Dimethoxyamphetamine hydrochloride was obtained as a stable monohydrate; 2,5-dimethoxyamphetamine hydrochloride deliquesces in moist air. We noted that literature values for the melting points of many amphetamine hydrochlorides differed considerably, and that our findings too were at variance; melting points seem to be affected by the presence of moisture absorbed from air.

1-Aryl-2-nitropropanes

The appropriately substituted β-methyl-β-nitrostyrene was reduced using sodium borohydride in methanol or ethanol at 30° (25). A large excess of reducing reagent was required before the yellow color of the nitrostyrene was completely discharged. Oximes appear to be the usual by-product, since on aqueous acid work-up, the corresponding phenylacetone (26) could be obtained. The nitropropane and phenylacetone were easily separated by silica gel column chromatography. The compounds were liquids, satisfactory analyses (C, H, and N) were obtained.

1-Aryl-2-propanols

The appropriately substituted phenylacetone was reduced using sodium borohydride in methanol. The alcohols were purified by column chromatography on silica gel.

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