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SYNTHESIS OF 3β-FLUORO DERIVATIVES OF 7-DEHYDROCHOLESTEROL AND OF ERGOSTEROL

R. I. Yakhimovich, N. F. Fursaeva, and V. E. Pashinnik

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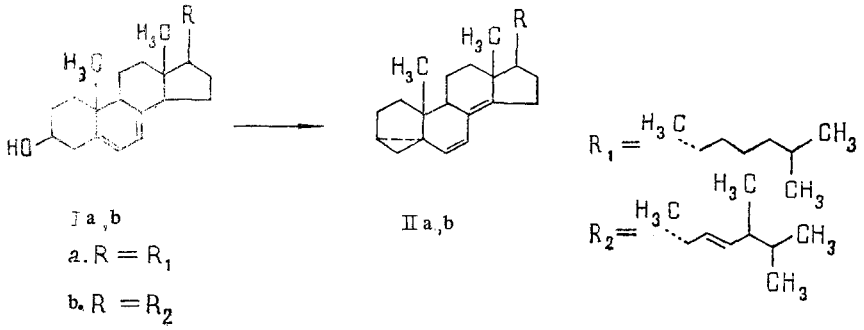
It has been established that the fluorination of 3β-hydroxy-$\Delta^{5,7}$-steroids, unlike that of 3β-hydroxy-Δ^{5}-steroids, does not lead to the formation of 3β-fluoro derivatives. The reaction products are 3α,5α-cyclo-$\Delta^{6,8(14)}$ compounds. Consequently, to obtain the 3β-fluoro derivatives of provitamins D — 7-dehydrocholesterol and ergosterol — the 5,7-diene system was first protected by the formation of a cycloadduct with 4-phenyl-1,2,4-triazoline-3,5-dione after which the adduct was fluorinated with morpholinosulfur trifluoride to the 3β-fluoro adduct, and then the 5,7-double bonds were regenerated by treating the adduct with a solution of sodium methanolate in methanol.

We have previously reported the synthesis of 3β-fluoro derivatives of vitamins D [1-3]. The main difficulty in their preparation is connected with the synthesis of the corresponding provitamins, since the direct fluorination of the vitamins and provitamins D does not form the 3β-fluoro derivatives. While the 3β-hydroxy group of cholesterol and of β-sitosterol is readily replaced by fluorine, in the fluorination of 7-dehydrocholesterol (Ia) and of ergosterol (Ib) with 2-choloro-1,1,2-trifluoroethylamine [4] or with morpholinosulfur trifluoride [5] the unsaturated hydrocarbon (II) were obtained with yields of about 90%. According to the results of elementary analysis, they had the empirical formulas $C_{27}H_{44}$ (for IIa) and $C_{28}H_{42}$ (for IIb), which was also confirmed by their mass spectra (presence of the molecular ions with m/z 366 and 378 and of fragment with m/z 253 [M^+ − 113 or 125 (side chain)].



Ia,b

a. R = R_1

b. R = R_2

IIa,b

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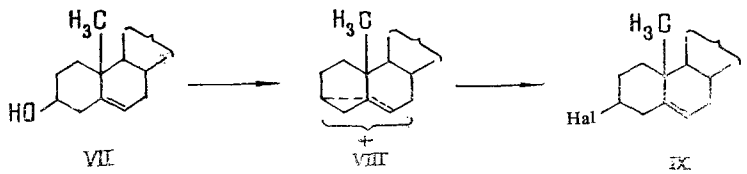
On this basis it could be assumed that in attempts to fluorinate provitamins such as (Ia) dehydration (or dehydrofluorination) takes place with the formation of some one of the trienes (III-VI). However, we immediately excluded the structures of cholesta-2,4,6-triene (III), cholesta-3,5,7-triene (IV), and cholesta-2,5,7-triene (V), since the UV spectra of the products (IIa) and (IIb) isolated showed an absorption maximum at 260 nm, while λ_{max} 306, 315, and the triplet λ_{max} 271, 282, and 293 nm, respectively, are characteristic for the UV spectra of compounds (III), (IV), and (V) [6]. The structure of cholesta-2,6,8(14)-triene (VI) having one isolated double bond and a heteroannular diene system appeared more probable. This structure was also rejected, since it did not correspond to the ^{1}H NMR spectrum of the hydrocarbon (IIa) contained only two one-proton doublets with centers at 6.17 ppm (J = 10 Hz), and 5.21 ppm (J = 10 Hz), showing the presence of only one disubstituted double bond. Moreover, the given values of the chemical shifts unambiguously show that there is another completely substituted double bond conjugated with it. Only $\Delta^{6,8(9)}$- and $\Delta^{6,8(14)}$-diene systems correspond to this condition.

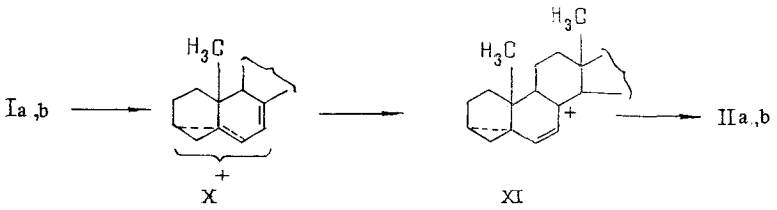
Furthermore, in the ^{1}H NMR spectrum of the hydrocarbon (IIa) there is a distinct quartet (center at 0.48 ppm, 1 H, J = 3 and 8 Hz), which is characteristic for the H atom of a cyclopropane molecular fragment. All this permitted the hydrocarbon obtained to be ascribed the structure of 3α,5α-cyclocholesta-6,8(14)-diene (IIa). We rejected the structure of 3α,5α-cyclocholesta-6,8(9)-diene on the basis that λ_{max} of about 275 nm is characteristic for the homoannular $\Delta^{6,8(9)}$-diene system, and this did not correspond to our results. A similar situation was found in the case of the fluorination of ergosterol (giving compound (IIb)).

Thus, the fluorination of 3β-hydroxy-$\Delta^{5,7}$-steroids takes place by a more complex mechanism than that of 3β-hydroxy-Δ^5-steroids. It is known [7, 8] that in the halogenation of 3β-hydroxy-Δ^5-steroids (VII) an intermediate cation (VIII) is formed which, on nucleophilic attack by Hal^- gives the 3β-Hal-Δ^5-cholestene (IX):



VII VIII IX

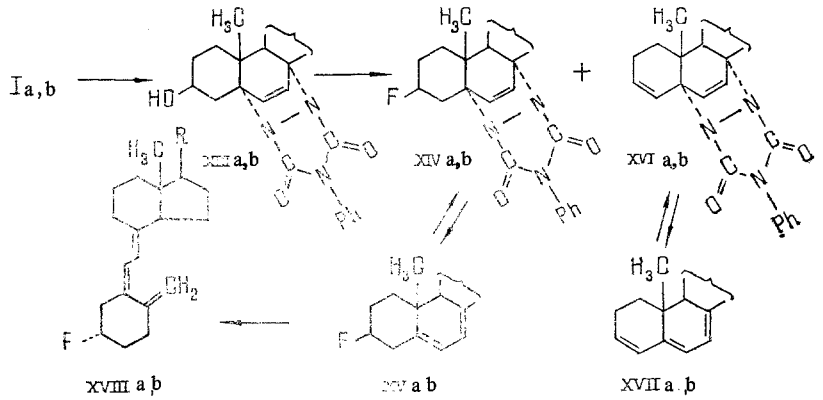
The presence of a Δ^7- double bond in each of provitamins (Ia, b) is probably responsible for the ready rearrangement of the cation (X) into the isomeric cation (XI), stabilized by the ejection of the proton at C_{14} with the formation of (IIa, b). The ease of the arrangement of the cations (X) → (XI) may also, apparently, serve as an explanation of the different course of the reaction as compared with the case of cholesterol:



X XI

Thus, starting from provitamins D_2 and D_3, as a result of the anomalous course of the fluorination reaction it is possible to obtain compounds of type (IIa, b), difficult to obtain by other methods, with preparative yields. These compounds are extremely reactive and permit the introduction of various functional groupings into the C-3, C-6, and C-14 positions and are therefore of independent interest for the synthesis of modified steroid hormones.

At the same time, it has become obvious that it is impossible to obtain 3β-fluoro-provitamins D by direct fluorination. We therefore performed the synthesis of 3β-fluoro-7-dehydrocholesterol and 3β-fluoro-7-dehydrositerosterol from 3β-fluorocholesterol and 3β-fluorositerosterol by allyl bromination and dehydrobromination and also by the use of the Bamford–Stevens reaction [3, 9]. Both these methods gave low yields of the 3β-fluoro-provitamins D_3 and D_5 and did not permit 3β-fluoro-provitamin D_2 to be obtained from ergosterol. We have therefore developed another method of obtaining 3β-fluoro derivatives, including the preliminary protection of the 5,7-diene system of the provitamin D by the formation of cycloadducts. As the dienophile we used 4-phenyl-1,2,4-triazoline-3,5-dione (XII) [10].



The fluorination of the adduct (XIIIa) obtained by the diene condensation of the provitamin (Ia) with the dione (XII) led to the formation of the corresponding 3β-fluoro derivative (XIVa) with a yield of about 65%. In this method of fluorination we observed no inversion of the configuration at C-3, which was shown unambiguously by the production of the adduct of 3β-fluorocholesta-5,7-diene (XVa) and the diode (XII), identical with the adduct (XIVa).

On the fluorination of the adduct (XIIa), compound (XVIa), containing no fluorine, was also formed (yield about 30%). Compound (XVIa) was apparently a dehydrofluorination product, since its ^{1}H NMR spectrum lacked the two multiplets in the 4.3-4.9 ppm region that are characteristic for the H atom of the >CHF grouping, but the signals of additional olefinic protons were observed (5.3-5.5 ppm). The treatment of compound (XVIa) with sodium methanolate in methanol led to the elimination of the protective grouping and to the formation of the known cholesta-3,5,7-triene (XVIIa) [11]. The structure of (XVIa) was definitely confirmed by its independent synthesis by means of the diene condensation of the triene (XVIIa) with the dione (XII).

It is known that (Ia) is readily regenerated from its adduct (XIIIa) with a yield of ~90% when it is boiled with $LiAlH_4$ in THF for 18 h [12]. However, under similar conditions the fluorinated adduct (XIVa) proved to be more stable and only on boiling for 60 h was it possible to obtain about 10-15% of the required provitamin (XVa). When THF was replaced by xylene with boiling at 140-150°C (4-6 h), the yield of the fluorodiene (XVa) rose to 30%. The protective grouping was eliminated more effectively when (XIVa) was boiled with a 7% solution of sodium methanolate in methanol for 30 min. In this case, (XVa) was obtained with a yield of 60%. Similar transformations took place in connection with ergosterol (Ib). The overall yield of the 3β-fluoro-provitamins (XV) amounted to 35% on the initial provitamins (I).

We have previously [2, 9] described the further transformation of the 3β-fluoro-provitamins (XVa, b) into the 3β-fluoro-vitamins D_3 and D_2 (XVIIIa, b).

EXPERIMENTAL

IR spectra were measured on a UR-20 spectrophotometer (in tablets with KBr or in CCl_4 solution); UV spectra, on an SF-4A instrument in C_2H_5OH; mass spectra, on an MKh-1309 mass spectrometer (at an energy of the ionizing electrons of 70 eV); and ^{1}H NMR spectra, on a Varian XL-100 instrument in $CDCl_3$; and specific rotations were measured on a Polamat A polarimeter. For column chromatography we used Al_2O_3 (Brockman activity grade II).

Fluorination of Cholesterol with Morpholinosulfur Trifluoride. A solution of 1 g of cholesterol in 50 ml of methylene chloride was treated dropwise at 5°C over 10 min with a solution of 1 ml of morpholinosulfur trifluoride in 25 ml of methylene chloride. Then the reaction mixture was treated with water. The organic layer was separated off and, by the usual treatment, 0.9 g (90%) of 3β-fluorocholesterol with mp 96-97°C (ethanol), $[\alpha]_D^{20} - 51.5°$ (c 0.5: chloroform) was obtained. According to the literature: mp 97-98°C (ethanol) [13] $[\alpha]_D$ −50° (chloroform) [14].

3α,5α-Cyclocholesta-6,8(14)-diene (IIa). A solution of 1 g of (Ia) in 50 ml of methylene chloride was treated with 1 ml of morpholinosulfur trifluoride or with 2-choloro-1,1,2-trifluoroethylamine as described above. The product was chromatographed on a column of Al_2O_3 in

petroleum ether, to give 0.7 g (74%) of the diene (IIa) with mp 53-55°C (acetone), $[\alpha]_D^{20}$ + 164.5° (*c* 1.0; chloroform). IR spectrum, ν_{max}^{KBr}, cm^{-1}: 1630, 1605, 1470, 1375; UV spectrum $\lambda_{max}^{C_2H_5OH}$, nm: 260 (ε 24,000). ^1H NMR spectrum (δ, ppm): 0.48 q (J = 3 and 8 Hz, 1 H, 3β-H); 0.79 s (3 H, 18-CH_3); 0.85 d (J = 6 Hz, 3 H, 21-CH_3); 0.92 d, (J = 6 Hz, 6 H, 26- and 27-CH_3); 0.98 s (3 H, 19-CH_3); 5.21 d (J = 10 Hz, 1 H, 7-H); 6.17 d (J = 10 Hz, 1 H, 6-H). Mass spectrum: (*m/z*): 366 (M, 62%), 351 (M—CH_3, 59%), 323 (M—C_3H_7, 3%), 308 (M—CH_3—C_3H_7, 4%), 281 (M—C_6H_{13}, 6%), 265 (7%), 253 (M—C_8H_{17}, 100%), 239 (19%), 228 (24%), 211 (21%), 199 (77%).

3α,5α-Cycloergosta-6,8(14),22-triene (IIb). The synthesis was performed in a similar manner to that of (IIa). The yield of the triene (IIb) amounted to 90%, mp 95-97°C (acetone); $[\alpha]_D^{20}$ +163.2° (*c* 1.0; chloroform). IR spectrum, ν_{max}^{KBr}, cm^{-1}: 1625, 1605, 1465, 1375. UV spectrum, $\lambda_{max}^{C_2H_5OH}$, nm: 260 (ε 23,000). ^1H NMR (δ, ppm): 0.47 g (J = 3 and 8 Hz, 1 H, 3β-B); 0.77 s (3 H, 18-CH_3); 1.02 s (3 H, 19-CH_3); 5.2-5.4 m (3 H, 7-, 22- and 23-H); 6.21 d (J = 10 Hz, 1 H, 6-H). Mass spectrum (*m/z*): 378 (M, 56%), 363 (M—CH_3, 47%), 253 (M—C_9H_{17}, 100%) 199 (67%).

Fluorination of the Adduct (XIIIa). Over 20 min at 5°C, a solution of 2 ml of one of the fluorinating agents mentioned above (the yield of the final product was independent of the agent used) in 60 ml of methylene chloride was added to a solution of 2 g of the adduct (XIIIa) with mp 156°C obtained as described by Barton et al. [12] in 100 ml of methylene chloride. After the usual working up, a product was obtained which was chromatographed on a column of Al_2O_3. Diethyl ether—petroleum ether (3:7) yielded 1.3 g (65%) of the fluorinated adduct (XIVa), R_f 0.55, mp 145-146°C (ethanol or petroleum ether), $[\alpha]_D^{20}$ —94.5° (*c* 1.0; chloroform); IR spectrum, ν_{max}^{KBr}, cm^{-1}: 1750, 1700 (amide), 1603 (olefin); UV spectrum, $\lambda_{max}^{C_2H_5OH}$, nm: 255 (ε 4400). ^1H NMR spectrum (δ, ppm): 0.82 s (3 H, 18-CH_3); 0.86 d (J = 6 Hz, 3 H, 21-CH_3); 0.86 d (J = 6 Hz, 3 H, 21-CH_3); 0.95 d (J = 6 Hz, 6 H, 26- and 27-CH_3); 0.98 s (3 H, 19-CH_3); 4.37 m and 4.81 m (J = 30 Hz, 1 H, CHF); 6.27 q and 6.47 q (J = 3 and 8 Hz, 2 H, 6- and 7-H); 7.51 m (5 H, C_6H_5).

The subsequent fractions of the same mixture of solvents yielded 0.6 g (30%) of the unsaturated adduct (XVIa), R_f 0.35, mp 186-188°C (decomp., petroleum ether), $[\alpha]_D^{23}$ — 56.4° (C 1.0; chloroform). IR spectrum, ν_{max}^{KBr}, cm^{-1}: 1761, 1699 (amide), 1605; ^1H NMR spectrum (δ, ppm): 0.18 s (3 H, 18-CH_3); 0.85 (d, J = 6 Hz, 3 H, 21-CH_3); 0.94 d (J = 6 Hz, 6 H, 26- and 27-CH_3); 1.02 s (3 H, 19-CH_3); 5.3-5.5 m (2 H, 3- and 4-H); 6.23 q and 6.45 q (J = 3 and 8 Hz, 2 H, 6- and 7-H); 7.43 m (5 H, C_6H_5).

The Fluorinated Adduct (XIVa) from (XVa). With ice cooling, a solution of 0.05 g of 4-phenyl-1,2,4-triazoline-3,5-dione (XII) in 5 ml of ethyl acetate was added to a solution of 0.1 g of (XVa) in 5 ml of ethyl acetate. After 20 min, the solvent was driven off in vacuum and the residue was crystallized from ethanol. This gave 140 ml (98%) of the fluorinated adduct (XIVa) with mp 145-146°C, identical with the sample obtained above.

The Unsaturated Adduct (XVIa) from (XVIIa). The condensation of 0.4 g of the triene (XVIIa) with 0.17 g of (XII) in 4 ml of ethyl acetate at 10°C followed by chromatography on Al_2O_3 in diethyl ether—petroleum ether (3:7) gave 0.3 g of (XVIa) with mp 186-188°C, identical with the sample obtained above.

Cholesta-3,5,7-triene (XVIIa). A. A mixture of 0.5 g of the adduct (XVIa) and a solution of sodium methanolate obtained from 2.5 g of metallic sodium and 40 ml of absolute methanol was boiled for 30 min, and then it was cooled and was acidified with dilute acetic acid and the product was extracted with benzene. After chromatography on Al_2O_3 in petroleum ether, 0.2 g of (XVIIa) was isolated in the form of an oil. Crystallization from acetone gave 0.12 g of white crystals with mp 67-68°C, $[\alpha]_D^{20}$ — 130° (*c* 0.5; chloroform); UV spectrum, $\lambda_{max}^{C_2H_5OH}$, nm: 302.5, 315, 330 (ε 12,400, 15,500, 1100 [sic]). According to the literature: mp 67-69°C (acetone), $[\alpha]_D$—122.4° (chloroform); UV spectrum, $\lambda_{max}^{C_2H_5OH}$, nm: 302.5, 315, 330 (ε 12,580, 15,720, 11,120) [11].

B. To a suspension of 1.25 g of finely disperse metallic sodium in 150 ml of hexane (prepared by repeated boiling in toluene and shaking with the subsequent displacement of the

solvent) was added 1 g of the ethyl ether of (Ia) with mp 104-106°C, $[\alpha]_D^{20}$ —110° (*c* 1.0 ; chloroform). UV spectrum $\lambda_{max}^{C_2H_5OH}$, nm: 282 (ε 12,280). At room temperature, a solution of 3.0 ml of amyl chloride in 60 ml of hexane was added slowly, over 1.5 h, to the mixture and it was then left overnight. After this, 200 ml of water was added to the reaction mixture and the organic layer was separated off, and after the usual working up and chromatography on Al_2O_3 in petroleum ether 0.4 g (45%) of (XVIIa) was isolated with mp 67-69°C (acetone), $[\alpha]_D^{20}$ — 130° (C 0.5; chloroform); UV spectrum, $\lambda_{max}^{C_2H_5OH}$, nm: 302.5, 315, 330 (ε 12,400, 15,500, 11,100).

3β-Fluorocholesta-5,7-diene (XVa). A. A solution of 1 g of the fluorinated adduct (XIVa) in 10 ml of xylene was boiled with 1 g of $LiAlH_4$ in an atmosphere of argon for 60 h. After the usual working up the product was chromatographed on Al_2O_3 in petroleum ether. This yielded 0.26 g (36%) of (XVa) with mp 105-106°C (acetone), $[\alpha]_D^{20}$ —149° (*c* 1.0, chloroform). UV spectrum, $\lambda_{max}^{C_2H_5OH}$, nm: 271, 282, 293 (ε 10,600, 10,900, 6350). According to the literature: mp 105-107°C (acetone); $[\alpha]_D^{20}$ —149° (chloroform); UV spectrum, $\lambda_{max}^{C_2H_5OH}$, nm: 271, 282, 293 (ε 10,700, 11,000, 6420) [15].

B. A mixture of 1 g of the fluorinated adduct (XIVa) and a solution of sodium methanolate prepared from 5 g of metallic sodium and 75 ml of absolute methanol was boiled for 30 min. The reaction mixture was worked up as described above for (XVIIa) and was chromatographed on Al_2O_3 in petroleum ether. This gave 0.41 g (60%) of (XVa) with mp 105-106°C, completely identical with the sample described above.

Fluorination of the Adduct (XIIIb). The fluorination of 2 g of the adduct (XIIIb) with mp 190-192°C, $[\alpha]_D^{20}$ —124° (*c* 0.5 ; chloroform), obtained by the method of Barton et al. [12], was carried out as described for the adduct (XIIIa). The product obtained was chromatographed on Al_2O_3 in benzene–acetone (93:7). This yielded 1.5 g (75%) of the fluorinated adduct (XIVb) with mp 173-174°C (decomp., acetone), $[\alpha]_D^{20}$ —129.3° (*c* 1.0 ; chloroform): IR spectrum, ν_{max}^{KBr}, cm^{-1}: 1760, 1700, 1605; UV spectrum, $\lambda_{max}^{C_2H_5OH}$, nm: 255 (ε 4240).

3β-Fluoroergosta-5,7,22-triene (XVb). A. A solution of 1 g of the adduct (XIVb) in 10 ml of xylene was boiled with 1 g of $LiAlH_4$ in an atmosphere of argon for 5 h. The product, obtained in the usual way, was chromatographed on Al_2O_3 in petroleum ether, which gave 0.3 g (41%) of (XVb) with mp 137-138.5°C (acetone) $[\alpha]_D^{20}$ —109.7° (*c* 1.0 ; chloroform); IR spectrum, ν_{max}^{KBr}, cm^{-1}: 1660, 1605, 1468; UV spectrum, $\lambda_{max}^{C_2H_5OH}$, nm: 272, 282, 293 (ε 9900, 10,800, 5800); ^1H NMR spectrum (δ, ppm); 0.61 s (3 H, 18-CH_3); 0.85 s (3 H, 19-CH_3); 1.01 d (J = 6 Hz, 3 H, 21-CH_3); 0.99 d (J = 6 Hz, 6 H, 26- and 27-CH_3); 1.03 d (J = 6 Hz, 3 H, 28-CH_3); 4.27 m and 4.74 m (J = 30 Hz, 1 H, CHF); 5.44 m, 5.48 m, and 5.71 m (4 H, 6-, 7-, 22-, and 23-H). Mass spectrum (*m/z*): 398 (M, 53%), 383 (M—CH_3, 14%), 378 (M—HF, 100%), 364 (M—HF—CH_3, 61%), 355 (M—C_3H_7, 44%), 337 (M—HF—C_3H_7, 21%), 271 (M— C_9H_{17}—H_2, 83%), 251 (71%), 246 (51%), 231 (43%).

Ergosta-3,5,7,22-tetraene (XVIIb). The mixture after the fluorination of (XIIb) (1.3 g) was boiled in xylene with $LiAlH_4$ for 5 h. After chromatographic separation on Al_2O_3 in petroleum ether, the first fractions yielded 0.17 g (20%) of (XVIIb) with mp 95.5-97.5°C (acetone), $[\alpha]_D^{20}$ —174° (*c* 1.0 ; chloroform); UV spectrum, $\lambda_{max}^{C_2H_5OH}$, nm: 315 (ε 19,950). According to the literature: mp 94-96°C [16]; UV spectrum, $\lambda_{max}^{C_2H_5OH}$, nm: 315 (ε 19,860) [6].

G. M. Segal' assisted in the recording and interpretation of the mass and ^1H NMR spectra.

SUMMARY

1. The fluorination of 3β-hydroxy-$\Delta^{5,7}$-steroids, unlike that of 3β-hydroxy-Δ^5-steroids, does not lead to the formation of 3β-fluoro derivatives. The reaction products are 3α, 5α-cyclo-$\Delta^{6,8(14)}$ compounds.

2. A method has been proposed for obtaining 3β-fluoro derivatives of provitamins D by the preliminary protection of the 5,7-diene system through the formation of a cycloadduct

(for example, with 4-phenyl-1,2,4-triazoline-3,5-dione), fluorination with morpholinosulfur trifluoride to give the 3β-fluorinated adduct, and the subsequent regeneration of the 5,7-double bonds by treating the adduct with a solution of sodium methoanolate in methanol.

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SYNTHESIS OF RACEMIC DOMINCALURE — THE AGGREGATION PHEROMONE OF THE LESSER GRAIN BORER *Rhyzopertha dominica*

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UDC 542.91:632.936.2

The sec-amyl esters of 2-methylpent-2E-enoic and 2,4-dimethylpent-2E-enoic acids, constituting the aggregation pheromone of the lesser grain borer *Rhyzopertha dominica*, have been synthesized stereospecifically in high yield from the products of the aldol condensation of propionaldehyde and isobutyraldehyde. The 2-methyl- and 2,4-dimethylpent-2E-enals were oxidized to the corresponding acids, which were converted into the chlorides and these into the corresponding sec-amyl esters. The geometric purity of the products was shown by their PMR spectra (250 MHz).

The lesser grain borer *Rhyzopertha dominica* is one of a number of dangerous pests of grain stocks. One of the methods of combating this insect may be the use of its aggregation pheromone, which has recently been identified as a mixture of S-(+)-sec-amyl esters (Ia and b) ("dominicalure") [1]. This pheromone possesses a high attractant activity, and in the present paper we consider a stereospecific synthesis of the racemic forms of both of its components, which have been obtained previously in comparatively low yield from methyl propyl and methyl isobutyl ketones [1].

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