The 3,6,7-Triacetate (III) and 3,6-Diacetate (II) of Cycloorbigenin B from (I). Cycloorbigenin B (I) (25 mg) was acetylated with 2 ml of acetic anhydride in 2 ml of absolute pyridine at room temperature for 48 h. The residue after the solvents had been evaporated off was chromatographed on a column with elution by chloroform. This yielded 6 mg of the triacetate (III), $C_{36}H_{54}O_9$, mp 257-259°C (from chloroform–hexane), $[\alpha]_D^{27}$ +21.5 ± 2° (c 0.38; benzene). ν_{max}^{KBr}, cm^{-1}. 3490 (CH_2 of a cyclopropane ring), 1750, 1720, 1260 (ester groups). Mass spectrum, m/z (%): M^+ 630 (0.8), 615 (5.4), 597 (1.4), 571 (38.4), 555 (30.7), 529 (11.6), 510 (84.6), 495 (19.9), 469 (14.5), 451 (100), 437 (17.2), 435 (19.9), 409 (15.3), 391 (24.4), 370 (11.7), 311 (11.7).

Continued elution of the column with chloroform led to the isolation of 11 mg of the amorphous diacetate (II), $C_{34}H_{52}O_8$, $[\alpha]_D^{30}$ +30 ± 2° (c 0.1; methanol), ν_{max}^{KBr}, cm^{-1}; 3580-3355 (OH), 1740, 1250 (ester groups). Mass spectrum, m/z (%): M^+ 588 (1.0), 573 (2.8), 529 (100), 513 (7.5), 500 (3.3), 499 (3.1), 473 (8.7), 469 (25), 468 (8.7), 453 (8.7), 451 (13.7), 439 (8.7), 409 (12.5), 269 (9.3), 171 (8.7).

Periodate Oxidation of Cycloorbigenin B. To 5 mg of genin (I) in 2 ml of methanol was added 20 mg of sodium periodate in 3 ml of water, and the mixture was left at room temperature for 30 min. Thin-layer chromatography of the reaction mixture in the chloroform–methanol (15:1) system in comparison with a sample of the initial substance showed that the genin (I) had been oxidized completely.

SUMMARY

A new cycloartane methylsteroid – cycloorbigenin B, which has the structure of (23R,24S)-16β,23; 16α,24-diepoxycycloartane-3β,6α,7β, 25-tetraol – has been isolated from the epigeal part of Astragalus orbiculatus Ledeb. (Leguminosae).

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GLYCOSYLATION OF TRITERPENOIDS OF THE DAMMARANE SERIES. X. REGIO- AND STEREOSELECTIVE SYNTHESIS OF 20(S)-PROTOPANAXADIOL 3-O-β-D-GLUCOPYRANOSIDE (GINSENOSIDE Rh_2)

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UDC 547.917+547.918+547.597

The regio- and stereoselective synthesis of ginsenoside Rh_2, which possesses antitumoral activity, has been effected by the glycosylation of 12β-acetoxydammar-24-ene-3β,20(S)-diol. Condensation with α-acetobromoglucose was carried out in the presence of silver oxide in dichloroethane at room temperature, and the yield of the desired glycoside amounted to 50%. A method for the selective protection of the C-12-OH group of dammar-24-ene-3β,12β,20(S)-triol [20(S)-protopanaxadiol] has been proposed.

20(S)-Protopanaxadiol 3-O-β-D-glucopyranoside (ginsenoside Rh_2) (1), which possesses antitumoral activity [1, 2] has been obtained by Japanese workers as the result of the partial hydrolysis of ginseng glycosides (ginsenosides Rb_1, Rb_2, Rb_3, Rc, and Rd [3], the aglycon of which is 20(S)-protopanaxasiol [dammar-24-ene-3β,12β,20(S)-triol or 3-epibetulafolienetriol] (2). We have sinthesized this compound together with four other glycosides by the condensation of the triol (2) with α-acetobromoglucose [4]. However, the absence of regio-

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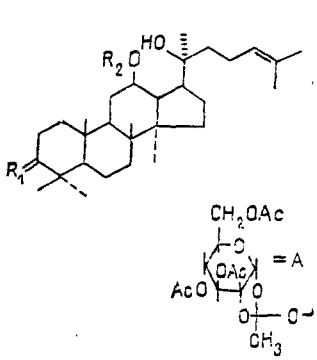
selectivity in the glycosylation of the triol (2) and the consequent difficulty of separating the mixture of glycosides with similar chromatographic mobilities restrict the use of this method for the preparative production of the monoglucoside (1).

The usual expedient employed for the regioselective glycosylation of compounds containing several hydroxy groups differing little in reactivity is the selective protection of the groups not participating in the reaction. Since it had been established previously that the tertiary C-20—OH group in the diacetate (3) is not glycosylated under these conditions [4], it was sufficient to protect the OH group at C-12. However, the direct acetylation of the triol (2) and partial deacetylation of the diacetate (3) led to one and the same compound — the monoacetate at C-3 (4). The 12-O-acetyl derivative (5) was obtained in the following way. Betulafolienetriol (6), isolated from birch leaves, was oxidized to the monoketone (7), which was acetylated under the usual conditions. The acetate of the ketone derivative (8) was then reduced with sodium tetrahydroborate in isopropanol to 12β-acetoxy-dammar-24-ene-3β,20(S)-diol(5).



1. R_1=—OGlc; R_2=H
2. R_1=—OH; R_2=H
3. R_1=—OAc; R_2=Ac
4. R_1=—OAc; R_2=H
5. R_1=—OH; R_2=Ac
6. R_1=—H; R_2=H
7. R_1=O; R_2=H
8. R_1=O; R_2=Ac
9. R_1=—OGlc(Ac)$_4$; R_2=Ac
10. R_1=—A; R_2=Ac

Condensation of the resulting 12-O-monoacetate (5) with α-acetobromoglucose was carried out in dichloroethane in the presence of silver oxide at room temperature and led to the formation of the desired glucoside (9) (50%) and the orthoester (10) (8%) (experiment 1), the structures of which were established on the basis of their IR and PMR spectra and elementary analyses. In addition, the presence of the orthoester grouping in compound (10) was confirmed by the ease of its acid hydrolysis. The formation of the orthoester (10) somewhat complicated the isolation of the desired glucoside (9), and for simplicity of isolation the orthoester (10) formed can be subjected to hydrolysis under mild conditions.

As is known, orthoesters are the most labile of sugar derivatives with respect to acids, and therefore the treatment of the reaction mixture with water containing a small amount of a weak acid led, without affecting the glycosidic bond, to the complete hydrolysis of the orthoester (10) to the initial 12-O-monoacetate (5), which was separated from the desired glycoside (9) fairly easily with the aid of column chromatography (experiment 2). The deacetylation of the glycoside pentaacetate (9) by sodium methanolate in methanol followed by crystallization from aqueous methanol gave a 90% yield of crystalline dammar-24-ene-3β,12β,-20(S)-triol 3-O-β-D-glucopyranoside (ginsenoside Rh_2) (1).

EXPERIMENTAL

IR spectra were recorded on a Specord 75 IR spectrophotometer in chloroform solution, and ^{1}H NMR spectra were measured on a Bruker WM-250 spectrometer with a working frequency of 250 MHz at 30°C in deuterochloroform. Chemical shifts are expressed in the δ scale relative to TMS. The accuracy of measurement was ±0.15 Hz. Optical rotations were measured on a Perkin—Elmer 141 polarimeter in a cell 10 cm long at 20°C, and the melting points of the substance were determined on a Boëtius stage.

Column chromatography was conducted on KSK silica gel (150 mesh) in the hexane—acetone (15:1 → 5:1) system. The individuality of the substances was checked with the aid of TLC in a fixed layer of silica gel in the hexane—acetone (3:2), benzene—chloroform—methanol (6:4:1) and benzene—ethanol (10:1) systems. Detection was carried out with 10% H_2SO_4 in ethanol and heating at 100-200°C. The elementary analyses of all the newly obtained compounds agreed with the calculated figures.

Betulafolienetriol [dammar-24-ene-3α,12β,20(S)-triol] (6) was isolated from an ethereal extract of Betula pendula leaves followed by chromatography on silica gel and crystallization from acetone; mp 195-196°C. According to the literature [5]: mp 197-198°C.

12β,20(S)-Dammar-24-en-3-one (7) was obtained by the oxidation of the triol (6) with chromium trioxide in pyridine, mp 196-198°C (acetone). According to the literature [6], mp 196-199°C (acetone).

12β-Acetoxy-20(S)-hydroxydammar-24-en-3-one (8) was obtained by the acetylation of the ketone (7) with acetic anhydride in pyridine at room temperature: amorphous, IR spectrum (ν, cm^{-1}): 1600, 1720, 3535. ^1H NMR spectrum (δ, ppm): 0.94 (s, 3H), 0.96 (s, 3H), 1.04 (s, 6H), 1.09 (s, 3H), 1.14 (s, 3H), 1.72 (s, 3H), 2.06 (s, 3H, OAc), 3.04 (s, 1H, OH), 4.73 (td, 1H, H_a-12), 5.17 (t, 1H, ^3J = 6.3 Hz, H-24).

12β-Acetoxydammar-24-en-3 β20(S)-diol (5) was obtained by the reduction of the acetylated ketone (8) with sodium tetrahydroborate in isopropanol with ice-bath cooling; yield 87%; amorphous, $[\alpha]_D^{20}$ −6.9° (c 1.07; chloroform). IR spectrum (ν, cm^{-1}): 1598, 1720, 3535. ^1H NMR spectrum (δ, ppm): 0.78 (s, 3H), 0.86 (s, 3H), 0.96 (s, 3H); 0.98 (s, 3H), 1.02 (s, 3H), 1.13 (s, 3H), 1.64 (s, 3H), 1.71 (s, 3H), 2.05 (s, 3H, OAc), 3.20 (dd, 1H, $^3J_1$ = 4.9 Hz, $^3J_2$ = 10.8 Hz, H_a-3), 4.73 (td, 1H, $^3J_1$ = $^3J_2$ = 10.0 Hz, $^3J_3$ = 5 Hz, H_a-12), 5.16 (t, 1H, ^3J = 6.3 Hz, H-24).

Condensation of 12β-Acetoxydammar-24-ene-3β,20(S)-diol (5) with α-acetoxybromoglucose. Experiment 1. A mixture of 1.08 g (2 mmole) of the acetate (5), 2.47 g (6 mmole) of α-acetobromoglucose, and 1.4 g (6 mmole) of silver oxide in 20 ml of absolute dichloroethane was stirred at room temperature for 6 h. Then it was diluted with chloroform and filtered from insoluble silver compounds The solvent was distilled off and the dry residue was chromatographed on a column of silica gel in the hexane–acetone (15:1 → 5:1) system. After chromatography, chromatographically homogeneous substances were isolated: 133 mg (12%) of (5), 124 mg (8%) of (10), and 853 mg (47.7%) of (9).

3β-(2',3',4',6'-Tetra-O-acetyl-β-D-glucopyranosyloxy)-12β-acetoxydammar-24-en-20(S)-ol (9). mp 223-225°C (ethanol), IR spectrum (ν, cm^{-1}): 1598, 1720, 1750, 3535. ^1H NMR spectrum (δ, ppm): 0.74 (s, 3H), 0.85 (s, 3H), 0.90 (s, 3H), 0.94 (s, 3H), 1.00 (s, 3H), 1.13 (s, 3H), 1.65 (s, 3H), 1.71 (s, 3H), 2.00-2.09 (s, 15H, 5 × OAc), 3.08 (dd, 1H, $^3J_1$ = 4.9 Hz, $^3J_2$ = 10.8 Hz, H_a-3), 3.69 (m, 1H, H-5'), 4.12-4.24 (m, 2H, 2H-6'), 4.54 (d, 1H, $J_{1',2'}$ = 7.5 Hz, H-1'), 4.73 td, 1H, $^3J_1$ = $^3J_2$ = 10.0 Hz, $^3J_3$ = 5.0 Hz, H_a-12), 5.04 (m, 2H, H-2', H-4'), 5.16 (t, 1H, ^3J = 6.5 Hz, H-24), 5.20 (t, 1H, ^3J = 9.5 Hz, H-3').

3β-[3',4',6']-Tri-O-acetyl-1',2'-O-(1-hydroxyethylidene)-α-D-glucopyranosyloxy]-12β-acetoxydammar-24-en-20(S)-ol (10), amorphous. IR spectrum (ν, cm^{-1}): 1600, 1720, 1751, 3535. ^1H NMR spectrum (δ, ppm): 0.78 (s, 3H), 0.85 (s, 3H), 0.95 (s, 3H), 0.98 (s, 3H), 1.00 (s, 3H), 1.13 (s, 3H), 1.64 (s, 3H), 1.71 (s, 3H), 1.73 (s, 3H, CH_3 of an ethylidene group), 2.00-2.11 (s, 12H, 4 × OAc), 3.08 (m, 1H, H_a-3), 4.73 (td, 1H, $^3J_1$ = $^3J_2$ = 10.0 Hz, $^3J_3$ = 5.0 Hz, H_a-12), 4.03-4.32 (m, 4H, H-5', 2H-6', H-2'), 4.89 (m, 1H, H-4'), 5.18 (m, 2H, H-24, H-3'), 5.69 (d, 1H, $J_{1',2'}$ = 5.0 Hz, H-1').

Experiment 2. A mixture of 8.46 g (16.8 mmole) of compound (5), 20.84 g (51 mmole) of α-acetobromoglucose, 13.9 g (51 mmole) of silver oxide, and 2 g of 4 Å molecular sieves in 100 ml of absolute dichloroethane was stirred at room temperature (22°C) for 3 h. The reaction mixture was diluted with chloroform and was filtered from insoluble silver compounds. The solvent was distilled off. The residue was treated with water, acidified with acetic acid (a few drops), and then with water and was dried. The dry residue was chromatographed on a column of silica gel. In the hexane–acetone (8:1) system the chromatographically pure monoacetate (5) in an amount of 3.225 g (38.1%) and then, in the hexane–acetone (5:1) system, the desired glucoside (9) in an amount of 7.04 g (50%) were obtained.

The acetylated glycoside (6.15 g) was saponified with a 1 N solution of sodium methanolate (1.7 ml) in absolute methanol (30 ml). This gave 4.7 g of chromatographically homogeneous compound (1), which, on crystallization from aqueous methanol, yielded 4.23 g of the crystalline ginsenoside Rh_2 (1). mp 220-225°C. According to the literature [3]: mp 218-220°C.

SUMMARY

1. The regio- and stereoselective synthesis of dammar-24-en-3β,12β,20(S)-triol 3-O-β--D-glucopyranoside (ginsenoside Rh_2) has been effected.

2. A method is proposed for the selective protection of the C-12-OH group of dammar-24-en-3β,12β,20(S)-triol.

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AROMATIC AMINO-CLAISEN REARRANGEMENT IN THE SYNTHESIS OF ELLIPTICINE

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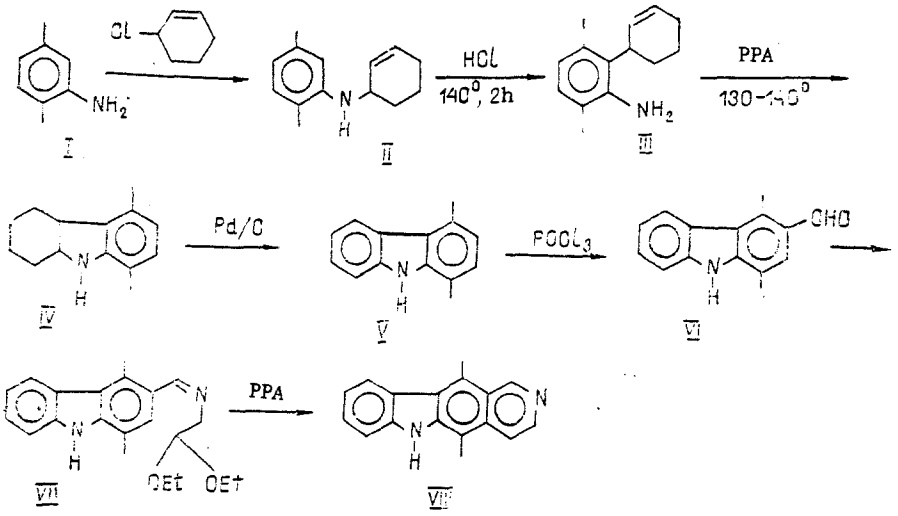
A convenient route is described for the preparation of 1,4-dimethylcarbazole — the key compound in the synthesis of the antitumoral alkaloid ellipticine. The interaction of 2,5-xylidine with 3-chlorocyclohexene led to N-(cyclohex-2-enyl)-2,5-xylidine (I), the two-hour heating of which at 140-150°C gave the product of an amino-Claisen rearrangement, 6-(cyclohex-2-enyl)-2,5-xylidine (II) with a yield of 82%. The intramolecular cyclization of compound (II) in polyphosphoric acid (130-140°C, 5 h) led to 5,6,7,8,12,13-hexahydro-1,4-dimethylcarbazole (III) in a yield of 75%. The dehydrogenation of substance (III) by boiling in trimethylbenzene in the presence of Pd/C gave 1,4-dimethylcarbazole (IV) with a yield of 87%. The conditions for performing the reactions and the physicochemical constants of the compounds obtained are given.

The alkaloid ellipticine from the leaves of the plant Ochrosia elliptica, family Apocynaceae, and also some of its synthetic analogues possess a high antitumoral activity [1, 2]. The synthesis of these substances has attracted the attention of many chemists in the last few years [2-5].



In this paper we describe a convenient method for obtaining 1,4-dimethylcarbazole — the key compound in the synthesis of ellipticine (scheme). When 3-chlorocyclohexene was heated with a fourfold excess of 2,5-xylidine (I), N-(cyclohex-2-enyl)-2,5-xylidine (II) was formed, and this was then subjected to aromatic amino-Claisen rearrangement with the formation of 6-(cyclohex-2-enyl)-2,5-xylidine (III), the yield of which amounted to 82% [6].

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