The effect of Imipramine on the Reserpine Toxicity in Adrenalectomised Rats

SIR,—Reserpine is highly toxic when administered to adrenalectomised rats (Gaunt, Renzi, Antonchak, Miller and Gilman, 1954; also Pennefather and Rand, personal communication). Garattini, Giachetti, Jori, Pieri and Valzelli (1961) have shown that hypothermia, blepharospasm and sedation induced by reserpine are prevented by pretreatment of rats with imipramine, a new antidepressant drug, as also are the occurrence and severity of gastric ulcer in restrained reserpine-treated rats. The present experiments were carried out to study the action of imipramine on the reserpine toxicity in adrenalectomised rats.

Reserpine in graded doses (1, 2·5, 4, 5 mg./kg.) was injected intraperitoneally into groups of rats adrenalectomised 6 days previously. The LD50 calculated by the method of Litchfield and Wilcoxon (1949) was 1·75 (0·49–6·30) mg./kg. Other groups of rats adrenalectomised 6 days previously were given imipramine 25 mg./kg. intraperitoneally 30 min. before similar doses of reserpine. The LD50 was 4·1 (2·2–7·4) mg./kg. Imipramine alone was not toxic to adrenalectomised rats. The confidence limits of these two LD 50 values overlap.

A comparison was next made of the effect of imipramine (25 mg./kg.) on the survival times of adrenalectomised rats receiving reserpine (5 mg./kg.). Male rats of the same weight and adrenalectomised 6 days previously were distributed in matched pairs into two groups each of 12 animals. The test rats were injected with imipramine. After 30 min. both the test group and the control group of the pairs were injected with reserpine. The mean survival-time was determined by inspecting the rats every 30 min. until the last had died. The results are shown in Table I. The significance was tested statistically by the British Pharmaceutical Codex (1959) method.

TABLE I

PROTECTION BY IMIPRAMINE OF RESERPINE TOXICITY IN ADRENALECTOMISED RATS

Drug and dose	No. of rats	Mean survival time in hr.	P
Reserpine 5 mg./kg.	12	7.9	
Imipramine 25 mg./kg. + Reserpine 5 mg./kg.	12	20·4	<0·001

These results show imipramine to delay the reserpine toxicity. Owing to the incompletely established pharmacological activities of imipramine and furthermore to the uncertainty of the causes of reserpine toxicity, it is difficult to define the mode of action of this protection. Nevertheless Garattini, Lamesta, Mortari, Palma and Valzelli (1961) showed that the toxicity of 5-HT is increased in adrenalectomised rats, and Sulser and Brodie (1961) suggested that imipramine or one of its metabolites acts by blocking free 5-HT. It may be that imipramine protects the adrealectomised rat from the toxic effects of reserpine by inactivating the 5-HT which is released.

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6-Methylcortisone Acetate 3-Enol Ethers—A New Group of Anti-inflammatory Agents

SIR,—Following our discovery of a new and highly efficient route to 6-methylated steroids, it has become possible to extend our work on corticoids to the 3-enol ethers of the now readily accessible 6α-methylcortisone acetate (I). The ethers listed in Table I were prepared by adaptation of known methods [cf. Ercoli and Gardi (1960)] viz. (*a*) reaction of (I) with the alkyl orthoformate/alkanol in the presence of toluene *p*-sulphonic acid and (*b*) by ether exchange. Anti-inflammatory activity was estimated by the turpentine-agar pellet assay described in an earlier communication [Bianchi, David and others (1961)]. The results in the Table were obtained by oral administration, employing prednisolone acetate as standard.

TABLE I

3-Enol ether	Anti-inflammatory activity Prednisolone acetate = 1
Ethyl	1·2
n-Propyl	2·2
i-Propyl	1·7
n-Butly	2·0
i-Butyl	2·1
n-Pentyl	1·1
Cyclopentyl	1·3
n-Hexyl	0·8
Cyclohexyl	1·7
n-Heptyl	0·8
n-Octyl	1·7
Benzyl	0·9
3'-Phenylpropyl	0·4

Maximal anti-inflammatory activity was shown by 6-methyl cortisone acetate 3-enol n-propyl ether and this compound is being examined further.

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