REVIEW

Recent Developments in our Knowledge of Steroids[1]

Roland Hardman[2,3]

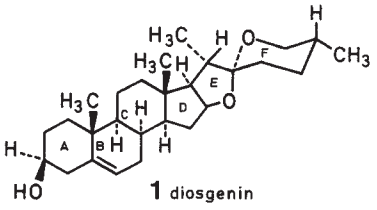
Received: October 14, 1986

Abstract: Annually, the American Chemical Abstracts has some 3 000 references to plant steroids or related compounds. This is a review of 34 selected papers mainly from the literature of 1984–1985. Plant steroids as raw material for the pharmaceutical industry; tissue culture for steroids; horticultural trials of species for sapogenins; the *in vitro* use of enzymes to increase the yield of sapogenins from plant material. New furostanol precursors of diosgenin; the cytotoxic activity of these and related compounds; their possible role in plant mineral metabolism. Microorganisms in the biotransformation of steroids; the exploitation of waste material as a source of sterols; the use of fungal spores on diatomaceous particles; the use of fungal protoplasts; hydrophobic resin as a product reservoir in such transformations. Brassinosteroids, their distribution as plant growth hormones; their microquantitative bioassay; physiological studies towards their use for enhancement of crop production; patented analogues obtained by partial synthesis. Ecdysones, their wide distribution in plants; their possible functions: effect on photosynthetic and respiratory rates; root protection against soil nematodes; dietary value in animal nutrition; their use in insect control. 29-Fluorophytosterols as pro-insecticides; fungal pregnanes as insecticides. Cardiac glycosides; ecological significance in plant-insect-bird relationships; new cardenolides, naturally occurring and those obtained by partial synthesis; the use of mesophyll cells in tissue culture; cross-breeding of *Digitalis* species. Steroidal alkaloids: reference to their annual review and to a steroidal antibiotic; the types of alkaloids now defineable in the Buxaceae and their chemotaxonomic significance for the new ones from the single genus family, Didymelaceae.

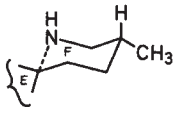
Introduction

Annually the American Chemical Abstracts contain some 3 000 references to plant steroids or steroids derived by partial synthesis from plant steroids. For this review I have selected 34 items to indicate the nature and range of recent developments.

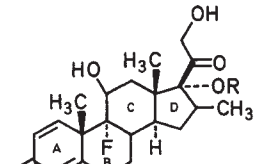
Plant steroids, having been produced by living cells, can provide the nuclei of the pharmaceutical steroids in a ready-made, precise stereo-configuration. Hence diosgenin (**1**), solasodine (**2**), and sterols may be used for the partial synthesis of the pharmaceutical steroids, such as the anti-inflammatory ones **3**; those that regulate the mineral metabolism **4**; anabolic agents **5**; progestogens **6** and estrogens **7**; their mixtures for the contraceptive; and even a steroidal anaesthetic **8**.



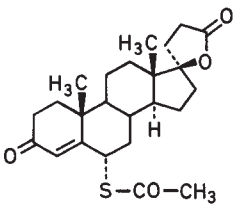
1 diosgenin



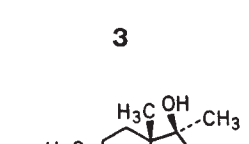
2 solasodine



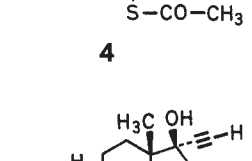
3



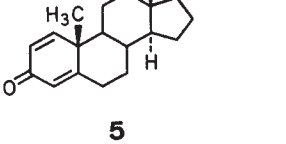
4



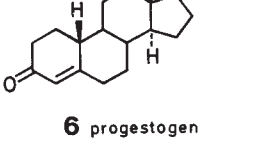
5



6 progestogen



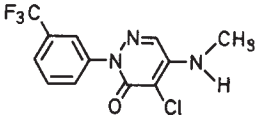
7 estrogen



8

Sapogenins and furostanol glyclosides

Without notable success in competing with the soil grown plants, the tissue culture of plant sources of diosgenin, e.g. *Dioscorea deltoidea*, continues. Commonly auxins and kinetins are used in the culture media. However, Tal et al. (1) used six chlorophyll-bleaching herbicides in cell suspension cultures of *D. deltoidea*. Norflurazon (**9**) gave an increased rate of diosgenin formation: 180 mg/l in 14 days, instead of 30 days, providing that norflurazon was added at day 7; delayed till that time because the biomass was decreased once norflurazon was present.



9 norflurazon

Meanwhile for diosgenin, the cultivation continues, principally in India, of *Dioscorea* species with deep-growing tubers (e.g. *D. floribunda*) and of those with shallow-growing tubers (e.g. *D. deltoidea*). Horticultural trials and surveys continue,

[1] Plenary lecture at the 34th Annual Congress of the Society for Medicinal Plant Research, Sept. 22–27, 1986 in Hamburg, Federal Republic of Germany.

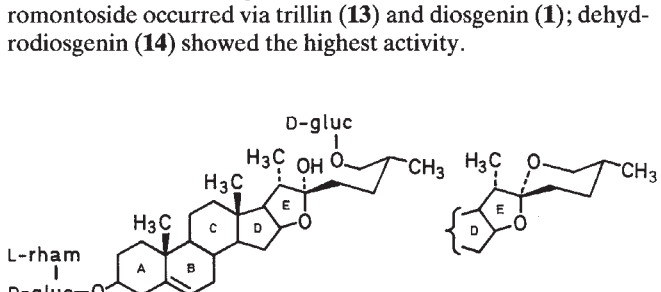
[2] Pharmacognosy Group, School of Pharmacy and Pharmacology, University of Bath, Bath, Avon, BA2 7AY, England.

[3] Address of correspondence: "Holly Leigh" Holt Road, Bradford on Avon, Wiltshire, BA15 1TR, England.

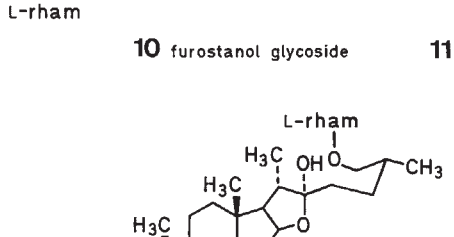
for example (2) with 19 species of *Dioscorea* tested (*D. deltoidea* being the best with 2.7 % diosgenin from the tuber) alongside rhizomes of 6 species of *Costus* (0.05–1.03 %) and 5 species of *Allium* (0.5–0.7 % in the underground organs and 0.96–2.32 % in the aerial parts) with *A. nutans* being the best of the *Allium* species. Ammal et al. (3) found that the highest yield of diosgenin came from a diploid race of *Costus speciosus* (minimum from tetraploid) when it was in flower and extracted from the rhizome.

The chemotaxonomic aspect, rather than the commercial one, was stressed when Hirai and colleagues (4) made the first report of a steroidal saponin **10** in the Palmae via the Fan Palm, *Trachycarpus fortunei*: from all parts they obtained the spirostanol glycoside, dioscin (**11**; 3β-chacotrioside of diosgenin) and its pro-saponin, the furostanol precursor (**10**; 3β-chacotrioside 26-glucoside).

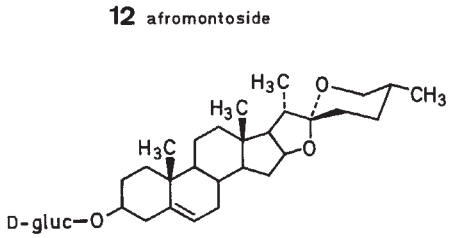
The novel afromotoside (**12**) has a 26-rhamnose unit in this furostanol glycoside, instead of the 26-glucose unit commonly found in the Fan Palm, the Dioscoreas, and many other steriodal saponin-yielding plants. It is claimed (5) as a new cytotoxic principle from Kenyan *Dracaena afromontana* (Agavaceae). In *in vitro* tests, against KB-cells from human carcinoma of the nasopharynx, structure activity increased from **12** to **14** as the step-wise methanolic acid hydrolysis of afromontoside occurred via trillin (**13**) and diosgenin (**1**); dehydrodiosgenin (**14**) showed the highest activity.



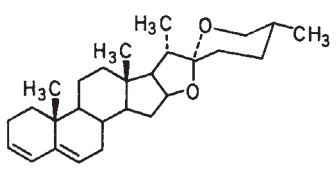
10 furostanol glycoside **11** dioscin spirostanol glycoside



12 afromontoside

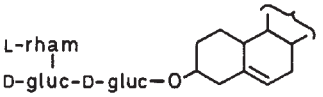


13 trillin

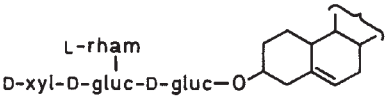


14 dehydrodiosgenin

Trigonella foenum-graecum, Fenugreek, is an annual legume which as the knee-high, unripe, nitrogen fixing crop, gives a high protein fodder. The ripe spice seed affords mucilage, fixed oil, protein, flavouring oleo-resin, and diosgenin. Unlike the Dioscorea tubers, etc., ripe Fenugreek seed has no free sapogenins. Instead it has the precursor furostanol glycosides (26-*O*-β-D-glucopyranosides). Gupta et al. (6) report the identification of two more such diosgenin precursors, 3β-tri- and tetra-saccharides [Trigofoenoside F (**15**) and G (**16**), respectively] to add to some six such furostanol glycosides already known from this seed.



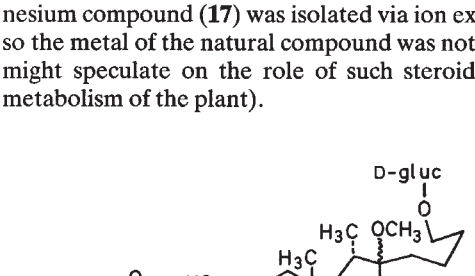
15 trigofoenoside F



16 trigofoenoside G

Elujoba et al. (7) report that the yield of sapogenin from the above precursor in Fenugreek seed was increased by 90 %, with the aqueous acid hydrolysis time reduced to 1.5 h, if the seed was first incubated at 45° C, at initial pH 4.0, with aeration for 4 days. This incubation period can be shortened by supplementing the seed's endogenous enzymes with "Naringinase D" (rhamnosidase + β-glucosidase + pectinase from *Aspergillus niger* and commercially available for debittering citrus fruit peel for fruit drinks), and this enzyme can be entrapped in alginate pellets for repeated re-use (7).

Aspidistra elatior is notable as the first member of the Liliaceae to yield a steroidal magnesium sulphate monohydroxide – as its pentahydroxyfurostanol glycoside, with the sulphate group *not* on a sugar but on the nucleus (8). The magnesium compound (**17**) was isolated via ion exchange resin and so the metal of the natural compound was not identified. (One might speculate on the role of such steroids in the mineral metabolism of the plant).

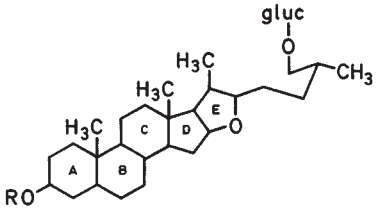


17

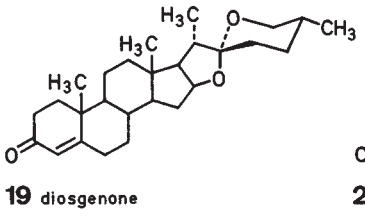
Micro-organisms in steroid transformations

The use of polymethylsiloxane resin as a product reservoir in steroid transformations has been illustrated by Saunders et al. (9): Fenugreek seed was defatted to get the useful oil, then extracted with methanol to get the crude mixture of furostanol glycosides **18** (R = di-, tri-, or tetrasaccharide). Instead of the high temperature acid hydrolysis of these (a high cost process),

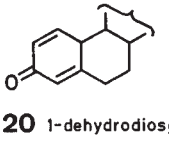
deglycosylation was effected with the mould *Fusarium solani* in the presence of the resin, to yield diosgenin (**1**) entrapped in the resin. The resin was sieved out, washed, and incubated with *Mycobacterium phlei* to afford androstanes **21** and **22** (via **19** and **20**) which were recovered from the resin by Soxhlet extraction with ethyl acetate.



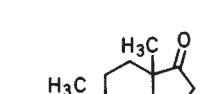
18 R = di- or trisaccharide



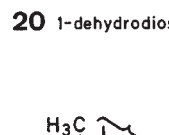
19 diosgenone



20 1-dehydrodiosgenone



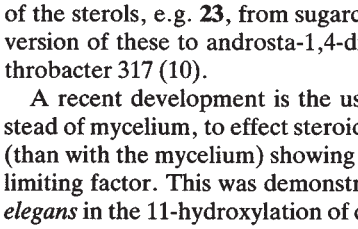
21 androsta-4-ene-3,17-dione



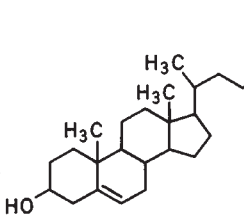
22 androsta-1,4-diene-3,17-dione

The exploitation of steroids from waste materials must always be considered and is illustrated by the solvent extraction of the sterols, e.g. **23**, from sugarcane press mud and the conversion of these to androsta-1,4-diene-3,17-dione (**22**) by Arthrobacter 317 (10).

A recent development is the use of fungal protoplasts, instead of mycelium, to effect steroid conversions at a faster rate (than with the mycelium) showing that the cell wall was a rate-limiting factor. This was demonstrated using *Cunninghamella elegans* in the 11-hydroxylation of cortexolone (**24**) for corticosteroid production (11). Also reported is the use of fungal spores, instead of mycelium, and entrapment of these in the pores of particles of diatomaceous earth (filter aid Celite 560) illustrated by the 11-hydroxylation of progesterone (**25**) (for corticosteroid production) by *Aspergillus ochraceus* (12).



23

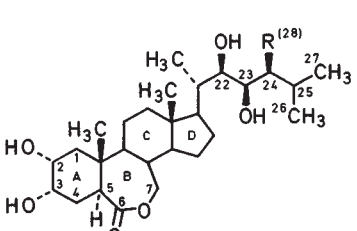


24 cortexolone

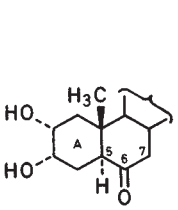
25 11α-hydroxyprogesterone

Brassinosteroids

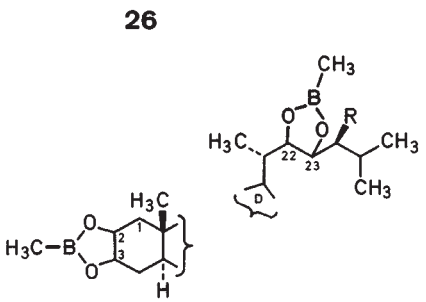
The group of plant growth promoting steroidal lactones, brassinosteroids, arose from the isolation in 1979 of brassinolide from the pollen of *Brassica napus*, oil seed rape (hence pollen available in quantity). Brassinolide, used as a 10 μM foliar spray on wheat seedlings, causes the third and fourth leaf to increase, root growth increases, the soluble protein and soluble reducing sugars increase, but the effect is dependent on age (13). Mixtures of two series of natural brassinosteroids are now recognised, differing in the structure of ring B **26** and **27** (R = H, CH_3, C_2H_5). A Japanese group (14) is very keen to demonstrate that *all* plants contain such steroids and they have succeeded in resolving and quantifying, at the nanogram level, these mixtures from plants as their bismethaneboronate derivatives **28** (via GC-CI-MS). When dealing with nanogram levels it is essential to have a very sensitive method of detecting the brassinosteroids in the fractions arising from the plant extraction procedure. This is done by a bioassay (15) known as the rice lamina inclination test: Fragments of lamina from rice seedlings are floated in the test solution. The curvature resulting from the growth under these conditions is measured. The Japanese found that IAA has the same type of activity as brassinolide but one needs 100,000 times more IAA to produce the same result as brassinolide, so that simple dilution excludes IAA. They also found that abscisic acid, kinetin, and N^6-benzyladenine inhibit this test, so that the bioassay will also detect anti-brassinolide compounds. Hence the brassinosteroids are considered to be yet another plant hormone like the auxins, gibberellins etc.



26



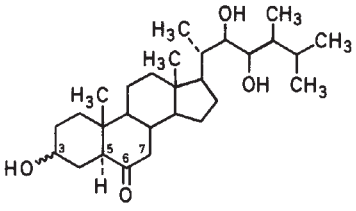
27



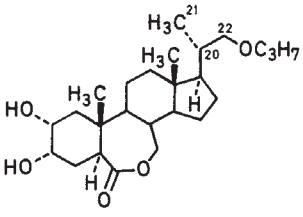
28

For plant growth promoting properties it was considered that both the 2α- and 3α-hydroxy groups were essential in these steroids but with the 2α-hydroxy group absent both the 3α- and 3β-hydroxy compounds, typhasterol (**29a**) and teasterone (**29b**), have been isolated from tea (*Thea sinensis*) leaves and both are equally active (16).

From the aspect of the commercial exploitation of this knowledge, it is essential that partial synthesis of active compounds should be achieved. Numerous patents have appeared. One reveals (17) that it is not essential to have the 22,23-dihydroxy groups of the natural steroids for growth promoting activity since a 22-ether, **30**, at 5 ppm markedly increased the growth of beet leaves.



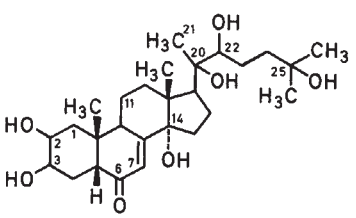
29 a (3α-OH) typhasterol
29 b (3β-OH) teasterone



30

Ecdysones

Steroids called ecdysones (because they cause ecdysis) are the moulting hormones of insects and crustaceans. Such steroids are only present in minute quantities in these creatures, but occur in greater structural variety and in much higher concentration in plants. By now they have been reported in about eighty five families. They do not protect the plant against insect attack in general. They have often been found in root bark and may protect the plant against soil nematodes. They are polyhydroxysteroids with an α,β-unsaturated keto system in ring B (6-keto as in the brasinosteroids) e.g. 20-hydroxyecdysone (β-ecdysone; **31**). Over forty such derivatives of cholestane, ergostane, stigmastane, pregnane and androstane, have been isolated from plants (some have weak insect moulting activity).



31 β-ecdysone

Preliminary studies on the effect of 20-hydroxyecdysone on photosynthetic and respiratory rates in isolated leaves of *Vicia faba* indicate that the steroid, only at low concentration (30 ppm), promotes accumulation of photosynthetic products without effect on the rate of respiration (19).

Fat hen (*Chenopodium album*) is a common weed taken by hens, suggesting that ecdysones may have a role in animal nutrition. This patent (21) claims that 20-hydroxyecdysone, derived from fat hen and other plants (e.g. *Serratula tinctoria* and *Spinacia oleracea*), as a single injection (50 g/kg), enhanced the weight gains of rats.

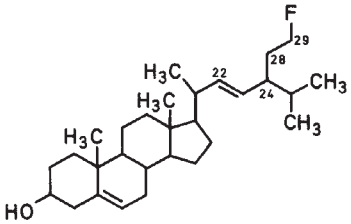
In the search for insecticides based on natural products, Kubo et al. (18) used crude extracts of the root bark of West African *Vitex madiensis* (Verbenaceae) to disrupt the moulting cycle of the agricultural pests, pink bollworm and armyworm. Droplet counter-current chromatrography revealed 0.4 % 20-hydroxyecdysone and 0.2 % ajugasterone in the fresh root bark.

Of course plant ecdysteroids have been applied topically to animal insect pests, a recent example being 20-hydroxyecdysone against ticks on camels: The lethal dose for nymphs and adults whether engorged or not, and the effect on their fertility, is described (20).

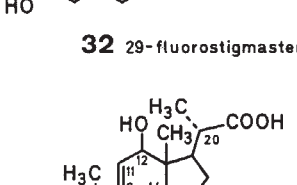
Other insecticides

Another approach to insect control is to exploit their inability to make sterols: for example, killing termites by feeding them with 29-fluorostigmasterol (**32**), when the insect's own enzymes release the fluorine as the poisonous trithiofluoro acetate: the subject of this US patent (22).

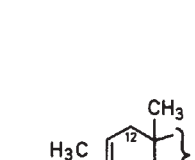
Fungi, pathogenic to insects, can also be extracted e.g. *Verticillium lecanii*, to afford two insecticidal hydroxypregnanecarboxylic acids, **33** and **34** (23).



32 29-fluorostigmasterol



33

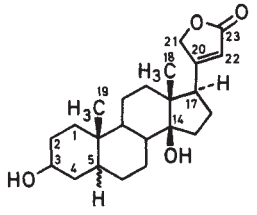


34

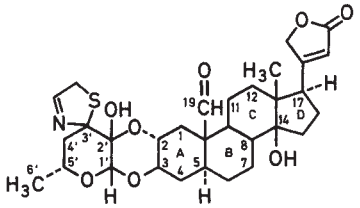
Cardenolides

The ecological significance of the cardenolides in *Asclepias* species (milkweeds, because of their latex) has been extensively reviewed (24). The latex is used as a cardiac arrow poison and the plants are poisonous to livestock (cattle, sheep, etc.) and birds, and the bitter taste of the cardenolides is the plant's protection. The cardenolides are not poisonous to the insects which feed on them. They have evolved in the presence of such plants. In its turn the insect uses the cardenolides to protect itself from birds, lizards and other predators. The plants have the 5α-isomer of digitoxigenin (**35a**) called uzarigenin (**35b**) as their characteristic genin, with their complex cardenolides in two series **36** and **37**. The insect removes the nitrogen and sulphur containing ring (via **36a** or **37a**, respectively) (no doubt using the elements to advantage) and then stores the bitter tasting cardenolides (**36b** or **37b**) in the bodies of larvae and adults, including the wings against vertebrate predators. Thus, when a bird bites the insect with its beak it immediately gets the bitter taste and rejects the insect or if it swallows it, the cardenolides cause it to vomit. Such insects advertise their toxicity to predators by noticeable patterning and pigmentation of their exteriors whereas other insects feeding on the same milkweed but avoiding predators by a low profile, e.g. keeping in the shadow, nocturnal feeding or feeding on roots, need not store the cardenolides and noticeable pigmentation or markings are absent from such insects. This has been well illustrated by feeding experiments of two beetles on the same sandhill milkweed (*A.*

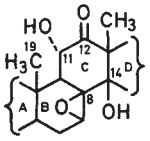
humistrata): the beetle with distinctive markings had high concentrations of cardenolides; the beetle without markings had no detectable cardenolides (25).



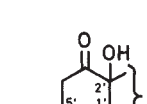
35 a (5α, *trans* A/B) uzarigenin
35 b (5β, *cis* A/B) digitoxigenin



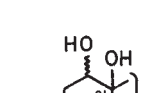
36



37

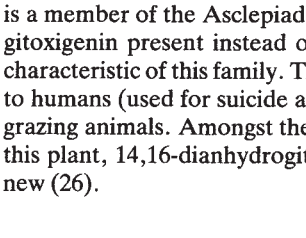


36 a or **37 a**



36 b or **37 b**

Exceptionally, *Cryptostegia madagascariensis*, a climbing shrub (ornamental vine) also common in Florida, Australia etc. is a member of the Asclepiadaceae with the 5β-compound, digitoxigenin present instead of the 5α-compound, uzarigenin, characteristic of this family. The plant is exceedingly poisonous to humans (used for suicide and homicide in Madagascar) and grazing animals. Amongst the six cardenolides identified from this plant, 14,16-dianhydrogitoxigenin-3-rhamnoside (**38**) was new (26).

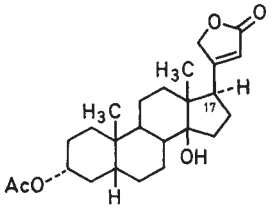


38

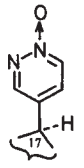
The cross-breeding of Digitalis species to produce plants of potential commercial value continues with hybrids dissimilar in morphology and cardenolide composition, e.g. hybrid *D. lutea* × *D. purpurea*: total purpurea glycosides + glucogitaloxin = 20.7 %; reciprocal cross: 2.6 % (27).

Tissue culture to afford cardenolides also continues, for example using cells of *D. purpurea*. Although all the organs of the plant contain digitoxin, the site of biosynthesis and accumulation of digitoxin was shown to be in the mesophyll cells of the leaf, by using isolated mesophyll cells, in culture, to convert labelled progesterone (e.g. **25**) to labelled digitoxigenin (**35**). Of five liquid cultures of cells, the green shoot-forming culture gave the highest production of digitoxin (28).

The partial synthesis of cardiotonic compounds is always present. To give one example related to digitoxigenin, it was found that the 3α-acetoxy compound (**39**) instead of the 3β-sugars had higher than expected activity in the guinea-pig atrial preparation and especially potent was this pyridazine oxide (**40**) (29).



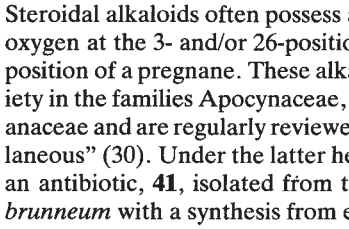
39



40

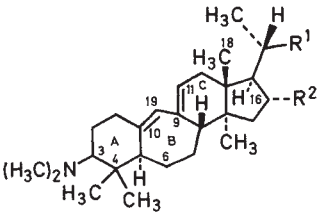
Steroidal alkaloids

Steroidal alkaloids often possess a nitrogen atom instead of an oxygen at the 3- and/or 26-position of cholesterol or at the 20-position of a pregnane. These alkaloids occur in very great variety in the families Apocynaceae, Buxaceae, Liliaceae and Solanaceae and are regularly reviewed under families and "Miscellaneous" (30). Under the latter heading Harrison (30) includes an antibiotic, **41**, isolated from the fungus *Geotrichum flavobrunneum* with a synthesis from ergosterol proposed by D. H. R. Barton. Reference (30) covers the literature from July 1982–June 1983.

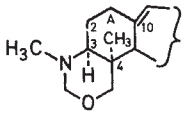


41

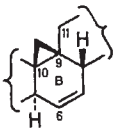
Two independent groups of workers (31, 32) have shown that the leaves of *Buxus* species yield 12 or more alkaloids which are 3,20-diaminopregnanes of 3 main types: **42** with a 9, (11) (10–19) *abeo*-diene system (R^1 = $NHCH_3$, R^2 = H); **43**, those with a tetrahydro-oxazine ring (arising from the 3-dimethylamino group and 4-methyl group of type **42**, so producing a pentacyclic structure) (R^1 = $NHCH_3$ or $N(CH_3)_2$, R^2 = H), and **44**, those with a cyclopropane ring involving carbons 9, 10 (R^1 = $N(CH_3)_2$, R^2 = $O_2CC(CH_3)$ = $CHCH_3$).



42

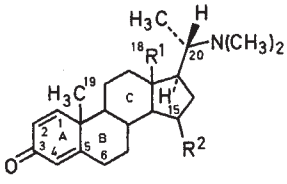


43



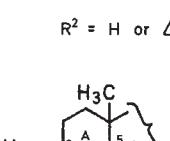
44

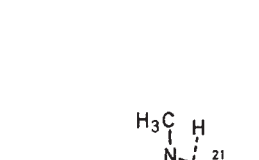
Thus, the range of biologically active steroids from plants continues to expand as does that from the animal kingdom, for example the six steroidal aminoglycosides, called Pavoninins, in the shark-repelling secretion of the Pacific sole (34) **48**. (Pavoninins I and II: R = Ac or H; III to VI: aminoglycoside at position 15 instead of position 7 and R = Ac; III and IV 3α- or 3β-OH with Δ^5; V and VI: 3α- or β-OH with Δ^6.)



45 R^1 = CH_3, CH_2OH, CHO

R^2 = H or Δ^{14}





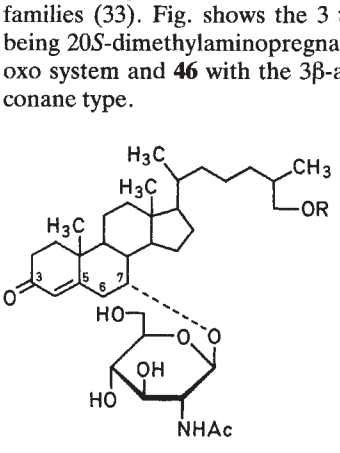
46 R^1 = CH_3, CH_2OH,

R^2 = H, α-HO, β-HO

R^3 = CH_3, CH_3CO

47 R^2 = H or Δ^{14}

The variety of such Buxaceae alkaloids has been extended by twelve (9 new) from the stem bark of *Didymeles cf. madagascariensis*, family Didymelaceae (with its single genus!) and so confirming previous botanical correlations between the two families (33). Fig. shows the 3 types of alkaloids: **45** and **46** being 20*S*-dimethylaminopregnanes, **45** with the 1 : 4-diene 3-oxo system and **46** with the 3β-amino group while (**47**) is the conane type.



48

References

(1) Tal, B., Rokem, J. S., Gressel, J., Goldberg, I. (1984) Phytochemistry 23, 1333–1335.
(2) Azarkova, A. F., Stikhin, V. A., Kabanov, V. S., Khotsialova, L. I., Maisuradze, N. I., Cherkasov, O. N., Rabinovich, A. M., Ivanov, V. B. (1984) Khim.-Farm. Zh. 18, 188–191.
(3) Ammal, E. K. J., Prasad, P. N. (1984) Curr. Sci. 53, 601–602.
(4) Hirai, Y., Sanada, S., Ida, Y., Shoji, J. (1984) Chem. Pharm. Bull. 32, 295–301.
(5) Reddy, K. S., Shekhani, M. S., Berry, D. E., Lynn, D. G., Hecht, S. M. (1984) J. Chem. Soc. Perkin Trans. 1 987–992.
(6) Gupta, R. K., Jain, D. C., Thakur, R. S. (1984) Phytochemistry 23, 2605–2607.
(7) Elujoba, A. A., Hardman, R. (1985) Planta Med. 51, 113–115.
(8) Konishi, T., Kiyosawa, S., Shoji, J. (1984) Chem. Pharm. Bull. 32, 1451–1460.
(9) Saunders, R. P., Hardman, R., Cheetham, P. S. J. (1985) Biotechnol. Bioeng. 27, 825–831.
(10) Goswami, P. C., Singh, H. D., Baruah, J. N. (1984) Curr. Sci. 53, 917–919.
(11) Sedlaczek, L., Dlugonski, J., Jaworski, A. (1984) Appl. Microbiol. Biotechnol. 20, 166–169.
(12) Broad, D. F., Foulkes, J., Dunnill, P. (1984) Biotechnol. Lett. 6, 357–362.
(13) Braun, P., Wild, A. (1984) in Adv. Photosynth. Res., Proc. Int. Congr. Photosynth. 6th 1983 (Sybesma, C., ed.) 3, pp. 461–464, Nijhoff, The Hague.
(14) Ikekawa, N., Takatsuto, S., Kitsuwa, T., Saito, H., Morishita, T. (1984) J. Chromatogr. 290, 289–302.
(15) Wada, K., Marumo, S., Abe, H., Morishita, T., Nakamura, K., Uchiyama, M., Mori, K. (1984) Agric. Biol. Chem. 48, 719–726.
(16) Abe, H., Ikekawa, N. (1984) Agric. Biol. Chem. 48, 2171–2172.
(17) Kerb, U., Eder, U., Kraehmer, H. (1984) (Schering A) Ger. Offen. DE 3, 305, 747, 23 Aug. 1984, 29 pp.
(18) Kubo, I., Matsumoto, A., Ayafor, J. F. (1984) Agric. Biol. Chem. 48, 1683–1684.
(19) Li, J. (1984) Zhiwu Shenglixue Tongxun 3, 25–26.
(20) Khalil, G. M., Shaarawy, A. A. A., Sonenshine, D. E., Gad, S. M. (1984) J. Med. Entomol. 21, 188–193.
(21) Szendrei, K., Bathory, M., Toth, I., Herke, I., Minker, E., Wolf, L. (1984) Hung. Teljes HU 29, 390, 30 Jan. 1984, 14 pp.
(22) Prestwich, G. D. (1984) U.S. US 4, 452, 793, 5 Jun. 1984, 9 pp.
(23) Grove, J. F. (1984) J. Chem. Soc. Perkin Trans. 1 1219–1221.
(24) Seiber, J. N., Lee, S. M., Benson, J. M. (1984) Isopentenoid Plants: Biochem. Funct. (Pap.-Symp.) 1982 (Nes, W. D., ed.), pp. 563–588, Dekker, New York.
(25) Nishio, S., Blum, M. S., Takahashi, S. (1983) Mem. Coll. Agric., Kyoto Univ. 122, 43–52.
(26) Sanduja, R., Lo, W. Y. R., Euler, K. L., Alam, M., Morton, J. F. (1984) J. Nat. Prod. 47, 260–265.
(27) Wichtl, M., Mangkudidjojo, M. (1984) Pharm. Ztg. 129, 686–689.
(28) Hagimori, M., Matsumoto, T., Mikami, Y. (1984) Plant Cell Physiol. 25, 947–953.
(29) Humber, D. C., Phillipps, G. H., Dodds, M. G., Dolamore, P. G., Machin, I. (1983) Steroids 42, 189–203.
(30) Harrison, D. M. (1984) Nat. Prod. Rep. 1, 219–224.
(31) Atta-ur-Rahman, Nisa, M., Zamir, T. (1984) Z. Naturforsch. B: Anorg. Chem., Org. Chem. 39B, 127–128.
(32) Mokry, P., Voticky, Z. (1984) Chem. Zvesti 38, 101–109.
(33) Sanchez, V., Ahond, A., Debray, M. M., Picot, F., Poupat, C. (1984) Bull. Soc. Chim. Fr. II, 71–76.
(34) Tachibana, K., Sakaitanai, M., Nakanishi, K. (1984) Science, (Washington, D.C.) 226 (4675) 703–705.