ALTERNATIVE SYNTHESES OF STEROIDAL MALEIMIDES*

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Received October 6th, 1982

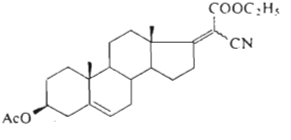
The described synthesis starts from the α-keto esters *VIII* and *XVI* which afford the maleimides *X* and *XVIII* *via* products of condensation with carbamoylmethylenetriphenylphosphorane (*IX* and *XVII*). In this way, the steroidal maleimides *X* and *XVIII* (structurally similar to the cardenolides), derived from 17β-androstanyl-(2-maleimide) and 21-nor-pregnanyl-(2-maleimide) were prepared. Other routes for their preparation have been studied.

The present paper describes some potentialities of synthetic utilization of condensation products of malonic acid derivatives with steroidal ketones described earlier[1].

For the synthesis of the maleimide *XVIII*, representig a homologue of the already described[2] series of steroidal maleimides *X*, we devised a synthetic approach *via* the unsaturated ester nitrile *VII*. Reduction[1] of the ester nitrile *I* afforded the saturated derivative *II* which was decarboxylated and hydrolyzed[1] to give the acid *III* (ref.[1]). This was acetylated to the acetyl compound *IV* according to the method published in the literature[3,4], the undesired steroidal anhydrides being destroyed by boiling with water[5]. The acid *IV* on treatment with oxalyl chloride in benzene[3,4] was converted into its chloride *V* which without isolation was treated with hydrogen cyanide using the method described previously[2]. The resulting cyanide *VI* was transformed into the ester nitrile *VII* by condensation with methoxycarbonylmethylenetriphenylphosphorane. The cyanide *VI* was characterized by the infrared band at 1 770 cm^{-1} whose wavenumber as well as intensity were comparable with those of the C=O band in acid chlorides (such as in *V*: 1 798 cm^{-1}; ref.[3]), and also by ^1H NMR and mass spectra. The latter contained no molecular ion; however, the fragment arising by loss of acetic acid from the molecular ion was well discernible. The ester nitrile *VII* was characterized by bands at 1 730, 1 638 and 1 439 cm^{-1} due to the conjugated ester grouping and also by the band at 2 230 cm^{-1} ascribed to the conjugated nitrile group. Characteristic feature was also the ^1H NMR signal of the proton at $C_{(23)}$ in the side chain ($\delta = 6{\cdot}32$). The observed chemical shift, corresponding to those of (*Z*)-ester nitriles prepared previously[2,6], indicates that also in this case the compound has the (*Z*)-configuration. Mass spectrum of the compound *VII* displays no molecular ion but the $(M^+ - CH_3COOH)$ fragment is again well discernible.

* Part CCLXXXI in the series On Steroids; Part CCLXXX: This Journal *48*, 937 (1983).

A direct synthetic way to the steroidal maleimide *XVIII* should have been acid cyclization[2] of the ester nitrile *VII* in a mixture of glacial acetic acid, concentrated sulfuric acid and acetic anhydride at elevated temperature. Analogously to a number of previous cases[2,6], this reaction failed due to a profound decomposition of the compound *VII* under the reaction conditions used.



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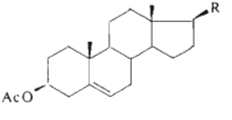
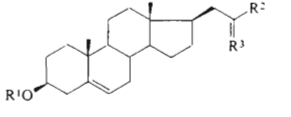
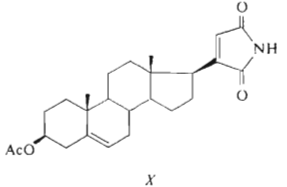


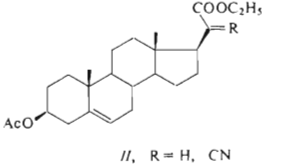
XI, R = COOH
XII, R = CH_2OH
XIII, R = CHO
XV, R = $CH_2CH(CN)COOC_2H_5$
XIV, R = $CH{=}C(CN)COOC_2H_5$



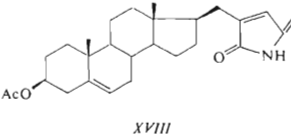
III, R^1 = H; R^2 = OH; R^3 = O
IV, R^1 = Ac; R^2 = OH; R^3 = O
V, R^1 = Ac; R^2 = Cl; R^3 = O
VI, R^1 = Ac; R^2 = CN; R^3 = O
VII, R^1 = Ac; R^2 = CN; R^3 = $CHCOOCH_3$
XVI, R^1 = Ac; R^2 = $COOC_2H_5$; R^3 = O
XVII, R^1 = Ac; R^2 = $COOC_2H_5$; R^3 = $CHCONH_2$



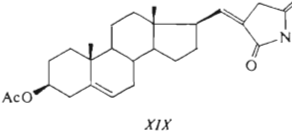
X



II, R = H, CN
VIII, R = O
IX, R = $CHCONH_2$



XVIII



XIX

We applied therefore a synthetic method, utilizing transformation of the α-keto ester into the maleimide *via* the product of Wittig condensation with carbamoylmethylenetriphenylphosphorane[7]. The reaction pathway was first checked on the sequence *II*→*VIII*→*IX*→*X*, leading to the known[2] maleimide *X*.

Using condensation products of malonic acid derivatives with steroidal carbonyl compounds[1], the α-keto ester *VIII* was obtained by the described[8] procedure *via* the saturated ester nitrile *II*; contrary to the original work[8], the compound *VIII* was prepared in the crystalline form, other physical properties being identical with those described[8]. Condensation[7] of the keto ester *VIII* with carbamoylmethylenetriphenylphosphorane, generated from carbamoylmethylenetriphenylphosphonium chloride[9] by treatment with 1,8-diazabicyclo[5,4,0]undec-7-ene as the base[10], afforded the unsaturated amido ester *IX* and further the described[2] maleimide *X* in a 16% yield.

The synthesis of the homologous maleimide *XVIII* started from the acetoxy acid *XI* (ref.[5]) which was reduced *via* the mixed anhydride by a described procedure[11,12], simplified by omitting the laborious filtration of the reaction mixture[13]. The resulting alcohol *XII* has been already mentioned in a patent[14] which reports only one physical constant. We have now characterized this compound also by other methods in complete agreement with its assumed structure.

Alcohol *XII* was oxidized to aldehyde *XIII* with pyridinium chlorochromate in dichloromethane. For the full characterization of *XIII*, infrared band at 2 730 cm^{-1} and a doublet at $\delta = 9{\cdot}79$ in its ^1H NMR spectrum with coupling constant 1·5 Hz were used. Aldehyde *XIII* was condensed with ethyl cyanoacetate in the presence of β-alanine and acetic acid under azeotropic removal of water according to the procedure described[8] for preparation of *I*. The obtained ester nitrile *XIV* was characterized by a band at 2 235 cm^{-1} due to the unsaturated nitrile in the IR spectrum, by a doublet ($\delta = 7{\cdot}46$) with coupling constant 11 Hz in the ^1H NMR spectrum, and by an $(M^+ - CH_3COOH)$ fragment (m/z 379) in its mass spectrum. The reaction can afford a mixture of (*Z*)- and (*E*)-isomers at the $C_{(20)}=C_{(22)}$ double bond. The ^1H NMR spectrum exhibits a higher background, particularly of the $C_{(20)}$ proton signal, and also a broader signal of the methyl at $C_{(13)}$ which indicates that it is composed of signals of the two isomers. We estimated the ratio of the isomers to be about 1 : 4 but direct configurational assignment from the available data was not possible. The attempted chromatographic separation of the isomers failed.

The conjugated double bond in the unsaturated ester nitrile *XIV* was reduced with sodium borohydride in tetrahydrofuran–ethanol at 0°C. Under these conditions almost no deblocking of the hydroxyl at $C_{(3)}$ occurred. The saturated ester nitrile *XV* of unknown configuration at $C_{(22)}$ was characterized by the IR-band at 2 255 cm^{-1} corresponding to the unconjugated nitrile group, and by a multiplet at $\delta = 3{\cdot}39$ due to the proton at $C_{(22)}$ in the ^1H NMR spectrum. Its mass spectrum again displayed an $(M^+ - CH_3COOH)$ fragment of mass by two units higher than that observed with the derivative *XIV*. Using the same method as described[8] for the reaction *II*→*VIII*,

the compound *XV* was converted into the α-keto ester *XVI*. In the IR spectrum of this compound all the three carbonyl bands merge into one strong band at 1 739 cm^{-1}.

The keto ester *XVI* was condensed with carbamoylmethylenetriphenylphosphorane[9] generated (unlike in the reaction of keto ester *VIII* in dichloromethane) from carbamoylmethyltriphenylphosphonium chloride[9] by 1,8-diazabicyclo[5,4,0]undec--7-ene[10] at room temperature under argon. The arising unisolated condensation product *XVII* was then converted into the maleimide *XVIII*, characterized by IR bands at 1 727 cm^{-1} and 1 778 cm^{-1}, corresponding to the maleimide carbonyls and by a narrow band at 3 439 cm^{-1} due to the N—H maleimide bond (the corresponding values for the homologous maleimide *X* were[2] 1 728, 1 775 and 3 445 cm^{-1}). Also the signal at $\delta = 6{\cdot}28$ in the ^{1}H NMR spectrum due to the proton on the maleimide double bond (for *X* found[2] $\delta = 6{\cdot}30$) confirms the assumed structure. The product gives a positive permanganate reaction and can be detected by UV light (254 nm) in thin-layer chromatography.

The attempted direct condensation of the aldehyde *XIII* with the phosphorane, generated from maleimide and hexaethylphosphorous triamide[15] in chloroform or boiling benzene was unsuccessful even when triphenylphosphine was used. The isomeric succinimide *XIX* which could be isomerized to the maleimide *XVIII* was not prepared.

EXPERIMENTAL

Melting points were determined on a Boetius melting point microscope (GDR). Optical rotations were measured at 25°C on a Perkin–Elmer 141 MC polarimeter, IR spectra were taken on a Zeiss UR-20 spectrometer. ^{1}H NMR spectra were determined in deuteriochloroform with tetramethyl silane as internal standard on a Tesla B-476 (60 MHz) instrument. Chemical shifts are given in ppm (δ-scale), coupling constants (J) and signal widths (W) in Hz. All values were obtained by first order analysis. Mass spectra were taken on an AEI MS 901 spectrometer. Column chromatography was performed on silica gel (according to Pitra; 60—120 μm) or on neutral alumina (Reanal, activity II), thin-layer chromatography was carried out on silica gel G (according to Stahl; Woelm). Before evaporation (at about 2 kPa), solutions of the compounds in organic solvents were dried over anhydrous sodium or magnesium sulfate. Analytical samples were dried over phosphorus pentoxide at 40°C and 26 Pa for 12 h. The identity of samples prepared by different routes was checked by comparison of their IR and ^{1}H NMR spectra, by thin-layer chromatography and mixture melting point determination.

3β-Acetoxy-5-pregnen-21-oic Acid (*IV*)

Acetic anhydride (20 ml) was added to a solution of hydroxy acid *III* (ref.[1]; 4·59 g; 13·5 mmol) in pyridine (30 ml). After standing for 24 h the mixture was mixed with water (20 ml) and refluxed to homogeneity (1 h). Water was added to the hot solution until slight turbidity occurred and the mixture was slowly cooled to +5°C. After standing at this temperature for 20 h, the separated crystals were collected on filter, washed with water and dried, yielding 5 g (99%) of the acid *IV*. Physical properties of the product were identical with those reported in the literature[3,4].

Methyl (22*Z*)-3β-Acetoxy-22-cyano-21-norchola-5,22-dien-24-oate (*VII*)

A) The acid *IV* (2 g; 5·35 mmol) was dissolved in benzene (40 ml) and the solution was evaporated. This procedure was repeated three times. The residue was dissolved in benzene (40 ml), oxalyl chloride (1·44 ml, 2·09 g; 7·8 mmol) was added and the mixture was stirred at room temperature for 30 min. The reaction course was monitored by dissolving samples of the reaction mixture in methanol and subjecting the solution to thin-layer chromatography in benzene–ether (5 : 1). The mixture was evaporated, the residue was three times coevaporated with dichloromethane (dried over phosphorus pentoxide) and finally dissolved in dichloromethane (40 ml). The solution was cooled to 0°C (ice) and treated with an ice-cold solution of methoxycarbonylmethylenetriphenylphosphorane (4·28 g; 12·8 mmol) in dichloromethane (40 ml) and with liquid hydrogen cyanide (dried over calcium chloride; 1·01 ml; 0·69 g; 25·7 mmol). The mixture was stirred in an ice-bath for 1 h and then at room temperature for 10 h. After evaporation, the residue was coevaporated three times with dichloromethane and chromatographed on a column of silica gel (250 g). As eluants we used successively benzene (500 ml), benzene–1% ether (500 ml) and benzene–5% ether. Two main fractions were obtained: the first (750 mg) was used for preparation of the pure cyanide *VI* (*vide infra*), the second (1 g) on crystallization from benzene–light petroleum afforded 520 mg (22%) of the ester nitrile *VII*, m.p. 165–167°C; $[\alpha]_D^{25}$ −63·8° (*c* 0·33, chloroform). IR spectrum (chloroform): 1 730, 1 246, 1 034 cm^{-1} (CH_3.COO), 1 730, 1 638, 1 439 cm^{-1} (=CH_2COOCH_3), 2 230 cm^{-1} (CN). ^1H NMR spectrum: 6·32 b d (1 H, $C_{(23)}$—H, J = 1), 5·38 m (1 H, $C_{(6)}$—H, W = 12), 4·58 m (1 H, $C_{(3)}$—H, W = 35), 3·79 s (3 H, CH_3O), 2·68–2·08 m (4 H, $C_{(20)}$—H_2 and $C_{(7)}$—H_2), 2·00 s (3 H, CH_3COO) 1·00 and 0·62 2 s (2 × 3 H, angular methyls). Mass spectrum (*m/z*): 379 (M—CH_3COOH), 364 (379—CH_3). For $C_{27}H_{37}NO_4$ (439·6) calculated: 73·77% C, 8·48% H, 3·19% N; found: 73·63% C, 8·77% H, 3·10% N.

B) Methoxycarbonylmethylenetriphenylphosphorane (2 g; 6 mmol) was added to a solution of the cyanide *VI* (1·5 g; 3·9 mmol) in benzene (40 ml) and the mixture was refluxed for 1 day. Another portion (500 mg; 1·5 mmol) of methoxycarbonylmethylenetriphenylphosphorane was added and after reflux for another day, the mixture was evaporated and the residue was chromatographed on silica gel (250 g) in benzene–ether (10 : 1 to 4 : 1). Crystallization of the main fraction (950 mg) afforded 840 mg (49%) of the ester nitrile *VII* of the same properties as the product prepared by procedure *A*.

3β-Acetoxy-21-cyano-5-pregnen-21-one (*VI*)

The first fraction (750 mg) from the chromatography of the ester nitrile *VII* (method *A*) was recrystallized from benzene–ether, affording 580 mg (28%) of the cyanide *VI*, melting at 241 to 243°C; $[\alpha]_D^{25}$ −62·6° (*c* 0·41, chloroform). IR spectrum (chloroform), cm^{-1}: 1 728, 1 258, 1 033 (CH_3COO), 1 770 (C=O), 2 255 (CN). ^1H NMR spectrum: 5·37 m (1 H, $C_{(6)}$—H, W = 13), 4·56 m (1 H, $C_{(3)}$—H, W = 35), 2·70–2·10 m (4 H, $C_{(20)}$—H_2 and $C_{(7)}$—H_2), 2·00 s (3 H, CH_3COO), 1·02 and 0·63 2 s (2 × 3 H, angular methyls). Mass spectrum (*m/z*): 323 (M—.CH_3COOH), 308 (323—H_2O). For $C_{24}H_{33}NO_3$ (383·5) calculated: 75·16% C, 8·67% H, 3·65% N; found: 75·42% C, 8·87% H, 3·40% N.

Ethyl 3β-Acetoxy-20-oxo-5-pregnen-21-oate (*VIII*)

The compound was prepared according to the literature[8] and the oily product obtained was chromatographed on a column of silica gel (100 g) in benzene–ether (50 : 2). Crystallization from light petroleum afforded the ester *VIII*, m.p. 89–92°C, in 84% yield. IR spectrum (chloro-

form), cm^{-1}: 1 745 sh, 1 730, 1 728 sh (C=O), 1 245 (CH_3COO), 1 671 (C=C), 1 091, 1 078, 1 033, 1 025 (C–O). Reported[8] 1 730 cm^{-1} (C=O), 1 243 cm^{-1} (COO), 1 091, 1 078, 1 033, 1 025 cm^{-1} (C—O). Other physical data are identical with the published ones[8].

3β-Acetoxy-17β-(2-maleimido)-5-androstene (*X*)

1,8-Diazabicyclo[5,4,0]undec-7-ene (96%, 516 μl, 525 mg; 3·45 mmol) was added under argon to a stirred mixture of carbamoylmethyltriphenylphosphonium chloride[9] (1·4 g; 4·3 mmol) and chloroform (40 ml). After 30 min of stirring at room temperature, a solution of the ester *VIII* (833 mg; 2 mmol) in chloroform (5 ml) was added and the mixture was set aside with intermittent stirring at room temperature for 8 days. After this time the starting keto ester was still present (according to thin-layer chromatography in benzene–ether 10 : 1), however, the composition of the mixture did not change further. It was evaporated with silica gel (10 g), applied on a column of silica gel (100 g) and eluted with benzene–ether 50 : 1 (2 l), 50 : 2 (2 l) and finally 50 : 4 (2 l). The following three fractions of increasing polarity were obtained: The first contained 440 mg of (thin-layer chromatography) starting compound *VIII*, the second (190 mg) consisted of at least four compounds (according to thin-layer chromatography), and the third (110 mg; 13%) which on crystallization from an acetone–ether–light petroleum mixture afforded 60 mg (7%) of the maleimide *X*, identical with an authentic sample[2]. The yield, related to the unreacted starting compound, is 28% of the crude and 16% of the recrystallized imide *X*.

3β-Acetoxy-21-nor-5-pregnen-20-ol (*XII*)

The acid *XI* (ref.[5]; 13 g; 36 mmol) and triethylamine (5·1 ml; 36 mmol) were dissolved in tetrahydrofuran (200 ml) and cooled. Ethyl chloroformate (3·4 ml; 35 mmol) was added at 0°C, followed after 20 min with a solution of sodium borohydride (6·9 g; 0·18) in water (250 ml). After standing at room temperature for 1 h, the mixture was poured into water acidified by hydrochloric acid and extracted with ether (3 × 250 ml). The combined ethereal extracts were washed successively with 5% hydrochloric acid, saturated potassium hydrogen carbonate solution and water, treated with charcoal, filtered, dried over anhydrous magnesium sulfate and evaporated. The residue was dissolved in dichloromethane and the solution filtered through a column of alumina (75 g) which was then washed with further dichloromethane (300 ml). The filtrate was concentrated, affording 9·74 g (78%) of the alcohol *XII*, m.p. 157–159°C (reported[14] m.p. 157–158°C); $[\alpha]_D^{25}$ −67·6° (*c* 0·52, chloroform). IR spectrum (chloroform), cm^{-1}: 3 630, 1 011, 1 001 (OH), 1 730, 1 263 and 1 034 (CH_3COO), 1 671 (C=C). ^1H NMR spectrum: 5·39 bd (1 H, $C_{(6)}$—H, J = 3·5), 4·58 m (1 H, $C_{(3)}$—H, W = 34), 3·63 b s (2 H, —CH_2—O—, W = = 11), 2·32 b d (2 H, $C_{(7)}$—H_2, J = 9), 2·15 s (3 H, CH_3COO), 1·04 and 0·68 2 s (2 × 3 H, angular methyls). For $C_{22}H_{34}O_3$ (346·5) calculated: 76·26% C, 9·89% H; found: 76·24% C, 10·00% H.

3β-Acetoxy-21-nor-5-pregnen-20-al (*XIII*)

Pyridinium chlorochromate (4·45 g; 20 mmol) was added to a solution of *XII* (3·46 g; 10 mmol) in dichloromethane (75 ml). After stirring for 2 h at room temperature the mixture did not contain any starting material (according to thin-layer chromatography in benzene–ether 4 : 1). The mixture was filtered through a column of alumina (100 g) which was then washed with dichloromethane (300 ml) and ether (100 ml). The filtrates were evaporated and the residue crystallized from ether, affording 1·8 g (52%) of the aldehyde *XIII*, m.p. 139–141°C, $[\alpha]_D^{25}$ −26·2° (*c* 0·3, chloroform); IR spectrum (chloroform), cm^{-1}: 1 724, 1 258 and 1 033 (CH_3COO), 1 714 shoulder, 2 730 (CHO), 1 671 (C=C). ^1H NMR spectrum: 9·79 d (1 H, CHO, J = 1·5),

5·39 m (1 H, $C_{(6)}$—H, $W = 14$), 4·60 m (1 H, $C_{(3)}$—H, $W = 34$), 2·31 b d (2 H, $C_{(7)}$—H_2, $J = 9$), 2·03 s (3 H, CH_3COO), 1·04 s (3 H, CH_3), 0·78 s (3 H, CH_3). For $C_{22}H_{32}O_3$ (344·5) calculated: 76·70% C, 9·36% H; found: 76·99% C, 9·06% H.

Ethyl (20*E*/*Z*)-3β-Acetoxy-22-cyano-21,24-dinorchola-5,20(22)-dien-23-oate (*XIV*)

A mixture of the aldehyde *XIII* (3·4 g; 10 mmol), benzene (40 ml), ethyl cyano acetate (2·26 g; 2·13 ml; 20 mmol), β-alanine (475 mg; 5·3 mmol) and glacial acetic acid (4 ml) was refluxed for 25 h with azeotropic removal of water, poured into water (100 ml) and extracted with ether (3 × 50 ml). The combined ethereal extracts were washed with saturated solution of potassium hydrogen carbonate, filtered with magnesium sulfate and charcoal and evaporated. The residue (4·8 g) was crystallized from ether–methanol to give 2·6 g (59%) of the ester nitrile *XIV*, m.p. 134–136°C; $[\alpha]_D^{25}$ −178° (*c* 0·29, chloroform). IR spectrum (chloroform), cm^{-1}: 2 235 (CN), 1 739 (CH_3COO and $COOC_2H_5$), 1 254 and 1 034 (CH_3COO). ^1H NMR spectrum: 7·46 d (1 H, $C_{(20)}$—H, $J = 11$), 5·30 m (1 H, $C_{(6)}$—H, $W = 15$), 4·32 m (1 H, $C_{(3)}$—H, $W = 40$), 4·25 q (2 H, OCH_2CH_3, $J = 7·3$), 2·64 m (1 H, $C_{(17)}$—H, $W = c.$ 40), 1·90 s (3H, CH_3COO), 1·34 t (3 H, CH_2CH_3, $J = 7·3$), 1·00 and 0·87 2 s (2 × 3 H, angular methyls). Mass spectrum (*m*/*z*): 379 (M − CH_3COOH), 364 (379 − CH_3), 213 ($C_{16}H_{21}$). For $C_{27}H_{37}NO_4$ (439·6) calculated: 73·77% C, 8·48% H, 3·19% N; found: 73·86% C, 8·81% H, 3·12% N.

Ethyl 3β-Acetoxy-22ζ-cyano-21,24-dinor-5-cholen-23-oate (*XV*)

Sodium borohydride (77 mg; 2·03 mmol) was added at 0°C to a stirred mixture of the ester nitrile *XIV* (1·4 g; 3·2 mmol), tetrahydrofuran (20 ml) and ethanol (10 ml). After stirring at 0°C for 3 h, the mixture was poured into water (200 ml), acidified with hydrochloric acid and extracted with ether (3 × 50 ml). The combined ethereal extracts were washed with 5% hydrochloric acid, potassium hydrogen carbonate saturated solution and water, filtered with anhydrous magnesium sulfate and charcoal and evaporated. The residue was crystallized from methanol, affording 1·1 g (78%) of the saturated ester nitrile *XV*, m.p. 123–125°C, $[\alpha]_D^{25}$ −41·5° (*c* 0·22, chloroform). IR spectrum (chloroform), cm^{-1}: 1 748 ($COOC_2H_5$), 1 739, 1 259, 1 033 (CH_3COO), 2 255 (CN). ^1H NMR spectrum: 5·30 m (1 H, $C_{(6)}$—H, $W = 13$), 4·29 m (1 H, $C_{(3)}$—H, $W = 45$), 4·19 q (2 H, OCH_2CH_3, $J = 7·3$), 3·39 m (1 H, $C_{(22)}$—H, $W = 35$), 2·22 b d (2 H, $C_{(7)}$—H, $J = 8$), 1·91 s (3 H, CH_3COO), 1·31 t (3 H, CH_2CH_3, $J = 7·3$), 0·99 and 0·62 2 s (2 × 3 H, angular methyls). Mass spectrum (*m*/*z*): 381 (M − CH_3COOH), 366 (381 − CH_3), 339 (366 − HCN), 213 ($C_{16}H_{21}$). For $C_{27}H_{39}NO_4$ (441·6) calculated: 73·44% C, 8·90% H, 3·17% N; found: 73·71% C, 8·80% H, 3·27% N.

Ethyl 3β-Acetoxy-21,24-dinor-22-oxo-5-cholen-23-oate (*XVI*)

The nitrile *XV* (883 mg; 2 mmol) was dissolved in a freshly distilled dried dimethylformamide (20 ml), the solution was evacuated (2 kPa) and the vacuum was destroyed by argon (repeated three times). Lithium hydride (19 mg; 2·4 mmol) was then added under argon. After stirring at 50°C (bath) for 30 min, the mixture was cooled to room temperature and anhydrous cuprous iodide (300 mg; 1·57 mmol) was then added under argon. The mixture was stirred at 50°C (bath) for 15 min, cooled to room temperature and oxygen was passed for 1 h through a sintered glas inlet into the stirred mixture. After cooling with ice to 0°C, 10% acetic acid (30 ml) was added, the mixture was poured into water (50 ml) and extracted with ether (3 × 20 ml). The combined ethereal extracts were filtered with charcoal and anhydrous magnesium sulfate and evaporated. Crystallization of the residue from ether–light petroleum afforded 360 mg (43%) of the ester

XVI, m.p. 130–133°C. IR spectrum (chloroform) cm^{-1}: 1 739 (CH_3COO + $COOC_2H_5$ + + C=O), 1 739, 1 256 and 1 031 (CH_3COO). Mass spectrum (*m/z*): 430 M^+, 370 ($M-CH_3COOH$), 254 ($C_{19}H_{26}$), 239 ($254-CH_3$). For $C_{26}H_{38}O_5$ (430·6) calculated: 72·53% C, 8·90% H; found: 72·74% C, 8·74% H.

3β-Acetoxy-20-(2-maleimido)-21-nor-5-pregnene (*XVIII*)

1,8-Diazabicyclo[5,4,0]undec-7-ene (96%, 525 mg; 0·516 ml; 3·45 mmol) was added under argon to a stirred mixture of carbamoylmethyltriphenylphosphonium chloride[9] (1·4 g; 4·3 mmol) in dichloromethane (40 ml). After stirring at room temperature for 30 min, a solution of the ester *XVI* (861 mg; 2 mmol) in dichloromethane (5 ml) was added. The mixture was set aside for 20 days at room temperature with intermittent stirring. After first 13 days the mixture was treated with another portion of a mixture of carbamoylmethyltriphenylphosphonium chloride[9] (700 mg; 2·15 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (96%; 0·25 ml; 1·67 mmol) in dichloromethane (5 ml) which prior the addition had been stirred at room temperature for 30 min.

The mixture was evaporated with silica gel (10 g) and chromatographed on a column of silica gel (200 g) in benzene–ether 50 : 1 (2 l), 50 : 2 (2 l) and finally 50 : 4 (2 l). Chromatographic fraction whose R_F corresponded to that of maleimide *X* (in benzene–ether 5 : 1) afforded 52 mg of a residue which was purified by preparative thin-layer chromatography (20 × 20 cm; 10 g of silica gel) in benzene–ether 5 : 1. This procedure gave 46 mg (5·4%) of the imide *XVIII*, melting at 230–235°C; $[\alpha]_D^{25}$ −45·2° (*c* 0·7, chloroform). IR spectrum (chloroform) cm^{-1}: 3 439 (NH), 1 727 and 1 253 (CH_3COO–), 1 629 (C=C), 1 727 and 1 778 (maleimide). ^1H NMR spectrum: 6·28 s (1 H, $C_{(3)}$–H), 5·37 m (1 H, $C_{(6)}$–H, $W = 12$), 4·53 m (1 H, $C_{(3)}$–H, $W = 45$), 2·30 b d (2 H, $(C_{(7)}-H_2$, $J = 8$), 2·01 s (3 H, CH_3COO–), 1·01 and 0·67 2 s (2 × 3 H, angular methyls). Mass spectrum (*m/z*): 365 ($M-CH_3COOH$), 350 ($365-CH_3$), 269 ($365-C_4H_2NO_2$), 255 ($269-CH_2$), 213 ($C_{16}H_{21}$). For $C_{26}H_{35}NO_4$ (425·6) calculated: 73·38% C, 8·29% H, 3·29% N; found: 73·11% C, 8·25% H, 3·47% N.

The authors are indebted to Dr L. Kalvoda for valuable advices, Dr A. Trka for measurement and interpretation of mass spectra, Mrs Z. Ledvinová for optical rotation measurements, Mrs K. Matoušková for measurement of IR *spectra and Dr J. Smolíková for their interpretation, and Mrs J. Jelínková for measurement of* ^1H NMR *spectra. The analyses were performed in the Analytical Laboratory of this Institute (Dr J. Horáček, Head).*

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Translated by M. Tichý.