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CYCLIZATION REACTIONS OF NITRILES.

28.* SYNTHESIS AND REACTIONS OF 3β-ACETOXY-2'-METHYL-5'-CYANOANDROST-5-ENO[17,16-c]PYRIDINE-6'(1'H)-THIONE

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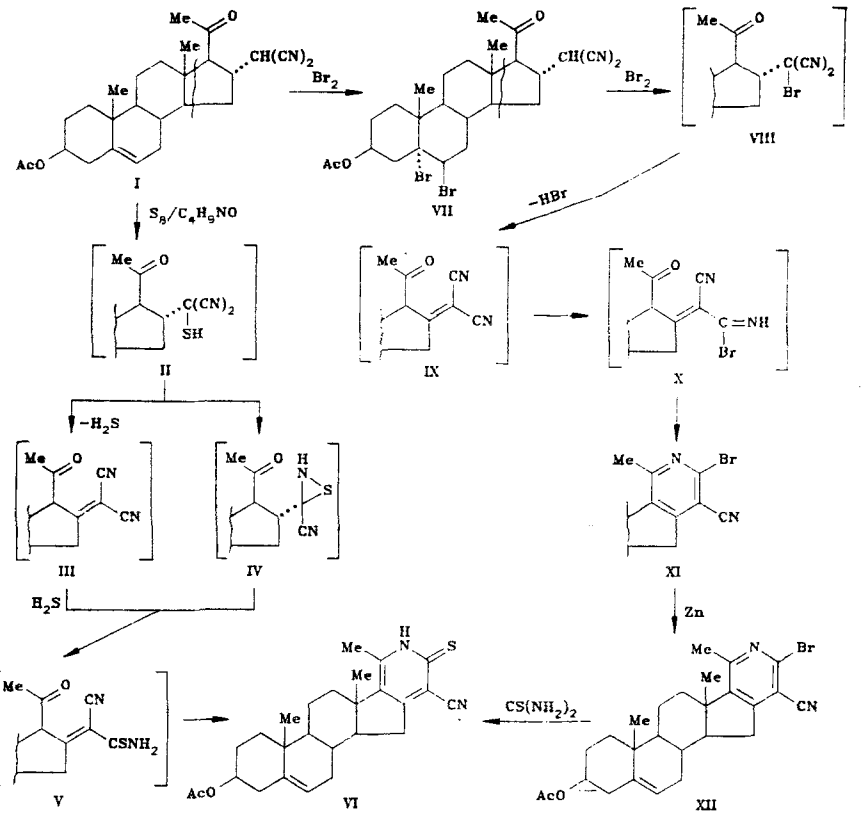
3β-Acetoxy-2'-methyl-5'-cyanoandrost-5-eno[17,16-c]pyridine-6'(1'H)-thione was obtained by thiylation of 16α-dicyanomethyl-3β-hydroxypregn-5-en-20-one acetate, and its alkylation by chloroacetonitrile and phenacyl bromide was studied. The same thione was also synthesized by treating the corresponding 6'-bromo-2'-methyl-5'-cyanoandrost-5-eno[17,16-c]pyridine with urea.

Derivatives of 1,5-ketonitriles are readily thiylated and brominated to the corresponding pyridine-2(1H)-thiones and 2-bromopyridines, which are used in the synthesis of various heterocyclic compounds [2, 3]. It was interesting to study the behavior of 16α-dicyanomethyl-3β-hydroxypregn-5-en-20-one acetate (I) [1] in these reactions.



*Communication 27, see [1].

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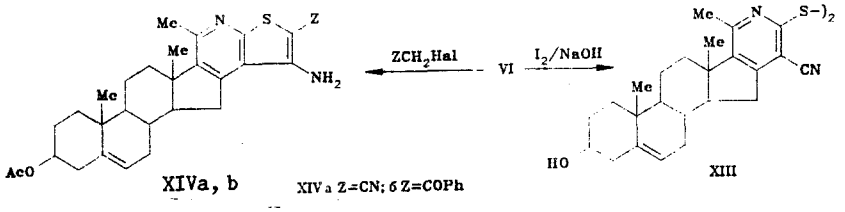
We found that adduct I reacts with powdered sulfur in an alcoholic medium in the presence of morpholine to form 3β-acetoxy-2'-methyl-5'-cyanoandrost-5-eno[17,16-c]pyridine-6'-(1'H)-thione (VI) in a high yield. It is possible that at the first stage, sulfur becomes implanted at the methine group of the adduct I with the formation of intermediate II. This is followed by elimination of hydrogen sulfide from this intermediate and its addition at one of the nitrile groups of the ylidene derivative III. An alternative path presumes the formation of iminothiirane IV. The two paths lead to ylidenecyanothioacetamide V, which cyclizes into androstenopyridine-6'(1'H)-thione VI.

In the reaction of dicyanomethylpregnenone acetate I with bromine, 3β-acetoxy-5α,6β-dibromo-16α-dicyanomethylpregnan-20-one (VII) was obtained. Further bromination of compound VII leads to 3β-acetoxy-6',5α,6β-tribromo-2'-methyl-5'-cyanoandrostano[17,16-c]pyridine (XI) (we did not determine the configuration of the bromine atoms, but this is indicated by the generally accepted data on the bromination of 5-unsaturated steroids [4, p. 174]). In analogy with the thiylation of compound I, it can be assumed that the reaction starts from an attack of the methine group of dibromide VII by bromine. Then this is dehydrobrominated to the ylidene derivative IX. Subsequent addition of hydrogen bromide to the nitrile group of intermediate IX leads to 1,5-ketobromoimine X, which can cyclize into tribromide XI. Compounds VIII-X are hypothetic.

The trans-diaxial configuration of the 5α,6β-bromides of type XI is most favorable for ready elimination of bromine [5]. In fact, treatment of the tribromo derivative XI by zinc dust leads to 6'-bromoandrost-5-eno[17,16-c]pyridine XII, and in its reaction with thiourea, androst-5-eno[17,16-c]pyridine-6'(1'H)-thione VI was isolated.

Oxidation of thione VI gives disulfide XIII. The reaction is accompanied by the hydrolysis of the ester group.



XIVa, b XIV a Z=CN; 6 Z=COPh XIII

Like other 3-cyano-2(1H)-pyridinethiones [6, p. 35], thione VI is alkylated by chloroacetonitrile and phenacyl bromide to 2'-substituted 3'-amino-3β-acetoxy-6'-methylandrost-5-eno[16,17-d]thieno[2,3-b]pyridine (XIVa, b). In accordance with the data in [6, p. 35], the reaction proceeds via the corresponding S-alkylation products.

EXPERIMENTAL

The UV spectra were run on a Specord UV-vis spectrophotometer in ethanol solutions. The IR spectra were recorded on a UR-20 spectrophotometer, in KBr tablets. The PMR spectra were recorded on a Bruker WM-250 spectrometer (250 MHz) in DMSO-D_6 solution. The course of the reactions and the individual state of the new compounds were controlled by TLC on Silufol UV-254 plates in a 5:3 acetone–hexane system. The mixtures were partitioned by column chromatography using silica gel L100/400 μ as the solid phase and a 3:5 acetone–hexane mixture as eluent.

3β-Acetoxy-2'-methyl-5'-cyanoandrost-5-eno[17,16-c]pyridine-6'(1'H)-thione (VI). A. A mixture of 1.25 g (3 mmoles) of adduct I, 0.3 g (9.4 mmoles) of finely divided sulfur, 1 ml of morpholine in 20 ml of ethanol is boiled for 12 h and then filtered hot. When the filtrate is cool, 15% hydrochloric acid is added to pH 7. The precipitate is filtered, purified chromatographically on a column and recrystallized from methanol. Yield 1.1 g (84%) of thione VI in the form of yellow crystals, mp 277...279°C (dec.). R_f 0.33. UV spectrum, λ_{max} (log ε): 236 (3.97), 311 (4.28), 391 nm (3.51). IR spectrum: 1731 (C=O) 2230 cm^{-1} (CN). PMR spectrum: 13.40 (1H, s, NH), 5.39 (1H, m, =CH), 4.47 (1H, m, CHO), 0.93 (3H, s, $C_{(18)}H_3$), 1.04 (3H, s, $C_{(19)}H_3$), 1.99 (3H, s, CH_3CO), 2.29 ppm (3H, s, 2'-CH_3). Found, %: C 71.3; H 7.2; N 6.4; S 7.1. $C_{26}H_{32}N_2O_2S$. Calculated, %: C 71.5; H 7.4; N 6.4; S 7.3.

B. A 0.34 g portion (4.5 mmoles) of thiourea is added to a solution of 0.73 g (1.5 mmole) of bromopyridine XII in 20 ml of ethanol, and the mixture is boiled for 5 h. A 0.84 ml portion (1.5 mmole) of 10% KOH solution is added to the cooled solution, and the mixture is heated to boiling. The reaction mixture is cooled and 15% hydrochloric acid is added

dropwise to pH 7. The yellow precipitate of compound VI is filtered and purified as described above. Yield, 0.3 g (46%), mp 278...279°C (dec.).

The compound is identical with the above sample.

3β-Acetoxy-5α,6β-dibromo-16α-dicyanomethylpregnan-20-one (VII). A solution of 0.13 ml (2.5 mmoles) of bromine in 5 ml of acetic acid is added dropwise at 25°C, with vigorous stirring, to a solution of 1.05 g (2.5 mmoles) of adduct I in 20 ml of glacial acetic acid at such a rate that the bromine is uniformly decolorated. The white precipitate that separates at the end of the addition of bromine is filtered after 30 min, washed with alcohol, and crystallized from 2-propanol. Yield, 0.4 g (28%), mp 181-182° R_f 0.60. IR spectrum: 1701 (CO), 1735 (O–C=O), 2260 cm^{-1} (weak CN). PMR spectrum: 5.32 (1H, m, 6-H), 5.03 (1H, m, 3-H), 1.36 (3H, s, $C_{(18)}H_3$), 1.44 (3H, s, $C_{(19)}H_3$), 2.02 (3H, s, CH_3OH), 2.47 ppm (3H, s, $(C_{(21)}H_3$). Found, %: C 53.4; H 5.6; Br 27.1; N 4.8. $C_{26}H_{34}Br_2N_2O_3$. Calculated, %: C 53.6; H 5.9; Br 27.4; N 4.8.

3β-Acetoxy-6',5α,6β-tribromo-2'-methyl-5'-cyanoandrostano[17,16-c]pyridine (XI). A solution of 0.08 ml (1.5 mmole) of bromine in 5 ml of acetic acid is added dropwise at 100°C, with vigorous stirring, to a solution of 0.87 g (1.5 mmole) of pregnanone VII in 20 ml of glacial acetic acid at such a rate that the bromine is uniformly decolorated. At the end of the evolution of hydrogen bromide, the reaction mixture is poured onto 5 g of ice. The yellow precipitate is filtered, washed with alcohol and recrystallized from ethanol. Yield 0.3 g (93%), mp 168...169°C. R_f 0.57. IR spectrum: 2220 (weak CN); 1732 cm^{-1} (C=O). Found, %: Br 36.8. $C_{26}H_{31}Br_3N_2O_2$. Calculated, %: Br 37.3%. Bromohydrin XI is unstable, it rapidly resinifies on storage, but its isolation for preparative purposes is not obligatory.

3β-Acetoxy-6'-bromo-2'-methyl-5'-cyanoandrost-5-eno[17,16-c]pyridine (XII). Zinc dust (0.12 g, 1.7 mmole) is added in portions with vigorous stirring, to a suspension of 0.65 g (1 mmole) of compound XI in 30 ml of ether and 0.06 ml of acetic acid. The mixture is stirred for 24 h at 25°C, and then left to stand for 24 h in a refrigerator. The precipitate is filtered, washed with 50% ethanol, and purified by column chromatography. After evaporation of the solvent, the residue is recrystallized from ethanol. Yield, 0.4 g (83%), mp 152...153°C. R_f 0.34. IR spectrum: 2220 (CN), 1732 cm^{-1} (C=O). PMR spectrum: 5.44 (1H, m, 6-H), 5.03 (1H, m, 3-H), 1.02 (3H, s, $C_{(18)}H_3$), 1.14 (3H, s, $C_{(19)}H_3$), 2.01 (3H, s, CH_3CO), 2.50 ppm (3H, s, 2'-CH_3). Found, %: C 64.5; H 6.6; Br 16.2; N 5.9. $C_{26}H_{31}BrN_2O_2$. Calculated, %: C 64.6; H 6.5; Br 16.5; N 5.8%.

(6'-Methyl-3β-hydroxy-3'-cyanoandrost-5-eno[17,16-c]pyridin-2-yl) Disulfide (XIII). A 10% solution of iodine in ethanol is added dropwise to a mixture of 0.44 g (1 mmole) of thione VI and 0.4 ml (1 mmole) of a 10% solution of NaOH in 20 ml of ethanol, until decoloration of iodine ceases. The reaction mixture is left to stand for 24 h, the precipitate is filtered, and recrystallized from ethanol. Yield, 0.3 g (77%) of disulfide XIII, mp 219...220°C. R_f 0.39, which is identical with that already described in [1].

3'-Amino-3β-acetoxy-6'-methyl-2'-cyanoandrost-5-eno[16,17-d]thieno[2,3-b]pyridine (XIVa). A 0.56 ml portion (1 mmole) of a 10% solution of KOH in water is added to 0.44 g (1 mmole) of thione VI in 4 ml of DMFA. Then 0.76 ml (1 mmole) of chloroacetonitrile is added rapidly, with stirring, in one portion, followed by another portion of 0.56 ml (1 mmole) of the alkali solution. After 5 min the mixture is diluted with 1.5 ml of water and the precipitate that separates is filtered, washed with alcohol, and recrystallized from acetic acid. Yield 0.3 g (69%), mp 297...298°C. R_f 0.37. IR spectrum: 3250, 3330, 3420, 1630 (NH_2), 1725 cm^{-1} (C=O), PMR spectrum: 6.58 (2H, s, NH_2), 5.32 (1H, s, =CH), 4.60 (1H, m, 3-H), 0.96 (3H, s, $C_{(18)}H_3$), 1.03 (3H, s, $C_{(19)}H_3$), 2.09 (3H, s, CH_3CO), 2.54 ppm (3H, s, 6'-CH_3). Found, %: C 70.3; H 7.1; N 8.7; S 6.4. $C_{28}H_{33}H_3O_2S$. Calculated, %: C 70.7; H 7.0; N 8.8; S 6.7.

3'-Amino-3β-acetoxy-2'-benzoyl-6'-methylandrost-5-eno[16,17-d]thieno[2,3-b]pyridine (XIVb) was obtained in a similar way as compound XIVa, starting from 0.44 g (1 mmole) of thione VI and 0.2 g (1 mmole) of phenacyl bromine. Yield, 0.39 g (70%), mp 269...270°C (dec.). R_f 0.54. UV spectrum, λ_{max} (log ε): 226 (4.10), 280 (3.99), 300 (4.00), 315 (4.04), 323 (4.02), 411 nm (3.86). IR spectrum: 3293, 3446, 1605 (NH_2), 1730 cm^{-1} (C=O). PMR spectrum: 7.4-7.8 (7H, m, NH_2 and C_6H_5); 5.33 (1H, m, =CH); 4.55 (1H, m, 3-H); 1.00 (3H, s, $C_{(18)}H_3$); 1.06 (3H, s $C_{(19)}H_3$); 2.07 (3H, s, CH_3CO); 2.56 ppm (3H, s, 6'-CH_3). Found, %: C 73.6; H 6.8; N 5.4; S 5.6. $C_{34}H_{38}N_2O_3S$. Calculated, %: C 73.6; H 6.9; N 5.1; S 5.8.

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SYNTHESIS OF ENANTIOMERS OF 3',4'-seco-2'-DESOXYTHYMIDINE

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455.6.07:541.63

The glycosylation of 1,3,4-tri-O-benzoyl-2-desoxy-β-D-ribopyranose by bis-trimethylsilylthymine in the presence of $SnCl_4$ and $F_3CSO_2OSiMe_3$ was studied. It was shown that the stereo-selectivity and directivity of the reaction are dependent on the choice of catalyst. The 1-(2-desoxy-β- and α-D-ribopyranosyl)-thymines obtained were converted into 3',4'-seco-2'-desoxythymidines.

In a continuation of our investigations on the synthesis of chiral acyclic analogs of nucleosides [1, 2], we synthesized 3',4'-seco-2'-desoxythymidine (preliminary communication, see [3]), a representative of a new class of analogs of 2'-desoxynucleosides without the $C_{(3')}$—$C_{(4')}$ bond.

As starting compound, we chose 1,3,5-tri-O-benzoyl-2-desoxy-β-D-ribopyranose (I), which is readily obtained from 2-desoxy-D-ribose [4]. We studied the condensation of pyranose I with bistrimethylsilylthymine in dichloroethane in the presence of $SnCl_4$ and $F_3CSO_2OSiMe_3$, two of the most frequently used catalysts in nucleoside synthesis [5]. When the reaction is carried out in the presence of $SnCl_4$, a complex mixture of products is formed. By using chromatography and crystallization, two main products IIa and IIIa were isolated and characterized. They are obtained in yields of 36% and 17%, respectively. The complex character of the occurrence of this reaction is probably explained by splitting of benzoic acid to form a glycal, followed by glycosylation. The formation of unsaturated nucleosides of type III has already been observed in the condensation of glycals [6, 7] and 1,3,4,6-tetra-O-acetyl-2-desoxy-D-glucopyranose [8] with trimethylsilyl derivatives of heterocyclic bases in the presence of Friedel—Crafts catalysts. (See scheme on page 780.)

The glycosylation of pyranose I in the presence of $F_3CSO_2OSiMe_3$ led to β- and α-anomers IIa and IVa in a ratio of 1:2.5, in an overall yield of 88%.

It should be noted that the use of the two above glycosylation reaction catalysts leads to different products: In the case of $F_3CSO_2OSiMe_3$, the α-anomer IVa is preferentially formed, while when $SnCl_4$ is used the main product is the β-anomer IIa.

Debenzoylation of compounds IIa-IVa led to high yields of nucleosides IIb-IVb, and subsequent acetylation gave derivatives IIc-IVc.

In the PMR spectra of the unsaturated compounds IIIa-c, a SSCC $J_{2',3'}$ 10.0-10.8 Hz is observed and a long-range SSCC, characteristic of 2-enopyranosides [6, 7]. The negative Cotton effect (CE) in the circular dichroism (CD) spectrum of nucleoside IIIb serves as a proof of the β-anomeric configuration [6, 7].

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