LETTER TO THE EDITOR

Absence of General Anaesthetic Properties in a Number of Terpenoid Hemisuccinates

SIR,—The demonstration of central depressant activity in a number of steroids (Seyle, 1942; Figdor and others, 1957 and refs. cited), one of which, sodium 21-hydroxypregnane-3,20-dione hemisuccinate (hydroxydione sodium) is employed clinically as a basal anaesthetic (e.g. Murphy, Guadagni and De Bon, 1955; Galley and Rooms, 1956) raises the question as to whether these compounds share a common mechanism of action with other general anaesthetics, many of which have been considered to act by a "physical" mechanism (Ferguson, 1939) in which favourable lipid solubility has long been considered a necessary prerequisite (see review by Butler, 1950). It has been further suggested (e.g. Warburg, 1921) that adsorption of the agent on or in the cell membranes produces the primary effects responsible for the anaesthesia and Mullins (1956) has presented a model of the membrane permitting visualisation of these changes. Stress is laid upon the importance of the molecular dimensions of the anaesthetic, an aspect which has also been emphasised by Wulf and Featherstone (1957). More recently, Pauling (1962) has divided general anaesthetics into two classes. Those capable of hydrogen bond formation, for example barbiturates and aliphatic alcohols, are regarded as specifically inhibiting the processes supplying energy for the maintenance of cerebral electrical activity, whilst those incapable of hydrogen bonding, for example the simple gaseous anaesthetics and the magnesium ion, are postulated to depress the electrical oscillations of the brain through hydrated microcrystal formation.

It seemed, therefore, to be of some interest to establish whether central depressant activity was present in alcohols possessing molecular weights between those of the simple aliphatic alcohols and those of the anaesthetically-active steroids. Since the water-soluble hydroxydione is known to suffer hydrolysis to the centrally-active lipid-soluble parent steroid (Figdor and others, 1957; Jakoby and Tomkins, 1956) we investigated several representative terpenoid hemisuccinates. Thus the hemisuccinates of menthol, borneol, citronellol, fenchol, farnesol, dehydroabietinol and podocarpinol were prepared by refluxing the alcohol with succinic anhydride in pyridine or quinoline and administered intravenously to mice in the form of their sodium salts, in doses of up to 500 mg./kg. These compounds, like the sodium salts of arachidyl, erucyl and dodecyl hemisuccinates, produced convulsions at or below this dose level and in no case was anaesthesia observed. Intraperitoneal injection into rats at doses up to 100 mg./kg. gave no effect. Hydroxydione itself is active in the mouse on intravenous injection at an AD50 of 21·5 mg./kg. (Figdor and others, 1957).

These results support the conclusions of Figdor and others (1957) that the steroidal general anaesthetics display a high degree of structural specificity as indicated by the marked reduction or loss of activity on hydroxylation, epoxidation or halogenation, or on introduction of nuclear unsaturation. Moreover, convulsant activity is present in certain analogues of hydroxydione and evidence has been advanced (Gordon and others, 1956) that the steroidal general anaesthetics act in a similar way to the barbiturates where it is well established that minor structural modifications can lead to convulsant activity (e.g. Swanson and Chen, 1939). It is tempting to view these facts in terms of Pauling's (1962) contention that anaesthetics capable of hydrogen bonding act by a specific mechanism and to regard the appearance of convulsant activity as a manifestation of retention of affinity for the receptors coupled with marked changes in intrinsic

activity (cf. Ariëns, 1954). If this picture is correct convulsant activity in these instances could result from a direct stimulant action, rather than from a preferential depressant action on the higher centres with functional release of automatic lower motor mechanisms as is generally considered to be the case in stage II, the excitement stage of general anaesthesia.

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