SYNTHESIS OF SOME 1,2-UNSATURATED ANALOGUES OF ANDROGENS WITH THE CYCLOPROPANE RING IN 4,5-POSITION*

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1,2-Unsaturated analogues of testosterone *XI* and *XVII* carrying the cyclopropane ring in position 4,5 were prepared from the corresponding 3-oxo derivatives *VIII* and *XIV via* the enol acetates *IX* and *XV* and the bromo ketones *X* and *XVI* followed by dehydrohalogenation with *sym*-collidine. Analogues of androstenedione *XXI* and testosterone *XIX* with the epoxide ring in 2β,19-position were prepared from the bromo ketone *XVI* with potassium methoxide.

In our earlier studies[1,2] dealing with steroids of potential biological activities the 1,2-unsaturated B-norsteroids carrying the cyclopropane ring in 4,5 position were found to show antiandrogenic action comparable with that of cyproterone acetate. In this paper we described the synthesis of similar analogues derived from the normal steroid series. They are represented by the analogues of testosterone *XI* and 19-hydroxytestosterone *XVII*. The syntheses of the ketones *VII*, *XIII*, *XIX*, and *XXI* which are the 4,5-cyclopropano analogues of testosterone and androstenedione are also described in this paper.

The starting compound for the synthesis of 19-unsubstituted derivatives – the allylic alcohol *II* – was prepared from the corresponding ketone by sodium borohydride reduction[3] using a mixture of ethyl acetate–methanol as solvent. The compound was characterized as the diol *I* and the diacetate *III*. Simmons–Smith methylenation afforded the cyclopropano derivative *V*, characterized as the diol *IV* and the diacetate *VI*. Jones' oxidation of the alcohol *V* gave the ketone *VIII*, which on hydrolysis yielded the desired cyclopropano analogue of testosterone *VII*. Oxidation of the diol *IV* afforded the corresponding analogue of androstenedione *XIII*. The β-configuration of the cyclopropane ring follows from our earlier studies[4,5] and was assigned by analogy. The double bond was introduced into the A ring as follows: The ketone *VIII* was transformed to the enol acetate *IX* on acid catalysed reaction with isopropenyl acetate. Addition of bromine afforded a bromo ketone. It has been shown[6,7] in the cholestane series that the sole product of this reaction is the stable

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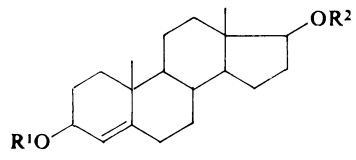
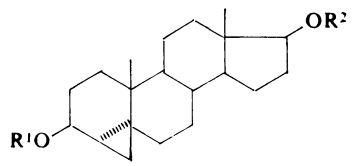
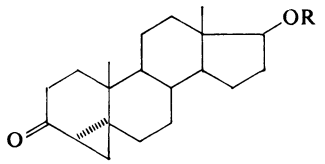


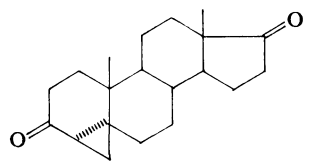
I, $R^1 = R^2 = H$
II, $R^1 = H$, $R^2 = Ac$
III, $R^1 = R^2 = Ac$



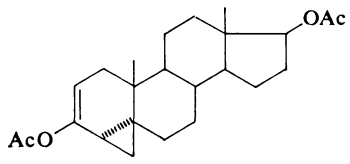
IV, $R^1 = R^2 = H$
V, $R^1 = H$, $R^2 = Ac$
VI, $R^1 = R^2 = Ac$



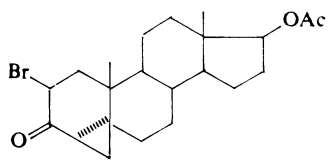
VII, R = H
VIII, R = Ac



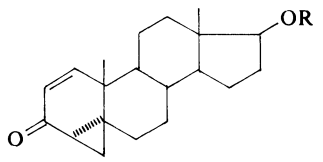
XIII



IX



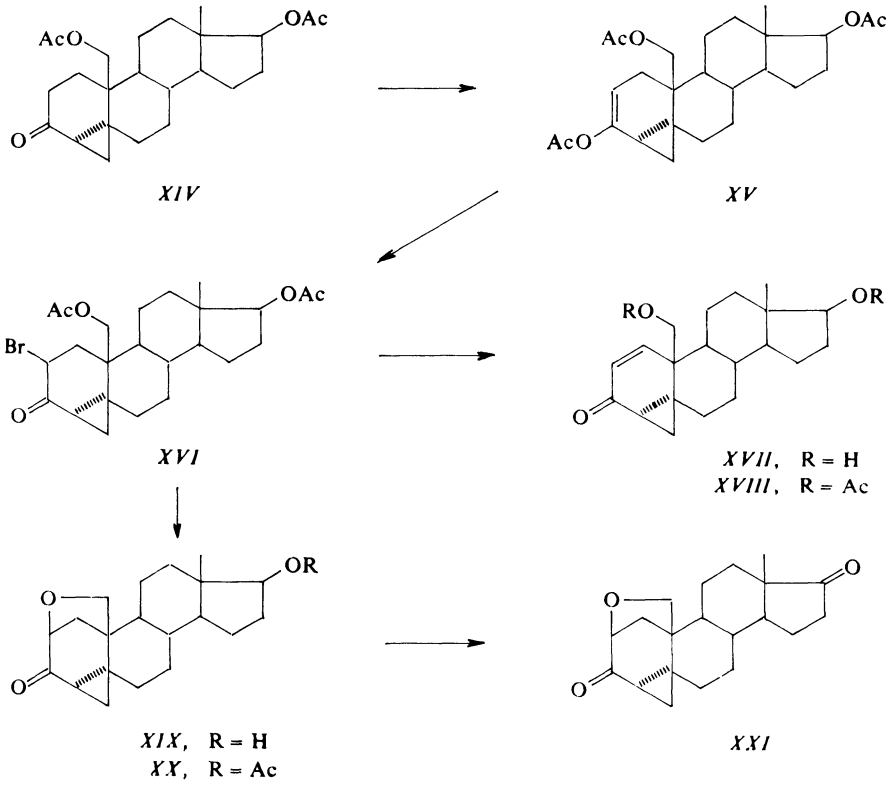
X



XI, R = H
XII, R = Ac

2β-bromo derivative and we therefore assign structure *X* to this bromo ketone. Subsequent reaction with *sym*-collidine and hydrolysis lead to the desired unsaturated cyclopropane analogue of testosterone *XI*. Similar reaction sequence was applied in the 19-hydroxylated series for the synthesis of the unsaturated analogue *XVII*.

On reaction with isopropenyl acetate the ketone[5] *XIV* afforded the enol acetate *XV*, bromine addition gave the bromo ketone *XVI* and reflux with collidine followed by hydrolysis yielded the required unsaturated compound *XVII*. The analogues of testosterone *XIX* and of androstenedione *XXI* with the epoxide ring in 2β,19 position were synthesized from the bromo ketone *XVI* on reaction with potassium methoxide followed by hydrolysis and oxidation. The biological evaluation of the compounds described in this paper is in progress.



EXPERIMENTAL

Melting points were determined on a Kofler block. Optical rotations were carried out in chloroform with an error of ±3°. The infrared spectra were recorded on the Zeiss UR 20 spectrometer in tetrachloromethane unless stated otherwise. Mass spectra were recorded on a JEOL JMS D-100 spectrometer. The identity of samples was checked by mixture melting point determination, by thin-layer chromatography and by spectral evidence. Usual working up of a solution implies washing the solution with 5% aqueous hydrochloric acid, water, 5% aqueous sodium hydrogen carbonate, water, drying over magnesium sulphate, and evaporation of the solvent under reduced pressure. Ligroin refers to the fraction of b.p. 40–60°C.

4-Androstane-3β,17β-diol (*I*)

The diacetate *III* (150 mg) in methanol (25 ml) was treated with a solution of potassium hydroxide (50 mg) in methanol (5 ml) and heated to 50°C for 3 h. Methanol was distilled off under reduced pressure, the residue was diluted with water and the product was taken into ether. The ethereal solution was washed with water, dried, and ether was removed. The crude product was crystallized from methanol to yield 105 mg of the diol *I*, m.p. 138–140°C, $[\alpha]_D^{20}$ +48° (*c* 1·0). For $C_{19}H_{30}O_2$ (290·4) calculated: 78·57% C, 10·41% H; found: 78·43% C, 10·26% H.

4-Androstane-3β,17β-diol 3,17-Diacetate (*III*)

The alcohol[3] *II* (230 mg) was acetylated with acetic anhydride (3 ml) in pyridine (4 ml) for 18 h at room temperature. The mixture was decomposed with ice, diluted with water, and the product was extracted into ether. Usual working up and crystallization from methanol afforded 187 mg of the diacetate *III*, m.p. 110–112°C, $[\alpha]_D^{20}$ 0° (*c* 1·2). For $C_{23}H_{34}O_2$ (374·5) calculated: 73·76% C, 9·15% H; found: 73·65% C, 9·04% H.

4β,5-Cyclopropano-5β-androstane-3β,17β-diol (*IV*)

The monoacetate[3] *V* (210 mg) in methanol (10 ml) was refluxed with a solution of potassium hydroxide (70 mg) in methanol (5 ml) for 1 h. The excess alkali was removed with acetic acid and methanol was distilled off *in vacuo*. The residue was diluted with water and the product was extracted with ether. Usual working up and crystallization from methanol yielded 115 mg of the diol *IV*, m.p. 156–157°C, $[\alpha]_D^{20}$ −31° (*c* 1·4). For $C_{20}H_{32}O_2$ (304·5) calculated: 78·89% C, 10·60% H; found: 78·92% C, 10·74% H.

4β,5-Cyclopropano-5β-androstane-3β,17β-diol 17-Acetate (*V*)

The Zn–Cu couple (0·5%) was prepared by adding zinc dust (44 g; Baker 60–200 mesh) into a solution of cupric acetate monohydrate (700 mg) in acetic acid (150 ml) at 50–60°C and shaking until the solution decolorizes. The solvent was poured off, the metal was washed first with acetic acid (150 ml) and then with eight portions of absolute ether (150 ml each). The metal was covered with absolute ether (300 ml), iodine (120 mg) and diiodomethane (45 ml) were added and the mixture was refluxed under argon for 2 h. After cooling off to the room temperature a solution of the olefin *II* (14 g) in tetrahydrofuran (40 ml) and absolute ether (50 ml) was added and the mixture was stirred at room temperature for 30 h in an argon atmosphere. It was diluted with ether, poured into 5% sodium hydrogen carbonate solution, the ethereal layer was washed with 5% sodium thiosulphate, water, dried, and the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column (600 g) ligroin–ether (2 : 3). Fractions containing the desired adduct were combined and solvents were distilled off. The residue was crystallized from acetone–ligroin to yield 11 g of the cyclopropano derivative *V*, m.p. 125 to 127°C, $[\alpha]_D^{20}$ −31° (*c* 1·3). Literature[3] records m.p. 119–121°C, $[\alpha]_D^{20}$ −29°. IR spectrum: 3 615 (hydroxyl), 3 070 (cyclopropane), 1 740, 1 250, 1 036 cm^{-1} (acetate). For $C_{22}H_{34}O_3$ (346·5) calculated: 76·26% C, 9·89% H; found: 76·18% C, 9·70% H.

4β,5-Cyclopropano-5β-androstane-3β,17β-diol 3,17-Diacetate (*VI*)

The alcohol *V* (180 mg) in pyridine (2 ml) was acetylated with acetic anhydride (1·5 ml) for 18 h at room temperature. Usual working up and crystallization from methanol afforded 145 mg of the diacetate *VI*, m.p. 106°C, $[\alpha]_D^{20}$ −61° (*c* 1·3). For $C_{24}H_{36}O_4$ (388·5) calculated: 74·19% C, 9·34% H; found: 74·25% C, 9·27% H.

4β,5-Cyclopropano-17β-hydroxy-5β-androstan-3-one (*VII*)

A solution of the acetate *VIII* (100 mg) in methanol (20 ml) was treated with potassium hydroxide (50 mg) in methanol (5 ml) and allowed to stand at 35°C for 8 h. The excess alkali was removed with acetic acid and the solvent was distilled off under reduced pressure. The residue was diluted with water and the product was isolated with ether. Usual working up and crystallization from ethyl acetate gave 64 mg of the alcohol *VII*, m.p. 198–200°C, $[\alpha]_D^{20}$ +70° (*c* 1·7). IR spectrum (in chloroform): 3 610, 1 054 (hydroxyl), 3 080 (cyclopropane), 1 673 cm^{-1} (carbonyl). For $C_{20}H_{30}O_2$ (302·4) calculated: 79·42% C, 10·00% H; found: 79·30% C, 9·89% H.

17β-Acetoxy-4β,5-cyclopropano-5β-androstan-3-one (*VIII*)

A solution of the alcohol *V* (6 g) in acetone (120 ml) was treated with excess Jones' reagent and allowed to stand at room temperature for 10 min. The excess oxidizing agent was removed with methanol and the mixture was treated dropwise and under stirring with water. The crystalline product was collected by succion, dissolved in ethyl acetate and the solution was washed with 5% sodium hydrogen carbonate, water, and dried. Evaporation of the solvent and crystalization from acetone–hexan yielded 5·1 g of the ketone *VIII*, m.p. 152–154°C, $[\alpha]_D^{20}$ +66° (*c* 1·4), in accordance with the literature[3]. IR spectrum: 3 075, 3 005 (cyclopropane), 1 734, 1 245, 1 045 (acetate), 1 683 cm^{-1} (carbonyl). For: $C_{22}H_{32}O_3$ (344·5) calculated: 76·70% C, 9·36% H; found: 76·61% C, 9·22% H.

4β,5-Cyclopropano-5β-androst-2-ene-3,17β-diol 3,17-Diacetate (*IX*)

A solution of the ketone *VIII* (5 g) in isopropenyl acetate (80 ml) was treated with conc. sulphuric acid (5 drops) and 40 ml were distilled off in the course of 2 h. Isopropenyl acetate (80 ml) and sulphuric acid were added and 60 ml were distilled off within 2 h. The rest of the acetate was removed under reduced pressure and the residue was dissolved in benzene–ligroin (1 : 1) and the solution was filtered through an alumina column. The filtrate was evaporated and the product was chromatographed on a silica gel column (150 g) in ligroin–ether (2 : 1). Fractions with the desired product were combined and solvents removed to yield 5·2 g of the oily TLC pure enol acetate *IX*, $[\alpha]_D^{20}$ +7° (*c* 1·3). For $C_{24}H_{34}O_4$ (386·5) calculated: 74·58% C, 8·87% H; found: 74·39% C, 8·71% H.

17β-Acetoxy-2β-bromo-4β,5-cyclopropano-5β-androstan-3-one (*X*)

A solution of the enol acetate *IX* (5·1 g) in tetrachloromethane (100 ml) was treated dropwise under stirring at 0°C with a solution of bromine (0·7 ml) in tetrachloromethane (40 ml). The mixture was washed with 5% sodium thiosulphate, 5% sodium hydrogen carbonate, water, dried, and solvent was removed *in vacuo*. The residue was chromatographed on a silica gel column (350 g) in benzene. The corresponding fractions were worked up and the crude product (3·7 g) was crystallized from acetone–water to afford 2·8 g of the bromo ketone *X*, m.p. 201–203°C, $[\alpha]_D^{20}$ +46° (*c* 1·2). IR spectrum: 3 080, 3 010 (cyclopropane), 1 734, 1 245, 1 046 (acetate), 1 696 cm^{-1} (carbonyl). For $C_{22}H_{31}BrO_3$ (423·4) calculated: 62·40% C, 7·38% H, 18·87% Br; found: 62·28% C, 7·29% H, 19·09% Br.

4β,5-Cyclopropano-17β-hydroxy-5β-androst-1-en-3-one (*XI*)

A solution of the acetate *XII* (120 mg) in methanol (30 ml) was hydrolysed with potassium hydroxide (40 mg) in methanol (5 ml) at 35°C for 8 h. The excess alkali was destroyed with acetic acid and methanol was distilled off under reduced pressure. The residue was taken into

ether and the ethereal solution was worked up in the usualy way. Crystallization from ethyl acetate yielded 65 mg of the alcohol *XI*, m.p. 187–189°C, $[\alpha]_D^{20}$ +307° (*c* 1·3). For $C_{20}H_{28}O_2$ (300·4) calculated: 79·95% C, 9·39% H; found: 79·78% C, 9·22% H.

17β-Acetoxy-4β,5-cyclopropano-5β-androst-1-en-3-one (*XII*)

A solution of the bromo ketone *X* (2·5 g) in *sym*-collidine (65 ml) was refluxed for 7 h. Collidine was distilled off *in vacuo* and the residue was diluted with water and the product was extracted with ethyl acetate. The extract was worked up as usual and the residue after evaporation of the solvent (2·3 g) was chromatographed over silica gel (300 g) in benzene. Fractions with the unsaturated derivative were combined and solvent removed to yield 700 mg of a crude product. Crystallization from ethyl acetate–methanol afforded 580 mg of the ketone *XII*, m.p. 142–143°C, $[\alpha]_D^{20}$ +301° (*c* 1·9). IR spectrum: 3 075, 3 025 (cyclopropane), 1 734, 1 245, 1 045 (acetate), 1 670, 1 615 cm^{-1} (carbonyl). For $C_{22}H_{30}O_3$ (342·5) calculated: 77·15% C, 8·83% H; found: 76·95% C, 8·77% H.

4β,5-Cyclopropano-5β-androstane-3,17-dione (*XIII*)

The diol *IV* (350 mg) in acetone (8 ml) was treated with excess Jones' reagent and allowed to stand at room temperature for 15 min. Methanol was added to remove the excess oxidizing agent, the mixture was diluted with water, and the product was taken into ethyl acetate. Usual working up and crystallization from ethyl acetate–ligroin afforded 285 mg of the dione *XIII*, m.p. 127°C, $[\alpha]_D^{20}$ +157° (*c* 1·7). IR spectrum: 3 080, 3 015 (cyclopropane), 1 745 and 1 690 cm^{-1} (carbonyls). For $C_{20}H_{28}O_2$ (300·4) calculated: 79·95% C, 9·39% H; found: 80·08% C, 9·26% H.

4β,5-Cyclopropano-5β-androst-2-ene-3,17β,19-triol 3,17,19-Triacetate (*XV*)

A solution of the ketone[5] *XIV* (3 g) in isopropenyl acetate (70 ml) was treated with conc. sulphuric acid (4 drops) and 40 ml were distilled off in the course of 2 h. The operation was repeated with additional 70 ml of isopropenyl acetate and the rest of the ester was removed *in vacuo*. The residue was dissolved in ether and the ethereal solution was washed with 5% sodium hydrogen carbonate, water, and dried. The product after evaporation of ether was chromatographed on a silica gel column (200 g) in benzene–ether (9 : 1). The corresponding fractions were worked up to yield 2·6 g of the triacetate *XV*, which resisted all attempts at crystallization, $[\alpha]_D^{20}$ +17° (*c* 1·4). For $C_{26}H_{36}O_6$ (444·5) calculated: 70·24% C, 8·16% H; found: 70·01% C, 8·05% H.

17β-Acetoxy-2β-bromo-4β,5-cyclopropano-5β-androstan-3-one (*XVI*)

The enol acetate *XV* (2·5 g) was dissolved in tetrachloromethane (50 ml), calcium carbonate (3·5 g) was added and the mixture was treated dropwise under stirring at 0°C with a solution of bromine (0·28 ml) in tetrachloromethane (20 ml). The slightly yellow mixture was washed with 5% sodium thiosulphate, 5% sodium hydrogen carbonate, water, dried, and the solvent was distilled off *in vacuo*. The residue (3·1 g) was chromatographed over silica gel (200 g) in ligroin–ether (3 : 2). Working up of the corresponding fractions and crystallization from methanol yielded 2 g of the bromo ketone *XVI*, m.p. 170–172°C, $[\alpha]_D^{20}$ +58° (*c* 1·6). IR spectrum: 3 080, 3 010 (cyclopropane), 1 741, 1 235, 1 040 (acetate), 1 697 cm^{-1} (carbonyl). For $C_{24}H_{33}BrO_5$ (481·4) calculated: 59·87% C, 6·90% H, 16·60% Br; found: 59·69% C, 6·81% H, 16·80% Br.

4β,5-Cyclopropano-17β,19-dihydroxy-5β-androst-1-en-3-one (*XVII*)

The acetate *XVIII* (80 mg) in tetrahydrofuran (1 ml) was treated with a solution of potassium hydroxide (20 mg) in methanol (1 ml) and allowed to stand at 45°C for 5 h. The alkali was neutralized with acetic acid and solvents were distilled off under reduced pressure. The residue was treated with water and the product was isolated with ethyl acetate. Usual working up and crystallization from ethyl acetate afforded 58 mg of the diol *XVII*, m.p. 240–242°C, $[\alpha]_D^{20}$ +298° (*c* 1·2). For $C_{20}H_{28}O_3$ (316·4) calculated: 75·91% C, 8·92% H; found: 75·80% C, 8·78% H.

17β,19-Diacetoxy-4β,5-cyclopropano-5β-androst-1-en-3-one (*XVIII*)

The bromo ketone *XVI* (1·9 g) in *sym*-collidine (60 ml) was refluxed for 5 h. Collidine was distilled off under reduced pressure, the residue was diluted with water, and the product was isolated with ether. Usual working up yielded 1·2 g of a solid which was chromatographed over silica gel (180 g) in ligroin–ether (2 : 1). Working up of the corresponding fractions and crystallization from methanol gave 420 mg of the olefin *XVIII*, m.p. 130–132°C, $[\alpha]_D^{20}$ +248° (*c* 1·3). IR spectrum: 3 075, 3 030 (cyclopropane), 1 742, 1 239 (acetate), 1 672 cm^{-1} (carbonyl). Mass spectrum: $M^{+\cdot}$ 400. For $C_{24}H_{32}O_5$ (400·5) calculated: 71·97% C, 8·05% H; found: 71·69% C, 8·01% H.

4β,5-Cyclopropano-17β-hydroxy-2β,19-epoxy-5β-androstan-3-one (*XIX*)

The bromo ketone *XVI* (1·2 g) in methanol (150 ml) was treated with a solution of potassium hydroxide (1·3 g) in methanol (30 ml) and allowed to stand at 35°C for 4 h. The excess alkali was neutralized with acetic acid, solvents were removed *in vacuo* and the product was isolated with ethyl acetate. Usual working up and crystallization from ethyl acetate yielded 760 mg of the alcohol *XIX*, m.p. 237–238°C, $[\alpha]_D^{20}$ −18° (*c* 1·4). IR spectrum (in chloroform): 3 610 (hydroxyl), 3 090 (cyclopropane), 1 701 (carbonyl), 1 057, 1 044, 1 022 cm^{-1} (ether). For $C_{20}H_{28}O_3$(316·4) calculated: 75·91% C, 8·92% H; found: 75·80% C, 8·78% H.

17β-Acetoxy-4β,5-cyclopropano-2β,19-epoxy-5β-androstan-3-one (*XX*)

The alcohol *XIX* (700 mg) was acetylated with acetic anhydride (3 ml) in pyridine (4 ml) at room temperature for 20 h. The reaction mixture was decomposed with ice, diluted with water, and the product was extracted with ether. Usual working up and crystallization from ethyl acetate yielded 600 mg of the acetate *XX*, m.p. 210–211°C, $[\alpha]_D^{20}$ −7° (*c* 1·6). IR spectrum: 1 720, 1 255, 1 025 (acetate), 1 701 cm^{-1} (carbonyl). For $C_{22}H_{30}O_4$ (358·5) calculated: 73·71% C, 8·44% H; found: 73·73% C, 8·42% H.

4β,5-Cyclopropano-2β,19-epoxy-5β-androstane-3,17-dione (*XXI*)

A solution of the alcohol *XIX* (320 mg) in acetone (8 ml) was treated with excess Jones' reagent and allowed to stand at room temperature for 15 min. The excess reagent was removed with methanol, the reaction mixture was diluted with water, and the product was taken into ethyl acetate. Usual working up and crystallization from methanol afforded 265 mg of the dione *XXI*, m.p. 193°C, $[\alpha]_D^{20}$ +49° (*c* 1·6). IR spectrum: 3 010 (cyclopropane), 1 745 and 1 711 (carbonyls), 1 056, 1 026, 1 012, 932, 908 cm^{-1} (epoxide). For $C_{20}H_{26}O_3$ (314·4) calculated: 76·40% C, 8·34% H; found: 76·32% C, 8·17% H.

The analyses were carried out in the Analytical Laboratory of this Institute by Mrs E. Sýkorová and Mrs E. Šípová under the direction of Dr J. Horáček. The IR *spectra were recorded by Mrs K. Matoušková under the direction of Dr J. Smolíková. The mass spectrum was recorded and interpreted by Dr A. Trka.*

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