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A pharmacokinetic investigation of the distribution and elimination of diethylpropion and its metabolites in man

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Analogue and digital computing techniques have been used to elucidate the pharmacokinetic parameters involved in the metabolism and excretion of diethylpropion and its metabolites in man. Rate constants for the various processes have been evaluated for the complex reaction scheme. The values of the rate constants are used as a basis for discussion of the relative importance of some of the metabolic routes.

The anorectic agent diethylpropion (A, Fig. 1) is rapidly and completely absorbed from the gastrointestinal tract (Schreiber, Bozian & others, 1965). In man, its metabolism occurs by two major routes:— *N*-dealkylation and keto-reduction. This metabolism is extensive, only about 2% of the parent compound being recovered within 30 h under acidic urine conditions, the basic metabolites *N*-ethylaminopropiophenone (C), aminopropiophenone (E), *N*-diethylnorephedrine (B), *N*-ethylnorephedrine (D), and norephedrine (F) accounting for *ca* 85% of the dose (Testa & Beckett, 1973).

The two routes combine to give a complex metabolic pattern (Fig. 1). Since this study was of the overall fate of diethylpropion, in man, any use of isolated enzyme systems to monitor individual steps in the metabolism was considered irrelevant, nor was it considered ethical to give subjects intravenous injections of the metabolic products. In the present study, therefore, use is made of computing techniques to obtain an insight into the various rate processes involved.

METHODS

Two of the male subjects used in the previous trials with diethylpropion (Testa & Beckett, 1973) were given, on separate occasions, oral doses in aqueous solution of: (a) aminopropiophenone (E) 10 mg as hydrochloride; (b) *N*-ethylaminopropiophenone (C) 20 mg as hydrochloride; (c) diethylpropion (A) 25 mg.

The conditions of the trials were as already described (Testa & Beckett, 1973), with urines maintained at an acid pH.

In trial (i) urines were examined for components E and F of Fig. 1, in (ii) for components C, D, E and F and in (iii) for components A, B, C, D, E and F. The analytical methods used were those of Testa & Beckett (1972).

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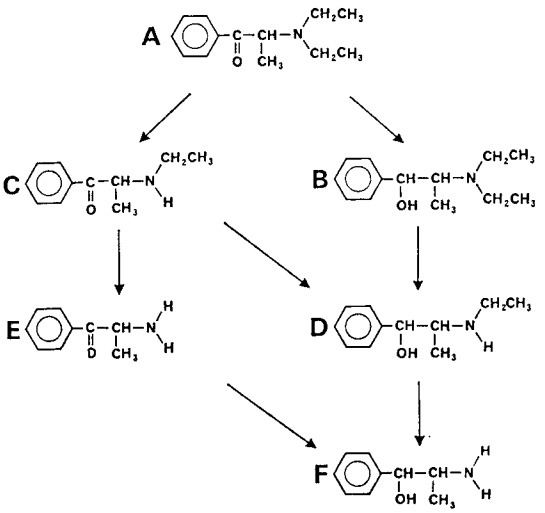

FIG. 1. Pathway for the production of the known metabolites of diethylpropion.

RESULTS AND DISCUSSION

(i) *Computer simulation of excretion after dosing with amino ketone E*

When the amino ketone E was given as an oral dose, 40–50% was recovered as the original compound or as metabolite F.

The pattern of excretion (see Fig. 3) was such as to indicate a "first pass" phenomenon as well as forms of tissue storage. A scheme such as that of Fig. 2 was found to be the simplest able to accommodate the experimental results. (The analogue computer program and definitions of symbols used in this and other parts of the overall analysis are given in the Appendix.) Tissue storage, denoted by subscript T, was found to be a necessary part of the compartmental model needed to describe the excretion of E in both subjects, but played only a minor role in the excretion of F in one subject and was not needed for the other.

Separate experiments using various subjects had already shown (Wilkinson & Beckett, 1968) that under conditions in which urine is maintained acid an oral dose of F in man can be quantitatively recovered from the urine unchanged. This lack of metabolism in man applies to both the diastereoisomeric forms of F (Beckett &

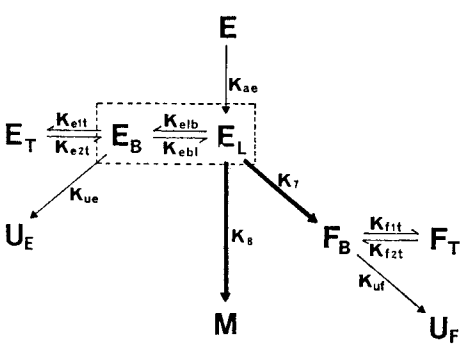

FIG. 2. Compartment model for the metabolism and excretion of compounds E and F after oral dosing with E.

Njikam, unpublished). It was therefore felt that after dosing with compound E, any material not accounted for as either E or F must have been lost as a metabolite of E rather than of F. For this reason the unknown metabolite(s) M is shown in Fig. 2 as emanating from E.

The rate of absorption of an oral dose of E is rapid, since E has a relatively low pKa value and a large partition coefficient (Vree, Muskens & van Rossum, 1972). In the analogue computer program the initial dose of E was therefore set as an initial condition for the integrator producing E_L, the assumption being made that K_{ae} is much greater than any other rate constant in the system. The equations and computer program for the model are given in the Appendix, and the fits obtained for the cumulative and rate curves found experimentally are shown in Fig. 3.

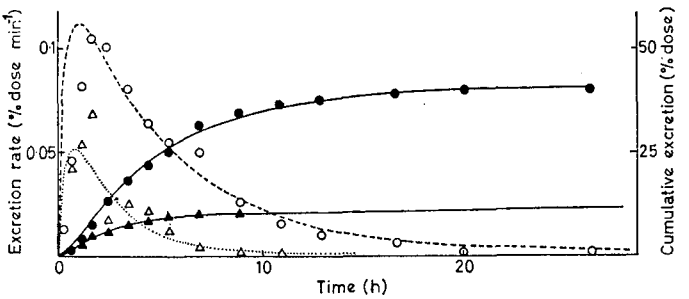

FIG. 3. Comparison of analogue computer generated curves with experimental points for the rate of excretion and cumulative excretion of compounds E and F, following oral dosing with 10 mg of the hydrochloride of E; triangles are for E, circles for F, open symbols for rate and closed for cumulative excretion.

(ii) *Computer simulation of excretion after dosing with amino ketone C*

By analogy with the model required after dosing with amino ketone E, that following dosing with the similar amino ketone C would be as in Fig. 4. Metabolism of the

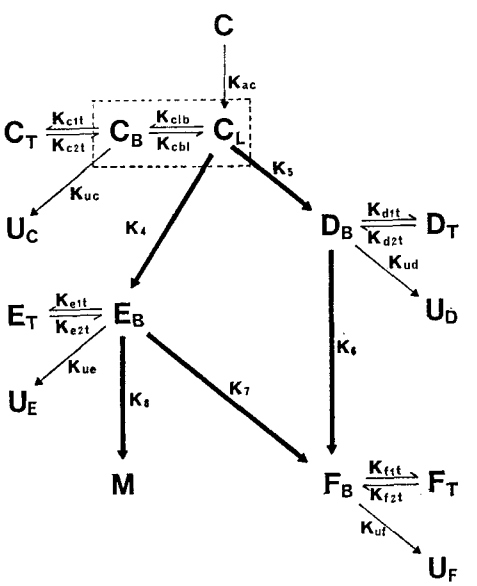

FIG. 4. Compartment model for the metabolism and excretion of compounds, C, D, E and F after dosing with C.

amino alcohol D other than to F is considered to be insignificant, since almost complete recovery of the parent drug and F in urine can be obtained when the analogous ephedrine and ψ-ephedrine are given to man under conditions of acid urine (Wilkinson & Beckett, 1968; Beckett & Njikam, unpublished). As with compound E, it is assumed that absorption of C is very fast. A "first pass" phenomenon is needed to account for the metabolism of C, but it is not now necessary to invoke it for E since E is produced inside the body rather than being led directly to the liver by the hepatic artery.

With only eight integrators available on the analogue computer it was not possible to solve the complete scheme of Fig. 4. However, the values of K_7 and K_{ue} are known from the analysis of data obtained after dosing with E. The proportion of E_B giving F_B can therefore be calculated. Since the total amount of E excreted in urine is known, the contribution of the path through E to F can be found. Of the total amount of F excreted, any not accounted for by this process must have come from D. The total amount of D excreted is also known, so that it is possible to calculate the ratio K_{ud} to K_6. The scheme in Fig. 4 can then be simplified to that in Fig. 5, and can be analysed for rate and cumulative plots of excretion of C and D using the computer program shown in Fig. 10. The computer generated curves and the experimental points are shown in Fig. 6.

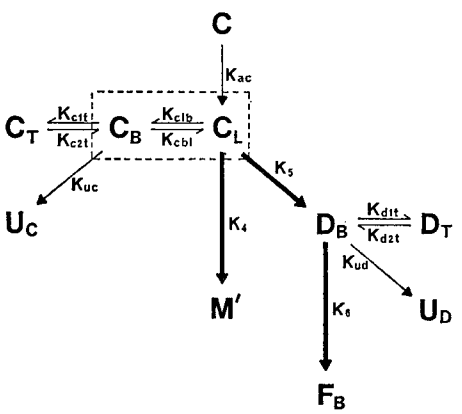

FIG. 5. Simplification of compartment model of Fig. 4 allowing solutions for C and D only.

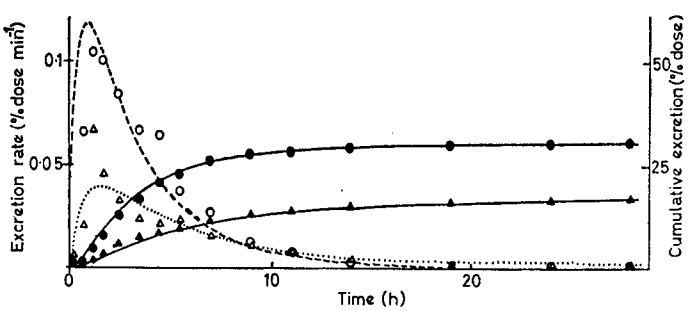

FIG. 6. Comparison of analogue computer generated curves with experimental points for the rate of excretion and cumulative excretion of compounds C and D following oral dosing with 20 mg of the hydrochloride of C; circles are for C, triangles are for D, open symbols for rate and closed for cumulative excretion.

(iii) *Computer simulation of excretion after dosing with diethylpropion (A)*

The complete model for urinary excretion following oral dosing with diethylpropion is shown in Fig. 7. Absorption of the drug is considered to be very fast, as with amino ketones E and C. Also, as in these instances, curve fitting of the ex-

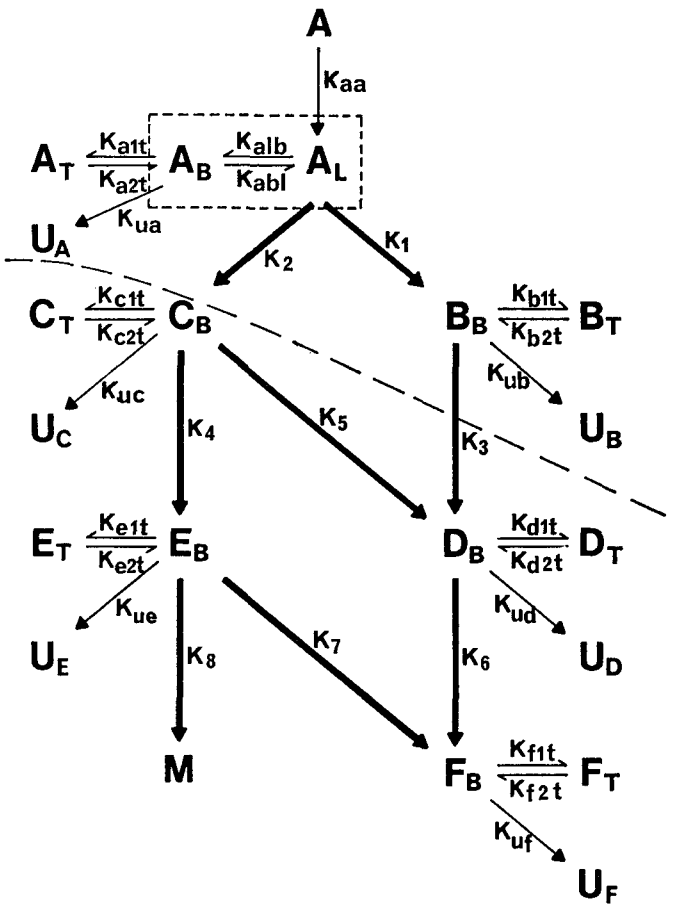

FIG. 7. Compartmental model for the metabolism and excretion of diethylpropion and its metabolites A, B, C, D, E and F following oral dosing with diethylpropion (A). The part of the diagram above the broken line was used to formulate a simplified model similar to that in Fig. 5 for solution by analogue computer.

perimental points demanded the inclusion of a "first pass" phenomenon for the administered drug. Since the limitations of the analogue computer used did not allow for specific solutions of the elimination characteristics of C, it was not necessary to include a "first pass" phenomenon for C (but see later). Administration of the methyl analogues of the compounds B and D leads to almost complete recovery of the dose as the amino alcohol F and the methyl analogues of B and D. Consequently, metabolism of B and D by routes other than dealkylation are ignored in Fig. 7. Furthermore, administration of compound C leads to *ca* 80% recovery of the initial dose as the basic compounds C, D, E and F and administration of A similarly leads to *ca* 80% recovery of the initial dose as the basic compounds A, B, C, D, E and F. On the other hand, administration of E gives only *ca* 50% recovery of

total drug as E and F (see p. 712). It therefore seems likely that metabolism of A and C by routes other than dealkylation and keto reduction may be ignored in comparison with such metabolism of E.

With the limited number of integrators the scheme could not be analysed completely by the analogue computer available. However, from the previous results of analysis after dosing with C and E, and knowing the total amounts of A, B, C, D, E and F excreted, it is possible to calculate the ratio K_{ub} to K_3 (see part ii). The part scheme indicated in Fig. 7 could therefore be solved and the rate constants of the part scheme found. The experimental points and computer generated curves are shown in Fig. 8.

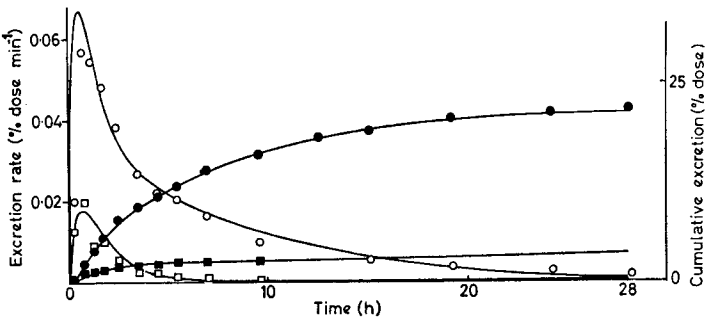

FIG. 8. Comparison of analogue computer generated curves with experimental points for the rate of excretion and cumulative excretion of compounds A and B following oral dosing with 10 mg of the hydrochloride of A; circles are for A, triangles for B, open symbols for rate and closed for cumulative excretion.

(iv) *Digital computer analysis of the metabolism of diethylpropion*

The absolute solution of the model of Fig. 7 by digital computing methods is theoretically possible. In practice it proved difficult to set up the correct convergent equations; and to arrive at a solution which is the true minimum of the equations and not merely one of several apparent minima which may be reached on the way. Attempts at *ab initio* solutions were therefore abandoned. However, using the rate constants obtained with the analogue computer, the rate equations for the overall scheme of Fig. 7 could be simultaneously integrated with respect to time using the digital computer. The digital output provided a set of curves to describe the excretion of the various products with time. Modifications of the rate constants were then made to obtain curves which fitted the empirical data more exactly.

Values for the rate constants obtained by analogue computer for the schemes of Figs 2 and 5 and the part scheme of Fig. 7 are shown in Table 1, and the computer curves and experimental points for the various situations are shown in Figs 3, 6 and 8. Discrepancies in the fits of the rate of excretion points to the computer curves in the early stages of urinary excretion can be ascribed to the placing of the dose directly into the appropriate liver compartment in the analogue simulation. This was necessary because of instrumental limitations, but is equivalent to setting an infinitely large rate of absorption. Table 1 also shows the rate constants used in the simultaneous solution of the complete scheme of Fig. 7 by digital computation, while the curves generated by the digital computer are compared with the experimental values in Fig. 9.

Considering the complexity of the system analysed, the curves obtained with the digital computer fit the experimental data very well and would seem to justify the

Table 1. *Analogue and digital computer values for the rate constants for distribution, metabolism and excretion of diethylpropion and its metabolites. The constants refer to the pathways shown in Figs 2, 5 and 7.*

	Rate constant K (h^{-1})	Values for subjects: PB	BT Analogue computation	BT Digital computation
Stage I				
	1	0·77	0·20	0·20
	2	1·35	0·98	0·98
	alb	0·16	0·03	0·03
	abl	0·52	0·50	0·50
	alt	0	0	0
	ua	0·28	0·28	0·28
	3	0·1	0·1	0·1
	blt	0·78	0·6	0·6
	b2t	0·49	0·75	0·7 5
	ub	0·27	0·24	0·24
Stage II				
	4	0·65	0·66	0·66
	5	0·30	0·22	0·22
	clb	0·91	0·86	0·86
	cbl	0·20	0·31	0·31
	clt	0·19	0·09	0·19
	c2t	0·46	0·46	0·46
	uc	0·25	0·52	0·45
	6	0·04	0·04	0·05
	dlt	0·02	0·02	0·02
	d2t	0·87	0·87	0·87
	ud	0·24	0·26	0·26
Stage III				
	7	0·87	0·92	1·92
	8	1·00	1·00	1·13
	elb	0·38	0·38	0·38
	ebl	0·02	0·02	0·02
	elt	0·13	0·16	0·16
	e2t	0·04	0·04	0·04
	ue	0·29	0·29	0·16
	uf	0·22	0·22	0·22
	f1t	0·04	0	0
	f2t	0·003	0	0

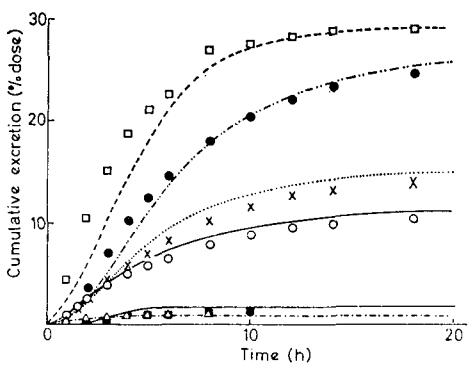

FIG. 9. Comparison of digital computer generated curves with experimental points for the cumulative excretion of compounds A, B, C, D, E and F following oral dosing with 25 mg of the hydrochloride of A. △ A. ○ B. □ C. × D. ■ E. ● F.

assumptions inherent in the scheme of Fig. 7. The results for the species A and B would be expected to fit the points, since these depend on rate constants which were the last to be assigned in the analogue computation stages. Of the other species

involved D, E and F fall very closely on the theoretical curves, and only C is excreted at a rate appreciably greater than predicted. It is possible to make a much more exact fit by including new rate processes. We have deliberately avoided this, and include only processes which seem justified on physiological grounds.

Of the 29 rate constants involved in the overall scheme (K_{aa} is excluded) and found by analogue computer, only five needed alteration for the purpose of the digital calculation, and of the five only three required amendment to any extent (K_7, K_{uc}, K_{ue}). A possible explanation of the need to alter these three lies in the use of the "first pass" model invoked in the analogue solutions for C and E given orally but not used subsequently for these compounds in the overall scheme for the metabolism of A given orally. Some of C and E could be in the "first pass" (liver) compartment after dosing with A, rather than all in central compartments C_B and E_B as shown in Fig. 7.

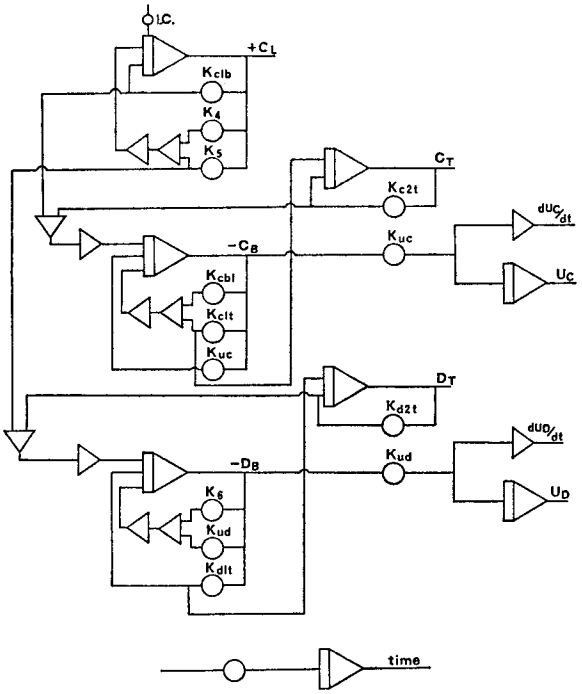

FIG. 10. Analogue computer program for the solution of the scheme in Fig. 5. A similar program is used for the schemes in Fig. 2 and part of Fig. 7.

In obtaining values for the rate constants of the two subjects (Table 1) by analogue computer, rate constants giving the best fit for one subject were obtained and then the best fit for the second subject was arrived at with as little change in the constants as possible. Even allowing for this, the values of the constants for the two subjects agree remarkably closely. Inter-subject variation is shown most clearly in the values of K_1 and K_{a1b}. However, these two constants represent processes which compete with one another and a high value of K_1 for subject PB (relative to subject BT) is matched by a high value for K_{a1b}. Given the very low amounts of A excreted by both subjects the differences may be more apparent than real.

The results, and interpretation of the results of analysis of the optical isomers

of the amino alcohols are dealt with elsewhere (Testa & Beckett, 1973; Beckett & Mihailova, 1974), but the remarkably small inter-subject variation in optical content may be noted, since it provides strong experimental confirmation for the agreement in rate constants found in the present work.

From considerations of the general success of the predictive value of the overall model we turn now to the value of the rate constants found for related processes.

(v) *Urinary excretion*

Conditions of acid urine were used in all trials with the intention of eliminating kidney tubular reabsorption of the compounds A to F. Under the conditions used the concentration of unionized drug in the kidney tubules is very much lower than that in the plasma, and this prevents tubular reabsorption (Beckett, Boyes & Tucker, 1968). In the absence of such reabsorption the rate constants for urinary excretion of these compounds would be expected to be identical and a reflection of the glomerular filtration rate provided that the various compounds show similar rates of passage from blood to urine after glomerular filtration (see Beckett, Salmon & Mitchard, 1969). Though no attempt was made to prejudge this in setting computer potentiometer values, the values for the rate constants K_{ua}(·28, ·28); K_{ub}(·24, ·27); K_{uc} (·25, ·25); K_{ud}(·26, ·24); K_{ue}(·29, ·29) and K_{uf}(·22, ·22) found show the expected constancy, with a mean of 0·26 and a range of 0·22–0·29 h^{-1}.

This agreement in values of K_u, and the general concordance of experimental results and analogue and digital computer simulations encourages other general conclusions regarding the calculated rate constants for the various metabolic reactions. The relative rates for one subject, BT, will be considered, but the same conclusions apply to the processes in the other subject.

(vi) N-*De-ethylation*

Both the tertiary amino compounds A and B are dealkylated more rapidly than the corresponding secondary amines C and D [K_2(·98) > K_4(·66) and K_3 (0·1 > K_6 (0·04)]. The amino ketones A and C are more rapidly dealkylated than the corresponding amino alcohols B and D [K_2(·98) > K_3 (0·1) and K_4 (·66) > K_6 (0·04).] *In vivo N*-dealkylation takes place mainly in the liver in a lipid environment and the relative rates of dealkylation of compounds A, B, C and D are in accord with the lipid/water partition coefficients of these compounds, viz: A > C, B > D, A $\gg$ B and C $\gg$ D (Beckett & Mihailova unpublished information).

(vii) *Keto reduction*

The rate constant for the reduction of the primary amino ketone E[K_7(·92)] is appreciably greater than those for reduction of A[K_1(·20)] and C[K_5 (·22)]. The latter rate constants are approximately equal in value. These differences between K_7 and K_1, K_2 are reflected in the different stereo selectivities of the reduction reactions (Testa, 1973; Beckett & Mihailova, 1974). The differences may also be because keto reductase systems in the kidney and liver favour hydrophilic substrates (Culp & McMahon, 1968), and compound E would then be a better substrate than A or C.

(viii) *Deamination*

After an oral dose of diethylpropion only 13% of the dose cannot be accounted for as the sum of the amines A to F recovered in urine. No other basic metabolites were detected. For reasons stated previously, compound E is involved primarily

in the additional metabolic route, which is therefore almost certainly deamination. The rate constant for this route [K_8(1·0)] is of the same order of magnitude as that for reduction of E[K_7(·92)].

(ix) *Main routes to the amino alcohols*

The rates of dealkylation of the tertiary (A) and secondary (C) amino ketones are two to four times those of carbonyl reduction of the same compounds K_2(·98), K_4(·66) > K_1(·20), K (·22). Since these reduction reactions are still much faster than the dealkylation reactions of the amino alcohols, it follows that the amino alcohols D and F are produced primarily by reduction of the amino ketones C and E respectively rather than by dealkylation of the alcohols B and D.

Acknowledgements

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APPENDIX

The following equations were used in the solution of the overall scheme of Fig. 7.

$$\frac{dA_L}{dt} = K_{aa}A + K_{ab1}A_B - (K_{a1b} + K_1 + K_2)A_L \quad (1)$$

$$\frac{dA_B}{dt} = K_{a1b}A_L + K_{a2t}A_T - (K_{ab1} + K_{a1t} + K_{ua})A_B \quad (2)$$

$$\frac{dA_T}{dt} = K_{a1t}A_B - K_{a2t}A_T \quad (3)$$

$$\frac{dU_A}{dt} = K_{ua}A_B \quad (4)$$

$$\frac{dB_B}{dt} = K_1A_L + K_{b2t}B_T - (K_{b1t} + K_{ub} + K_3)B_B \quad (5)$$

$$\frac{dB_T}{dt} = K_{b1t}B_B - K_{b2t}B_T \quad (6)$$

$$\frac{dU_B}{dt} = K_{ub}B_B \quad (7)$$

$$\frac{dC_B}{dt} = K_2A_L + K_{c2t}C_T - (K_{c1t} + K_{uc} + K_4 + K_5)C_B \quad (8)$$

$$\frac{dC_T}{dt} = K_{c1t}C_B - K_{c2t}C_T \quad (9)$$

$$\frac{dU_C}{dt} = K_{uc}\, C_B \quad .. \quad .. \quad .. \quad .. \quad .. \quad .. \quad .. \quad .. \quad (10)$$

$$\frac{dD_B}{dt} = K_3\, B_B + K_5\, C_B + K_{d_2t} D_T - (K_{d_1t} + K_{ud} + K_6)\, D_B \quad .. \quad (11)$$

$$\frac{dD_T}{dt} = K_{d_1t}\, D_B - K_{d_2t}\, D_T \quad .. \quad .. \quad .. \quad .. \quad .. \quad .. \quad (12)$$

$$\frac{dU_D}{dt} = K_{ud}\, D_B \quad .. \quad .. \quad .. \quad .. \quad .. \quad .. \quad .. \quad .. \quad (13)$$

$$\frac{dE_B}{dt} = K_4\, C_B + K_{e_2t}\, E_T - (K_{e_1t} + K_{uE} + K_7 + K_8)\, E_B \quad .. \quad .. \quad (14)$$

$$\frac{dE_T}{dt} = K_{e_1t}\, E_B - K_{e_2t}\, E_T \quad .. \quad .. \quad .. \quad .. \quad .. \quad .. \quad (15)$$

$$\frac{dU_E}{dt} = K_{ue}\, E_B \quad .. \quad .. \quad .. \quad .. \quad .. \quad .. \quad .. \quad .. \quad (16)$$

$$\frac{dF_B}{dt} = K_6\, D_B + K_7 E_B + K_{f_2t}\, F_T - (K_{f_1t} + K_{uf})\, F_B \quad .. \quad .. \quad (17)$$

$$\frac{dF_T}{dt} = K_{f_1t}\, F_B - K_{f_2t}\, F_T \quad .. \quad .. \quad .. \quad .. \quad .. \quad .. \quad (18)$$

$$\frac{dU_F}{dt} = K_{uf}\, F_B \quad .. \quad .. \quad .. \quad .. \quad .. \quad .. \quad .. \quad .. \quad (19)$$

The scheme in Fig. 2 was solved using equations (15), (16), (18) and (19) and

$$\frac{dE_L}{dt} = K_{ae}\, E_L + K_{eb1}\, E_L + K_{e1b}\, E_B - (K_{e1b} + K_7 + K_8)\, E_L \quad .. \quad (20)$$

$$\frac{dE_B}{dt} = K_{e1b}\, E_L + K_{e_2t}\, E_T - (K_{eb1} + K_{e_1t} + K_{ue})\, E_B \quad .. \quad .. \quad (21)$$

$$\frac{dF_B}{dt} = K_7\, E_L + K_{f_2t}\, F_T - (K_{f_1t} + K_{uf})\, F_B \quad .. \quad .. \quad .. \quad .. \quad (22)$$

The scheme in Fig. 5 was solved using equations (9), (10), (12) and (13) and

$$\frac{dC_L}{dt} = K_{ac}\, C_L + K_{a1b}\, C_B - (K_{cb1} + K_4 + K_5)\, C_L \quad .. \quad .. \quad (23)$$

$$\frac{dC_B}{dt} = K_{c1b}\, C_L + K_{c_2t}\, C_T - (K_{cb1} + K_{c_1t} + K_{uc})\, C_B \quad .. \quad .. \quad (24)$$

$$\frac{dD_B}{dt} = K_5\, C_L + K_{d_2t}\, D_T - (K_{d_1t} + K_{ud} + K_6)\, D_B \quad .. \quad .. \quad (25)$$

K_{a1b}, K_{c1b}, K_{e1b}	are the respective rate constants for passage of material from the "first pass" compartments A_L, C_L, E_L to the "body" compartments A_B, C_B, E_B
K_{ab1}, K_{cb1}, K_{eb1}	are the rate constants for the reverse pathways from the "first pass" to "body" compartments
K_{a_1t}, K_{b_1t}, K_{c_1t}, K_{d_1t}, K_{e_1t}, K_{f_1t}	are the respective rate constants for passage of material from "body" compartments A_B, B_B, C_B, D_B, E_B, F_B to "tissue" compartments A_T, B_T, C_T, D_T, E_T, F_T
K_{a_2t}, K_{b_2t}, K_{c_2t}, K_{d_2t}, K_{e_2t}, K_{f_2t}	are the rate constants for the pathways from "tissue" to "body" compartments
K_1, K_2, K_3, K_4, K_5, K_6, K_7, K_8	are rate constants for metabolism
K_{ua}, K_{ub}, K_{uc}, K_{ud}, K_{ue}, K_{uf}	are rate constants for urinary excretion