[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX S.A.]

Steroids. XLIV.[1] Synthesis of Δ^4-Pregnene-11α,21-diol-3,20-dione Diacetate, the 11-Epimer of Corticosterone Acetate

BY FRANZ SONDHEIMER, G. ROSENKRANZ, O. MANCERA AND CARL DJERASSI[2]

RECEIVED DECEMBER 22, 1952

Pregnane-3α,11α-diol-20-one diacetate (II) with lead tetraacetate gave the 21-acetoxy compound (III), which was partially saponified to the 11-monoacetate (IV). N-Bromoacetamide oxidation at C-3 and acetylation furnished pregnane-11α,21-diol-3,20-dione diacetate (Vb), which on bromination and dehydrobromination with semicarbazide hydrochloride yielded Δ^4-pregnene-11α,21-diol-3,20-dione diacetate (Ib). A similar series of transformations was performed in the 5α (allo) series. In this case the final double bond introduction was carried out through tribromination, sodium iodide treatment and chromous chloride reduction.

A program aimed at the synthesis of the 11α-hydroxy analogs of the various adrenal hormones has been under way for some time in these laboratories, and syntheses of 11α-hydroxyprogesterone,[3] 11α,17α-dihydroxyprogesterone[4] and 11α,17α,21-trihydroxyprogesterone[4,5] have already been described. We now wish to record the preparation of 11α,21-dihydroxyprogesterone (Δ^4-pregnene-11α,-21-diol-3,20-dione, the 11-epimer of corticosterone) as the diacetate Ib, by two different routes. The synthesis of this compound has previously been described by Gallagher,[6] who prepared it from 3α,-11α-diacetoxyetianic acid[7a] by the diazoketone method. It was however not obtained in the crystalline state, and was probably not pure.[7b] The free compound Ia has very recently been obtained through the microbiological oxidation of desoxycorticosterone with *Aspergillus niger*[8] as well as by the incubation of 11α-hydroxyprogesterone with adrenal breis.[5a]

The preferred of our two routes utilized as starting material pregnane-3α,11α-diol-20-one diacetate (II) which may be obtained by the side chain degradation of 11α-hydroxylithocholic acid,[7a] from 11α-hydroxyprogesterone,[1] or from pregnan-3α-ol-11,20-dione.[9] Acetoxylation of II at C-21 was effected by means of lead tetraacetate in acetic acid,[10] and the resulting pregnane-3α,11α,21-triol-20-one triacetate (III) was partially saponified by means of potassium hydroxide in aqueous methanol.[3,4] The 11-monoacetate (IV) thus formed was not obtained crystalline, but was oxidized directly by means of N-bromoacetamide in aqueous *t*-butyl alcohol at 10°[11] to pregnane-11α,21-diol-3,20-dione 11-monoacetate (Va), which on acetylation furnished the 11,21-diacetate (Vb). The Δ^4-double bond introduction was effected in *ca.* 60% yield through bromination in acetic acid to the 4-bromo compound VI, which on treatment with semicarbazide hydrochloride (*inter al.* reference 11), followed by cleavage of the semicarbazone with *p*-hydroxybenzaldehyde,[12] was converted to the beautifully crystalline Δ^4-pregnene-11α,21-diol-3,20-dione diacetate (Ib).

The second, less satisfactory, route proceeded *via* compounds of the 5α (allo) series. Allopregnane-3β,11α-diol-20-one diacetate (VII)[13] was acetoxylated at C-21 and the resulting triacetate VIII partially saponified in the same way as described above for the 5β ("normal") series. The 11-monoacetate IX in this series was a crystalline compound, which on partial acetylation gave the 11,21-diacetate (X), oxidized by means of chromic acid to allopregnane-11α,21-diol-3,20-dione diacetate (XIb). The latter could alternatively be obtained by a method analogous to that used in the 5β series, *viz.*, N-bromoacetamide oxidation of IX to the corresponding 3-ketone XIa, followed by acetylation at C-21. The double bond introduction into XIb was effected through tribromination in chloroform to give a crude 2,4,17-tribromide (*cf.* reference 3), followed by treatment with sodium iodide and reduction with chromous chloride.[14] The resulting oil was shown to contain the Δ^4-3-ketone Ib, but the crystalline material could only be obtained with difficulty (see Experimental Section).

Compound Ib is being tested biologically and the results will be reported later.

Experimental[15]

Pregnane-3α,11α,21-triol-20-one Triacetate (III).—A solution containing 9.5 g. of pregnane-3α,11α-diol-20-one

(1) Paper XLIII, O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **75**, 1286 (1953).

(2) Department of Chemistry, Wayne University, Detroit, Michigan.

(3) O. Mancera, J. Romo, F. Sondheimer, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **17**, 1066 (1952).

(4) J. Romo, G. Rosenkranz, C. Djerassi and F. Sondheimer, THIS JOURNAL, **75**, 1277 (1953). (Steroids XLI.)

(5) (a) J. Romo, A. Zaffaroni, J. Hendrichs, G. Rosenkranz, C. Djerassi and F. Sondheimer, *Chemistry and Industry*, 783, 834 (1952); (b) see also H. L. Herzog, E. P. Oliveto, M. A. Jevnik and E. B. Hershberg, THIS JOURNAL, **74**, 4470 (1952).

(6) T. F. Gallagher, "Recent Progress in Hormone Research," Vol. I, Academic Press, Inc., New York, N. Y., 1947, p. 95.

(7) (a) W. P. Long, C. W. Marshall and T. F. Gallagher, *J. Biol. Chem.*, **165**, 197 (1946). (b) While this manuscript was being prepared a report appeared by A. Lardon and T. Reichstein (*Pharm. Acta Helv.*, **27**, 287 (1952)) in which the synthesis of crystalline 11-epicorticosterone diacetate (Ib) from sarmentogenin was described.

(8) J. Fried, R. W. Thoma, J. R. Gerke, J. E. Herz, M. N. Donin and D. Perlman, THIS JOURNAL, **74**, 3962 (1952).

(9) F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, *ibid.*, **75**, 1282 (1953).

(10) *Cf.* T. Reichstein and C. Montigel, *Helv. Chim. Acta*, **22**, 1212 (1939).

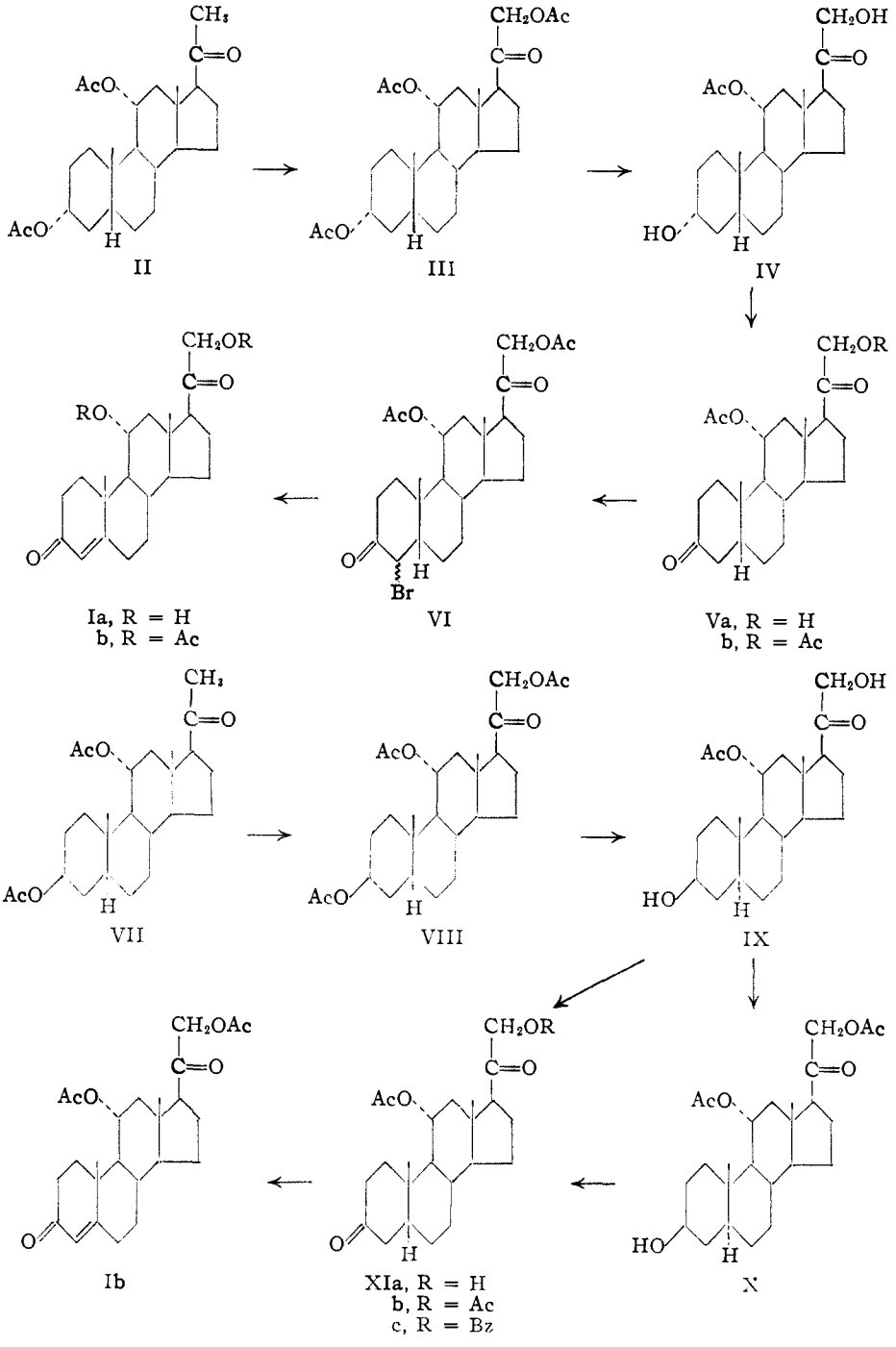
(11) *Cf.* T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, THIS JOURNAL, **74**, 483 (1952).

(12) *Cf.* V. R. Mattox, E. L. Woroch, G. A. Fleisher and E. C. Kendall, *J. Biol. Chem.*, **197**, 261 (1952).

(13) C. Djerassi, E. Batres, J. Romo and G. Rosenkranz, THIS JOURNAL, **74**, 3634 (1952).

(14) G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, *ibid.*, **72**, 4077 (1950).

(15) Melting points are uncorrected. Unless noted otherwise, rotations were determined in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are grateful to Srta. Paquita Revaque for these measurements as well as for the infrared spectra, which were obtained on a Perkin-Elmer model 12C spectrometer with sodium chloride prism. Thanks are due to Srta. Amparo Barba and staff for the microanalyses, and to Srta. Carmen Velasco for technical assistance.



diacetate (II)[1,7,9] (m.p. 136–139°) and 10.85 g. of lead tetraacetate (Arapahoe Chemicals, Boulder, Colo.; 90% pure) in 250 cc. of glacial acetic acid and 4.2 cc. of acetic anhydride was heated at 75° for 16 hours (all the tetraacetate had been consumed by this time). The solution was poured into water, and the product was isolated with ether. Crystallization from acetone–hexane furnished 4.58 g. (42.5%) of the triacetate III with m.p. 170–175°, $[\alpha]^{20}D$ +76°. The analytical sample was recrystallized from methanol, and exhibited m.p. 182–184°, $[\alpha]^{20}D$ +80°, $\lambda_{max}^{CHCl_3}$ 1718 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 67.81; H, 8.28.

Saponification of the mother liquors with potassium hydroxide in methanol (room temperature, 1 hour), chromatography of the oily product on alumina, followed by acetylation of the crystalline fractions eluted with ether–chloroform (3:1), furnished 2.37 g. (25%) of starting material II with m.p. 138–141°.

Pregnane-11α,21-diol-3,20-dione 11-Monoacetate (IV).—A solution of 4.0 g. of potassium hydroxide in 10 cc. of water and 40 cc. of methanol was slowly added to 4.5 g. of the above triacetate III dissolved in 400 cc. of methanol, with ice cooling in an atmosphere of nitrogen. The solution was allowed to attain room temperature and then allowed to stand for 1 hour. The excess base was neutralized with acetic acid, most of the solvent was removed under vacuum, water was added to the residue, and the product was extracted with ether. The crude 11-monoacetate IV (3.77 g.) was obtained as a yellow oil, which was not purified.

N-Bromoacetamide (2.66 g.) was added to a cooled solution of the crude monoacetate IV in 100 cc. of *t*-butyl alcohol containing 2.5 cc. of water, the solution was kept at 10° for 6 hours and then in the refrigerator (*ca.* 4°) for 12 hours. Water was added, the product was extracted with ether, and the ether extract was washed with sodium thiosulfate solution and water. Crystallization from acetone–hexane yielded 1.5 g. (41% based on III) of the diketone Va with m.p. 158–162°. The analytical sample showed m.p. 169–171°, $[\alpha]^{20}D$ +56°, $\lambda_{max}^{CHCl_3}$ 1718 and 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 71.19; H, 8.92.

The 11,21-diacetate Vb was prepared with acetic anhydride in pyridine (1 hour, steam-bath). It was crystallized from acetone–hexane and exhibited m.p. 142–144°, $[\alpha]^{20}D$ +72°, $\lambda_{max}^{CHCl_3}$ 1736, 1718 and 1700 cm.$^{-1}$, no free hydroxyl band.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.63; H, 8.71.

When the mother liquors, remaining after removal of the crystalline diketone Va, were acetylated and the product chromatographed, *ca.* 15% of the 3,11,21-triacetate III was recovered.

Δ^4-Pregnene-11α,21-diol-3,20-dione Diacetate (Ib) from Pregnane-11α,21-diol-3,20-dione Diacetate (Vb).—A solution of 0.79 g. of the diacetate Vb in 30 cc. of C.P. acetic acid was treated with 0.3 cc. of a solution of bromine in acetic acid (containing 95 mg. Br_2/cc.). The same bromine solution (3.0 cc.) containing 155 mg. of anhydrous sodium acetate (*cf.* reference 11) was then added dropwise. The solution, as soon as it had become decolorized after the end of the addition, was poured into water, and the amorphous

bromo compound VI (0.83 g.) was collected by filtration. It could not be crystallized.

Anal. Calcd. for $C_{25}H_{35}O_6Br$: Br, 15.64. Found: Br, 14.91.

The crude bromo compound (0.83 g.) dissolved in 50 cc. of glacial acetic acid was added to a solution of 0.54 g. (3 moles) of semicarbazide hydrochloride and 0.40 g. (3 moles) of sodium acetate in 50 cc. of 96% acetic acid. The reaction mixture was allowed to stand at room temperature in an atmosphere of nitrogen for 4 hours, a solution of 0.18 g. of semicarbazide hydrochloride and 0.13 g. of sodium acetate in 10 cc. of acetic acid was then added, and the reaction was allowed to proceed at room temperature under nitrogen for another 2 hours. A suspension of 2.0 g. of *p*-hydroxybenzaldehyde and 0.13 g. of sodium acetate in 40 cc. of water were added, and the homogeneous reaction mixture was left at room temperature for 15 hours. Most of the acid was removed under vacuum, the residue was diluted with water, extracted with ether, and the extract washed well with sodium carbonate solution. The oily product crystallized after standing for several days. Crystallization from acetone–hexane, and chromatographic purification of the mother liquors on alumina furnished a total of 0.46 g. (59% based on the dihydro compound Vb) of the Δ^4-3-ketone Ib as long transparent needles with m.p. 139–142°, raised on further crystallization to m.p. 144–146°, $[\alpha]^{20}D$ +158°, λ_{max} 240 mμ, log ϵ 4.23, $\lambda_{max}^{CHCl_3}$ 1748, 1736 and 1660 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 70.08; H, 8.13.

Allopregnane-3β,11α,21-triol-20-one Triacetate (VIII).—Lead tetraacetate (13.6 g.) was gradually added during 2 hours to a solution of 12.0 g. of allopregnane-3β,11α-diol-20-one diacetate (VII)[13] in 400 cc. of C.P. glacial acetic acid containing 6.6 cc. of acetic anhydride, kept at 80°. After a further 10 hours at 80°, all the tetraacetate had reacted, the mixture was poured into ice-water, and the product was extracted with ether. Crystallization from acetone–hexane gave 8.46 g. (62%) of the triacetate VIII with m.p. 132–136°. The analytical sample showed m.p. 138–140°, $[\alpha]^{20}D$ +55°, λ_{max}^{mull} 1736 and 1720 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 68.48; H, 8.47.

The mother liquors were partially saponified by the procedure described directly below, and the product was chromatographed on alumina. In this way 1.19 g. (10.5% based on VII) of allopregnane-3β,11α,21-triol-20-one 11-monoacetate IX with m.p. 218–223° and 1.25 g. (11.5% recovery) of allopregnane-3β,11α-diol-20-one 11-monoacetate[3] with m.p. 174–176° were obtained. The yield of triacetate VIII taking into account these materials was therefore 84%.

Allopregnane-3β,11α,21-triol-20-one 11-Monoacetate (IX).—A solution of 5.0 g. of potassium hydroxide in 20 cc. of water and 30 cc. of methanol was added to an ice-cooled solution of 8.0 g. of the triacetate VIII in 500 cc. of methanol, strictly under nitrogen. After 1 hour at room temperature the product was isolated as described above for the corresponding 5β derivative IV. Crystallization from ether yielded 5.16 g. (78%) of the 11-monoacetate IX with m.p. 220–225°. Recrystallization from acetone gave the analytical specimen with m.p. 225–230° or 230–236° (when introduced in the bath at 215°), $[\alpha]^{20}D$ +26°, $\lambda_{max}^{CHCl_3}$ 1720 and 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.25. Found: C, 70.04; H, 9.00.

Allopregnane-11α,21-diol-3,20-dione Diacetate (XIb) from Allopregnane-3β,11α,21-triol-20-one 11-Monoacetate (IX). (a) **Via the 11,21-Diacetate X.**—The crude 11,21-diacetate X was prepared by treating 7.2 g. of the 11-monoacetate IX in 50 cc. of dry pyridine cooled in Dry Ice, slowly with 2.0 cc. (1.15 moles) of redistilled acetic anhydride, leaving the solution at −10° for 22 hours, adding ice-water and extracting with ether. It was a yellow oil, which could not be induced to crystallize. It was dissolved in 150 cc. of glacial acetic acid, and a solution of 1.4 g. (1.2 equivalents) of chromium trioxide in 50 cc. of 80% acetic acid was added dropwise with stirring during 30 minutes. After 2 hours at room temperature water was added, and the product was isolated with ether in the usual way. Crystallization from acetone–hexane and chromatographic purification of the mother liquors on alumina furnished 3.40 g. (43%) of the 3,20-dione XIb with m.p. 141–145°. The analytical sample exhibited m.p. 146–147°, $[\alpha]^{20}D$ +78°, $\lambda_{max}^{CHCl_3}$ 1750, 1736, 1724 and 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.74; H, 8.45.

(b) **Via the 11-Acetate XIa.**—The 11-monoacetate IX (1.0 g.) in 15 cc. of *t*-butyl alcohol and 1 cc. of water was treated with 0.42 g. (1.2 moles) of N-bromoacetamide at 10°. After another 5 hours at 10° water was added and the product was extracted with ether. Crystallization from acetone–hexane gave 0.57 g. (57%) of the 3,20-dione-11-acetate XIa with m.p. 148–152°. The analytical sample showed m.p. 155–157°, $[\alpha]^{20}D$ +61°, $\lambda_{max}^{CHCl_3}$ 1718 and 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.82; H, 9.05.

The 11,21-diacetate XIb with m.p. 146–147° was prepared with acetic anhydride and pyridine (steam-bath, 30 minutes) and proved to be identical (mixture melting point, infrared spectrum) with that prepared by method (a).

The 11-monoacetate XIa could be regenerated from XIb by saponification of the latter with alcoholic potassium hydroxide for 30 minutes at room temperature under nitrogen.

Allopregnane-11α,21-diol-3,20-dione 11-Acetate 21-Benzoate (XIc).—This substance was prepared from the corresponding 11-monoacetate XIa with benzoyl chloride and pyridine for 1 hour at room temperature. It was crystallized from acetone–hexane and had m.p. 205–207°, $[\alpha]^{20}D$ +93°, λ_{max} 230 mμ, log ϵ 4.25, $\lambda_{max}^{CHCl_3}$ 1736, 1718 and 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{38}O_6$: C, 72.85; H, 7.74. Found: C, 72.56; H, 7.66.

Δ^4-Pregnene-11α,21-diol-3,20-dione Diacetate (Ib) from Allopregnane-11α,21-diol-3,20-dione Diacetate (XIb).—The diacetate XIb (1.5 g.) in 75 cc. of C.P. chloroform was treated with 5 drops of a saturated solution of hydrogen bromide in acetic acid, and then dropwise with 1.8 g. (3.2 mols) of bromine in 30 cc. of C.P. chloroform. The solution was allowed to stand overnight, was then poured into water, and the chloroform layer was washed with sodium carbonate solution, dried and evaporated. The resulting crude 2,4,17-tribromide was heated under reflux with 4 g. of sodium iodide in 75 cc. of methyl ethyl ketone for 16 hours, whereupon water was added. The Δ^4-2-iodo-17-bromo compound was extracted with ether, the extract was washed with sodium thiosulfate solution, dried and evaporated under reduced pressure. The orange oil (λ_{max} 244 mμ, log ϵ 4.10) dissolved in 75 cc. of acetone was treated in an atmosphere of carbon dioxide with a solution of chromous chloride prepared[14] from 10 g. of chromic chloride. After 10 minutes at room temperature water was added, and the product was extracted with ether. The residual oil (λ_{max} 242 mμ, log ϵ 4.11) was chromatographed on alumina, and the fractions eluted with benzene–ether were combined (340 mg., λ_{max} 240 mμ, log ϵ 4.15). Paper chromatography of this product[15] revealed that it consisted of three entities. The most abundant (*ca.* 60% of total) was the least polar, and was shown to be the desired Δ^4-pregnene-11α,21-diol-3,20-dione diacetate (Ib) through mixed paper chromatography and sulfuric acid curve comparison. The impure product could not be induced to crystallize. It was therefore chromatographed twice more on alumina; repeated recrystallization of the solid fractions from acetone–hexane then yielded a very small amount of Ib with m.p. 140–144°, undepressed on admixture with the material described before.

Under identical conditions of tribromination in chloroform, sodium iodide and chromous chloride treatment, 21-acetoxyallopregnane-3,20-dione was converted to crystalline desoxycorticosterone acetate in *ca.* 15% yield.

MEXICO CITY 17, D.F.

(16) We would like to thank Dr. A. Zaffaroni of our Biochemistry Department for these measurements.