Compounds VIII-XVIII (all were colorless except X and XV, which were yellowish) were crystalline substances, insoluble in water, except for the hydrochloride of IX, which was soluble in organic solvents. For analysis they were purified by crystallization from 1:1 dioxane—water (VIII, XII, XV, XVII), propanol (IX), 50% isopropanol (X), butanol (XI), DMF (XIII, XIV), dioxane (XVI), or 1:1 DMF—water (XVIII).

1-(p-Chlorophenyl)-2,3-dihydroimidazo[2,1-b]quinazolin-5(1H)-one (XIX). A mixture of 2.72 g (0.01 mole) or 2-(p-chlorophenylamino)quinazolin-4(3H)-one (IId) and 3.72 g (0.02 mole) of 1,2-dibromoethane in 25 ml of DMF was refluxed for 8 h, whereupon 2.1 g (0.025 mole) of sodium bicarbonate was carefully added and heating was continued for a further hour, After cooling, the precipitate was filtered off and washed with water. The yield was 2.65 g (98%) of colorless crystals, mp 192-194°C (from 1:1 DMF—water). Found, %: C 64.3, H 3.9, Cl 11.8, N 14.3. $C_{16}H_{11}ClN_3O$. Calculated, %: C 64.8; H 3.8; Cl 11.9; N 14.2. The hydrochloride of XX was obtained as colorless crystals, mp 160-162°C (from 2:1 acetone—methanol). Found, %: Cl 20.8. $C_{16}H_{12}Cl_2N_3O$. Calculated, %: Cl 21.3.

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SYNTHESIS OF 16-ALKYL(ARYL)PSEUDOSOLASODINES

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As part of our search for new methods of cleaving solasodine we have studied the oxidation of solasodine diacetate (I) with sodium dichromate in acetic acid. In the reaction the tetrahydrofuran and piperidine rings were opened and 3β-acetoxy-26-acetylamino-5-cholestene-16,22-dione (IIa) was formed as the principal product. A by-product of the reaction was the previously described 3β-acetoxy-5-bisnorcholene-22,16-lactone (III). Similar oxidation in the sapogenin series [1] gives the sapogenoic acids, which also contain the 1,4-dicarbonyl system. The carbonyl groups in sapogenoic acids [2] are known to differ in reactivity. The carbonyl group at position 16 is more reactive, suggesting that several reactions, particularly the Grignard reaction, may be selective.

The Grignard reaction with IIa has been proposed for the introduction of alkyl and aryl substituents into position 16 of the steroid molecule.

Reaction of IIa with methylmagnesium iodide gave after treatment of the reaction product with ethyl alcohol 16-methyl-22-ethoxy-26-acetylamino-5-furosten-3β-ol (IV). Its PMR spectrum showed a singlet signal from the C_{16} methyl group (1.15 ppm) and signals from the ethyl

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TABLE 1. Chemical Shifts of Compounds II, IV-VI (δ, ppm)

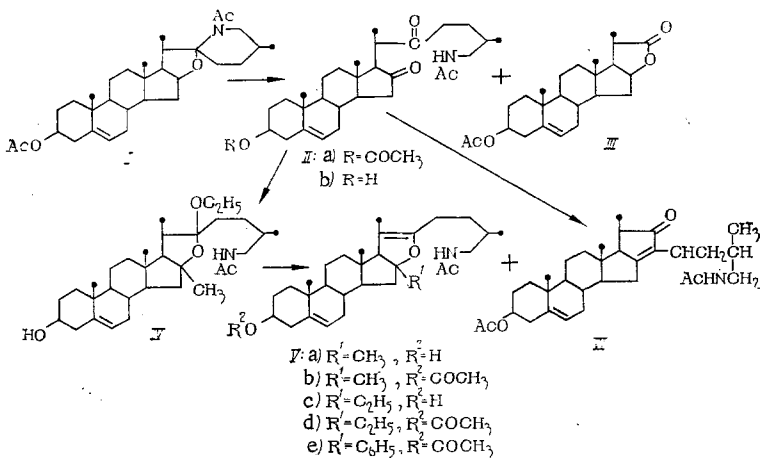
Compound	Angular CH_3 (C_{19}, C_{18})		CH_3 at C_{20}	CH_3 at C_{25}	OAc NHAc	H at C_3	H at C_6	2H at C_{26}	NH	R at C_{16}	Comments
IIa	0,80,	1,02	1,02d	0,88d	1,93 1,96	4,55m	5,33m	3,08m	6,20m	—	
IV	0,85,	1,06	1,43d	0,89d	—	3,65m	5,32m	3,07m		1,15s	With added CD_3OD
Va	0,61,	0,95	1,50s	0,85d	1,90	3,64m	5,25m	3,05m	5,92m	1,15s	
Vb	0,62,	0,98	1,50s	0,89d	1,92	4,53m	5,31m	3,07m	5,99m	1,16s	
Vc	0,63,	0,97	1,51s	0,85d	1,93	3,50m	5,32m	3,07m	5,62m	1,16t	
Vd	0,62,	0,97	1,52s	0,87d	1,91 1,98	4,55m	5,31m	3,07m	5,79m	0,92t	Signal of the ethyl group in deutero-chloroform
Ve	0,76,	1,01	1,50s	0,86d	1,9 1,97	4,53m	5,32m	3,08m	5,79m	7,31m	
VI	0,52,	1,02	1,15d	0,76d	1,96 1,98	4,58m	5,32m	—	6,77m	—	

Note: s) singlet; d) doublet; t) triplet; m) multiplet.

group (1.22 ppm, triplet; 3.65 ppm, quartet) (Table 1). Formation of IV implies that introduction of the methyl group at position 16 is accompanied by cyclization to a hemiketal [2], which on treatment with alcohol would easily give the ketal IV. A similar hemiketal, obtained as a by-product from the cleavage of solasodine to dehydropregnenolone acetate, is easily dehydrated under acidic conditions forming pseudosolasodine O,N-diacetate [3]. On treatment of IV with alcoholic hydrogen chloride an alcohol molecule was eliminated and N-acetyl-16-methylpseudosolasodine (Va) was formed, acetylation of which with acetic anhydride in pyridine yielded 16-methylpseudosolasodine O,N-diacetate (Vb). This could also be prepared without isolating the intermediate hemiketal.

We prepared 16-ethylpseudosolasodine O,N-diacetate (Vd) and 16-phenylpseudosolasodine O,N-diacetate (Ve) by reaction of IIa with ethylmagnesium bromide and with phenylmagnesium bromide followed by dehydration and acetylation.

As a byproduct from the preparation of Ve we isolated [1-keto-2-(β-methyl-γ-acetylaminopropyl)-5-methylcyclopent-2-eno[16,17-c]androst-5-en-3β-ol-3-acetate (VI). Its formation seems to be due to intramolecular aldol condensation of II. We synthesized VI by an independent method by refluxing II in aqueous alcoholic potassium hydroxide [4]. The substances did not show depression of the melting point of a mixed sample and had identical IR and PMR spectra. The PMR spectrum of VI lacked the signal due to the C_{16} proton and contained a signal from the C_{21} methyl group (1.48 ppm, doublet). The IR spectrum contained an absorption band characteristic for conjugation with the carbonyl double bond (1690 cm^{-1}).



Thus, we have synthesized 16-alkyl(aryl)pseudosolasodine O,N-diacetates by the Grignard reaction.

These reactions in the solasodine series as compared to those involving sapogenins differ in that Grignard reaction of sapogenoic acids followed by dehydration under acidic conditions leads to cyclization of the tetrahydropyran ring (ring F) forming 16-alkylsapogenins [2]. Acetylation and isomerization under forcing conditions are necessary to convert the latter into 16-alkylpseudosapogenins.

The known method [5] can be used to convert 16-methylpseudosolasodine O,N-diacetate to 16-dehydro-16-methylpregnane, which is a key intermediate in the synthesis of several steroid preparations containing a methyl or methylene group at position 16 (Betamethasone, Superlutin, and Melengestrol acetate).

EXPERIMENTAL

The IR spectra were recorded with a Perkin-Elmer instrument in vaseline oil and the PMR spectra with a JNM 4H-100 instrument in deuterochloroform with tetramethylsilane as internal standard, if no special conditions are noted. Chemical shifts are referred to the δ scale. Chromatography was carried out on a thin layer of Silufol with 1:1 cyclohexane–acetone, developed with a 1% solution of vanillin in 10% aqueous perchloric acid. Preparative chromatography was carried out on L 40/100 silica gel (Chemapol).

Oxidation of Solasodine O,N-Diacetate (I). A solution of 8 g (0.08 mole) of sodium dichromate in 50 ml of 70% acetic acid was added in one stage to a stirred solution of 20 g (0.04 mole) of I in 150 ml of 70% acetic acid at room temperature. The mixture was heated to 55-60°C and stirred at this temperature for 1.5 h. After addition of 5 g of sodium sulfate, the reaction mixture was heated to remove excess sodium dichromate and, without cooling, poured into ten times the quantity of hot water (70-80°C). After filtration and drying the precipitate was recrystallized from acetone. We obtained 11.8 g (57.5%) of IIa (Table 2). The acetone mother liquor was evaporated to dryness and the residue was chromatographed on a silica-gel column. Benzene eluted 1.8 g (12%) of III, mp 208-210°C [3]. Ethyl acetate–chloroform eluted a further 1 g (5%) of IIa.

3β-Hydroxy-26-acetylamino-5-cholestene-16,22-dione (IIb). A solution of 5 g of IIa in 60 ml of 2% methanolic sodium hydroxide was allowed to stand for 2 h at room temperature. The solution was neutralized with acetic acid and evaporated to dryness; after addition of water to the residue, filtration yielded 4.18 g of IIb.

Ethyl 16-Methyl-26-acetylamino-5-furostene-3,22-diol (IV). A solution of 10 g of IIa in 150 ml of dry benzene was added over a period of 1 h to a solution of methylmagnesium iodide (from 2.4 g of magnesium) in 50 ml of dry ether that had previously been cooled to 0°C; the temperature was maintained at 0-3°C. The reaction mixture was refluxed and stirred thoroughly for 3 h and allowed to stand for 12 h at room temprature. The mixture was poured into a saturated aqueous solution of ammonium chloride. The precipitate was filtered off, washed with water, dried, and triturated with alcohol. We obtained 6.1 g (60%) of IV.

16-Methylpseudosolasodine N-Acetate (Va). After dissolving 4.0 g of IV in 60 ml of warmed ethyl alcohol, 6 ml of concentrated hydrochloric acid was added, and the solution was allowed to stand for 3 h at room temperature. The solution was neutralized with ammonium hydroxide, and after removal of the alcohol under vacuum, the residue was diluted with water and Va was filtered off. We obtained 3.9 g of Va (Table 2).

16-Methylpseudosolasodine O,N-Diacetate. Method 1. A solution of 3.9 g of Va in 10 ml of dry pyridine and 3 ml of acetic anhydride was allowed to stand for 12 h at room temperature. The solution was poured into water; Vb was filtered off, washed with water, and dried. The yield was 3.8 g.

Method 2. Reaction of 10 g of IIa with methylmagnesium iodide under the conditions described above gave after decomposing the reaction product with ammonium chloride solution 10.5 g of precipitate, which was dehydrated with 100 ml of alcohol and 10 ml of concentrated hydrochloric acid and acetylated with acetic anhydride, as in method 1. We obtained 4.8 g (48%) of Vb.

16-Ethylpseudosolasodine O,N-Diacetate (Vd). This compound was prepared following method 2 for Vb. The yield was 50%. Saponification of Vb with 2% methanolic potassium hydroxide gave Vc (Table 2).

TABLE 2. Physicochemical Properties of the Compounds

Compound	Melting point, deg	Solvent for crystallization	R_f	IR spectrum λ, cm^{-1}	Found, %		Bruto-formula	Calc., %	
					C	H		C	H
IIa	178—80	Acetone	0,41	3280, 1730, 1710, 1630	73,24	9,27	$C_{31}H_{47}NO_5$	72,47	9,24
IIb	212—4	"	0,27	3280, 3100, 1730, 1710, 1640	73,70	9,53	$C_{29}H_{45}NO_4$	73,85	9,62
IV	156—8	Ethyl alcohol	—	3280, 1660	74,21	10,30	$C_{32}H_{53}NO_4$	74,51	10,35
Va	176—8	Acetone	0,43	3280, 3100, 1650	76,28	10,16	$C_{30}H_{47}NO_3$	76,71	10,08
Vb	132—4	80% aqueous acetone	0,55	3300, 1740, 1650	74,83	9,69	$C_{32}H_{49}NO_4$	75,10	9,65
Vc	167—70	Acetone	0,46	3320, 3100, 1660	76,29	10,20	$C_{31}H_{49}NO_3$	76,97	10,23
Vd	145—6,5	"	0,55	3280, 1730, 1645	74,85	9,55	$C_{33}H_{51}NO_4$	75,38	89,78
Ve	155—8	"	0,55	3320, 1730, 1650	77,43	8,97	$C_{37}H_{51}NO_4$	77,44	8,95

16-Phenylpseudosolasodine O,N-Diacetate (Ve). The Grignard reaction was carried out under the conditions described above. After decomposing the reaction product and filtering off the precipitate, the benzene layer was evaporated to dryness and the residue was combined with the filtered precipitate. Chromatography on silica gel gave 1.8 g of biphenyl (elution with benzene) and 9.9 g of an oily product (elution with chloroform). The latter was dehydrated and acetylated as described above. Crystallization from acetone gave 1.5 g of IIa; chromatography of the mother liquor on silica gel yielded 2.7 g of Ve and 0.9 g of VI (Table 2).

[1-Keto-2-(β-methyl-γ-acetylaminopropyl)-5-methylcyclopent-2-eno][16,17-c]androst-5-en-3β-ol 3-Acetate (VI). After 1 g of IIa in 170 ml of aqueous methanol had been refluxed with 15 g of potassium hydroxide for 3 h, the solution was neutralized with acetic acid and the methanol was removed by vacuum distillation; VI was then extracted with methylene chloride. Chromatography on silica gel gave 0.5 g of VI.

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