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The inhibition of human platelet 5-hydroxytryptamine uptake by tricyclic antidepressive drugs. The relation between structure and potency

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Thirty-five compounds related to the antidepressive drug imipramine in chemical structure have been examined for their capacity to inhibit the uptake of 5-hydroxytryptamine by human platelets *in vitro*. Substitution by small-sized electropositive groups in positions 2 or 3 of a benzene ring gave compounds more active than the prototype, 3-chloroimipramine being five times as potent on this test. Alteration of the characteristic seven-membered ring of the antidepressive drugs reduced the activity while substitution in the basic side-chain destroyed it. The tertiary amines were more potent inhibitors than their demethylated derivatives. In this and other ways the active structure for the inhibition of 5-HT uptake by human blood platelets differs from that for the inhibition of noradrenaline uptake by the rat heart.

The antidepressive drug, imipramine, [*N*-(dimethylaminopropyl) iminodibenzyl hydrochloride], is a potent inhibitor of the active transport of 5-hydroxytryptamine (5-HT) into human blood platelets (Marshall, Stirling & others, 1960). Stacey (1961) found it to be much the most active in this respect of forty compounds comprising drugs of widely different pharmacological properties, together with compounds related to 5-HT and the endogenous catecholamines. Imipramine was some fifty times more active than the two next most potent compounds, cocaine and chlorpromazine. Long & Lessin (1961) failed to observe this superiority of imipramine over chlorpromazine when studying ox platelets, but confirmed it when they subsequently employed human platelets (1962).

The *N*-desmethyl derivative of imipramine (desipramine) and the chemically closely related ("isosteric") compounds amitripyline and *N*-desmethylamitriptyline (nortriptyline), all of which are used clinically in the treatment of depression, also inhibit the uptake of 5-HT by platelets (Yates, Todrick & Tait, 1964).

This *in vitro* activity is paralleled by the observation that patients receiving therapy with imipramine and desipramine gradually lose up to 80% of the original 5-HT content of their platelets (Marshall & others, 1960; Yates, Todrick & Tait, 1963).

Haefely, Hurlimann & Thoenen (1964b) demonstrated a similar inhibition by tricyclic antidepressive drugs of the re-uptake of noradrenaline at sympathetic nerve endings. Since there is much evidence that this re-uptake phenomenon is a physiological process of major significance in the disposal of the adrenergic transmitter (Brown & Gillespie, 1957; Kirpekar, Cervoni & Furchgott, 1962; Haefely, Hurlimann & Thoenen, 1964a; Thoenen, Hurlimann & Haefely, 1964; Iversen, 1966), the hypothesis has been put forward that imipramine exerts its antidepressive action by

inhibiting the uptake of noradrenaline by nerve endings in the central nervous system, thereby potentiating and prolonging the action of the transmitter (Bunney & Davies, 1965; Klerman & Cole, 1965; Schildkraut, 1965).

The present paper reports the investigation of the inhibition of platelet 5-HT uptake by an extended series of derivatives of imipramine, further derivatives of amitriptyline and some other antidepressive drugs containing modifications to the central seven-membered ring.

The work was carried out in the hope firstly, of throwing light on the spatial configuration of the amine uptake mechanism, and secondly, of establishing some correlation between inhibitory potency against amine uptake in a human test system and clinically assessed antidepressive activity. The latter issue will be discussed subsequently.

EXPERIMENTAL

Methods

The method described in a previous paper (Yates & others, 1964) was used with two modifications: (i) the platelet counting was omitted since it did not appear to be essential to a study of comparative drug activity; (ii) the volume of platelet-rich plasma taken for each test was the original 1·5 ml. Incubations were carried out using final drug concentrations in the series 10^{-n}M and 3×10^{-n}M where n is an integer; this gives an almost uniform logarithmic decrement. For any one compound, after preliminary experimentation to find the correct concentration range, tests were made at either three or four concentrations.

Thirteen compounds in the following categories received more intensive investigation than the rest, viz. about twelve incubations in all, and the data were subjected to a statistical analysis (see Appendix). (*a*) Drugs in clinical use. (*b*) Compounds which were highly active. (*c*) Compounds of particular interest for structure-activity relations.

For the remaining 22 of the total of 35 compounds tested, the inhibitory potency was determined graphically from about eight estimates (Finney, 1964). The data from an earlier paper (Yates & others, 1964) have been included in the results and in the statistical analysis where appropriate. Most of the data were obtained in the course of four separate periods of work, each lasting a few months, spread over four years. The prototype compound, imipramine, was tested during each phase as a reference standard. The absolute inhibitory potency of imipramine in the four phases differed slightly but significantly. Allowance has been made for this in the statistical analysis (see Appendix).

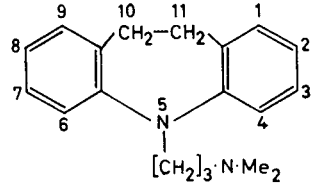
Since a wide variation in inhibitory potency was observed in the series of compounds the absolute measured potency has been expressed in terms of the negative logarithm of the concentration of the drug which causes 50% inhibition of 5-HT uptake (pI 50). This scale is recognized as having advantages for pharmacological studies; on it, the most potent compound has the highest value, a difference of 1 unit indicates a ten-fold difference in potency and a difference of 0·3 unit a two-fold difference in potency.

RESULTS

Table 1 lists the compounds possessing the imipramine nucleus which have been tested, their structure and their experimentally determined pI 50 values. The final column gives their activity as a percentage of that of the imipramine standard of

Table 1. *Inhibition of human platelet 5-HT uptake by compounds possessing the imipramine* (I) *nucleus*

I



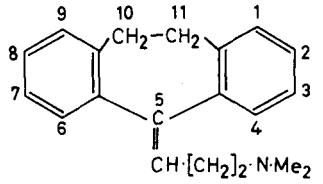
Compound	Nuclear substituents in positions 2	3	10	Side-chain substituents (in β-position)	Terminal amino-group	Salt	pI50	Experimental phase	Potency relative to imipramine (= 100) (comparison within phase)
Imipramine[1]	H	H	H	H	NMe_2	Hydrochloride	5·54	A	
							5·78	B	100
							5·62	C	
							5·73	D	
Desipramine[2]	H	H	H	H	NHMe	Hydrochloride	5·02	A	30
Desdimethylimipramine	H	H	H	H	NH_2	Hydrochloride	5·13	D	25
2-Hydroxyimipramine	OH	H	H	H	NMe_2	Hydrochloride	5·41	D	48
2-Hydroxydesipramine	OH	H	H	H	NHMe	Acid fumarate	5·13	A	39
2-Hydroxydesipramine glucuronide	O $C_6H_{10}O_6$	H	H	H	NHMe	Internal salt	3·61	B	0·7
10-Hydroxyimipramine	H	H	OH	H	NMe_2	Base	5·22	B	28
10-Hydroxydesipramine	H	H	OH	H	NHMe	½ Neutral fumarate, H_2O	4·37	B	3·9
10-Methyldesipramine	H	H	Me	H	NHMe	Hydrochloride	4·79	D	11
Imipramine *N*-oxide	H	H	H	H	NMe_2O	Base	4·11	B	2·1
3-Chloroimipramine[3]	H	Cl	H	H	NMe_2	Hydrochloride	6·50	B	520
2-Methoxyimipramine	OMe	H	H	H	NMe_2	Hydrochloride	6·03	C	260
3-Methoxyimipramine	H	OMe	H	H	NMe_2	Hydrochloride, ½H_2O	6·09	C	290
3-Methoxydesipramine	H	OMe	H	H	NHMe	Hydrochloride	5·22	D	31
3-Methylthioimipramine	H	SMe	H	H	NMe_2	Hydrochloride	5·72	C	125
3-Methylsulphinylimipramine	H	S(O)Me	H	H	NMe_2	Acid oxalate	5·57	C	89
3-Isopropylthiodesipramine	H	$SCHMe_2$	H	H	NHMe	Hydrochloride	4·74	C	13
3-Isopropylsulphinylimipramine	H	$S(O)CHMe_2$	H	H	NMe_2	Acid oxalate	4·89	C	19
3-Dimethylsulphamoxylimipramine	H	SO_2NMe_2	H	H	NMe_2	Hydrochloride	4·73	C	13
3-Dimethylsulphamoxyldesipramine	H	SO_2NMe_2	H	H	NHMe	Hydrochloride	4·71	C	12
Imipramine methochloride	H	H	H	H	NMe_3	Chloride	6·12	C	320
N-Hydroxydesipramine	H	H	H	H	N(OH)Me	Base	<3·5	B	<0·5
10-Oxoimipramine	H	H	O	H	NMe_2	Acid fumarate	4·64	B	7·3
Trimipramine[4]	H	H	H	Me	NMe_2	Hydrochloride	3·92	C	2·0
3-Chloro-β-methylimipramine	H	Cl	H	Me	NMe_2	Hydrochloride	3·85	C	1·7
Opipramol[5]	H	H	10,11Δ	H		Dihydrochloride	4·30	D	3·7

[1] In clinical use as an antidepressive drug under the name of Tofranil (Geigy).
[2] In clinical use as an antidepressive drug under the name of Pertofran (Geigy).
[3] On clinical trial under the name of Anafranil (Geigy).
[4] In clinical use as an antidepressive drug under the name of Surmontil (May and Baker).
[5] In clinical use as an antidepressive drug under the name of Insidon (Geigy).

the phase in which they were tested (this causes certain minor inconsistencies in rank-order between the last two columns). Table 2 lists similar data for compounds in which the nitrogen atom in position 5 is replaced by a carbon atom; included also are chlorpromazine and two drugs that have received clinical use in the treatment of depression, orphenadrine (Robinson, 1961) and thiazesim (Freeman, Oktem & others, 1965).

Table 2. *Inhibition of human platelet 5-HT uptake by compounds possessing the amitriptyline* (II) *nucleus and certain other compounds*

II



Compound	Nuclear substituents in positions: 2	3	Bridge at 10–11	5	Terminal amino-group	Salt	pI50	Experimental phase	Potency relative to imipramine (=100) (comparison within phase)
Amitriptyline[1]	H	H	$-CH_2-CH_2-$	C-	NMe_2	Hydrochloride	5·28	A	54
Nortriptyline[2]	H	H	$-CH_2-CH_2-$	C-	NHMe	Hydrochloride	5·00	A	29
Desdimethylamitriptyline	H	H	$-CH_2-CH_2$	C-	NH_2	Hydrochloride	5·04	B	18
10,11Δ-Amitriptyline ..	H	H	-CH=CH-	C-	NMe_2	Hydrochloride	4·83	B	11
10,11Δ-Nortriptyline ..	H	H	-CH=CH-	C-	NHMe	Hydrochloride	4·89	B	13
Protriptyline[3]	H	H	-CH=CH-	C-	NHMe	Hydrochloride	5·05	C	27
Thiazenone[4]	—	—	See note 5	—	NMe_2	Hydrochloride	3·77	C	1·4
Chlorpromazine	H	Cl	-S-	N-	NMe_2	Hydrochloride	4·41	A	7·4
Orphenadrine	H	H	No bridge	C-[6]	NMe_2	Hydrochloride	3·90	D	1·5

[1] In clinical use as an antidepressive drug under the names of Laroxyl (Roche), Saroten (Warner) and Tryptizol (Merck).
[2] In clinical use as an antidepressive drug under the names of Aventyl and Allegron (Eli Lilly).
[3] In clinical use as an antidepressive drug under the name of Concordin (Merck).
[4] On clinical trial as an antidepressive drug under the name of Thiazesim (Squibb).
[5] 5-(Dimethyl aminoethyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4 (5H)-one hydrochloride.
[6] Orphenadrine has a methyl group at C-4 and the side chain at C-5 is $-O-(CH_2)_2$. It is in clinical use under the name of Disipal (Brocades).

The information derived from the statistical analysis of the thirteen most important compounds (given in detail in Table A of the Appendix), may be conveniently summarized in the following ranking list; in this, compounds or groups of compounds having potencies different at the 5% significance level are separated by solid lines:

3-Chloroimipramine 520,/imipramine methochloride 320, 3-methoxyimipramine 290, 2-methoxyimipramine 260,/3-methylthioimipramine 125, imipramine 100, 3-methylsulphinylimipramine 89, amitriptyline* 54,/desipramine 30, nortriptyline 29, protriptyline 27, desdimethylimipramine 25, desdimethylamitriptyline 18.

The compounds are almost completely separated into groups by the significance test. This non-random distribution is to some extent a fortuitous result of the choice of significance level, but it also reflects the selection of compounds; the more active 3-substituted compounds came wholly from the imipramine series while the less active 10,11Δ-compounds came from the amitriptyline series.

Although these thirteen compounds were regarded as being of particular interest and were given both more extended experimental investigation and arithmetical analysis, the pI50 values obtained graphically for the remaining compounds may be

* Amitriptyline is significantly less potent than 3-methylthioimipramine and imipramine, but not significantly different from 3-methylsulphinylimipramine.

assumed to be subject to the same error variance; a working figure for the difference in pI50 which indicates a potency difference at the 5% significance level can be calculated. In round numbers, it will be 0·2 for in-phase comparisons. For interphase comparisons the correct difference to take is (pI50 Drug A − pI50 standard A) − (pI50 Drug B − pI50 standard B); to be significant, it must not be less than 0·25.

General structure—activity relations

The series of compounds listed in Tables 1 and 2 provide examples of modification of the basic structure of the prototype compound, imipramine, as follows:

1. On the terminal nitrogen atom. 2. By substitution in the aliphatic side-chain. 3. By substitution in the 2 position of a benzene ring. 4. By substitution in the 3 position of a benzene ring. 5. By substitution in the 10 position (ethylene bridge). 6. By alteration of the seven-membered central ring.

1. Potency is maximal for the quaternary salt of imipramine and falls off through imipramine to desipramine, but there is no further loss of potency with the removal of the last methyl group: the same pattern holds for the amitriptyline series as far as it goes (the quaternary salt was not tested). The tertiary and secondary amines can be compared in four other instances: the highly active 3-methoxy- and the fairly potent 10-hydroxyimipramine are markedly more effective than their desmethyl analogues; the comparatively inactive pairs 10,11Δ-amitriptyline and 10,11Δ-nortriptyline and 3-dimethylsulphamoxylimipramine and 3-dimethylsulphamoxyldesipramine do not differ significantly.

There is only one compound with an alkyl substituent other than the methyl group, viz. opipramol, which carries a substituted piperazine ring; this has very little activity. Finally, addition of → O or substitution of –Me by –OH on the terminal *N*-atom causes almost complete loss of inhibitory activity.

2. Two compounds substituted in the β-position of the side-chain, trimipramine and 3-chlorotrimipramine, are practically without activity.

3. Only four compounds substituted in the 2-position of a benzene ring have been tested, three of which are natural metabolites: 2-hydroxyimipramine is half as active as the parent substance while 2-hydroxydesipramine has the same activity as its less potent parent; 2-hydroxydesipramine glucuronide, which is the main excretion product from both drugs, is practically inactive. 2-Methoxyimipramine is, however, more potent than imipramine and not significantly less active than its 3-methoxy isomer.

4. Substitution in the 3-position of the benzene ring has been examined in some detail in an attempt to assess the influence of electromeric effects. The synthesis of compounds substituted with electronegative groups has not been possible, but electropositive substituents in the 3-position appear to increase potency; 3-chloroimipramine is five times as potent as the parent substance and 3-methoxyimipramine three times as potent. A series with 3-substituents of graded electropositivity was then examined. The results (Tables 1 and 3) show no correlation with degree of electropositivity but can be interpreted as indicating a steric factor since all compounds containing substituent groups larger than –S(O)Me are uniformly low in activity (12–19, imipramine = 100).

Table 3. *Effect of size of substituent group at position* 3 *on inhibitory potency of imipramine derivatives*

3-Substituent group	Relative potency (Imipramine = 100)	Molecular radius (Å)
– Cl	520	1·8
– O – Me	290	2·8
– S – Me	125	3·6
– S – Me ↓ O	89	—
O Me ↑ / – S – N ↓ \ O Me	13	—

5. Since the possession of an ethylene bridge in the 10,11-position is the characteristic of the antidepressive drug molecule, as distinct from the tranquillizer molecule, it might have been thought that substitution in the 10-position would have had a marked adverse effect on the activity. However, 10-hydroxyimipramine possesses a quarter of the activity of the parent substance though its desmethyl derivative is much less active; 10-oxoimipramine is also only weakly active.

6. Substitution at the 5-position of the central ring of N– by C= gives amitriptyline which is slightly but significantly less potent than imipramine, though the singly and doubly demethylated compounds in the two series do not differ significantly. Dehydrogenation of the 10,11-bridge of amitriptyline results in a five-fold loss of potency (from 54 to 10). The activity of nortriptyline (29) also falls (to 13) on dehydrogenation: a shift of the double bond from the 5 γ-position of nortriptyline to the 10,11-position of protriptyline does not alter the activity. Replacement of the 10,11-bridge of 3-chloroimipramine by a sulphur atom (chlorpromazine) results in a marked loss of potency, from 520 to 8·5; an unbridged compound (orphenadrine) which was tested, though still less active (1·5), is not strictly comparable as the side-chain contains an ether linkage.

DISCUSSION

The tricyclic antidepressive drug molecule, which includes both the imipramine and amitriptyline series of compounds, can be modified or substituted in many positions of differing potentiality. The present series of compounds includes only a small number of modifications or substitutions at each position; any generalizations must be regarded with caution, but three provisional rules appear to emerge:

(*a*) Activity is practically destroyed ($<2\%$) either by substitution of a methyl group in the β-position of the three-carbon side-chain or by substitution of other groups for the methyl groups or hydrogen atoms attached to the terminal N-atom of the side-chain, or both.

(*b*) Alteration of the central ring, either by replacing the N-atom in position 5 with C= or C– or by doubling the 10,11-bond or by monovalent substitution on the 10,11-bridge reduces the activity much less, broadly to one quarter to one half of that of the parent compound.

(*c*) Substitution in position 2 and 3 of a benzene ring can in certain instances increase the activity above that of imipramine but two conditions may require to be fulfilled, as (i) the increase in activity has only occurred with electropositive substituents (but few neutral and no electronegative substituents have been tested), and (ii) the substituent group must not be more than a certain size or the activity drops to one tenth of that of imipramine.

Since 2-methoxyimipramine is as active as 3-methoxyimipramine, the increase in activity on substitution can hardly be purely an electromeric induction effect on the N-atom in position 5.

As the mode of action of imipramine has been postulated to consist of interference with the uptake of noradrenaline, its molecule might be supposed to fit closely with the system responsible for this in the membrane of the nerve ending; it should also fit, but not quite so closely, with the adrenergic receptor. Hypotheses have been developed concerning the chemical structure of the adrenergic receptor based on the relative specificities of a wide range of noradrenergic agonists and antagonists. The primary point of attachment is anionic; Belleau (1960) and Bloom & Goldman (1966) have put forward evidence to support the view that the phosphate ion of ATP is involved but the results of Triggle (1965) and Graham & Al Katib (1966) favour the carboxylate ion of protein.

It has been argued that the agonist (noradrenaline) must possess a more specific structure than an antagonist since it has to perform a more specialized function following attachment; the same may reasonably be expected to hold good for the uptake mechanisms which appear to be basically similar whether the amine involved is noradrenaline or 5-HT. This lower specificity requirement may account for the wide range of chemical structures found among compounds interfering with amine uptake, e.g. imipramine, cocaine, metaraminol, prenylamine, guanethidine.

Iversen (1966) has analysed the specificity as "Uptake$_1$" inhibitors of a group of amines structurally related to noradrenaline. This in no way resembles the structure activity relationship found for the imipramine series in respect of 5-HT uptake inhibition, since methylation of hydroxy-groups and *N*-alkylation decrease inhibitory potency while side-chain methylation increases it.

Uptake inhibitors might be expected to be similar in structure to α-adrenergic blocking drugs and the latter do in fact inhibit the platelet 5-HT uptake system though they are less active than the tricyclic antidepressive drugs (Todrick, unpublished results). Bloom & Goldman (1966) suggest that the steric hindrance of the bulky cationic head is the primary factor with the α-blocking drugs; if there is any parallelism between the two systems, this may account for the increase in activity with increasing numbers of methyl groups on the terminal N-atom in the imipramine series.

In considering basic drugs, the effect of the degree of ionization on the activity must be taken into account. The imipramine series being comparatively insoluble in water, the pK_a is normally obtained by extrapolation. The available data are given in Table 4 (this includes only extrapolated figures or estimates by methods where extrapolation was considered unnecessary).

The pK_a for the imipramine quaternary salt may be assumed to be >13; these figures therefore provide no explanation for the increase in activity with increasing methylation of the terminal N-atom in the unsubstituted imipramine; the lower pK_a might partially account for the inactivity of trimipramine.

Table 4. pK_a *Values of imipramine and derivatives*

Compound	Method	pK_a in water	Experimenters
Imipramine	A	10·0	Schmidt (personal communication)
	B	9·57	Moody (unpublished results)
Desipramine	A	10·6	Schmidt (personal communication)
	B	10·43	Moody (unpublished results)
Desdimethylimipramine ..	B	10·19	Moody (unpublished results)
Trimipramine	C	8·0	Rhone Poulenc Research Laboratories, (personal communication)

Methods: A Titration in aqueous methyl cellosolve with extended extrapolation.
B Titration in aqueous solution with measurement of fluorescence change.
C Titration in 10% ethanol in water; not extrapolated.

There are in current use numerous laboratory tests characterizing compounds with a clinical antidepressive action; this of itself is perhaps the best evidence that no one is wholly satisfactory and that "in the meantime pharmacological characterization of antidepressant agents should be based on the use of a battery of tests outlined in several comparative studies" (Gyermek, 1966).

Table 5 compares the results obtained with eleven antidepressive drugs and two tranquillizers of similar chemical structure in some current tests.

Table 5. *Comparison of six tests for the assessment of antidepressive action*

Compound	Ro 4–1284 antagonism[1]	Noradrenaline potention of cat nictitating membrane[2] A	Noradrenaline potention of cat nictitating membrane[2] B	Potentiation of amphetamine hyperthermia[3] (increase in area under curve)	Inhibition of noradrenaline uptake by rat heart[4] pI50	Inhibition of 5-HT uptake by human platelets[5] pI50	5-HT potentiation of cat nictitating membrane[2]
Imipramine	—	++	++	+6·5	7·4	5·7	+++
Desipramine	++	+++	+++	+6·3	8·15	5·0	++
Desdimethylimipramine	++			+6·5	7·0	5·1	
2-Hydroxyimipramine ..		++		+3·8		5·4	+
3-Chloroimipramine ..	O	+				6·5	++
Amitriptyline	O	+	+		7·0	5·3	+
Nortriptyline	++	+++	+		7·6	5·0	++
10,11Δ-Imipramine ..	O	+++			7·5		++
10,11Δ-Desipramine ..	++	+++			8·2		++
10,11Δ-Amitriptyline ..	O	O				4·8	O
10,11Δ-Nortriptyline ..	O	++				4·9	+
Promazine (10–11 bridge replaced by S)	O	—			7·4		—
Desmethylpromazine ..	+	—			7·1		—

[1] Bickel & Brodie (1964). [2] A. Sigg & others (1965) as quoted in Gyermek (1966). B. Haefely & others (1964b). [3] Theobald, Buch & others (1966). [4] Callingham (1967). [5] Present work.
— = Blockage. O = No effect. + = Active/moderate potentiation. ++ = Very active/marked potentiation. +++ = Very marked potentiation.

The tests listed possess certain individual characteristics:

(*a*) The RO–4–1284 variant of the reserpine antagonism test (Bickel & Brodie, 1964) has consistently shown secondary amines (e.g. desipramine) to be more potent than tertiary amines (e.g. imipramine); only 2 out of 40 tertiary amines tested were found to possess any activity at all. Hjelte & Richter (1967), who used a different form of reserpine antagonism test, did not, however, confirm the inactivity of the tertiary amine structure.

(*b*) In the cat nictitating membrane test (Sigg, Soffer & Gyermek, 1963) the secondary amines consistently potentiated noradrenaline more effectively, except for the iminostilbene pair; in a later investigation, Haefely & others (1964b) did not find nortriptyline superior to amitriptyline.

(*c*) The other test in which noradrenaline is specifically involved, namely the study of "Uptake$_1$" by the perfused rat heart (Iversen, 1965; Callingham, 1967) again demonstrated a consistent superiority of the desmethyl series of antidepressive drugs. The difference disappeared in pairs of compounds of lower activity.

(*d*) The effect of 5-HT on the cat nictitating membrane can hardly be regarded as other than "pharmacological," whereas that of noradrenaline may be claimed to be "physiological." The potentiation of the action of 5-HT may therefore be a more artificial test than noradrenaline potentiation; of four pairs tested, the desmethyl compound is superior in two but imipramine is superior to desipramine and the iminostilbenes are equipotent.

(*e*) In the platelet 5-HT uptake test the active tertiary compounds were found to be superior to their desmethyl derivatives though the difference disappeared in less active pairs.

(*f*) Data for the amphetamine hyperthermia potentiation test are scarce but imipramine and desipramine were essentially equipotent.

We hope later to assess the relative value of different laboratory tests of antidepressive action in comparison with the findings of clinical trials. The problems in such a comparison are great, reflecting not only the complexity of clinical assessment in depression, but also the fact that some compounds have an additional (directly sedative) cerebral action. As a preliminary comment, however, our laboratory ranking of drug activity is at least in broad general concordance with clinical reports.

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