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SHORT COMMUNICATION

The stereochemistry of carbonyl reduction of diethylpropion and related amino-ketones in man

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THE MAIN routes of metabolism of diethylpropion have been established;[1] these are outlined in Fig. 1. Under conditions of acidic urine to minimise tubular reabsorption of bases, 85–90 per cent of a dose of A could be accounted for in the urine of four subjects as compounds A to F (see Fig. 1). Furthermore there was only slight intersubject variation in the relative proportions of these amines and of the enantiomorphs of the amino-alcohols B, D and F. In this presentation the average values only will be used.

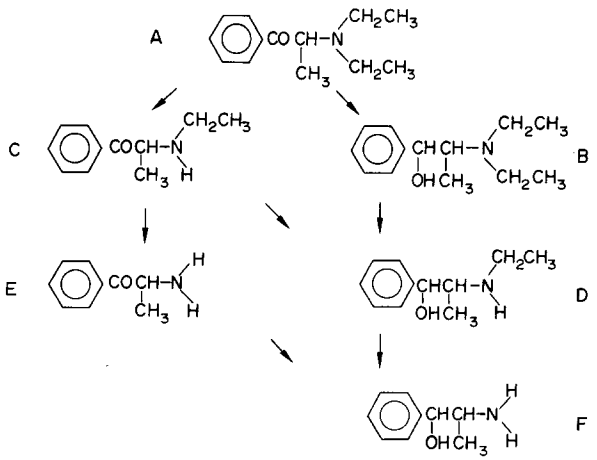

FIG. 1. Pathways for the production of the known metabolites of diethylpropion.

The relative cumulative recoveries of different metabolic products in urine do not indicate the relative importance of routes yielding particular compounds if more than one route leads to the compound and it is also further metabolised. For instance, 26 per cent of F but only 3 per cent of E was recovered in urine[1] even though twice as much diethylpropion is eliminated from the body via compound E (see later). Metabolic rate constants and excretion rate constants must be established from the cumulative urine data before the latter can be utilised to provide information concerning the relative involvement of alternative metabolic pathways.

A pharmacokinetic treatment of the data of excretion of compounds A to F after oral doses of diethylpropion (A) has recently been made using an analogue and digital computer programme to evaluate the rate constants of metabolism and excretion of these compounds.[2] Good agreement was obtained between experimental results and computer simulations to describe the cumulative excretion curves, e.g. see Fig. 2 for excretion of A and B after oral A and analogue computing and Fig. 3 for digital computing of the simultaneous cumulative excretion of the amines A–F after an oral dose of diethylpropion (A).

The metabolic and excretion rate constants for one of the subjects (Table 1) was used in Fig. 4 in conjunction with the average excretion of the amines in four subjects. The rate constants of excretion for these amines were very similar i.e. 0·28, 0·24, 0·25, 0·26, 0·29 for A–E. This indicates that tubular reabsorption of these compounds has been eliminated so that there is a common rate constant which is a reflection of glomerular filtration rate, if it is assumed that the rate of movement of these drugs from blood to urine passing down the kidney tubules[3] is similar because the partition coefficients of these compounds are not too dissimilar. The rate for F would be smaller because of its much greater water solubility in the unionised form which probably accounts for its overall smaller (i.e. 0·22) rate constant of urinary excretion.

TABLE 1. COMPUTER DERIVED RATE CONSTANTS FOR ONE SUBJECT FOR THE METABOLISM AND EXCRETION OF DIETHYLPROPION AND ITS METABOLITES
(see Ref. 2 for more details)

K_1	0·20	K_{ua}	0·28
K_2	1·0	K_{ub}	0·24
K_3	0·10	K_{uc}	0·25
K_4	0·66	K_{ud}	0·26
K_5	0·22	K_{ue}	0·29
K_6	0·04	K_{uf}	0·22
K_7	0·90		
K_8	1·0		

The 13 per cent of the drug unaccounted for is considered to involve E (possibly by deamination) because (a) F is not metabolised in man and the methyl-analogues of B and D are not metabolised except by *N*-dealkylation and (b) if C is given orally, the equivalent of 80 per cent of the dose can be recovered as C,D,E and F but, if E is given only the equivalent of 50 per cent of the dose can be recovered as E and F in urine and (c) no other bases were observed in urine after a dose of E except E and F i.e. the basic group had been removed in the metabolism. Only the fate of the 98 per cent of the compound not excreted as A is considered, and the "first-pass" through the liver is involved for the parent drug given orally but not for the products of its metabolism.[2]

Using this information, it is possible to compute the relative importance of different metabolic pathways on the metabolism and urinary excretion of diethylpropion (A) and its metabolic products (B–F) but at this stage ignoring the stereoisomeric composition of each amine (see Fig. 1). Reasonable agreement resulted between the average of the compounds excreted in four subjects using the rate constants of one subject to compute the percentage involvement of each compound in the network of metabolic pathways.

There is a much greater involvement of carbonyl reduction in the formation of amino-alcohols B, D and F than of de-ethylation in either the metabolism or formation of these amines. Of the 20 per cent of the diethylpropion (A) being reduced to B, only 5·5 per cent is de-ethylated. The sum of 17 per cent of the diethylpropion (A) appearing in urine as the amino-alcohol D, involves 15 per cent from reduction of C plus 5·5 per cent by de-ethylation of B, minus 3·5 per cent lost by de-ethylation of D. Likewise the 22·5 per cent of F in the urine involves 19 per cent by reduction of E and only 3·5 per cent by de-ethylation of D.

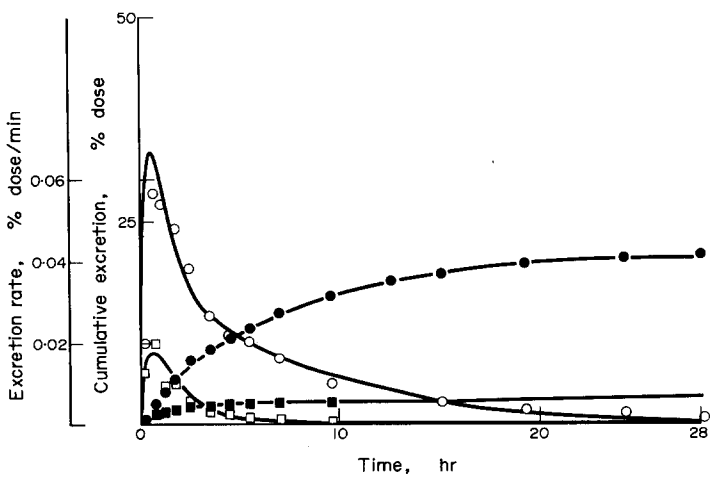

FIG. 2. Comparison of analogue computer generated curves with experimental points for the rate of excretion and cumulative excretion of compounds A and B following oral dosing with 10 mg of the hydrochloride of A. (□) Rate of excretion of A; (■) cumulative excretion of A; (○) rate of excretion of B; (●) cumulative excretion of B.

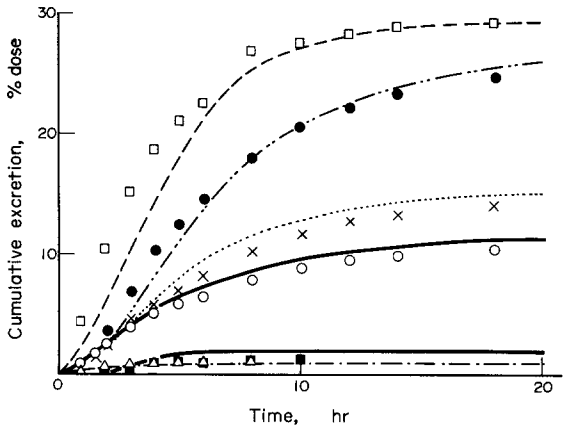

FIG. 3. Comparison of digital computer generated curves with experimental points for the cumulative excretion of compounds A,B,C,D,E and F following oral dosing with 25 mg of the hydrochloride of A. (△) A; (○) B; (□) C; (×) D; (■) E; (●) F.

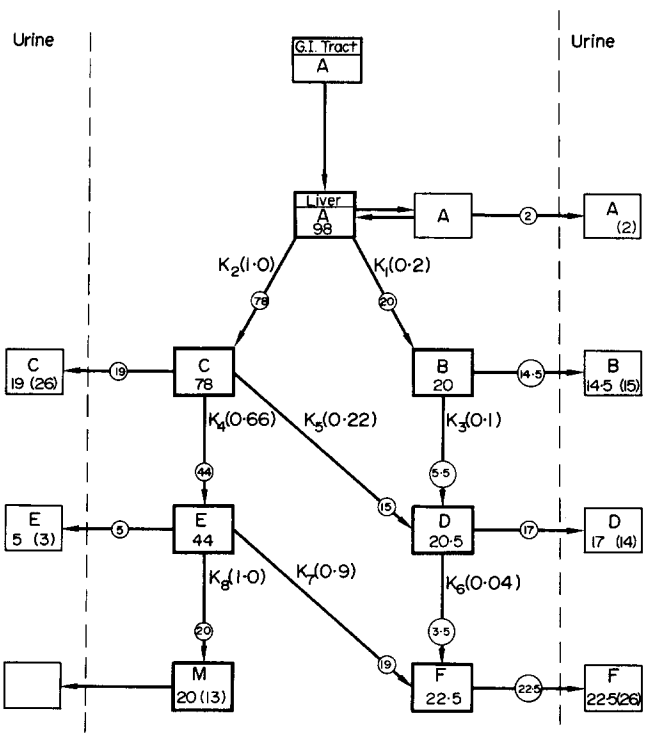

FIG. 4. The relative importance of different metabolic pathways in the metabolism and urinary excretion of diethylpropion (A) and its metabolic products (B–F).

□ Calculated percentage of diethylpropion dose produced *in vivo* as the stated product.

-○- Calculated percentage of diethylpropion dose involved in the route indicated.

□ a □ Calculated and observed percentage respectively of diethylpropion dose recovered in the urine as the stated compounds.

K Rate constants for the routes indicated.

Percentage of dose unaccounted for as recovered total bases in urine.

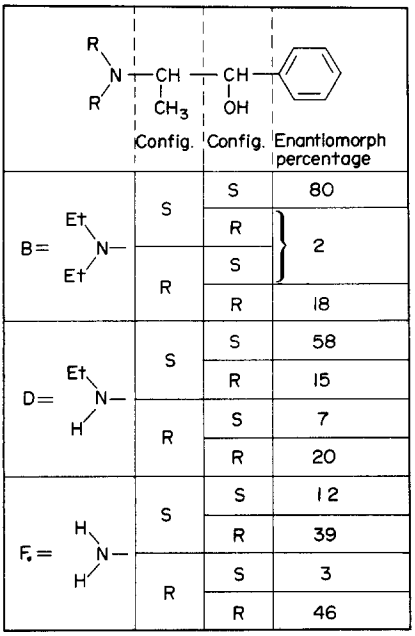

FIG. 5. The percentage enantiomorphic composition of the amino-alcohols B,D and F excreted in man after oral doses of diethylpropion (A). Average of four subjects; acidic conditions of urine (from Testa and Beckett[1]).

The average percentage of the free enantiomorphs in each of the amino-alcohols B, D and F excreted in the urine of the four subjects is shown in Fig. 5. The stereochemistry of reduction of the carbonyl group of A, C and E to give these enantiomorphs will now be considered.

Diethylpropion was given as the racemic mixture. Although the aminoketones E and C derived by successive metabolic *N*-de-ethylation of A also contain one asymmetric centre, they are concluded to be racemic mixtures because *N*-dealkylation is not a significantly stereoselective process and because their enantiomorphs racemise rapidly since their asymmetric centre possessing one H-atom is attached directly to a conjugated carbonyl group.

It is further concluded that stereochemical preference plays a minor role in the contribution of de-ethylation routes to the observed enantiomorphic proportions of the aminoalcohols B, D and F because (a) these routes are much less important than the carbonyl reduction routes to these compounds and (b) little stereochemical preference has been shown in the *N*-dealkylation of "amphetamines" and "ephedrines".[4,5]

Thus the proportions of enantiomorphs of B, D and F are considered to be a reflection of the relative hydrogen transfer of a keto-reductase to the 2S and 2R enantiomorphs of the amino-ketones A, C and E respectively. Likely conformation of the amino-ketones at the enzyme active site will now be considered.

The carbonyl and phenyl group will be in the same plane because of conjugation; this group combination is regarded as important in the binding of the substrate. The ionised basic group to give an ionic reinforced H-bond interaction with the receptor is also considered important in the enzyme-substrate interaction so that the directional influence is important. The relative alignment of these two groups at the receptor for the amino-ketone A with the 2S configuration is shown in (I), Fig. 6; the 2R configuration fits in a similar manner (II) with just the interchange of the C_2–Me and C_2–H groups. It is further postulated that the H transfer from the active site to the carbon of the carbonyl group occurs from below the plane of the molecule as depicted; in I it occurs from the left hand side because this side is not hindered by the C_2–Me whereas the two *N*-ethyl groups hinder the approach via the right hand side. In the 2R configuration (II), the approach from the bottom left hand portion is obstructed by the downward projecting C_2–Me but there is now greater freedom of movement for the two *N*-ethyl groups (Me interaction replaced by H interaction) which allows H-transfer from the right hand side. Also the 2S configuration in conjunction with the requirement of fit of a similar area and ion-reinforced hydrogen bond allows better fit at the receptor than with configuration 2R, and accounts for the four-fold overall less reduction of the 2R than the 2S configuration.

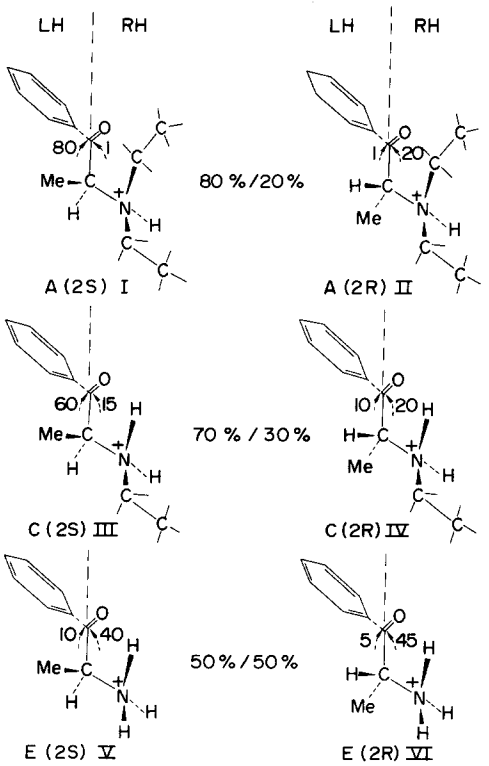

FIG. 6. The stereochemistry of carbonyl reduction in man of the amino-ketones, diethylpropion and its mono- and di-desmethyl metabolic products. The numbers indicate the importance of attack on the C of the carbonyl group from the sides indicated.

The successive removal of *N*-ethyl groups in the 2S configuration should progressively reduce the steric hindrance from the lower right hand side and thus increase the relative importance of the H-transfer to carbonyl from this direction; this occurs i.e. RH/LH is 4, 0·25 and 0·01 for E, C and A respectively. The removal of *N*-ethyl groups in the 2R configuration should also progressively increase the attack from the lower right against the lower left hand side; the results from C to E (IV to VI) are in accordance with the prediction but the increased flexibility introduced by removing these groups also allows some attack from the left side as the steric hindrance of the C_2–Me is reduced since conformational changes can be accommodated. Further support for this contention lies in the lessened importance of the C_2-Me to control the overall rate of reduction of the carbonyl group as the *N*-ethyl groups are successively removed i.e. 2S/2R reduction is 4, 2·5 and 1 for tertiary (A), secondary (C) and primary (E) amino-ketones respectively.

The results indicate that the rates of reduction of the amino-ketone diethylpropion (A) and the stereochemistry of the products of reduction are influenced significantly by the stereochemistry of the group adjacent to the carbonyl function and that the relative importance of this steric control of reduction can be influenced by the size of the groups attached to the basic centre. It is stressed that the conclusions are based on the overall rate processes *in vivo* in man rather than being based upon studies on isolated enzymes. It is hoped that the approach outlined in the present work will prove useful in studies with the object of producing generalisations which will help in the establishment of principles for drug design.

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