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THE ACID-CATALYSED RACEMISATION MECHANISM OF CATECHOLAMINES

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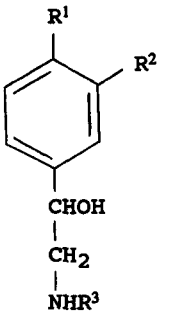
Abstract - The racemisation rates of (-)-adrenaline (1), (-)-isoprenaline (2), (-)-2-(3,4-dimethoxyphenyl)-2-hydroxy-N-isopropylamine (3), (+)-2-(4-methoxyphenyl)-2-hydroxy-N-isopropylethylamine (4), (+)-2-phenyl-2-hydroxy-N-isopropylethylamine (5), (-)-phenylephrine (6), and (+)-1-phenylethanol (7) were compared. The racemisation rates decreased in the following order: **7 > 1 ≈ 2 > 3 ≈ 4 >> 5, 6.** In general, the reactivity of the series of the phenylethanolamine compounds (1) - (6) was seen to increase sharply as the electron-releasing ability of the *p*-substituent of the aromatic nucleus increases. The results strengthen the notion that the acid-catalysed racemisation of catecholamines proceeds *via* a quinonoid-type intermediate.

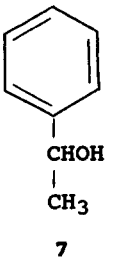
Each of adrenaline (1) and isoprenaline (2) possesses a point of asymmetry at the β-carbon atom; and the pharmacological activity at α- and β-adrenoceptors resides predominantly in the R(-)-enantiomers.[1,2] Although the racemisation of adrenaline (1) has been the subject of a number of investigations, most of these studies centered around the stability of adrenaline (1) under certain conditions.[3-6] Schroeter and Higuchi[7] have suggested that the acid-catalysed racemisation of adrenaline (1) is an S_N1 reaction and that the reaction involves an initial protonation of the β-hydroxy group, leading to the formation of a carbonium ion intermediate. Following studies[8] of the methanolysis of catecholamines and related compounds, it was suggested that the acid-catalysed racemisation of catecholamines may proceed *via* a quinoidal intermediate and not *via* an S_N1-type reaction.

Since we have been interested in the role played by the β-hydroxy group of catecholamines in drug-receptor interactions,[9] it was thought that the reactivity of the β-hydroxy group and/or mechanism of racemisation may give some insight in the role played by the β-hydroxy group in the drug-receptor interactions of the catecholamines (1) and (2). In order to assess the effect of the electron-withdrawing ammonium group as well as the effect of the different *p*-substituents on the reactivity of the β-carbon atom, the racemisation rate of a selected number of compounds (1) - (7) were determined under specified conditions.

RESULTS AND DISCUSSION

The racemisation studies were conducted by monitoring the change of optical rotation of different enantiomers (1) - (7) in 1.0M hydrochloric acid *versus* time at constant temperature. (-)-Adrenaline (1), (-)-isoprenaline hydrochloride (2), (-)-phenylephrine hydrochloride (6) and (+)-1-phenylethanol (7)





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1. $R^1 = R^2 = OH$, $R^3 = CH_3$
2. $R^1 = R^2 = OH$, $R^3 = CH(CH_3)_2$
3. $R^1 = R^2 = OCH_3$, $R^3 = CH(CH_3)_2$
4. $R^1 = OCH_3$, $R^2 = H$, $R^3 = CH(CH_3)_2$
5. $R^1 = R^2 = H$, $R^3 = CH(CH_3)_2$
6. $R^1 = H$, $R^2 = OH$, $R^3 = CH_3$

were obtained commercially. The methoxy compounds (3)[10] and (4) were synthesised and the racemic mixtures were resolved by classical methods. The obtained enantiomers were sufficiently pure for the racemisation studies. (+)-Phenylethanolamine (5) was synthesised *via* a stereo specific route from (+)-styreen oxide. Experimental values of the racemisation reaction constants, **k**, of compounds (1) - (7) are summarised in **Table 1.**

From the data in **Table 1** it is clear that the catecholamines (1) and (2), which possess *p*-hydroxy groups, racemise markedly faster than compounds (3) and (4) possessing *p*-methoxy groups. Phenylethanolamine (5) and phenylephrine (6), which are both devoid of *p*-sustituents, are for all practical purposes unreactive towards acid catalysed racemisation. A comparison of the racemisation rates of the phenylethanolamines (1) - (6) with that of 1-phenylethanol (7), revealed that (7) racemises faster than these compounds. The fact that (7) racemises faster than the *p*-substituted compounds (1) - (4), was

Table 1. Rate constants for the acid-catalised racemisation of (1) - (7) in 1.0M hydrochloric acid at 30.1 °C.

Compound	Rate constant, **k** min^{-1}
(-)-Adrenaline (1)	$(4.1 \pm 0.2) \times 10^{-4}$
(-)-Isoprenaline (2)	$(4.5 \pm 0.3) \times 10^{-4}$
(-)-Dimethoxy compound (3)	$(1.0 \pm 0.1) \times 10^{-4}$
(+)-Methoxy compound (4)	$(1.5 \pm 0.1) \times 10^{-4}$
(+)-Phenylethanolamine (5)	$(8.4 \pm 0.2) \times 10^{-7}$
(-)-Phenylephrine (6)	$(3.2 \pm 0.3) \times 10^{-7}$
(+)-Phenylethanol (7)	$(1.8 \pm 0.2) \times 10^{-3}$

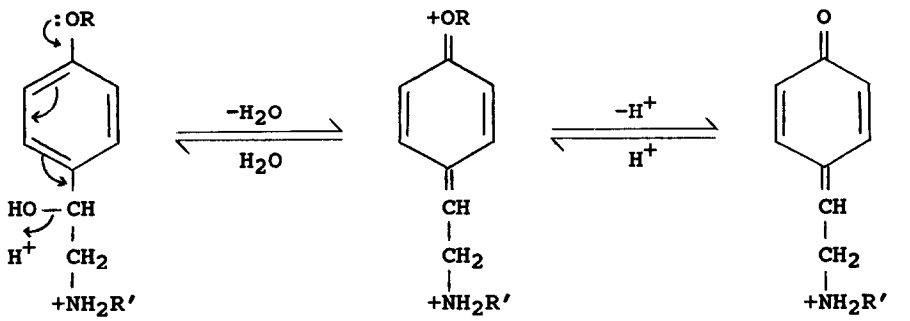
unexpected, especially since the reactivity of (7),[11,12] and (1),[7] is ascribed to the ability of the aromatic nucleus to stabilise the partial positive charge of a carbonium ion intermediate by delocalisation. It is generally visualised that unimolecular substitution will be facilitated by *p*-substituents, such as *p*-hydroxy and *p*-methoxy groups, on the aromatic nucleus which increases the effective length of the conjugated system and hence the electron density at the carbon atom constituting the reaction site.[13,14]

The results indicate that the metastable intermediates involved in the racemisation of (5) and (6) are of very high energy, and that a *p*-hydroxy group, or *p*-methoxy group, is of fundamental importance in lowering the energy of the metastable intermediates of the phenylethanolamine-type compounds. The unreactivety of (5) and (6) towards acid-catalysed racemisation, and the fact that (7) racemise faster than the *p*-substituted phenylethanolamines (1) - (4), can not be readily explained by simply assuming a S_N1-type mechanism for the racemisation of the phenylethanolamine compounds (1) - (6). Since the aromatic nucleus of phenylethanolamine (5) possess the same conjugating ability as (7) to stabilise a possible carbonium ion intermediate on the β-carbon atom, the unreactivety of compounds (5) and (6), and the observation that the *p*-substituted compounds (1) - (4) reacts slower than (7), can only be attributed to the presence of the amino group.

At the low pH of the reaction medium the amino group of compounds (1) - (6) would, however, predominantly exist as a positively charged ammonium moiety. In view of the results obtained, it may be argued that in the presence of an acid, catecholamines will probably not lose the β-hydroxy group to produce a carbonium ion intermediate directly, since the electron-withdrawing ammonium group in $[C_6H_5CH(OH)CH_2NH_2R]^+$ will decrease the ease of carbonium ion formation on the β-carbon atom, and should therefore retard unimolecular substitutions at the β-carbon atom.[15] The stabilising effect of the aromatic nucleus on a possible carbonium ion intermediate, centered on the β-carbon atom of the phenylethanolamines (1) - (6), may be outweighed to a high degree by the destabilising electron-withdrawing effect of the ammonium group.

Proposed reaction mechanism. In accepting the probability that the formation of a carbonium ion in the vicinity of the ammonium group is undesirable, the racemisation reaction can be explained in terms of the mechanism shown in **Scheme 1.** The simplest plausible mechanism for acid catalysed racemisation would involve an initial loss of the β-hydroxy group resulting in the formation of a highly metastable intermediate (II). Since (II) is achiral, the possible equilibrium between (I) and (II) may lead to a loss of optical activity. The fact that the racemisation rate of the *p*-hydroxy compounds (1) and (2) is higher than that of the *p*-methoxy compounds (3) and (4), indicate that the metastable intermediates involved in the racemisation of (3) and (4) are of higher energy than the metastable intermediates involved for the *p*-hydroxy compounds (1) and (2). This difference in stability may be ascribed to the fact that π-electrons are released more readily by the *p*-hydroxy group than by the *p*-methoxy group.[16-18] The metastable intermediate (II, R = H), of the *p*-hydroxy compounds (1) and (2), may additionally stabilise itself by formation of a quinonoid intermediate (III). Obviously, the quinonoid intermediate (III) is not possible in compounds (3) and (4).

Scheme 1.



I II III

R = H, CH_3
R'= CH_3, $CH(CH_3)_2$

EXPERIMENTAL

Optical rotations were measured at 30.1°C at 589 mμ (sodium D-line) with a Zeiss circle polarimeter and a 10 cm jacketed cell fitted with a centrifugal pump and a constant temperature bath. M.p.s. were determined with a Gallenkamp melting point apparatus and are uncorrected. Microanalyses of the compounds agreed with calculated values within ±0.4%. The resolved compounds afforded i.r., ^{1}H n.m.r., and mass spectral data consistent with their structures. ^{1}H n.m.r. spectra were recorded on a Varian T60. The mass spectrometic analyses were carried out with a VG 70-70E mass spectrometer fitted with a saddle-field FAB gun. Ionisation was accomplished by a beam of neutral Xenon atoms of approximately 8keV energy and 1mA emission current. The ion accelerating voltage was 8kV. The samples, dissolved in glycerol, were introduced into the source using a stainless steel target attached to direct insertion probe.

Resolution of (3). Racemic 2-(3,4-dimethoxyphenyl)-2-hydroxy-N-isopropylethylamine (3) was synthesised as described in the literature.[10] To a hot solution of the free base of racemic (3) (4.78 g, 0.02 mol) in ethanol (20 ml) was added a solution of (+)-tartaric acid (3.00 g, 0.02 mol) in ethanol (30 ml). After the mixture was refluxed for 10 min, it was allowed to cool slowly and stand at room temperature for 4 h to yield colourless crystals of the bitartrate of (-)-(3) (1.5 g, 19%). The resultant (+)(-)-diastereoisomer was recrystallised from ethanol to constant m.p. and optical rotation; m.p. 128-130°C; $[\alpha]^{30}$ -7.1 (c = 3.89, H_2O); m/z 240 (M^++1) (FAB); Anal. ($C_{17}H_{27}NO_9$) C, H, N.

(-)-2-(3,4-dimethoxyphenyl)-2-hydroxy-N-isopropylethylamine hydrochloride (3). The (+)(-)-diastereoisomer (3.89 g, 0.01 mol) was dissolved in water (50 ml) and treated with sodium carbonate (1.17 g, 0.011 mol). The precipitated free base (2.11 g, 88%) was filtered, dried and used without further purification. A mixture of the the free base (1.20 g, 0.005 mol), benzyl chloride (0.633 g, 0.005 mol) and palladium on charcoal (5%, 0.1 g) in ethanol (80 ml) was hydrogenated at room temperature and atmospheric presure. After uptake of the theoretical amount of hydrogen (0.005 mol) was completed, the mixture was filtered and the filtrate was concentrated under reduced pressure. Addition of anhydrous diethyl ether to the ethanol solution yielded colourless crystals of the hydrochloride of (-)-(3) (1.01 g, 73%); m.p. 178-179°C; $[\alpha]^{30}$ -36.0 (c = 2.39, H_2O); (60 MHz; solvent DMSO-d6; standard Me_4Si)

1.23 (6H, d, J 6 Hz, $-CHMe_2$), 2.83–3.35 (3H, m, $-CH_2-NH-CHMe_2$), 3.74 (3H, s, OMe), 3.78 (3H, s, OMe), 4.85–5.11 (1H, m, -CH(OH)-), 6.92–7.02 (3H, m, ArH); m/z 240 (M^++1) (FAB); Anal. ($C_{13}H_{22}ClNO_3$) C, H, Cl, N.

Synthesis of 2-(4-methoxyphenyl)-2-hydroxy-N-isopropylethylamine (4). 4-Methoxybenzaldehyde (1.36 g, 0.01 mol) was treated with dimethylsulphonium methylide (0.01 mol) in dimethylsulphoxide (70 ml) to afford 4-methoxyphenyl-ethylene oxide.[19] A mixture of the crude epoxide (1.3 g, 0.01 mol) and isopropylamine (30 ml) was sealed in a stainless steel reaction vessel and heated at 50°C for 12 h. The solution was concentrated *in vacuo* to yield (4) (1.2 g, 57%); m.p. 84–86°C; (60 MHz; solvent $CDCl_3$; standard Me_4Si) 1.20 (6H, d, J 6 Hz, $-CHMe_2$), 2.60–2.98 (3H, m, $-CH_2-NH-CHMe_2$), 3.78 (3H, s, OMe), 4.53–4.77 (1H, m, -CH(OH)-), 6.90 (2H, d, J 9 Hz, ArH), and 7.3 (2H, d, J 9 Hz, ArH); m/z 209 (M^+, 7%), 137 (MeO-Ar-CH=OH^+, 44%), and 72 (CH_2=$NHPr^{i+}$, 100%); Anal. ($C_{12}H_{19}NO_2$) C, H, N.

Resolution of (4). (+)-Tartaric acid (3.00 g, 0.02 mol) in ethanol (30 ml) was added to a solution of the free base of racemic (4) (4.18 g, 0.02 mol) in ethanol (15 ml). The mixture was refluxed for 10 min. After evaporation, the residual oil was dissolved in boiling water (80 ml) and allowed to cool slowly and stand at room temperature for 8 h to yield colourless crystals of the bitartrate of (+)-(4) (1.87 g, 26%). The resultant (+)(+)-diastereoisomer was recrystallised from water to constant m.p. and optical rotation; m.p. 96–98°C; $[\alpha]^{30}$ +41.4 (c = 3.59, H_2O); m/z 210 (M^++1) (FAB); Anal. ($C_{16}H_{25}NO_8.H_2O$) C, H, N.

(+)-2-(4-Methoxyphenyl)-2-hydroxy-N-isopropylethylamine hydrochloride (4). The (+)(+)-diastereoisomer (3.59 g, 0.01 mol) was dissolved in water (50 ml) and treated with sodium carbonate (1.17 g, 0.011 mol). The precipitated free base (1.88 g, 90%) was filtered, dried and used without further purification. A mixture of the free base (1.045 g, 0.005 mol), benzyl chloride (0.633 g, 0.005 mol) and palladium on charcoal (5%, 0.1 g) in ethanol (80 ml) was hydrogenated at room temperature and atmospheric presure. After uptake of the theoretical amount of hydrogen (0.005 mol) was completed, the mixture was filtered and the filtrate was concentrated under reduced pressure. Addition of anhydrous diethyl ether to the ethanol solution yielded colourless crystals of the hydrochloride of (+)-(4) (0.99 g, 81%); m.p. 120–122°C; $[\alpha]^{30}$ +39.1 (c = 2.25, H_2O); (60 MHz; solvent D_2O; standard Me_4Si) 1.83 (6H, d, J 7 Hz, $-CHMe_2$), 3.63–4.13 (3H, m, $-CH_2-NH-CHMe_2$), 4.26 (3H, s, OMe), 5.33–5.67 (1H, m, -CH(OH)-), 7.43 (2H, d, J 9 Hz, ArH), 7.83 (2H, d, J 9 Hz); m/z 210 (M^++1) (FAB); Anal. ($C_{12}H_{20}ClNO_2$) C, H, Cl, N.

Synthesis of (+)-2-phenyl-2-hydroxy-N-isopropylethylamine (5). A mixture of commercially obtained (+)-styreen oxide (0.6 g, 0.005 mol) and isopropylamine (5 ml) was sealed in a stainless steel reaction vessel and heated at 50°C for 12 h. The solution was concentrated *in vacuo* to yield (+)-(5) (0.72 g, 81%); m.p. 72–74°C; $[\alpha]^{30}$ +50.0 (c = 1.79, 0.1M HCl, 98%); (60 MHz; solvent $CDCl_3$; standard Me_4Si) 1.07 (6H, d, J 6 Hz, $-CHMe_2$), 2.57–2.87 (3H, m, $-CH_2-NH-CHMe_2$), 4.53–4.77 (1H, m, -CH(OH)-), and 7.30–7.40 (5H, m, ArH); m/z 179 (M^+, 14%), 107 (Ar-CH=OH^+, 43%), and 72 (CH_2=$NHPr^{i+}$, 100%); Anal. ($C_{11}H_{17}NO$) C, H, N.

Polarimetric determinations. 0.1 Molar solutions were prepared by dissolving (7) (122.0 mg, 0.001 mol) and the hydrochlorides of (2) (247.7 mg, 0.001 mol), (3) (275.5 mg, 0.001 mol), (4) 245.5 mg, 0.001 mol) and (6) (203.7 mg, 0.001 mol) in 1.0M hydrochloric acid (10 ml). 0.1 Molar solutions of (1) and (5) where prepared by dissolving the free bases of (1) (183.2 mg, 0.001 mol) and (5) (179.0 mg, 0.001 mol) in 1.10M hydrochloric acid (10 ml). The rates of racemisation of the thermostated 0.1 molar solutions were determined by measuring the change in optical rotation with respect to time. All rate coefficients quoted were determined from:

$$\ln\alpha_o - \ln\alpha_t = kt,$$

where α_o is the angle of rotation for a given solution of compounds (1) – (7) at the start of the experiment and α_t is the angle of rotation at time equal to t.

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REFERENCES

1. Pratesi, P.; Grana,E. *'Advances in Drug Research'*. (Edited by N.J. Harper and A.B. Simmonds) Vol 2, Academic Press, London and New York, **1965**, p. 130.
2. Patil, P.N.; Miller, D.D.; and Trendelenburg, U. *Pharmacol. Rev.* **1974**, *26*, 323-392.
3. Haddock, L.A. *Quart. J. Pharmacol.* **1933**, *6*, 496-501.
4. Florence, G.; Shapira, G. *Arch. phys. biol.* **1944**, *17*, 94-95.
5. Berry, H.; West, G.B. Quart. *J. Pharm. Pharmacol.* **1944**, *17*, 242-248.
6. Hellberg, H. *J. Pharm. Pharmacol.* **1955**, *7*, 191-197.
7. Schroeter, L.C.; Higuchi, T. *J. Am. Pharm. Assoc.* **1958**, *47*, 426-430.
8. Venter, D.P.; Greef, D.F. *Tetrahedron*, **1980**, *36*, 305-307.
9. Venter, D.P.; Oliver, D.W.; Dreyer, A.C. *S. Afr. J. Sci.* **1988**, *84*, 400-403
10. Venter, D.P.; Dreyer, A.C.; Langenhoven, J.H.; Dekker, T.G. *S. Afr. J. Sci.* **1988**, *84*, 393-395.
11. Grunwald, E.; Heller, A.; Klein, F.S. *J. Chem. Soc.* **1957**, 2604-2613.
12. Gould, E.S. *'Mecanism and Structure in Organic Chemistry'*, Holt, Rinehart and Winston, New York, **1962**, pp. 283-284.
13. Jorge, J.A.L.; Kiyan, N.Z.; Miyata, Y.; Miller, J. *J. Chem. Soc., Perkin Trans. 2*, **1981**, 100-103.
14. Vitullo, V.P.; Grabowski, J.; Sridharan, S. *J. Chem. Soc., Chem. Commun.* **1981**, 737-738.
15. Hine, J.; Lee, D.E. *J. Am. Chem. Soc.* **1952**, *74*, 3182-3183.
16. Bordwell, F.G.; Boutan, P.J. *J. Am. Chem. Soc.* **1956**, *78*, 854-860.
17. Brown, H.C.; Okamoto, Y. *J. Am. Chem. Soc.* **1958**, *80*, 4979-4987.
18. McDaniel, D.H.; Brown, H.C. *J. Org. Chem.* **1958**, *23*, 420-427.
19. Corey, E.J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353-1364.