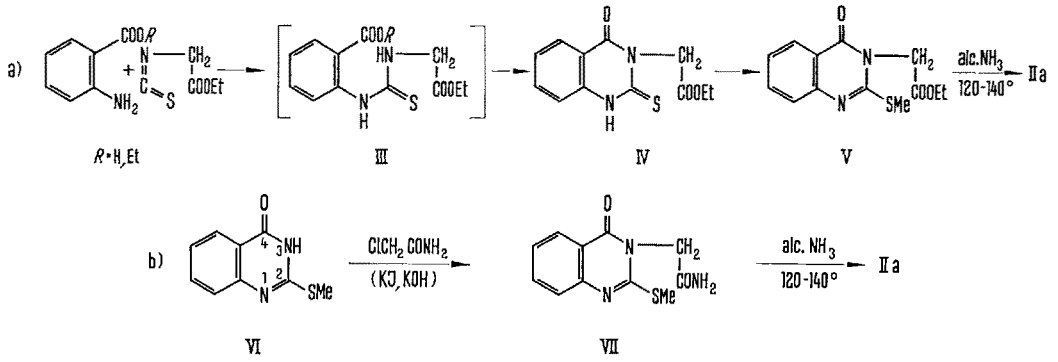
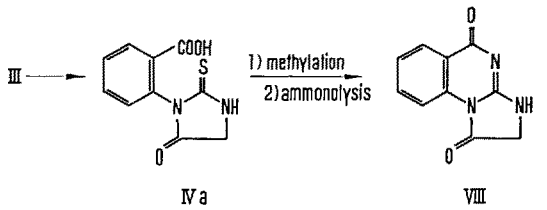


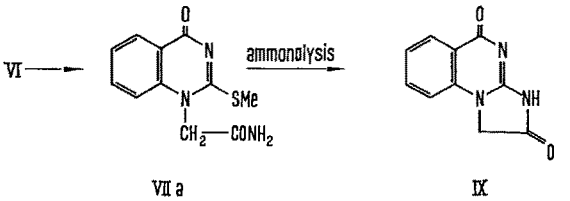
Ethyl (2-thioxo-4-oxo-1, 2, 3, 4-tetrahydro-3-quinazolinyl)-acetate (IV, mp.: 216–7°, incorr.; found: C 54.80 H 4.68 N 10.80 S 12.08; $C_{12}H_{12}N_2O_3S$ requires C 54.54 H 4.58 N 10.60 S 12.12) was prepared by refluxing either anthranilic acid or ethyl anthranilate with ethyl isothiocyanatoacetate in alcohol; methylation gave the S-methyl derivative (V, mp.: 107–8°; found: C 56.63 H 5.23 N 10.10 S 11.62; $C_{13}H_{14}N_2O_3S$ requires C 56.10 H 5.07 N 10.06 S 11.52) and ammonolysis and ring closure of the latter, effected by heating with alcoholic ammonia, led to a product (mp.: about 340°, incorr., decomp.; found: C 59.94 H 3.68 N 21.07; $C_{10}H_7N_3O_2$ requires C 59.70 H 3.55 N 20.89) which, in all respects (mp., mixed mp., IR-spectrum) proved to be identical with the condensation product from anthranilic acid and S-methyl-2-thiohydantoin.

(2-Methylmercapto-3, 4-dihydro-4-oxo-3-quinazolinyl)-acetamide (VII, mp.: 245–46°, incorr., decomp.; found: C 53.05 H 4.60 N 16.86 S 12.56; $C_{11}H_{11}N_3O_2S$ requires C 53.00 H 4.45 N 16.86 S 12.86) was prepared by reaction of 2-methylmercapto-4(3 H)-quinazolinone (VI) with chloroacetamide in the presence of potassium iodide and potassium hydroxide. Ammonolysis and ring closure was effected as above and led to a product (mp.: about 340°, incorr., decomp.; found: C 60.01 H 3.59 N 21.14; $C_{10}H_7N_3O_2$ requires C 59.70 H 3.55 N 20.89) which too proved in all respects to be identical with the products mentioned above.

Attention should be called to the fact that neither the synthesis via a nor that via b *alone* proves the structure of IIa unequivocally. Ring closure of III could lead namely, under the conditions employed, by subsequent esterification even in the case R=H instead of IV to the isomeric thiohydantoin derivative IVa which, after methylation and ammonolysis, should lead to VIII, an isomer of IIa:



VI, on the other hand, might react with chloroacetamide at N^1 instead of N^3, leading to VIIa and, after ammonolysis to IX, *another* isomer of IIa:



However, the fact that *both* syntheses give the *same* product, offers an unequivocal proof of its structure.

Thus the condensation product of anthranilic acid and S-methyl-2-thiohydantoin and that of methyl anthranilate with ethyl N-cyano-glycinate[5] has been proved to be 2,51 H, 3 H-imidazo (2,1-b) quinazolinedione (IIa).

Zusammenfassung. Die Struktur des Kondensationsproduktes aus Anthranilsäure und S-Methyl-2-thiohydantoin, bzw. aus Anthranilsäuremethylester und N-Cyanglycinäthylester[5] wurde als die eines 2,5-(1 H, 3 H) Imidazo(2,1-b) chinazolindions bewiesen.

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Steroids. The Stereochemistry of Grignard Additions to Steroidal Ketones

The addition of methyl magnesium halide to 12-pregnanones[1–3] and 17-a-*D*-homoandrostanones[4] proceed contrary to the 'rule of rear attack'[5,6]. These abnormal additions led us to survey the reactions of methyl magnesium halide and methyl lithium with steroidal ketones. It revealed the fact that in all cases recorded, the yield of axial alcohol is at least 50%. Since the analogy between the addition reaction of Grignard reagent and lithium aluminum hydride to ketones has been well authenticated[7], and as the latter reaction has been studied at greater length, a comparison of the results obtained with these

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Lithium aluminum hydride reduction and Grignard reaction of steroidal ketones

Position of the carbonyl group	Steric hindrance	Lithium aluminum hydride reduction Series	Yield of alcohol in % axial	equatorial	MeMgX or MeLi reaction Series	Yield of alcohol in % axial	equatorial	References
3	unhindered	5α	10	90	5α	50	50	[14,18,19,25], see also [20]
7	intermediate	5α	50	50	5β	75	25	[10,26,27,28], cf. [29]
12		5α	50	50				[1–3], cf. [30,31]
2		5α	52	37				[10]
1		5α	65	35				[32]
17a					Δ5	76		[4]
4	hindered	5α	90	7				[11]
6		5α	94	6	5α	90		[11,12,33–35], cf. [36]
11		5β and Δ5	90	5	5α and 5β	85		[37–39,40–43]

two reagents with steroidal ketones seemed appropriate (see Table).

BARTON summarised the results of hydride reduction of steroidal ketones with the generalisation that unhindered ketones give the equatorial alcohol as the major product, whereas the reduction of hindered ketones yields mainly the axial alcohol[8]. DAUBEN et al. studied the stereochemical features governing hydride reductions of alkylcyclohexanones[9] and of steroid ketones[10], and suggested that two effects determine the stereochemistry of the alcohol composition: (i) product development control and (ii) steric approach control.

Polar substituents or double bonds at close proximity to a carbonyl group may introduce new steric or stereoelectronic effects, and thus influence the alcohol composition in lithium aluminum hydride reductions. Thus, while lithium aluminum hydride reduction of 4- and 6-cholestanones yields the axial alcohol as the major product[11,12], cholest-5-en-4-one and 3,5-cyclocholestan-6-one affords mainly the equatorial alcohol ([11–13] see also [14,15]). COMBE and HENBEST have shown that polar substituents can influence the stereochemical course of lithium aluminum hydride reduction of cyclohexanones[16]. To a lesser degree, the influence of solvents have been shown in such reductions[1,10,16,17]. In the examples included in the Table, except for the minor influences of solvent, other influences discussed above have been excluded, and in our opinion the results in the Table are to a large extent a true measure of the steric hindrance.

We now suggest that DAUBEN's concept of product development and steric approach control, originally proposed to explain the stereochemistry of hydride reductions, can be extended to include Grignard additions. The steric approach control becomes important even in unhindered ketones, because of the bulky nature of Grignard reagents. Thus, while lithium aluminum hydride reduction of 3-cholestanone gives 90% equatorial alcohol[14,18], addition of methyl Grignard reagent affords 56% of axial alcohol and only 42% of equatorial alcohol[19]. It is of interest to note that the reaction of 3-cholestanone with phenyl magnesium bromide also yields a 1:1 mixture of axial and equatorial phenylcholestanols[20]. The results of these two Grignard reactions suggest that the influence of the size of the alkyl (aryl) group presumably does not affect the stereochemical course of the addition reaction. In this context, it might be mentioned, that whereas 4-t-butylcyclohexanone, where the t-butyl group acts as an anchoring group[21], on reduction with lithium aluminum hydride gives 90% of the trans alcohol[22], the same ketone on treatment with methyl Grignard reagent yields the epimeric carbinols in 1:1 ratio[23].

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Ketones of intermediate steric hindrance give with lithium aluminum hydride approximately a 1:1 mixture of axial and equatorial alcohols. With methyl magnesium halide, the axial alcohol predominates distinctly. Thus the 'abnormal' mode of Grignard addition to 12-pregnanones and 17-a-*D*-homoandrostanones is the predicted one[24]. In the case of the hindered 4-, 6- and 11-ketones, both reactions afford the axial alcohol as the major product.

It is apparent that the results of lithium aluminum hydride reduction and Grignard addition with steroidal ketones are similar, and it seems that the same factors influence the stereochemistry of these two nucleophilic addition reactions.

Zusammenfassung. – Die Anlagerung von Methylmagnesiumhalogeniden an unkonjugierte sechsgliedrige Ringketone der Steroidreihe ergibt bei ungehinderten Ketonen ungefähr eine 1:1-Mischung von axialen und äquatorialen Alkoholen. Mit zunehmender sterischer Hinderung des Ketons bildet sich, ähnlich wie bei Reduktionen mit Lithiumaluminiumhydrid, mehr vom axialen Alkohol.

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Chemistry Department, McGill University, Montreal (Canada), June 4, 1962.

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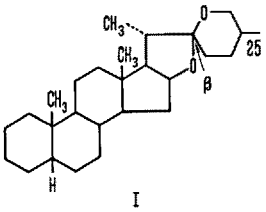
Nomenclature of Steroidal Sapogenins[1]

Nomenclature of steroidal sapogenins is covered under rules proposed at Stockholm (Sweden) in 1953, adopted as tentative at Zurich (Switzerland) in 1955[2] and published as definitive by the International Union of Pure and Applied Chemistry in 1960[3]. Unfortunately, sapogenin stereochemistry was not fully understood when the proposed rules were formulated. During the ensuing seven-year period the stereochemistry of the sapogenin skeleton was elucidated. The correct formulas were not, however, incorporated in the definitive nomenclature rules of 1960, which are based on structures published earlier in the tentative rules.

The present status of the Definitive Rules requires use of the formulas as shown, and the parent names 5α,22β-



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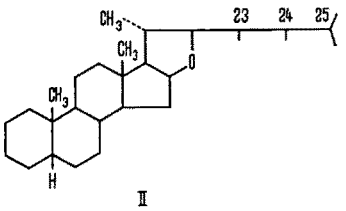
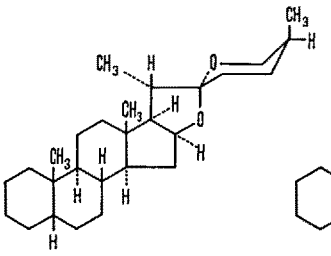


II

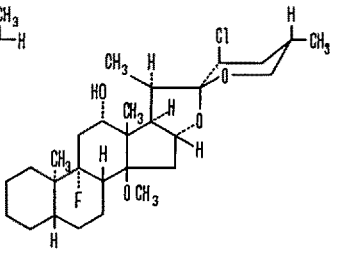
spirostan or 5β,22β-spirostan (I), and 5α- or 5β-furostan (II). In neither parent is there provision for designating known stereochemical variations possible at carbon 25; in both cases configurational representations at carbon 22 are equivocal. Furthermore, the structures of tigogenin and dihydrotigogenin published in the Rules as illustrative examples are incomplete and incorrect in light of present concepts[4]. Tentative Rules have already been published[5] which purport to remedy the situation. FIESER and FIESER have published opinions on this subject[6].

We wish to offer an alternate approach in the hope that our suggestions ultimately will receive formal adoption and in the meantime will extricate sapogenin nomenclature from the confusion of its recent past[7] and place it on a logical and general basis. Accomplishment of this immediate objective requires adoption of three ideas that already have won varying degrees of acceptance in nomenclature: (1) use of the parent name; (2) application of α- and β-configurations to an extended but nearly planar ring system as in present steroid practice; and (3) employment of the R- and S-designation of configuration at asymmetric centers not included in the planar ring system[8].

As parent names of hexacyclic steroidal sapogenins we recommend 5α,25R-, 5α,25S-, 5β,25R-, and 5β,25S-spirostan (III), in which the stereochemistry at each asymmetric center is implicitly and uniquely defined. The



III



IV

α- and β-terminology applies to all carbon atoms in rings A, B, C, D, and E, where an inversion of the skeleton at any center is expressed by numbering that center and designating the new configuration as α or β. The configuration so expressed is that of the free substituent at

[1] A summary of the personal views of the authors. Presented by the authors to an *ad hoc* Committee on Steroid Nomenclature (sponsored by the National Academy of Sciences and the National Research Council, and supported by a grant from the U.S. Air Force Office of Scientific Research) that met in Columbus, Ohio, October 13–15, (1961), under the chairmanship of R. C. ELDERFIELD.

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