Phytochemistry, 1969, Vol. 8, pp. 1319 to 1322 Pergamon Press. Printed in England.

REPORT

RECENT WORK ON PLANT PRODUCTS OF THERAPEUTIC INTEREST

(*Received* 11 *February* 1969)

A SYMPOSIUM with this title was organized for the Phytochemical Society by Professor J. W. Fairbairn (School of Pharmacy, University of London) and Dr. P. C. Spensley (Tropical Products Institute, London), and it was held in London on 7 January 1969. Some ninety members attended and under the chairmanships of Professor T. W. Goodwin (University of Liverpool) and Professor W. B. Whalley (University of London) the speakers reviewed current knowledge of pharmacologically active substances obtained directly from plants or by partial synthesis from plant compounds.

Dr. K. Jewers (Tropical Products Institute), in his talk on "Anti-tumour agents", described the value of chemotherapy as a means of controlling cancer, the methods used for screening anti-tumour agents and the problems arising from the use of these systems for selecting new drugs for clinical trial. Plants have been used by man for the treatment of malignant diseases for thousands of years; recent investigations have resulted in the isolation of a number of plant products which demonstrate anti-neoplastic activity. Several of these compounds have been used for the treatment of human cancers and others show sufficient activity in rodents to warrant clinical evaluation against human malignant tumours.

Colchicine and its derivatives are of historic importance as it was the work of Dustan and his colleagues during the 1930's on colchicine which demonstrated the existence of cytotoxic substances. The clinical applications of colchicine, demecolcine, and trimethylcolchicinic acid were described. More recent investigations on the periwinkle, *Vinca rosea*, which led to the discovery of the two clinically useful dimeric indole alkaloids, vinblastine and vincristine, and four additional active alkaloids were also discussed. These discoveries have renewed interest in plants as sources of anti-tumour agents, and have led to the discovery of a number of alkaloids with reproducible anti-tumour activity in rodents. The activities of the alkaloids narciclasine, camptothecin, ellipticine, acronycine, aristolochic acid, tylocrebrine, thalicarpine, (±)-tetrandrine, cissampereine, emetine, tubulosine, β-solamarine, solapalmitine, and solapalmitenine were then reviewed. Structure/activity studies were indicated where information was available.

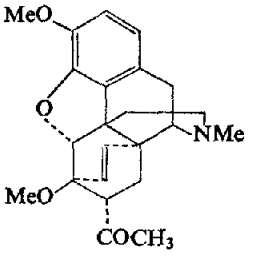
Also reported as anti-tumour agents were compounds having a lignan, tannin, naphthaquinone, or quinone methide structure. Podophyllotoxin and its derivatives have been the subject of considerable clinical interest, and lapachol is undergoing clinical evaluation. α/β-Unsaturated lactones are known to induce a variety of physiological actions including cytotoxicity. Recent investigations have shown that a number of sesquiterpenoids and steroids containing this functionality possess anti-tumour activity, and the results of this work were given. Finally, the clinically useful fungal metabolites were briefly discussed.

A paper on "Some novel derivatives of the opium alkaloids" by Dr. K. W. Bentley

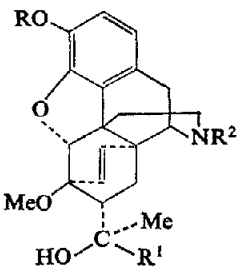
(Pharmaceutical Research Laboratories, Reckitt & Sons Ltd., Hull) followed. He said an attempt had been made to achieve some separation of desirable and undesirable effects of morphine-like analgesics by the construction of compounds more rigid and more bulky in molecular shape than morphine and the synthetic analgesics. This end was approached utilizing a medically valueless by-product of opium processing, namely the alkaloid thebaine which very readily undergoes stereospecific Diels–Alder reactions to give a range of reactive products. Using one of these products, the ketone (I), a series of bases, unprecedented in extent in the analgesic field, of general structure (II) was obtained. The series of phenols (II, R=H, R^2=Me) includes the most potent analgesics ever reported, showing activities up to 10,000 times that of morphine. The principal use for such compounds so far has been the immobilization and capture of large wild game, 1 mg being sufficient to immobilize a 2-ton rhinoceros, and they clearly have great potential for use in veterinary practice, although their addictive potential makes them unsuitable for human use.

The series of compounds of structure II, where R^2 is other than a methyl group, includes compounds of great potential interest. Many of these are morphine antagonists analogous in structure and activity to *N*-allylnormorphine (including the most potent antagonists so far reported), whereas others are analgesics several hundred times more potent than morphine, yet ineffective in suppressing abstinence symptom in addicted monkeys withdrawn from morphine. Such compounds have a pharmacological profile not previously encountered in work on analgesics.

A study of the variation of activity in several closely related homologous series, obtained by varying one of the groups R^1 and R^2 in structure (II, R=H or Me), reveals a pattern not previously encountered in the analgesic field and has led to the hypothesis that the analgesic receptor surface in the central nervous system is more extensive than previously assumed.



(I)



(II)

Professor F. Korte (University of Bonn), due to illness, was unable to give his lecture entitled "Cannabis". Instead, at very short notice, a most important aspect of this subject was ably described by Dr. P. A. L. Chapple, medical director of the Chelsea Drug Addiction Treatment Centre of the National Addiction and Research Institute, London. Professor Fairbairn in his introductory remarks to Dr. Chapple's talk said the plant, *Cannabis sativa* L., from which hashish, marihuana, pot, etc. is prepared, presents at least two problems. Are there two distinct varieties, var. *sativa* which is cultivated for its fibre and is non-narcotic, and var. *indica* which produces the narcotic resin? Some authorities (e.g. Korte) are of the opinion that there are two distinct chemical varieties with gradations between. Traditionally the female plant alone is used for narcotic purposes but the further question arises as to whether the male is active; recent work in Brazil suggests that this is so. Phytochemical

studies have shown that the narcotic resin contains a series of cannabinoids based on olivetol and a terpene moiety. The only really active substance so far isolated is *trans*, Δ9-tetrahydrocannabinol.

Dr. Chapple also said the nature and potency of cannabis was markedly variable in different countries; that used in Great Britain was potent. He outlined some of the work done at the Chelsea Centre and the type of disturbed patient involved. It was clear that such people did not start drug-taking with cannabis. There were now indications that subsequent dependence on cannabis was greater than previously had been supposed. Following heavy cannabis smoking, some individuals might fail to distinguish between real and imagined danger. If cannabis was not available a variety of other drugs was taken by the addicts. In time some cannabis users changed to the more dangerous LSD and heroin addicts also had passed through a cannabis-taking stage and would use cannabis if heroin was not available. Some aspects of the Institute's research were difficult; it was not possible to detect, for example by means of a urine test, that someone had recently taken cannabis. Furthermore, only tincture (alcoholic solution) of cannabis could be legally prescribed and its pharmacological properties were in dispute.

Dr. W. M. Hollyhock (London) gave a brief survey of "Psychotomimetic and hallucinogenic drugs," suggesting a need for care in defining them, as well as for distinguishing between drugs whose primary effect was to mimic some of the manifestations of psychosis, and those which produced toxic confusional or allied states as a result of overdosage. He concluded with a note on recently discovered amphetamine derivatives and their possible relation to earlier work on the toxic principle from *Myristica fragrans*, with a suggestion that the latter studies showed the need for caution in extrapolating from one toxic effect (liver damage) to another (psychotic symptoms).

Dr. R. Hardman (Bath University) dealt with "Steroids." He reviewed those of established importance to man's well-being and included the cardiotonic glycosides, the antibiotic, fusidic acid, the vitamin D_2 precursor, ergosterol and others chiefly derived from plant steroids by chemical and microbiological means. These were a group comprising the corticosteroids; the oestrogens, progestogens and the oral contraceptives; the androgens; and the anabolic agents. For this widely ranging pharmacological group it had been estimated that the world's total steroid raw material had been 1000 tons (1,000,000 kg) in 1968, of which plant steroids provided 86 per cent, animal steroids 6 per cent and total synthesis 8 per cent. The plant sources of steroid were stigmasterol from cultivated soybean in the United States of America, and the steroidal sapogenins; hecogenin from the sisal industry of Tanzania, and diosgenin from tubers of wild species of *Dioscorea* (non-edible yams) currently collected in Mexico, Central America, India and Asia. Of these, diosgenin was the most important and it was expected that over 1,000,000 kg of it would be required in 1973 with the increasing world demand for the medicinal steroids and the fertility control compounds. Important species of *Dioscorea* and the processing of their tubers were described. Because attempts at cultivating the wild Dioscoreas had not been altogether successful, Dr. Hardman's group had been investigating "stand-by" sources of diosgenin. Such sources were the seed of the legume, *Trigonella foenum-graecum* L., (fenugreek), a 90-day crop in many parts of the world, and the fruits of species of *Balanites*—wild trees and shrubs indigenous to Africa and India. Besides a breeding programme for high diosgenin-yielding strains of fenugreek, Dr. Hardman's group were also investigating ways of increasing the yield of diosgenin from *Dioscorea* tubers, fenugreek seed, *Balanites* fruits and other plant materials in their post-harvest condition. Squalane (2,6,10,15,19,23-hexamethyl-*n*-tetra-

cosane) had given favourable results and had been included in a British patent recently granted to the National Research Development Corporation.

In the final lecture, Professor Fairbairn described "Some recent work on the role of alkaloids in plants". After reviewing the earlier ideas on the function of alkaloids, he reported current work on the problem, especially that of his own school on the alkaloids of *Conium maculatum* L. and *Papaver somniferum* L. For both plants they had shown that the alkaloids were not "slowly accumulating heaps of metabolic sludge"; instead the alkaloidal pattern was found to fluctuate rapidly during active growth. Furthermore the major alkaloids, coniine and morphine respectively, were not end-product substances but were metabolized into further "non-alkaloidal" substances. In *Conium maculatum* the bound forms were associated with the reversible conversion of coniine to γ-coniceine which was established by use of radioactive tracer experiments. By analogy with the NAD cycle it was suggested that the conium alkaloids may be the active end of co-enzymes concerned with oxidation-reduction processes in this plant. In *Papaver somniferum*, the morphine present has also been shown to be rapidly metabolized in the latex into a series of compounds, some alkaloid-like, others more polar or bound forms. Some of these were translocated to the ovules and seeds in which they were stored. On germination they broke down to form alkaloids and alkaloid-like substances. Preliminary experiments suggest that these compounds may be necessary for seed viability. *In vitro* experiments with the isolated latex both before and after centrifugation show that the biosynthesis of morphine from simple amino acids is affected in a heavy fraction obtained at $1000 \times g$. If a special organelle is concerned with the formation of the alkaloids this gives additional support to the idea that the alkaloids play a significant role in the life of the plant.

ROLAND HARDMAN

Pharmacognosy Group,
Bath University of Technology,
Claverton Down,
Bath.