is no evidence that extraneuronal catecholamines are stored in this type of amine granules, disappearance of extraneuronal fluorescence after reserpine cannot be used to test the specificity.

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Fibrinolytic Activity of some Biarylcarboxylic Acids

BUFFERED solutions of certain aromatic acids dissolve human plasma clots when incubated with them *in vitro*[1,2]. The most active in this respect have proved to be arylcarboxylates, which possess an additional free rotating phenyl ring, for example, *N*-phenylanthranilates[3], 5-benzyloxysalicylates[4] and diphenylethylacetate[5]. It was suggested that non-condensed aryl rings in the presence of an acidic functional group are required to render a highly active fibrinolytic agent[5].

To check this suggestion we tested for fibrinolytic activity the twenty-two biarylcarboxylates presented in Table 1. The standard clots of recalcified human plasma were incubated for 18 h at 37° C and immersed in *tris*-buffered solutions of sodium salts of the compounds being investigated. The range of concentrations investigated was 1–100 mmoles/l. Solutions more alkaline than *p*H 8·0 were rejected. Details of procedure have been described by von Kaulla[6] and in a previous paper[5].

The results are presented in Table 1. It can be seen that simple diphenylcarboxylic acids (No. 4 and No. 5) are inactive, but when the carboxylic group is attached to the ring through an alkyl or alkylene chain (No. 1 and No. 2) but not through an alkoxy chain (No. 3) there is rather high fibrinolytic activity.

Compounds with both phenyl rings bridged through the oxygen atom (No. 6 and No. 7) are inactive, but if instead of oxygen the —NH— group is inserted *N*-phenylanthranilates can be obtained and these compounds are active fibrinolytics[3]. Here are presented only the most active compounds (No. 8, No. 9 and No. 10). Compound No. 11 is given as an example of the undesirable effect of hydroxylation on the fibrinolytic activity of *N*-phenylanthranilic acid.

If a one carbon atom group represents the bridge between two phenyl rings the fibrinolytic activity is observed only when the functional carboxylic group is attached directly to this methylene bridge (No. 14), but not to the phenyl ring (No. 12 and No. 13). Any further substitution of the methylene bridge is undesirable (No. 15 and No. 16) especially when the heavy chlorine atom is introduced (No. 16).

Diphenylethane *o*-carboxylate derivatives (No. 17 and No. 18) are active, but the translocation of the carboxylic group from the ring into an alkoxy side chain abolishes the fibrinolytic activity (No. 19) in a similar fashion to that in compounds No. 3 and No. 7.

Table 1. FIBRINOLYTIC ACTIVITY OF SOME BIARYLCARBOXYLIC ACIDS

No.	Formula R_1	Z	R_2	Range of fibrinolytic concentrations (mmoles/l.)
1*	–	–	*p*—CH(COOH)$CH_2CH=CHCH_3$	3–5
2	–	–	*p*—CH(COOH)CH_2CH_3	7–17
3*	–	–	*p*—OCH(COOH)$CH_2CH_2CH(CH_3)_2$	±4 trace of activity
4	–	–	*o*—COOH	no activity
5	–	–	*m*—COOH	no activity
6*	–	—O—	*p*—CH(COOH)$CH_2CH_2CH(CH_3)_2$	±4 trace of activity
7*	–	—O—	*p*—OCH(COOH)$CH_2CH_2CH(CH_3)_2$	no activity
8†	*m*—CF_3	—NH—	*o*—COOH	1·5–4
9	*p*—F	—NH—	*o*—COOH	5–18
10	–	—NH—	*o*—COOH	7–17
11	*p*—OH	—NH—	*o*—COOH	no activity
12	–	—CH_2—	*o*—COOH	no activity
13	–	—CO—	*o*—COOH	no activity
14	–	—CH/COOH/—	–	50–70
15	–	—C/OH//COOH/—	–	70–130
16	–	—C/Cl//COOH/—	–	no activity
17	*p*—Cl	—CH_2CH_2—	*o*—COOH	6–18
18	–	—CH_2CH_2—	*o*—COOH	18–36
19*	–	—CH_2CH_2—	*p*—OCH(COOH)$CH_2CH_2CH(CH_3)_2$	no activity
20	–	—CH_2NH—	*o*—COOH	8–12
21	–	—CH_2S—	*o*—COOH	15–40
22	–	—CH_2SO_2—	*o*—COOH	no activity

* These compounds supplied by Dr. F. Barzaghi of the Vister Pharmacological Laboratory, Italy.
† This compound was supplied by Dr. R. A. Scherrer from Parke Davis Co.

In the molecule of diphenylethane-*o*-carboxylic acid the ethylene bridge has been changed for isosteric —CH_2NH— or —CH_2S— groups. Compounds thus obtained (No. 20 and No. 21) are slightly more active than the parent structure (No. 18); however, diphenylmethylsulphonyl-*o*-carboxylic acid (No. 22) is inactive.

In summary, the chemical structure of biarylcarboxylic acids cannot be considered as the general requirement to render a highly active fibrinolytic agent, because 2-aryl-substituted benzoic acids like phenoxy-, benzoyl-, benzylsulphonyl- and benzyl- derivatives as well as diphenylcarboxylic acids themselves do not dissolve plasma clots. It should, however, be emphasized that phenylamino-, β-phenylethyl-, benzylamino-, benzyloxy- and benzylthio-derivatives are the most active synthetic fibrinolytics so far known. The further substitution within the ring of an active biphenylcarboxylate structure may potentiate or abolish fibrinolytic activity depending on the substituent used.

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