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Review Article

Biological activity in steroids possessing nitrogen atoms: recent advances

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WHEN the biological activities of steroids possessing nitrogen atoms were reviewed two years ago (Alauddin & Martin-Smith, 1962 a, b) it was predicted that a great deal of attention would be focussed on compounds of this class in the future. As anticipated, nitrogenous steroids possessing pharmacological properties not previously found within the group have been discovered—the most notable of these new properties being anti-inflammatory activity, anti-hypercholesterolaemic activity, digitalis-like activity, coronary dilatatory activity and central nervous system depressant activity. At the same time new nitrogenous steroids have been prepared which show weak androgenic, oestrogenic, progestational and anti-tumour activity (suggesting perhaps, that more potent agents exhibiting these types of activities await discovery within the nitrogen-containing steroid group) whilst the numbers of nitrogenous steroids showing high anabolic activity or antibacterial properties have also grown. It thus seemed desirable to extend the original reviews to these recent developments. The present survey covers the literature appearing since the publication of the two preceding reviews was completed, up to the end of 1963, although several 1964 references have been included and the opportunity has been taken to make reference to earlier contributions then unavailable to the authors.

Advances in the synthetic nitrogenous steroid field

Perhaps the most spectacular advances in the realm of synthetic nitrogenous steroids are connected with the preparation and biological testing of further steroids possessing heterocyclic rings incorporating nitrogen atoms, although many of the compounds so obtained still await full pharmacological evaluation and some of the claims concerning activity, which are based solely on routine assay procedures designed to detect compounds of potential interest, may need modification in the light of further studies. Differences in the activity of steroids as evidenced in screening assays and under conditions more closely akin to those of potential therapeutic application have been stressed by Bush (1962). Apart from new aza-steroids and new homo aza-steroids in which a nitrogen function has been substituted for a ring methylene group (for example, Engel & Rakhit, 1962; Huisman, Speckamp & Pandit, 1963; Kutney, Johnson & Vlattas, 1963; Kutney, Vlattas & Rao, 1963; Mazur,

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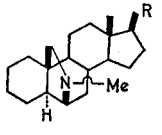
1963; Morgan, 1963; Morisawa, Kishida & Tanabe, 1963; Shoppee, Lack & Roy, 1963; Shroff, 1963; Uskokovic, Toome & Gut, 1962) prepared since the field was last reviewed (Rosseels, 1961; Tökés, 1963), several diaza-steroids have been prepared. These embrace both the heteroannular type (Doorenbos & Singh, 1961; 1962), giving an extension of the earlier work leading to a diazaequilenin-like molecule (Bhide, Tikotkar & Tilak, 1960), and the homoannular type in which a carbocyclic ring of the steroid nucleus can be considered to have been replaced by a pyrazole ring (Vida & Gut, 1963a), a pyrimidine ring (Caspi & Piatak, 1963a) or a pyridazine ring (Caspi, Grover & Piatak, 1963), thus extending earlier work in which ring A of the steroid nucleus was replaced by substituted pyridazine rings (Weisenborn, Remy & Jacobs, 1954). A further extension of this type of replacement of ring A of the steroid molecule is represented by the preparation of compounds in which an isoxazole ring is the replacing entity (Vida & Gut, 1963b). The biological properties shown by these compounds, when all have been tested, should be of theoretical interest, since the only modified steroid hormone so far discovered, in which a methylene carbon atom of the nucleus has been replaced by an atom of another element, and which shows enhancement of the activity characteristic of the parent compound, would appear to be 17α-methyl-2-oxa-5α-androstan-17β-ol-3-one (oxandrolone) (Fox, Minot & Liddle, 1962; Pappo & Jung, 1962). Certainly the pyrazole derivative prepared by Vida & Gut (1963a) was inactive as an androgen, anabolic agent, oestrogen or anti-oestrogen just as the steroidal 4-aza-5-en-3-ones prepared earlier by Dorfman, Uskokovic & Gut (1960) showed only weak anabolic or androgenic activities.

The first examples of aza-steroids in which a nitrogen atom replaces a carbon atom common to two rings of the steroid nucleus have been prepared (Meltzer & others, 1963a,b; Meyers, Ralhan & Munoz, 1963). The compounds so far reported include 8-aza-19-nortestosterone, 8-aza-19-norprogesterone and 8-azaoestrone and it will be interesting to learn of their biological activities particularly of the derived quaternary salts in view of the anti-shock properties of a structurally related compound reported by Osborne, Winbury & Govier (1963). It remains to be seen whether bisaza steroidal quaternary salts involving replacement of C-10 and C-13 by nitrogen will be prepared. These compounds, which will exhibit optical isomerism at the 10-aza- and 13-aza- quaternary nitrogen atoms, should be of great interest with respect to the relationship between chemical structure and neuromuscular-or ganglion-blocking activity. A further new type of aza-steroid is furnished by 17-azaprogesterone in which the carbon atom bearing the steroid side chain has been replaced by a nitrogen atom (Rakhit & Gut, 1964).

Many new nitrogenous steroids in which the perhydrocyclopentenophenanthrene nucleus is fused to a heterocyclic ring system have also been prepared, mainly as potential new anabolic agents. In addition to further derivatives of steroidal [3,2-*c*]-pyrazoles (for example, de Ruggieri, Gandolfi & Chiaramonti, 1962a; de Ruggieri, Gandolfi & Guzzi, 1963c; Fried & others, 1963a; Hirschmann & Patchett, 1963; Hirschmann &

others, 1963; Palmer, 1963; Patchett, Arth & Schwam, 1963; Schaub & Weiss, 1963), steroidal [2,3-*d*]-isoxazoles (for example, Marchetti & Donini, 1961; de Ruggieri & others, 1962a; Caspi & Piatak, 1963b; Manson & others, 1963) and steroidal [3,2-*d*]-thiazoles (for example, Doorenbos & Dorn, 1962; Holton & Necoechea, 1962; Clinton, 1963; Zderic & others, 1963), earlier representative members of which were discussed by Alauddin & Martin-Smith (1962a), a number of new fused steroidal heterocyclic compounds have been reported. The examples involving a 5-membered heterocyclic ring embrace steroidal [3,2-*b*]-pyrroles (Orr & Bowers, 1962), [16,17-*b*]-pyrroles (Mueller & Jiu, 1961), [3,2-*b*]- and [3,4-*b*]-indoles (Doorenbos & Wu, 1962), [3,4-*c*]-pyrazoles (Clinton & others, 1961, 1962), [17,16-*c*] -pyrazoles (for example, Moore, Holton & Wittle, 1962; de Ruggieri, Gandolfi & Chiaramonti, 1963a,b; Robinson, Bruce & Oliveto, 1963), [16,17-*c*]-pyrazoles (Dodson, 1960; Morita, 1963; Sciaky & Facciano, 1963), [3,2-*c*]-isoxazoles (de Ruggieri & others, 1962a), [6,7-*d*]-isoxazoles (Caspi & Piatak, 1962), [2,3-*d*]-thiazoles (Bowers & Edwards, 1963; Kraemer & others, 1963), [11,9-*d*]-thiazoles (Kitagawa & others, 1963), [12,11-*d*]-thiazoles (Takeda & Komeno, 1960), [17,16-*d*]-isothiazoles and [17,16-*d*]-thiazoles (Takeda & Komeno, 1962),



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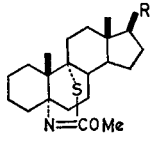

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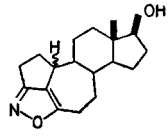


III

[2,3-*d*]-triazoles (Nathansohn, Testa & Di Mola, 1962; Fried, Buchschacher & Mrozik, 1963), [16,17]-1,2-diazabicyclo [3,2,0]-heptenes (Moore & others, 1962) and a D-homo-17-aza-[17,16-*a*]-indole (Hassner & Haddadin, 1962a). Those involving a six-membered ring include [17,16-*b*]-pyridines (Ketcheson & Taurins, 1960), [3,2-*d*]-pyrimidines (de Ruggieri & others, 1962a; de Ruggieri & others, 1963c; Smith, Teller & Foell, 1963; Zderic & others, 1963), [17,16-*d*]-pyrimidines (Ketcheson & Taurins, 1960; Smith & others, 1963), [2,3-*b*]-pyrazines (Jellinck & Irwin, 1963), [2,3-*e*]- and [4,3-*e*]-dihydro-*m*-oxazines (Kuehne, Konopka & Lambert, 1962), [2,3-*g*]- and [4,3-*g*]-pteridines (Bardos & others, 1963; Raman, Chmielewicz & Bardos, 1963), and finally [17,16-*b*]-quinolines (Hassner & Haddadin, 1962b), the preparation of this last group as potential anti-tumour agents being inspired by earlier reports (Buu-Hoi & Cagniant, 1944) of haemolytic properties in quinolino-steroids. An example involving a seven-membered ring is afforded by an androsteno [17,16-*e*]-1,2-diazepin-4-one (Moore & Pandya, 1964). In addition, several novel bridged heterocyclic nitrogenous steroidal systems have been prepared, including the types shown in I, II and III (Ledger & McKenna, 1963; Kitagawa & others, 1963; Roussel-UCLAF, 1963a; Kitagawa & Sato, 1964).

Compound III is claimed to possess anabolic properties.

The preparation of nitrogenous steroids in which the nitrogen atom forms part of an appended rather than a fused heterocyclic system has also continued. Among such compounds of biological interest, where the appended heterocycle forms a spiro system, are certain 16-spiro-dihydropyrazole derivatives (Werder & Brueckner, 1962), several 3-spiro-tetrahydrothiazole derivatives (Djerassi, Crossley & Kielezewski, 1962) and a number of lactams of 17β-amino-17α-(2-carboxyethyl)-androstane derivatives (Nysted & Burtner, 1962; Patchett, Arth & Hoffman, 1963; Patchett, Arth & Schwam, 1963; Patchett & others, 1962) which are nitrogen isosteres of the anti-aldosterone spirolactones and some of which (Burtner & Nysted, 1960) exhibit similar properties to the spirolactones.

In addition to the anti-accelerator activity shown by steroids substituted at C-16 by a piperidino ring (Swaine & Waud, 1960) steroids possessing appended piperidine rings at various positions have proved active as agents exerting a digitalis-like action (Nysted, 1958) or potentiating the contraction of striated muscle (Loomis, 1963), as central nervous system depressants (Babcock, 1959), as antihypertensive agents (Hershberg, 1960; Sterling, 1963), as antimicrobial agents (Counsell, 1963), as weak mineralotrophic (Szporny & Meszaros, 1962) and thymolytic agents (Dorfman & others, 1961; Stephenson, 1963), as antihypercholesterolaemic agents (Counsell & Klimstra, 1962; Tiernan, 1962) and as weakly active progestational (Kincl & Dorfman, 1963a,b) or oestrogenic (Takabatake & Ariyoshi, 1962) agents. It will also be interesting to learn of the biological properties of a number of 16α-substituted amino-glucocorticoid hormones which include 16α-piperidino-derivatives (Hoffman, Kissman & Weiss, 1962).

Steroids possessing appended pyrrolidine or morpholine rings, in several instances, appear to exhibit activities analogous to those just listed for the piperidine derivatives (for example, Camerino, Sciaky & Sala, 1962; Clinton, 1962; Gailliot & Robert, 1960; Hull, 1963; Marshall, 1961; Nysted, 1960; Panouse, Schmitt & Brunaud, 1961a,b; Gedeon Richter, 1963; Sciaky, 1962; Nakagawa, Mori & Tanaka, 1963), whilst a number of piperazine derivatives possess glucocorticoid activities (Brown & Sarett, 1963; Dömök & Szporny, 1963) and digitalis-like action is characteristic of several steroids possessing a substituted thiazole ring in the 17β-position (Ralls & Bergstrom, 1957; Takamura & others, 1963a,b).

The preparation of cyano- and thiocyanato-steroids has continued (for example, Cantrall, Littell & Bernstein, 1964a,b; Christiansen & Johnson, 1963; Crabbé & others, 1963; Julia, Linarès & Simon, 1963; Kissman, Hoffman & Weiss, 1961; Lednicer & Babcock, 1962; Nagata & others, 1961; Ueda & Mosettig, 1963; Valcavi, 1963). It would seem that in general the introduction of a cyano-group into a steroid hormone molecule greatly reduces the activity of the parent compound (Jen & Wolff, 1962; Kissman, Hoffman & Weiss, 1962) and some members of the group appear to actually exhibit antihormonal properties (Cella, 1960; Lincoln & Hogg, 1957; Mazur, 1957) although yet others are claimed to

be anabolic/androgenic agents (Bowers, Edwards & Orr, 1963), progestational or oestrogenic agents (de Ruggieri, 1962) or glucocorticoid agents (Fried, 1958). Certain 2α-cyano-compounds are stated to be useful as central nervous system depressants (Kissman & others, 1962). Interestingly, anti-inflammatory activity has been demonstrated in various 6β-nitro-steroids (Abildgaard, 1961) and antihypertensive activity is stated to be present in certain 16-nitromethylpregnenes (Dodson, 1959).

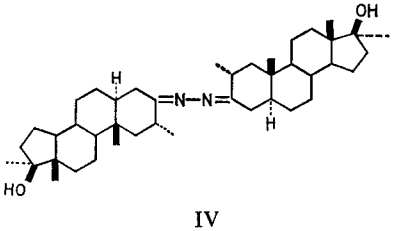
Several 21-azido analogues of glucocorticoids (Boland, 1961; Brown & others, 1961) have been shown to retain glucocorticoid activity, thus demonstrating extension of such properties to this group from steroidal diazoketones (Christensen, Steinberg & Hirschmann, 1958) and arylazo compounds (Dodson, 1957) known earlier. Perhaps the most dramatic discovery in this area, however, has been the demonstration that certain steroidal azines based on the androstane skeleton possess potent anabolic activity (de Ruggieri, Gandolfi & Chiaramonti, 1962b).

Further new nitrogenous steroids of great biological interest are afforded by several diaza-steroids in which carbon atoms of the steroidal side chain have been isosterically replaced by nitrogen atoms and which have proved to be inhibitors of cholesterol biosynthesis (Counsell & others, 1962b; Counsell, Klimstra & Ranney, 1962a; Ranney & Counsell, 1962a,b; Velluz & others, 1962).

A variety of nitrogenous steroids possessing various biological properties which have mainly been reported in the patent literature and which were not covered in the two previous reviews (Alauddin & Martin-Smith, 1962a,b) have been listed in a recently published compendium of steroidal drugs (Applezweig, 1962a).

ANABOLIC AGENTS

A number of new nitrogenous steroids possessing what is generally described as anabolic activity—despite objections which have been raised to the use of this term on account of its misleading connotations (Bush, 1962)—have been reported within the past two years. In addition to further representatives belonging to the group in which the steroid nucleus



IV

is fused to a heterocyclic ring, a new class of nitrogenous steroidal anabolic agents has been discovered in the androstane 3,3′-azines (de Ruggieri, & others 1963d; de Ruggieri & others, 1962b), the most potent of which is dimethazine, 2α,17α-dimethyl-17β-hydroxy-5α-androstane-3,3′-azine (IV). This compound, which, on oral administration, is stated to induce

an appreciable weight gain in adult rats, to show greater myotrophic activity than methyltestosterone, oxymetholone, stanozolol or testosterone propionate in castrated rats and to induce greater nitrogen retention in adult male rats than methyltestosterone (Matscher, Lupo & de Ruggieri, 1962) while exhibiting no oestrogenic, progestational or corticoid activity (Lupo, Matscher & de Ruggieri, 1962), can perhaps be regarded as an example of drug latentiation, especially in view of the obvious parallel to the relationship between prontosil red and sulphanilamide. On injection dimethazine is, however, less potent than testosterone and the nitrogenous steroids, 2-cyano-17β-hydroxy-5α-androst-2-ene caproate, stanozolol, 2-(*NN*-diethylaminomethylene)-17β-hydroxy-17α-methyl-5α-androstan-3-one and dihydrotestosterone-3-isonicotinyl hydrazone in the levator ani, ventral prostate and seminal vesicle weight gain tests in the rat (Dorfman & Kincl, 1963a). Dimethazine has been further shown to be without effect on the pituitary gland of castrated female rats (Beghelli & Mavrulis, 1962), to have a beneficial effect on bone regeneration in rats (Mavrulis & Pezzoli, 1962) and to have a higher activity in the levator ani test than methyltestosterone (Bianco & others, 1962).

In the heterocyclic field, clinical studies have shown that stanozolol (17β-hydroxy-17α-methylandrostano-[3,2-*c*]-pyrazole) may be a useful anabolic agent in man (Howard & Furman, 1962; Tainter & others, 1963), and, from nitrogen balance studies in the rat, 17β-hydroxy-17α-methylandrostano-[2,3-*d*]-isoxazole appears to be an even more potent agent than stanozolol (Arnold, Potts & Beyler, 1963a), although the initial claims of high potency in stanozolol have been questioned (Edgren, 1963).

Structure-action studies with some androstano- and androsteno-[2,3-*d*]-isoxazoles (Manson & others, 1963) have shown that the presence of a 4-ene or 4,6-diene system reduces anabolic activity where C-19 is present (Arnold, Potts & Beyler, 1963b) as is also true for the corresponding acetates (Caspi & Piatak, 1962), but that in the 19-nor series, where anabolic activity is present, it is more pronounced in the 4-ene than in the corresponding fully saturated compound. Unlike the situation with the corresponding 4-enes or 4,6-dienes of the [3,2-*c*]-pyrazole series, no oestrogenic activity is observed with the 4-enes or 4,6-dienes of the [2,3-*d*]-isoxazole series possessing a C-19 methyl group. The presence of a 17β-hydroxyl group seems crucial for high potency. Interestingly, 17β-hydroxyandrostano-[2,3-*d*]-isoxazole is inactive by the oral route but shows comparable activity to the corresponding 17α-methyl compound when given parenterally, thus providing a parallel to the situation pertaining between testosterone and 17α-methyltestosterone. Esterification of the hydroxyl group of 17β-hydroxyandrostano-[2,3-*d*]-isoxazole with 3-cyclohexylpropionic acid affords a potent anabolic agent with long duration of action and minimal androgenicity. A good myotrophic to androgenic ratio appears also to be present in 17β-hydroxy-17α-methyl-androstano-[3,2-*c*]-isoxazole (Arnold & others, 1963b; Donini & Montezemolo, 1961) where the side of the isoxazole ring involved in the ring fusion has been changed. This compound would seem to show negligible

progestational activity and to have a low inhibitory effect on pituitary gonadotrophin production. Insertion of methyl groups at C-4 to give 17β-hydroxy-4,4,17α-trimethylandrost-5-eno-[2,3-*d*]-isoxazole results in a compound which, like 2α-cyano-17β-hydroxy-4,4,17α-trimethylandrost-5-en-3-one, produces marked adrenocortical hypertrophy in mature female rats and blocks ACTH-induced thymolysis (Potts, Burnham & Beyler, 1963).

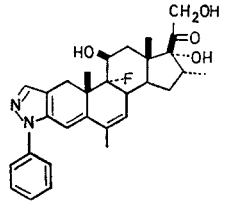
In addition to the anabolic properties of certain androstano-[3,2-*c*]-pyrazoles (Junkmann & Suchowsky, 1962) and [2,3-*d*]-triazoles (Nathansohn & others, 1962) a good anabolic to androgenic ratio is present in various androstano-[3,2-*d*]-thiazoles (Holton & Necoechea, 1962; Zderic & others, 1963). However, the androstano-[17,16-*c*]-pyrazoles so far prepared have nearly all proved devoid of hormonal activity (de Ruggieri, & others, 1963b), although weak anti-ovulatory properties are present in 3β-hydroxyandrostano-[17,16-*c*]-pyrazole and 3β-acetoxy-20-oxo-5-pregneno-[17,16-*c*]-pyrazole (Kincl & Dorfman, 1963b) and 3-methoxy-1,3,5(10)-oestratrieno-[17,16-*c*]-pyrazole, while without oestrogenic activity has been shown to possess antihypercholesterolaemic properties (Robinson & others, 1963). Similar lack of hormonal properties were found in the case of the androstano-[3,2-*d*]- and [17,16-*d*]-pyrimidines prepared by Smith & others (1963) although in this case antibacterial activity was present. The low degree of hormonal activity in the androstano-[17,16-*c*]-pyrazoles is perhaps of some significance in the light of the interesting suggestion (Bush, 1962) that the receptor site responsible for androgenic activity might be capable of accepting androgenic steroids in either of two positions in which the C-3 to C-17 axis is rotated through 180° in the plane of the steroid nucleus.

Two other nitrogenous steroids showing good anabolic to androgenic ratios are 2-(aminomethylene)-17α-methyl-5α-androstan-17β-ol-3-one and 2-(diethylaminoethylene)-17α-methyl-5α-androstan-17β-ol-3-one which on oral administration to rats had anabolic to androgenic ratios respectively 8 and 6 times that of testosterone (Zderic & others, 1963), whilst anabolic properties have been reported for 3-pyrrolidino-17α-methyl-5α-androst-2-en-17β-ol-4-one (Sciaky, 1962).

NITROGENOUS STEROIDS SHOWING ANTI-INFLAMMATORY ACTIVITY

Apart from further examples of latentiation or attempted latentiation of various anti-inflammatory steroids through esterification with nitrogen-containing acids (for example, Brunner & Finkelstein, 1960; Dorfman & others, 1961; Engelhardt, 1963; Thomae, 1963; Upjohn, 1960), oxime formation (Poos & Sarett, 1963) or carbamate formation (Brown & others, 1962; Lange & Amundson, 1962), anti-inflammatory activity has been demonstrated in some 20-alkylamino-steroids (Georgian, Kerwin & Wolff, 1961), in certain androsteno and pregneno [3,2-*c*]-pyrazoles (for example, Fried & others, 1963a; Harnik, 1963; Hirschmann & others, 1963; Steelman & others, 1963; Tishler, Steinberg & Hirschmann, 1962) and in several pregneno [3,2-*d*]-triazoles (Fried, Buchschacher & Mrozik, 1963). Although the [3,2-*c*]-pyrazole of hydrocortisone exhibited a

decreased anti-inflammatory activity as compared to hydrocortisone itself, potent activity is present in the [3,2-*c*]-pyrazoles of a number of glucocorticoids bearing substituents in the 6 or 16 positions. As well as their high potency these compounds are characterised by their lack of sodium retention activity (Fried & others, 1963a, Hirschmann & others, 1963). The [3,2-*c*]-2′-phenylpyrazole of 9α-fluoro-6,16α-dimethyl-Δ^6-hydrocortisone (V) has been claimed to be the most potent anti-inflammatory steroid yet known, being some 2000 times as potent as



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hydrocortisone in the rat systemic granuloma assay (Steelman & others, 1963). Other compounds of the series include the [3,2-*c*]-pyrazole of 16α-methylcortisone which has four times the activity of the parent steroid (Steelman & others, 1963) and the [3,2-*c*]-pyrazole of 9α-fluoro-16α-methylhydrocortisone which has 10 to 20 times the activity of hydrocortisone (Hirschmann & others, 1963). That a high degree of structural specificity would seem to be associated with anti-inflammatory activity is shown by the complete absence of activity in 6,16α-dimethyl-2′-phenyl-4,6-pregnadiene-11β,17α,21-triol-3,20-dione-[3,2-*d*]-3′-H-1′,2′,3′-triazole whereas the corresponding 3′-phenyltriazole exhibits an activity some 190 times that of hydrocortisone in the rat systemic granuloma assay (Fried, Buchschacher & Mrozik 1963).

The hydroxamic analogue of cortisone, 17α-hydroxy-3,11-dioxo-aetiochol-4-enohydroxamic acid, like its *O*-methyl derivative, proved devoid of anti-inflammatory activity (Kierstead, Faraone & Goldberg, 1963) as also appears to be the case with the *N*-acetyl derivatives of the 11-amino isostere of hydrocortisone and closely related compounds (Oliveto & Rausser, 1961; Scherico, 1962). Low or negligible anti-inflammatory activity was found to be present in 2α-cyano-9α-fluoro-16α-hydroxy-hydrocortisone-16,17-acetonide (Kissman & others, 1962), in 21-piperidino-21-deoxyprednisolone (Dorfman & others, 1961; Stephenson, 1963) and in the 20-oxime or 3-oxime of cortisone-21-acetate (Sarrett, Patchett & Steelman, 1963). Although highly active in the local granuloma inhibition assay, a series of 21-carbamate derivatives of hydrocortisone showed little systemic activity on subcutaneous injection (Brown & others, 1962).

ANTI-HYPERCHOLESTEROLAEMIC AGENTS

Apart from one or two exceptions (Nysted, 1960) anti-hypercholesterolaemic activity has been found to be characteristic of nitrogenous steroids

belonging to two main groups. The first group consists of β-dialkylaminoethyl ethers of 3-hydroxy steroids (for example, Birkenmeyer & others, 1961, 1962; Cantrall & others, 1963; Gordon & others, 1961; Phillips & Avigan, 1963; Velluz, 1963) and the second group consists of the steroids in which carbon atoms of the side chain have suffered isosteric replacement by nitrogen. In addition, 3-methoxy-1,3,5(10)-oestratrieno-[17,16-*c*]-pyrazole has been found to retain the antihypocholesterolaemic properties of oestradiol while being virtually devoid of oestrogenic activity as measured in the mouse uterotrophic assay (Robinson & others, 1963), thus affording an excellent example of a synthetic steroid in which two biological properties characteristic of a natural hormone have been dissociated.

The preparation of the side chain diaza-steroids which include 22,25-diazacholestanol (Counsell & others, 1962b), 22,25-diazacholesterol Counsell & others, 1962b), 20,25-diazacholesterol (Counsell, Klimstra & Ranney, 1962a), 22,25-diaza-19-norcholesta-1,3,5(10)-trien-3-ol (Velluz & others, 1962) and some closely related compounds, was inspired by the known inhibitory action of cholesterol upon its own biosynthesis—feedback control (Siperstein, 1960)—and it was reasoned that the nitrogen isosteres might well be more firmly bound to the surface of the feedback-inhibited enzyme (Counsell, Klimstra & Ranney, 1962a). It would now appear that these compounds exert their hypocholesterolaemic effects primarily via a mechanism involving blockade of the *in vivo* conversion of desmosterol into cholesterol (Dvornik & Kraml, 1963; Ranney & others, 1963) and not, as was claimed earlier, via inhibition of hydroxymethylglutarylcoenzyme A reductase (Ranney & Counsell, 1962a,b; Sachs & Wolfman, 1963; Thompson, Du Pont & Robbins, 1963). Thus their primary site of action may well be the same as that of the 3-(β-dialkylaminoethoxy)-steroids which also block the *in vivo* conversion of desmosterol into cholesterol (Gordon & others, 1961; Phillips & Avigan, 1963).

Daily oral administration of 22,25-diazacholestanol in the form of its dihydrochloride to rats at a level of 5 mg/kg for 10 days reduced the plasma cholesterol levels by 24% (Ranney & Counsell, 1962a,b) while in man, it was found to lower the serum cholesterol levels and the β-lipoprotein cholesterol content in hypercholesterolaemic patients (Sachs & Wolfman, 1963), but at the expense of progressive accumulation of desmosterol. The 20,25-diaza isostere of cholesterol was found to be the most active member of the series and on oral administration to rats rendered hypercholesterolaemic with 6-propylthiouracil it exhibited 15 times the hypocholesterolaemic potency of triparanol (Counsell, Klimstra & Ranney, 1962). No oestrogenic activity was present in 22,25-diaza-19-norcholesta-1,3,5(10)-trien-3-ol as evidenced by experiments on castrated female rats (Velluz & others, 1962).

In the 3-(β-dialkylaminoethoxy)-group three compounds, namely 3β-(β-dimethylaminoethoxy)-androst-5-en-17-one oxime, 3β-(β-diethylaminoethoxy)-androst-5-en-17-one methoxime hydrochloride and 3β-(β-dimethylaminoethoxy)-pregn-5-en-3-one, are stated to show at least 20

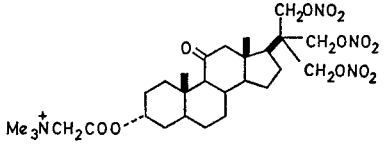
times the hypocholesterolaemic activity of triparanol in rats (Cantrall & others, 1963).

CENTRAL NERVOUS SYSTEM DEPRESSANTS

Anticonvulsant and sedative properties appear to be present in several groups of nitrogenous steroids. These include various steroidal monoximes (Babcock, 1958; Wechter, Schroeter & Buhler, 1961) and dioximes (Babcock & Wechter, 1962; Wechter, 1962; Upjohn, 1962a,b), a number of 17β-acetamido-androstane derivatives (de Ruggieri, Ferrari & Gandolfi, 1963), certain sterol aminoalkyl carbonates (Bergstrom, 1959), and aminoalkanoates (Marshall, 1963), and 2-cyano-1,4-pregnadiene-3,20-dione (Kissman & others, 1962) as well as various 3-aminopregnane derivatives (Schmitt, Brunaud & Panouse, 1961a,b; Schmitt & others, 1962) related chemically to the alkaloid funtumidine, the tranquillising properties of which were mentioned in the two earlier reviews. Similarly, central nervous system depressant activity as evidenced by induction of loss of the righting reflex in the mouse has been shown for several 2β-,6β- and 16β-morpholino-steroids, one of which, 2β-morpholino-3α-hydroxy-5α-pregnan-20-one, protected mice from leptazol-induced seizures at a dose one third of that necessary to produce loss of the righting reflex (Sugrue, 1963). In no case, however, was a degree of anaesthesia sufficient for surgery produced, nor was anti-Parkinson activity present.

VASODILATORY AGENTS

A striking example of the application of the supporting moiety theory is afforded by the preparation of several bis and tris nitratomethyl steroids and related nitrate esters such as VI which can be regarded as analogues



VI

of glyceryl trinitrate and which have proved to be potent coronary vasodilatory agents (for example, Bertin, 1962; Bertin, Nedelec & Locatelli, 1962; Bertin & others, 1962a; Roussel-UCLAF, 1962a, 1963b,c). Similar activity has been demonstrated in nitrogenous analogues such as 3α-acetoxy-11-oxo-20-dimethylaminoethyl-21-dimethylaminopregnane (Roussel-UCLAF, 1962b) whilst papaverine-dehydroepiandrosterone-3-monosulphate, which can be regarded as a steroid-latentiated presentation of papaverine, exhibited coronary vasodilator activity and inhibited histamine-induced bronchospasm and histamine-induced contraction of the guinea-pig small intestine (Setnikar, 1963). The synthesis of compounds of these types suggests many further applications of steroids as supporting moieties and latentiating agents, and it will be interesting

to discover what new drugs will be inspired by the success achieved with the compounds just discussed.

SEX HORMONAL ACTIVITY

The attempts so far recorded to synthesise nitrogenous steroids exhibiting potent androgenic, oestrogenic or progestational activity have not met with any marked success, although weak activity has been encountered in several instances. The preparation of amino isosteres of the steroidal oestrogens and related nitrogenous steroids has continued (for example, Bernstein, Cantrall & Littell, 1962; Schwenk & Gold, 1962; Suzui, Sawai & Chuma, 1962; Tsuda & others, 1963) and application of the α-aminonitrile synthesis to the preparation of a number 17-alkyl-17-dimethylamino-steroids resulted in a new oestrogenic compound, 17β-*NN*-dimethylamino-17α-methyl-3-methoxyoestra-1,3,5(10)-triene (Lednicer & Babcock, 1962). Nitrogenous oestrogen derivatives have played an important part in support of arguments attempting to more closely delineate the molecular requirements for oestrogenic activity (Patton & Dmochowski, 1963). Since replacement of a hydrogen atom of the C-2 methyl group in 2-methyloestrone by a dialkylamino-group leads to a marked decrease in oestrogenic potency as is also observed in 2-nitro-oestradiol and 4-nitro-oestradiol, it is conceivable that the fall in oestrogenic potency is a reflection of the lessened ability of the phenolic hydroxyl group on C-3 to enter intermolecular hydrogen bonding with the receptor, having its origin in steric hindrance, in intramolecular hydrogen bonding or in a combination of the two (cf. Brown, Eglinton & Martin-Smith, 1962).

Oestrone dimethylhydrazone proved only one thirtieth as active as oestrone in increasing the uterine weight of immature rats while the dimethylhydrazone derivatives of pregnenolone, progesterone and ethisterone proved to be without progestational activity (McKinney & Payne, 1961). The dimethylhydrazones of several androgenic steroids also showed a marked decrease in activity compared to the parent compound, and in the case of the 3-dimethylhydrazone of methyltestosterone the anabolic activity was depressed to a greater extent than the androgenic activity (McKinney & Payne, 1961; Wiley & Chang, 1963). On the other hand, the benziloyl hydrazones of testosterone-17-heptanoate and oestrone-3-heptanoate (Gleason & Parker, 1959), like various other steroidal ester hydrazones (Frosst, 1960) showed a marked prolongation of action as compared to the esters from which they are derived. The benziloyl hydrazone of 17α-hydroxyprogesterone-17-heptanoate, however, showed little difference in activity from 17α-hydroxyprogesterone-17-heptanoate (Gleason & Parker, 1959). The epimeric mixture of 17-cyanohydrins derived from 3,17-dioxo-oestr-4-ene has been reported to exhibit oestrogenic activity (de Ruggieri, 1962), while oestrogenic as well as progestational activity is stated to be present in various 4,9-androstadieno-[3,2-*c*]-pyrazoles (Hirschmann, 1963). Anti-ovulatory activity of one fifth and of one hundredth of that observed with norethisterone was found

in 3β-hydroxyandrostano-[17,16-*c*]-pyrazole and 3β-acetoxy-20-oxo-5-pregneno-[17,16-*c*]-pyrazole respectively (Kincl & Dorfman, 1963b) when administered orally to rats. On subcutaneous injection to rats, the anti-ovulatory activities of 3β-hydroxyallopregnane-20-*N*-acetylhydrazone, 3β-hydroxyallopregnane-20-nicotinylhydrazone, 16-dimethylaminoethylene-3β-hydroxyandrostan-17-one and 3,17-dioxo-16-piperidinomethylandrost-4-ene were respectively one fourteenth, one hundredth, one hundredth and one hundredth times that of norethisterone (Kincl & Dorfman, 1963a). Weak progestational activity was also found for 5α-thiocyanato-17α-ethynyloestrenolone and 5α-thiocyanatopregnan-3,20-dione as evidenced by the rabbit endometrial carbonic anhydrase test (Miyake, 1962).

Attention has also been given to the preparation of nitrogenous steroids capable of functioning as "antihormones," i.e. of antagonising endogenously formed hormones. Not only should such antihormones be of value in treating conditions such as prostate hypertrophy but it is conceivable that anti-oestrogens and antiprogestogens might prove of value in controlling fertility. Moreover, antihormones might prove of value in the elucidation of the intimate mechanisms of action of the natural hormones (Applezweig, 1962b). In some instances attempts have been made to secure steroids capable of directly antagonising the natural hormone and in other instances attention has been directed towards the production of antibodies capable of neutralising the endogenously formed hormones.

Examples of nitrogenous steroids resulting from the first approach are 3,11-dioxo-17-oximinoandrost-4-ene which is claimed to exhibit anti-oestrogenic and antimineralocorticoid properties (Nagata, Narisada & Sugasawa, 1962), certain 4-alkylamino-derivatives of testosterone and nortestosterone which are claimed to possess anti-androgenic activity (Suzuki, 1963), a number of steroidal [12,11-*d*]-thiazoles which are stated to exhibit antiprogestational properties (Yeneno, 1963) and various 17-iminosteroids which possess the ability to inhibit the response to testosterone propionate of the seminal vesicles and ventral prostate glands of castrated male rats, although without effect on endogenous androgens in intact male rats (Saunders & others, 1963). Anti-oestrogenic activity, as measured by the ability to inhibit oestrone-induced uterine growth in rats, was observed with the isonicotinylhydrazone of 17β-hydroxy-3-oxo-5α-androstane, with 3β-acetoxy-16β-carbamoyl-17α-isopregn-5-en-20-one, with 17β-hydroxy-17α-methyl-2-methylaminomethylene-5α-androstan-3-one and with 2-aminomethylene-17β-hydroxy-17α-methyl-5α-androstan-3-one (Dorfman & Kincl, 1963b), but only at massive doses. The piperidino-, pyrrolidino- and morpholino-ethers of oestrone and oestradiol also inhibit oestrone-induced uterine growth in rats but exhibit certain oestrogenic effects as well (Takabatake & Ariyoshi, 1962).

As a means of achieving antihormonal antibody production Erlanger & others (1957) prepared protein derivatives of testosterone and cortisone in which the steroid molecule was covalently bound to bovine serum albumin, and found that the products did indeed exhibit antigenic proper-

ties in rabbits. The encouraging results of this earlier work led to the synthesis of conjugates of progesterone, deoxycorticosterone and oestrone with bovine serum albumin (Beiser & others, 1959; Erlanger & others, 1959) but the results were by no means clear-cut (Lieberman & others, 1959). Nevertheless, oestrone conjugates of human serum albumin, formed by reaction of the 17-isocyanate derived from oestrone with the albumin to give the corresponding 17-carbamido-protein conjugate, were prepared (Goodfriend & Sehon, 1960, 1961a,b) and it was found that specific antibodies were produced to both the oestrone residue and the protein carrier. Thus it was established that the oestrone residue could indeed act as a haptenic group in inducing the formation of a steroid-specific antibody, but the antibody site complementary to the oestrone residue was found to be capable of accommodating other steroid molecules as well. The oestrone protein complex was itself devoid of oestrogenic activity and its antiserum proved capable of neutralising the 6-hr uterotrophic activity of exogenous oestrone in immature female rats. Further work involving the passive immunisation of sheep with oestrone bovine serum albumin, testosterone bovine serum albumin, hydrocortisone bovine serum albumin and aldosterone bovine serum albumin resulted in the production of anti-sera which were then found on administration to mice to be capable of blocking the effects of the appropriate steroid (Neri & Tolksdorf, 1962). At present insufficient data are available to permit of firm conclusions, but, in the light of the encouraging results so far, it would seem that complex nitrogenous steroids where the nitrogenous moiety is a protein may well have an important role to play in providing sera for the therapy of disorders which involve overproduction of steroid hormones.

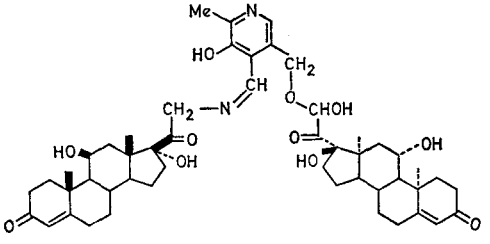
OTHER ACTIVITIES

Further compounds in which the steroidal nucleus can be regarded as acting as a supporting moiety bearing a hydrazide, hydrazone or isonicotinylhydrazone radical have been prepared (Volovel'skiĭ, 1961) and like the earlier compounds of the series (Volovel'skiĭ, 1957a,b) proved to have antitubercular activity. Tuberculostatic activity has also been demonstrated in 11-aminotigogenin (Jeger, Anner & Kalvoda, 1959) whilst antibacterial properties are characteristic of some 20- and 21-alkylamino pregnane derivatives (Nakama & Satake, 1959; Uchino & others, 1960; Varela & Kincl, 1962) and 17-ethylamino-1,3,5(10)-oestratien-3-ol (Misao, Sawai & Suzuki, 1962). *In vitro* activity against Gram-positive organisms, particularly certain strains of *Staphylococcus aureus*, was found for four steroidal [3,2-*d*]- and [17,16-*d*]-2′,6′-diaminopyrimidines (Smith & others, 1963) although these compounds proved incapable of protecting mice against a penicillin-resistant strain of *Staph. aureus*.

Antifungal properties are present in certain hydrazides, disemicarbazones and dithiosemicarbazones derived from hyodeoxycholic acid (Panizo & Laorga, 1958) and in a number of 18-dimethylamino-20-pregnenes (Pappo & Baran, 1959) and *N*-alkyl-17-amino-1,3,5(10)-oestratrien-3-ols (Misao, Sawai & Suzuki, 1962) whilst sterol complexes with piperazine

have proved useful as anthelmintic agents (Robeson, 1963). Antiviral activity is claimed to be present in *p*-toluenesulphonyl-dehydrocholamide (Ueda & others, 1962) and in *N*-dodecanoyl-4-cholylamino-1-naphthalenesulphonamide (Ueda, Kato & Toyoshima, 1958).

The results of attempts to secure antitumour activity in nitrogenous steroids have not been very encouraging. Thus further studies with nitrogen mustard derivatives of oestrogens (Nogrady, Vagi & Adamiewicz, 1962) have indicated that only weak anticancer properties are present in these compounds, although a degree of antitumour activity has been claimed for 6-aza-steroids (Lettre & Knof, 1959), the oxime of lanosta-8,24-dien-3-one (Mori, Gandhi & Schwenk, 1962) and a number of steroidal dihydro-1,3-oxazines (Kuehne & others, 1962). Preliminary biological screening indicated little antitumour activity in several steroidal [2,3-*d*]-isoxazoles (Caspi & Piatak, 1963b). The pteridino-steroids which were prepared as folic acid antagonists with the steroidal supporting moiety designed to confer favourable lipid solubility and cellular transport properties upon the antifolic 2,4-diaminopteridines (Bardos & others, 1963; Raman, Chmielewicz & Bardos, 1963) likewise showed little antitumour activity although 17β-acetoxy-5α-androstano-[4,3-*g*]-2′,4′-diaminopteridine is stated to have given a statistically significant inhibition of approximately 50% in one test—the sarcoma 180 assay—at 150 mg/kg/day (Bardos & others, 1963).



VII

Other biological properties shown by nitrogenous steroids which have been reported include hypoglycaemic activity for a series of aromatic sulphonyl carbamic esters of steroids (Heymons & Liebig, 1961) which are stated to be active on oral administration, and choleretic action for amides formed between various bile acids and amino-acids (Amiard & Heymès, 1958), while some *N*-substituted 17-amino-oestratrienes are claimed to be useful as hair tonics (Suzuki & others, 1963). The 21-glycylglycinate of prednisone has been shown to be without effect on the survival of adrenalectomised male golden hamsters but to increase the level of glutamic-pyruvic-transaminase in the liver (Oriol-Bosch & Voigt, 1961). Similarly 17β-aminoandrost-4-en-3-one has been shown to have very low androgenic and anabolic potencies but to increase the concentration of carbonic anhydrase in the seminal vesicles of intact male rats (Oriol-Bosch & Voigt, 1961). These two compounds thus afford examples of nitrogenous steroids in which there has been a dissociation of the

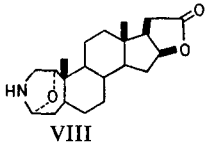
hormonal and enzyme-inducing activities characteristic of the parent compounds and give further examples of action of nitrogenous steroids on enzyme systems (for example, Levey, 1953).

The interest in the combination of steroids with nucleotides which was mentioned in the first of these reviews (Alauddin & Martin-Smith, 1962a) has now been extended to studies of the reaction of steroids with pyridoxine derivatives (Monder & White, 1962) in an attempt to explain how steroids may affect transaminase activity, and it has been shown that on oxidation by cupric ions to the corresponding 21-aldehydes, corticosteroids possessing an hydroxylic function at C-21 form Schiff bases of type VII with pyridoxamine.

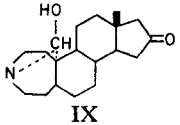
Steroidal alkaloids

SALAMANDER ALKALOIDS

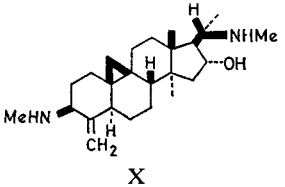
There would seem to have been no further biological investigations reported on the alkaloids of the 2a-aza-A-homoandrostane group although the results of further chemical studies have been published which have led to the elucidation of the structure of samandaridine as VIII (Habermehl, 1963) and to the reassignment of the structure of cycloneosamandione as IX (Habermehl & Goettlicher, 1963).



VIII



IX



X

ALKALOIDS FORMALLY DERIVED FROM PREGNANE

A further review of the occurrence, chemistry and pharmacological properties of the steroidal alkaloids belonging to the pregnane group has appeared (Janot, 1963) and some 20 new members of this group have been characterised.

New mono-acid bases of the pregnane type are irehamine which is 3β-hydroxy-20α-methylaminopregn-5-ene (Truong-Ho & others, 1963b) and thus the *N*-methyl derivative of holafebrine, paravallaridine which is 16α-hydroxyparavallarine (Beugelmans, Kan & Le Men, 1963), latifolinine which is 3-oxoconan-4-ene (Qui Khuong-Huu, Yassi & Goutarel, 1963) and norlatifoline which is 3β-hydroxy-*N*-demethylconan-5-ene (Qui Khuong-Huu, Yassi & Goutarel, 1963). These last two alkaloids, like latifoline (Janot, Qui Khuong-Huu & Goutarel, 1962) therefore represent examples of mono-acid conanine derivatives possessing an oxygen function at C-3 in place of the more usual nitrogen function. In addition, the structure of irehine has been elucidated as 20α-dimethylamino-3β-hydroxypregn-5-ene (Truong-Ho & others, 1963b). New alkaloids belonging to the holarrhimine sub-group of the pregnane diacid bases are epiheteroconessine which is 3α,20α-bis(dimethylamino)-pregn-5-ene (Lábler & Šorm, 1963a; Tschesche & Otto, 1962), irehdiamine A which is 3β,20α-diaminopregn-5-ene, irehdiamine B which is 20α-amino-3β-methylamino-

pregn-5-ene (Truong-Ho, Qui Khuong-Huu & Goutarel, 1963a), the pachysandrines A & B which possess an esterified hydroxyl group at C-4 (Tomita, Uyeo & Kikuchi, 1964) and cyclobuxine (X) Brown & Kupchan 1962a,b) and the cyclomicrophyllines A, B & C (Nikano & Terao, 1964) which represent examples of a new type of pregnane alkaloid incorporating a cyclopropane ring and retaining additional carbon atoms on C-4 and on C-14. In addition, the structure of kurchessine has been elucidated. It is 3β,20α-bis(dimethylamino)-pregn-5-ene (Lábler & Šorm, 1963a). New di-acid conanine derivatives are concuressine which is 3α-dimethylamino-conan-5-ene (Lábler & Šorm, 1963a), dihydroconcuressine which is 3α-dimethylamino-5α-conanine (Lábler & Šorm, 1963a) and malouphyllamine which is 3β-acetamido-5α-conanine (Janot & others, 1963).

The structure of α-hydroxyconessine has been confirmed as 3β-dimethylamino-4β-hydroxyconan-5-ene (Goutarel, Conreur & Parello, 1963) and kurchamine has been assigned the structure, 3-aminoconan-17-ene with unspecified stereochemistry (Tschesche & Otto, 1962). A new base isomeric with kurchamine and which has been assigned the structure 3-methylamino-*N*-demethyl-conan-17-ene has been termed kurchimine and a further base, designated kurcholessine, isolated (Tschesche & Otto, 1962).

The existence of yet other alkaloids belonging to the pregnane group is suggested by the isolation of the 3α-epimer of conessine and 3α-dimethylamino-5α-conanine together with 3α,20α-(bisdimethylamino)-pregn-5-ene and 3β-,20α-(bismethylamino)-pregn-5-ene from the methylated mother liquors remaining after the isolation of conessine from *Holarrhena antidysenterica* (Lábler & Šorm, 1963b) and by the isolation of a new *Funtumia* alkaloid, funtulatine (Oletta, 1963).

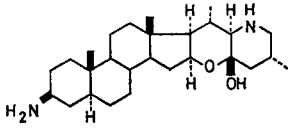
The trimethylammonium quaternary salts derived from funtumine and funtumidine have been claimed to possess 1/75th the neuromuscular blocking potency of tubocurarine (Blanpin & Bretaudeau, 1961; Blanpin & Pierre, 1961) which is of interest since they are monoquaternary, not bisquaternary, salts. Their other pharmacological properties are stated to be similar to those of the parent alkaloids. Pharmacological studies with the three possible isomers of malouetine involving the configurations of the nitrogen atoms, namely the 3β,20β-, 3α,20α- and 3α,20β-bis-(trimethylammonium)-5α-pregnanes, have shown that all three compounds possess neuromuscular-blocking activity comparable to that exhibited by malouetine itself on the rabbit gastrocnemius preparation, all being shorter acting than tubocurarine (Khuong Huu-Lainé & Pinto-Sconamiglio, 1964). The action of all four compounds is abolished by physostigmine and eserine.

ALKALOIDS FORMALLY DERIVED FROM CHOLESTANE

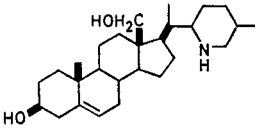
Two new skeletal types are now recognised within the cholestane group and these are represented by solanocapsine (XI) which has been shown to lack the usual spiro-structure (Schreiber & Ripperger, 1962) and by veralkamine (XII) a new alkaloid isolated from *Veratrum album* subspecies *lobelianum* (Tomko & Bendik, 1962).

BIOLOGICAL ACTIVITY IN STEROIDS POSSESSING NITROGEN ATOMS

Several comprehensive surveys of the occurrence of the solanidane and spirosolane alkaloids have been published (Schreiber & others, 1961; Schreiber, 1963a,b). The medicinal applications of extra-European *Solanum* species amongst primitive peoples have also been reviewed (Stopp, 1961) and a detailed study has been reported of the action of the solanum alkaloids on the chemoreceptors of the potato beetle, *Leptinotarsa decemlineata* Say (Stürckow, 1961). Solasodine has been shown to possess cardiotonic and antiphlogistic effects at 5–10 mg/kg in mice in addition to lowering sensitivity to pain stimuli (Turova, Seifulla & Belykh, 1961).



XI



XII

Solasodamine has been shown not to be an individual alkaloid but to be in fact solasonine monohydrate (Briggs, 1961; Briggs, Cambie & Hoare, 1961). Similarly solauricine has proved to be a mixture of solasonine and solamargine whilst the so-called alkamine, solauricidine was a mixture of solasodine and solasodine galactoside (Briggs, 1961; Briggs & others, 1961). Soladulcamaridine, originally classed as an alkamine of the solanidane type (Rasmussen & Boll, 1958) has now been proved to be a mixture of alkamines of the spirosolane type, consisting of solasodine, 5,6-dehydrotomatidine and 3,4 : 5,6-bis(dehydro)tomatidine (Boll, 1962). A number of new glycosidic alkaloids have been reported (for example, Bognár & Makleit, 1962; Makleit, Gaál & Bognár, 1962), including three new representatives from *Solanum dulcamara* which have been termed the α-, β- and γ-solamarines (Boll, 1962) and two new members from *Solanum laciniatum* which have been termed solaradixin and solaradinine (Bite, Jókay & Pongrácz-Sterk, 1962). β_1-Tomatine, which had previously been prepared from tomatine (α-tomatine) by partial acid hydrolysis giving cleavage of the xylose unit (Kuhn, Löw & Trischmann, 1957) has now been found to be of natural occurrence in the leaves of two mutants of *Lycopersicon esculentum* Mill. (Schreiber, 1963c).

The position of attachment of the second hydroxyl group in leptinidine has been shown to be C-23 (Kuhn & Löw, 1962) whilst by means of optical rotatory dispersion studies (Boll & Sjöberg, 1963) it has been shown that the differences existing within the side chains between the tomatidine and 5α-solasodan-3β-ol series are such that tomatidine has the 22βN,25*S* configuration and 5α-solasodan-3β-ol has the 22αN,25*R* configuration.

ALKALOIDS POSSESSING THE JERVI SKELETON

Further detailed pharmacological studies on the anti-accelerator action of veratramine (Hawkins, 1962) have shown that the alkaloid is acting

as a physiological antagonist to adrenaline whilst further careful structure-action studies within the ceveratrum ester group (Kupchan, 1961; Kupchan & others, 1961a,c; 1962a) have served to confirm earlier conclusions (Kupchan, Hensler & Weaver, 1961b) concerning the indispensability of esterification of the hydroxyl groups at positions 3 and 15 of protoverine for the presence of high antihypertensive potency. It was further concluded that although the absence of esterification of the alcoholic functions at both the 6 and 7 positions is not disadvantageous, absence of an ester group at position 7 alone does result in marked loss of potency. Esterification of the hydroxyl group at position 16 with either acetic acid or isobutyric acid is disadvantageous as is oxidation of this function to the corresponding ketone, whilst esterification of the hydroxyl at position 4 may lead to a loss of activity. Acetonide formation involving the hydroxyl groups on positions 14 and 15 results in a pronounced fall in potency.

The full chemical structures of sabine and its acetylated (at the hydroxyl group on position 3) derivative sabadine have been elucidated (Kupchan, Gruenfeld & Katsui, 1962). Unlike the related alkamines germine, protoverine, veracevine and zygadenine, sabine lacks a masked α-ketal system in ring A. It is 3β,4α,12α,14α,16β,17α,20β-heptahydroxy-5β-cevane. Similarly, the structure of verticine (*syn* peimine) has been shown to be 3β,6α,20β-trihydroxy-5α-cevane (Ito & others, 1963) whilst sipeimine (*syn* imperialine) has been shown to be a 3β-hydroxy-6-oxo-cevane derivative with an additional unplaced hydroxyl group (Liu & others, 1961).

Theoretical aspects

Recently there has been much speculation about the nature of androgen-receptor interaction, and nitrogenous steroids have played a role in experiments designed to gain more information bearing on this problem. Whereas with glycogenic activity, progestational activity or oestrogenic activity it seems generally accepted that interaction between the steroids concerned, and their receptors, involves the β face of the steroid molecule (Bush, 1961, 1962; Sarett, 1959; Sarett & others, 1963)—since with some exceptions bulky β-substituents attached to the steroid nucleus tend to abolish activity whereas α-substituents do not, thus suggesting that the β-substituents sterically hinder formation of the receptor complex—the position concerning mineralocorticoid or androgenic activity is particularly confused (Bush, 1962). In fact it has been suggested that α-face attachment, as is believed to occur in the binding of steroids to plasma albumin (Westphal & Ashley, 1959), may well be involved in mineralocorticoid and androgenic activity (Bush, 1962; Ringold, 1961) despite many anomalies, but apart from difficulties in interpretation arising from solubility, transport, absorption, distribution and biotransformation factors there remains the uncertainty as to whether a substituent group projecting from the steroid molecule coincides with a hump or a trough in the receptor surface. If the former situation pertains interaction between the steroid molecule concerned and the receptor would be

expected to be difficult or impossible, but if the second situation is the case, interaction with the receptor might even be strengthened due to increased van der Waals bonding.

To test the α-face hypothesis of androgenic attachment, several androgen analogues possessing an oximino group at C-19 or having a nitrile function replacing the C-19 methyl group were prepared and tested for androgenic activity (Wolff & Jen, 1963; Wolff, Jen & Kwok, 1963). Since the van der Waals radius of the nitrile group in the plane perpendicular to the steroid ring system is greater than that of the methyl group and since such a steric change on the β-face would hardly be expected to influence α-face attachment, the fact that the nitriles did not show the activity characteristic of the corresponding methyl compounds was taken to mean that androgens, like the glucocorticoids, progestogens and oestrogens interact with their receptors at the β-face.

A number of interesting vicinal amino-steroidal alcohols have recently been reported (Ponsold, 1963a,b,c) and it will be of some theoretical interest to learn of their biological properties in view of their conformational rigidity and the importance of the β-aminoethanol system as an active moiety or "stripped down" drug (Gero & Reese, 1956; Gero & Withrow, 1957)—being an integral part of the molecules of so many antispasmodic, local anaesthetic, sympathomimetic and antihistaminic drugs.

The potent neuromuscular blocking properties of C-curarine I and toxiferine I (Waser, 1959) which possess fully rigid molecules whose interonium distance can be seen to be *ca.* 9·7 Å from inspection of models (Haining & Johnston, 1962) coupled with the results of conductance studies on the flexible decamethonium molecule which have shown its interonium distance in aqueous solution to be *ca.* 9·5 Å (Elworthy, 1963), make it apparent that the original two-point attachment theory of neuromuscular blockade involving anionic receptor sites separated by *ca.* 14 Å (Paton & Zaimis, 1949, 1951) needs modification, and it is of great interest that several 3β,17β-bisquaternaryammonium androstane derivatives, in which the interonium distance can vary from 10·5 to 11·2 Å (as ring A passes from boat to chair), exhibit potent non-depolarising neuromuscular blockade of short duration (Biggs, Davis & Wien, 1964; May & Baker, 1963). One of these derivatives, 3β,17β-dipyrrolidin-1′-yl-5α-androstane bismethiodide has been found devoid of androgenic, oestrogenic and progestational activity in man. The detailed comparative pharmacological properties of the different members of the series will be of theoretical significance since increase in the size of the substituents on the cationic head in the flexible polymethylene bisquaternary series causes the average interonium distance to increase (Elworthy, 1963) and such variation will be minimised in the steroidal series. Apart from the fact that the possible interonium distances seem significantly higher than the 9·5–9·7 Å previously mentioned (a range also proposed by Carey & others, 1959), the lack of impedence to interaction with the receptors from the angular methyl groups projecting from the β-face of the steroid nucleus at C-10 and C-13, is of theoretical importance; so too is the presence of activity in

3α,17β-bistrimethylammonium-5α-androstane where the quaternary heads lie on opposite sides of the plane of the steroid nucleus. It remains to be seen whether bisquaternary salts having the 3α,17α-configuration in which the interonium distance can vary from 9·3 Å (ring A as chair) to 11·0 Å (ring A as boat) will exhibit similar activity.

Conclusion

If the progress in the nitrogenous steroid field achieved within the two years since the earlier reviews (Alauddin & Martin-Smith, 1962a,b) were completed, as indicated by the present review, can be taken as a criterion of future interest in the field, it may be anticipated that many nitrogenous steroidal drugs will be introduced in the coming years, and that still further contributions to the theoretical aspects of drug action will be forthcoming from this field. The successful development of photochemical reactions applicable to nitrogenous steroids (for example, Barton & Beaton, 1961; Barton & Morgan, 1961, 1962; Barton & others, 1960; Robinson & others, 1961; Tanasescu, Hodosan & Jude, 1960), the successful development of microbiological transformations applicable to nitrogenous steroids (de Flines & others, 1962; Kupchan & others, 1963; Mazur & Muir, 1963; Sato & Hayakawa, 1963, 1964) and the discovery of microbiological amidation of steroids (Smith & others, 1962) open new opportunities for the production of still further nitrogenous steroids and suggest that an active interest in the field will be maintained for some years.

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