679. *Steroids Derived from Hecogenin. Part II.*[1] *Some Ring* C-*Seco-derivatives.*

By Peter Bladon and W. McMeekin.

The Baeyer–Villiger oxidation of hecogenin acetate gives, besides the known hecololactone acetate, some 5% of the isomeric isohecololactone acetate. Derivatives of this lactone and of the corresponding acid are described.

The reaction between methyl hecolate and an excess of phenylmagnesium bromide or phenyl-lithium proceeded only to the stage of the phenyl ketone (VI). This ketone was readily cyclised to the enol ether (VII).

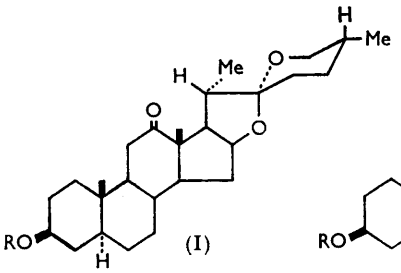
The lactam produced by Beckmann rearrangement of hecogenin acetate oxime was converted into derivatives of hecolic acid, this being a proof of the structure (X) for the lactam.

In 1954 Rothman, Wall, and Eddy[2] reported the formation of a lactone by the Baeyer–Villiger oxidation of hecogenin acetate (I; R = Ac). This lactone, to which they gave the name hecololactone acetate, was hydrolysed to the corresponding acid, hecolic acid. The transformations which the lactone and the acid underwent led these workers to ascribe[3] to them the undoubtedly correct structures (II; R = Ac) and (III; R = R′ = H).

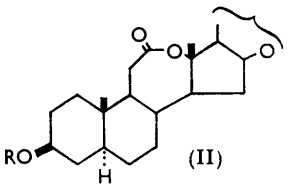
Methyl hecolate (III; R = H, R′ = Me) seemed a suitable starting material for a Barbier–Wieland reaction. We prepared hecolic acid by the second of two published

[1] Part I, Bladon and McMeekin, *J.*, 1960, 2191.
[2] Rothman, Wall, and Eddy, *J. Amer. Chem. Soc.*, 1954, **76**, 527.
[3] Rothman and Wall, *J. Amer. Chem. Soc.*, 1955, **77**, 2228, 2229.

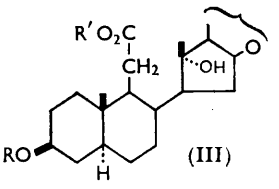
methods,[2] involving oxidation of hecogenin with peracetic acid in a two-phase system in the presence of sulphuric acid. The resulting crude lactone mixture was hydrolysed directly to a mixture of acids that gave on crystallisation 82% of hecolic acid and 5% of a



(I)



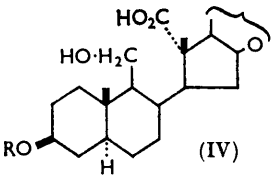
(II)



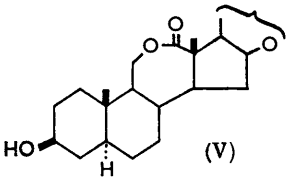
(III)

second, isomeric acid which we call isohecolic acid (sparing solubility of the former in chloroform made this separation feasible). Isohecolic acid formed a methyl ester, whose diacetate no longer had infrared absorption characteristic of a hydroxyl group These facts show that isohecolic acid has structure (IV; R = R′ = H), formed by the alternative fission of ring C.

Isohecolic acid readily lactonised *in vacuo* above its melting point, giving a lactone (V), characterised as its acetate and benzoate.



(IV)



(V)

The melting points in the iso series are in general higher than in the isomeric series, and the optical rotations also differ. In the infrared spectra carbonyl absorption of the iso-compounds tends to occur at lower frequency than in the normal series.

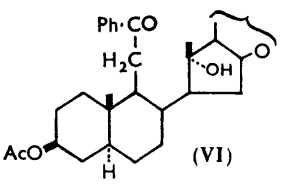
Two fractions of neutral material were encountered in the preparation of the acids. The first was a mixture of unchanged hecogenin, tigogenin, and 9(11)-dehydrohecogenin, the last two being known impurities in the hecogenin used (cf. ref. 2). The second was a mixture of unhydrolysed (or perhaps recyclised) lactones. Hydrolysis of this gave hecolic and isohecolic acid, together with a small quantity of a third acid (acid C), which were separated by crystallisation. Acid C is not a mixture of hecolic and isohecolic acid since its optical rotation is more negative than that of either. So far the small amount available has precluded further work on it. It is possibly the 13β-hydroxy-isomer of hecolic acid.

Treatment of methyl hecolate with an excess of phenylmagnesium bromide under the usual Barbier–Wieland conditions [4] or with phenyl-lithium resulted in the uptake of only one mole of reagent. The product, in neither case crystalline, had an ultraviolet spectrum ($\lambda_{max.}$ 242 mμ) similar to that of propiophenone [5] ($\lambda_{max.}$ 242 mμ), consistently with its formulation as the phenyl ketone (VI). On acetylation followed by brief treatment with boiling acetic acid, this compound was dehydrated to a crystalline product formulated as (VII; R = Ac). The ultraviolet spectrum ($\lambda_{max.}$ 205, 218, 263 mμ) was fairly consistent with this formulation, its difference from that of the analogous β-methylstyrene [5] ($\lambda_{max.}$ 251 mμ) being attributable to the influence of the ethereal oxygen atom. Good yields of this compound were obtained only under anhydrous conditions, since, when it was heated

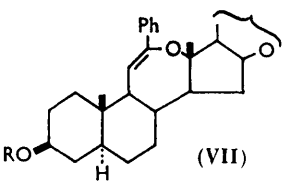
[4] Riegel, Moffett, and McIntosh, *Org. Synth.*, 1955, Coll. Vol. III, p. 237.
[5] Gillam and Stern, " An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Edward Arnold Ltd., London, 2nd edn., 1957, p. 277.

with aqueous acetic acid, the ring opened and 3β-acetoxy-12-phenyl-12,13-seco-5α,25D-spirost-13-en-12-one (VIII) was formed. In contrast, the enol-ether system was unaffected by alkali, which gave the free alcohol (VII; R = H).

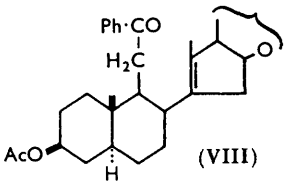
Attempts to oxidise the enol ether (VII; R = Ac) and the phenyl ketone (VIII) with a view to obtaining the lower homologue of hecolic acid were unsuccessful.



(VI)



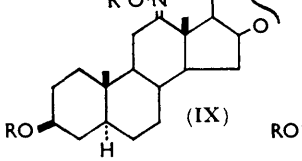
(VII)



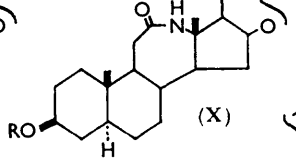
(VIII)

Rearrangement [6] of the oxime [7] (IX; R = Ac, R′ = H) of hecogenin acetate by toluene-*p*-sulphonyl chloride in pyridine yields a lactam (hecololactam), that had been tentatively assigned structure (X; R = Ac) rather than (Xa) on the basis of the ultraviolet spectrum of the related lactam (XIV) derived from 9(11)-dehydrohecogenin acetate oxime (XIII; R = Ac, R′ = H). Since the two isomeric lactones derived from hecogenin were now available, this hypothesis could be tested by conversion of the lactam into the corresponding lactone. According to White,[8] the *N*-nitroso-derivative of a substituted amide or lactam readily loses nitrogen on gentle heating, to yield an ester or lactone. This reaction has already been used successfully in the steroid series by Sato and Latham,[9] in the conversion of *ON*-diacetyldihydrotomatidine and *ON*-diacetyldihydrosolasodine into dihydroneotigogenin and dihydrotigogenin respectively.

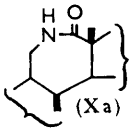
Nitrosation of the lactam acetate (X; R = Ac) by dinitrogen tetroxide in carbon tetrachloride (the reagent used by Sato and Latham) was unselective, attack on the sapogenin side-chain being difficult to control. However, treatment of the lactam acetate in acetic acid and acetic anhydride with sodium nitrite at 0° gave directly (*i.e.*, without isolation of the nitroso-derivative and without heating) hecololactone acetate (II; R = Ac)



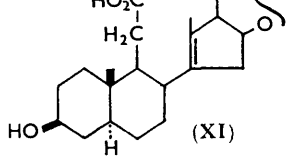
(IX)



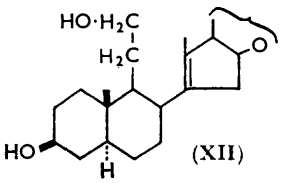
(X)



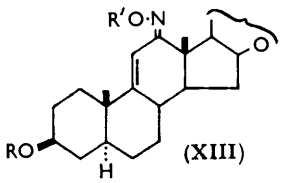
(Xa)



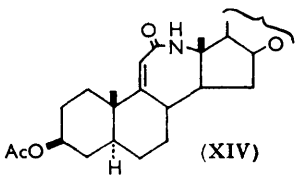
(XI)



(XII)



(XIII)



(XIV)

in 8—10% yield. The material in the mother-liquors failed to crystallise, but methanolic potassium hydroxide and acidification of the solution converted it into a crystalline acid in 90% yield. This is assigned structure (XI), since lithium aluminium hydride reduced it to the known [1] diol (XII). As this acid is derived from hecolic and not isohecolic acid, it

[6] Mazur, *J. Amer. Chem. Soc.*, 1959, **81**, 1454.
[7] Anliker, Rohr, and Heusser, *Helv. Chim. Acta*, 1955, **38**, 1171.
[8] White, *J. Amer. Chem. Soc.*, 1955, **77**, 6008, 6011, 6014.
[9] Sato and Latham, *J. Org. Chem.*, 1957, **22**, 981.

follows that the lactam must have structure (X). The possibility that the lactam was a mixture is also eliminated.

The oxime (XIII; R = Ac, R′ = H) of 9(11)-dehydrohecogenin acetate was rearranged in an analogous manner to the unsaturated lactam acetate (XIV) (cf. Mazur [6]), but in this case some of the intermediate oxime toluene-*p*-sulphonate (XIII; R = Ac, R′ = *p*-$C_6H_4Me{\cdot}SO_2$) could be isolated. Heating this ester with acidic ethanol converted it into the unsaturated lactam acetate. The unsaturated lactam acetate was recovered unchanged after treatment with sodium nitrite in acetic acid and acetic anhydride.

Experimental

M. p.s were determined on a Kofler block; with certain compounds two m. p.s were observed, with intermediate resolidification; in these cases the first m. p. is enclosed in parentheses below and is only an approximate value. With acids which show this effect the second m. p. is that of the lactone.

Unless otherwise stated, optical rotations were measured for chloroform solutions, and ultraviolet spectra for ethanol solutions. Alumina for chromatography was deactivated by treatment with 10% aqueous acetic acid (5 ml. per 100 g.). Extracts were dried over sodium sulphate before evaporation.

Baeyer–Villiger Oxidation of Hecogenin Acetate.—Hecogenin acetate (100 g.) in chloroform (1·5 l.) and acetic acid (600 ml.) was treated with 30% aqueous hydrogen peroxide (60 ml.) and a 10% v/v solution (40 ml.) of sulphuric acid in acetic acid. The mixture was left for 11 days at room temperature with occasional shaking. The chloroform layer was washed with water several times, mixed with a large volume of water, and steam-distilled until all the solvent was removed. The crude mixture of lactones was filtered off, washed with water, and roughly dried (m. p. 290—295°).

The above mixture was saponified by potassium hydroxide (100 g.) in refluxing methanol (1 l.) and water (100 ml.) for 2 hr. Dilution with water (total volume 3 l.) and filtration afforded neutral material (*A*) (1·9 g.), m. p. 228—230°. The filtrate was acidified with concentrated hydrochloric acid (to Congo Red), and the precipitated acids were filtered off, washed with water, and dried *in vacuo* below 40° [yield, 100 g.; m. p. (197°) 225—258°].

The acids were continuously extracted with hot acetone, and the extracts were concentrated under reduced pressure until crystals formed. These and three further crops obtained by further concentration of the mother-liquors and progressive addition of chloroform, had m. p. (187—203°) 250—254° (82 g.) and were substantially pure hecolic acid. A pure sample of the *hemihydrate* obtained by recrystallisation from acetone–chloroform had m. p. (195°) 260—264°, $[\alpha]_D$ −67·9° (*c* 0·8 in dioxan) (Found, on sample dried at 50°/0·01 mm.: C, 69·0; H, 9·8%; equiv., 470, 473; loss on drying at 105°/0·01 mm., 1·3. $C_{27}H_{44}O_6,0{\cdot}5H_2O$ requires C, 68·5; H, 9·6%; equiv., 474; loss on drying, 1·9%), $\nu_{max.}$ (in Nujol) 1724 cm.$^{-1}$ and hydroxyl band. Rothman, Wall, and Eddy [2] record m. p. (187°) 253—255°, $[\alpha]_D$ −66·3° (in dioxan), for the anhydrous material.

The chloroform mother-liquors from the fourth crop, when kept overnight, gave a fifth crop, m. p. (177—200°) 265—270° (5 g.). Recrystallisation from acetone gave 3β,11-*dihydroxy*-11,12-*seco*-5α,25D-*spirostan*-12-*oic acid* (*isohecolic acid*) (IV; R = R′ = H) as prisms, m. p. (239—240°) 285—290° (3·2 g.). A pure sample had m. p. (236—238°) 275—280°, $[\alpha]_D$ −62·9° (*c* 1·02 in dioxan) (Found, on sample dried at room temperature *in vacuo*: C, 69·7; H, 9·8%; Equiv., 465, 468. $C_{27}H_{44}O_6$ requires C, 69·8; H, 9·6%; equiv., 465), $\nu_{max.}$ (in Nujol) 1724 cm.$^{-1}$ and hydroxyl band.

Evaporation of the mother-liquors from the fifth crop gave a solid residue which was dissolved in chloroform and ether and shaken with dilute aqueous potassium hydroxide, the emulsion which was formed being broken by addition of sodium sulphate. The lower aqueous layer was separated, extracted with ether, filtered through kieselguhr, and acidified. The precipitated acid was isolated by two extractions with dichloromethane. Evaporation of the dried extracts and two recrystallisations of the residue from acetone afforded isohecolic acid, m. p. (230—235°) 279—283°, $[\alpha]_D$ −62·6° (*c* 0·78 in dioxan) (600 mg.). The combined chloroform and ether extracts were dried and evaporated to give solid neutral material (*B*) (4·9 g.). Recrystallisation gave material, m. p. 262°, $[\alpha]_D$ −67·7° (*c* 0·95) (Found: C, 72·4; H, 9·6. Calc.

for $C_{27}H_{42}O_5$: C, 72·6; H, 9·5%). This material is a mixture of lactones, and the infrared spectrum was similar to that of a mixture of hecololactone and isohecololactone. Acetylation gave material of m. p. 293—298°.

Chromatography of the Neutral Material A.—The material (500 mg.) was dissolved in benzene and chromatographed on alumina (50 g.). Elution with ether gave successively (slightly impure) tigogenin, m. p. and mixed m. p. 209—211°, hecogenin, plates, m. p. and mixed m. p. 257—258°, and 12-oxospirost-9(11)-en-3β-ol, m. p. and mixed m. p. 227—230°, $\lambda_{max.}$ 238 mμ (ε 11,400) (cf. Djerassi, Martinez, and Rosenkranz [10]).

Further Treatment of the Neutral Material B.—A portion (2 g.) was refluxed with 10% aqueous potassium hydroxide (10 ml.) in methanol (40 ml.) for 30 min. After dilution with water and filtration from an insoluble fraction (15 mg.; m. p. 292—295°) the solution was extracted with a mixture of benzene, chloroform, and ether. Evaporation of this extract gave material of m. p. 268—275° (40 mg.). The aqueous layer was acidified and the precipitated acids were filtered off and dried [1·78 g.; m. p. (190°) 257—259°]. Six recrystallisations from acetone gave *acid C* (56 mg.), m. p. (214—217°) 254—256°, $[\alpha]_D$ −68·8° (*c* 0·955 in dioxan) (Found: C, 70·3; H, 9·8. $C_{27}H_{44}O_6$ requires C, 69·8; H, 9·6%), $\nu_{max.}$ (in Nujol) 1704 cm.$^{-1}$ and hydroxyl peak. From the mother-liquors from the fourth, fifth, and six crystallisations was obtained a further quantity (171 mg.) of acid C, m. p. (204—208°) 252—261°, $[\alpha]_D$ −69·4° (*c* 1·03 in dioxan). This acid tended to separate as a gel on recrystallisation unless seed-crystals were present.

From the mother-liquors of the first three recrystallisations were obtained, successively, hecolic acid (1·25 g. from chloroform), m. p. (189—193°) 259—265°, and isohecolic acid (121 mg. from acetone), m. p. (230°) 283—285°.

Methyl Isohecolate.—Isohecolic acid with an excess of ethereal diazomethane gave the *methyl ester* (IV; R = H, R′ = Me), needles (from methanol), m. p. (132—134°) 196—198°, $[\alpha]_D$ −55·4° (*c* 0·85) (Found: C, 70·4; H, 9·9. $C_{28}H_{46}O_6$ requires C, 70·3; H, 9·7%), $\nu_{max.}$ (in Nujol) 1724, (in CS_2) 1721 cm.$^{-1}$. With acetic anhydride and pyridine at room temperature overnight this gave the *methyl ester* 3β,11-*diacetate*, prisms (from ether–isopentane), m. p. 117—119°, $[\alpha]_D$ −51·0° (*c* 0·925) (Found: C, 68·5; H, 9·1. $C_{32}H_{50}O_8$ requires C, 68·3; H, 9·0%), $\nu_{max.}$ (in Nujol) 1724, (in CCl_4) 1739 cm.$^{-1}$, no absorption in the hydroxyl region.

Isohecololactone.—Isohecolic acid (250 mg.) was heated to 240°/0·01 mm. It melted, evolved water, and resolidified. The temperature was raised to 260—280°, the lactone then subliming. A second sublimation followed by two recrystallisations from dichloromethane–ether gave 3β,11-*dihydroxy*-11,12-*seco*-5α,25D-*spirostan*-12-*oic acid* 12,11-*lactone* (*isohecololactone*) (V), m. p. 285°, $[\alpha]_D$ −81·3° (*c* 0·96) (Found: C, 72·5, 72·5; H, 9·8, 9·7. $C_{27}H_{42}O_5$ requires C, 72·6; H, 9·5%), $\nu_{max.}$ (in Nujol) 1720, (in CS_2) 1724 cm.$^{-1}$, which with acetic anhydride and pyridine gave the *acetate* (V; R = Ac), needles (from dichloromethane–ether), m. p. (250°) 292—294°, $[\alpha]_D$ −81·1° (*c* 1·3) (Found: C, 71·55; H, 9·1. $C_{29}H_{44}O_6$ requires C, 71·3; H, 9·1%), $\nu_{max.}$ (in Nujol) 1727, (in CS_2) 1739 cm.$^{-1}$, and with benzoyl chloride and pyridine gave the *benzoate*, m. p. 295—297° (from dichloromethane–acetone), $[\alpha]_D$ −75·5° (*c* 0·802) (Found: C, 74·65; H, 8·7. $C_{34}H_{46}O_6$ requires C, 74·15; H, 8·4%), $\nu_{max.}$ (KCl disc) 1724 cm.$^{-1}$.

Derivatives of Hecolic Acid.—The following were made for comparison with the isohecolic acid derivatives: methyl hecolate (III; R = H, R′ = Me), m. p. (78—80°) 163—164°, $[\alpha]_D$ −67° (*c* 1·45), $\nu_{max.}$ (KCl disc) 1724, (in Nujol) 1733 cm.$^{-1}$. Hecololactone (II; R = H), m. p. 259—261° (from dichloromethane–ether), $[\alpha]_D$ −56·5° (*c* 1·29), $\nu_{max.}$ (in Nujol) 1741, (in CS_2) 1736 cm.$^{-1}$. Hecololactone acetate, prisms (from dichloromethane–ether), m. p. (250°) 298—300°, $[\alpha]_D$ −65·0° (*c* 0·98), $\nu_{max.}$ (in Nujol) 1740, (in CS_2) 1739 cm.$^{-1}$. *Hecololactone benzoate*, needles (from dichloromethane–acetone), m. p. 307—310°, $[\alpha]_D$ −63·2° (*c* 0·95) (Found: C, 74·4; H, 8·2. $C_{34}H_{46}O_6$ requires C, 74·2; H, 8·4%), $\nu_{max.}$ (KCl disc) 1739, 1718 cm.$^{-1}$. Methyl hecolate 3-acetate (III; R = Ac, R = Me), m. p. 120—124°, $[\alpha]_D$ −73·2° (*c* 1·34) (Found: C, 69·4; H, 9·7. Calc. for $C_{30}H_{48}O_7$: C, 69·2; H, 9·3%), $\nu_{max.}$ (in Nujol) 1730, (in CCl_4) 1739 cm.$^{-1}$. Except for the last compound these constants are in good agreement with those recorded by Rothman, Wall, and Eddy [2] (cf. methyl hecolate 3-acetate, m. p. 99—101°, $[\alpha]_D$ −62·7°).

Reaction between Methyl Hecolate and Phenylmagnesium Bromide.—Phenylmagnesium bromide was prepared from magnesium turnings (10 g.), bromobenzene (45 ml.), and ether (500 ml.) in the usual way. Methyl hecolate (12 g.) in benzene [600 ml.; dried by distilling off a portion of the solvent (100 ml.)] was added. The mixture was refluxed with stirring for

[10] Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 303.

6 hr., then treated with dilute hydrochloric acid and the product was isolated in the usual way by extraction with ether, followed by steam-distillation to remove biphenyl. It gave a yellow froth (12·7 g.), $\lambda_{max.}$ 206 (ε 17,500), 242 mμ (ε 9750), and was treated with pyridine (50 ml.) and acetic anhydride (50 ml.) overnight at room temperature. Working up with ether gave a froth (13·4 g.), $\lambda_{max.}$ 205 (ε 16,000), 242 mμ (ε 9030). This was boiled in acetic acid (25 ml.). After 1 min. a large amount of solid separated. As much as possible of the acetic acid was evaporated under reduced pressure, and the cooled mixture was diluted with di-isopropyl ether (50 ml.). The solid was filtered off, the filtrate evaporated, and the residue treated a second time with boiling acetic acid (10 ml.) to give a second crop of solid. (Weight of first two crops 7·0 g.; m. p. 255—257°.) The material in the mother-liquors was treated a third time with boiling acetic acid, and the material was worked up by dilution with ether and washing with aqueous potassium hydrogen carbonate. Crystallisation of the product from di-isopropyl ether gave a third crop of solid, m. p. 250—252° (0·85 g.). The material in the mother-liquors failed to yield any more solid and had $\lambda_{max.}$ 206 (ε 23,700) and 244 mμ (ε 11,300).

Further crystallisation of the solid gave 3β-*acetoxy*-12-*phenyl*-12a-*oxa*-C-*homo*-5α,25D-*spirost*-11-*ene* (VII; R = Ac) as needles, m. p. 257—259° (from chloroform–methanol), m. p. 254—256° (from dichloromethane–ether), $[\alpha]_D$ −70·5° (*c* 0·64) (Found: C, 76·7; H, 8·6. $C_{35}H_{48}O_5$ requires C, 76·6; H, 8·8%), $\lambda_{max.}$ 205 (ε 11,900), 218 (ε 10,250), 263 mμ (ε 13,100); $\nu_{max.}$ (in Nujol) 1739, 1647, 1605, 1582, 1240, 772 cm.$^{-1}$.

An attempt to isolate the solid product after cyclisation with acetic acid by adding water failed. Solid already formed dissolved on warming and could not be induced to separate again. The amorphous product had $\lambda_{max.}$ 205 (ε 19,700) and 242 mμ (ε 11,350).

3β-*Hydroxy*-12-*phenyl*-12a-*oxa*-C-*homo*-5α,25D-*spirost*-11-*ene* (VII; R = H), obtained by hydrolysis of the acetate with boiling methanolic potassium hydroxide, formed needles (from methanol), m. p. 192—194°, $[\alpha]_D$ −75° (*c* 0·8) (Found: C, 78·6; H, 9·5. $C_{33}H_{46}O_4$ requires C, 78·2; H, 9·15%), $\lambda_{max.}$ 212 (ε 11,300), 263 mμ (ε 13,000), $\nu_{max.}$ (in Nujol) 3390, 1647, 1626, 1605, 1580, 770 cm.$^{-1}$.

The *benzoyl derivative* (benzoyl chloride and pyridine) formed needles (from chloroform–methanol), m. p. 274—277°, $[\alpha]_D$ −76° (*c* 0·6) (Found: C, 78·8; H, 8·5. $C_{40}H_{50}O_5$ requires C, 78·7; H, 8·25%), $\lambda_{max.}$ 214 (shoulder) (ε 18,000), 224 (ε 22,000), 264 mμ (ε 10,400), $\nu_{max.}$ (in Nujol) 1730, 1644, 1608, 1275, 764 cm.$^{-1}$.

Treatment of Methyl Hecolate with Phenyl-lithium.—Methyl hecolate (1 g.) in ether (100 ml.) was refluxed with ethereal 0·78M-phenyl-lithium (15 ml., 6 mol.) for 3 hr. Working up in the usual way (with steam-distillation to remove biphenyl) gave a yellow froth (0·96 g.), $\lambda_{max.}$ 209 (ε 13,000), 242 mμ (ε 8500). A portion of this (50 mg.) was treated with acetic anhydride and pyridine then with boiling acetic acid. The product was chromatographed on alumina, to yield 3β-acetoxy-12a-oxa-12-phenyl-C-homo-5α,25D-spirost-11-ene, m. p. and mixed m. p. 258—260° (eluted with 4 : 1 light petroleum–benzene), and hecololactone acetate, m. p. and mixed m. p. 294—296° (eluted with 1 : 1 light petroleum–benzene).

3β-*Acetoxy*-12-*phenyl*-12,13-*seco*-5α,25D-*spirost*-13-*en*-12-*one* (VIII).—The phenyl enol ether (VII; R = Ac) (501 mg.) was heated on the steam-bath with acetic acid (10 ml.) and water (1 ml.) for 3 hr.; it dissolved except for a trace of amorphous material, which was filtered off. The filtrate was diluted with water and the precipitate filtered off, dissolved in acetic acid, and reprecipitated with water. 3β-*Acetoxy*-12-*phenyl*-12,13-*seco*-5α,25D-*spirost*-13-*en*-12-*one* (VIII) was amorphous and had m. p. 86—91°, $[\alpha]_D$ −40° (*c* 1·175) (Found: C, 76·5; H, 8·9. $C_{35}H_{48}O_5$ requires C, 76·6; H, 8·8%), $\lambda_{max.}$ 206 (ε 20,000), 241 mμ (ε 16,300), $\nu_{max.}$ (KCl disc) 1727 (OAc), 1678 (Ph ketone), 1590 and 1570 (conjugated benzene ring), 1447 (benzene ring), 1239 (OAc), 758, and 697 cm.$^{-1}$ (monosubstituted benzene ring).

Oxidation of the Phenyl Enol Ether (VII; R = Ac) *and of the Phenyl Ketone* (VI).—The following oxidising agents were used in attempts to oxidse the phenyl enol ether (VII; R = Ac): ozone, chromium trioxide in acetic acid, chromium trioxide in aqueous sulphuric acid, potassium permanganate in acetone, osmium tetroxide, perbenzoic acid, and performic acid. In most cases there resulted acidic and neutral fractions from which no crystals were obtained (except benzoic acid, m. p. 120°, formed by chromium trioxide in acetic acid). Oxidation of the crude (acetylated) phenyl ketone (VI), formed by the action of phenyl-lithium on methyl hecolate, with chromium trioxide in acetic acid gave similar results.

Hecogenin Acetate Oxime (IX; R = Ac, R′ = H).—Hecogenin acetate (4·72 g.) and hydroxylamine hydrochloride (2·1 g.) in pyridine (50 ml.) were heated to 90° for 3 hr. Ethanol

(10 ml.) was added to dissolve the oil, and after 30 min. an excess of water was added. The precipitated solid was filtered off (4·66 g.; m. p. 318—320°). A specimen of this oxime, recrystallised from chloroform–acetone, had m. p. 318—320°, $[\alpha]_D$ −1·7° (*c* 0·785) (Found: C, 71·5; H, 9·0; N, 3·15. Calc. for $C_{29}H_{45}NO_5$: C, 71·4; H, 9·3; N, 2·9%). Mazur [6] recorded m. p. 318—321°, $[\alpha]_D$ −2·4°.

Hecogenin Oxime.—Saponification of the foregoing acetate gave *hecogenin oxime* (IX; R = R = H) as plates (from aqueous methanol), m. p. 256—260°, $[\alpha]_D$ +3° (*c* 1·0) (Found: C, 72·8; H, 9·35; N, 2·9. $C_{27}H_{43}NO_4$ requires C, 72·8; H, 9·7; N, 3·15%). Anliker, Rohr, and Heusser [7] record m. p. 317—318°, $[\alpha]_D$ ±0°, for a hemihydrate prepared in an unspecified manner. Their m. p. is similar to that of the 3β-acetate and the analytical figures quoted are in good agreement with this formulation. Acetylation of hecogenin oxime or its 3β-acetate with acetic anhydride and pyridine at room temperature gave the diacetate (IX; R = R′ = Ac), m. p. 194—196°, $[\alpha]_D$ +16° (*c* 1·1) (Found: C, 70·2; H, 8·7; N, 2·3. Calc. for $C_{31}H_{47}NO_6$: C, 70·3; H, 8·95; N, 2·65%). Anliker *et al.*[7] record m. p. 185°, $[\alpha]_D$ +7·9°.

Hecololactam Acetate.—Hecogenin acetate oxime (2·43 g.) in pyridine (50 ml.) was treated with toluene-*p*-sulphonyl chloride (1·9 g.) at room temperature for 4 days. Water was added till a slight cloudiness appeared, kieselguhr was added, and the solution filtered. Acidificaton of the filtrate precipitated the lactam (2·75 g.) which was isolated by ether-extraction. Crystallisation from aqueous acetone gave 3β-acetoxy-12a-aza-c-homo-5α,25D-spirostan-12-one (hecololactam acetate) (X; R = Ac) as needles, m. p. 234—236°, $[\alpha]_D$ −72·0° (*c* 1·19) (Found: C, 71·62; H, 8·8; N, 3·04. Calc. for $C_{29}H_{45}NO_5$: C, 71·4; H, 9·3; N, 2·9%). If the reaction mixture was worked up after 20 hr. the product consisted of the lactam acetate (1·4 g.) and unchanged oxime (1·03 g.), which were easily separated since the former is only precipitated from aqueous pyridine solution on acidification. Mazur [6] records m. p. 231—234°, $[\alpha]_D$ −70°.

Hecololactam.—The foregoing lactam acetate (500 mg.) in methanol (300 ml.) was refluxed with potassium hydroxide (1·5 g.) in a little water for 2 hr. Addition of an excess of water precipitated 3β-*hydroxy*-12a-*aza*-c-*homo*-5α,25D-*spirostan*-12-*one* (*hecololactam*) (X; R = H) which recrystallised from aqueous methanol as prisms, becoming opaque at 100°, m. p. (150—160°) 202—205°, $[\alpha]_D$ −61·7° (*c* 0·94) (Found, in material dried at 100°/0·01 mm.: C, 70·4; H, 9·5; N, 3·15. $C_{27}H_{43}NO_4,H_2O$ requires C, 69·95; H, 9·8; N, 3·0. Found, in material dried at 132°/0·01 mm.: C, 71·55; H, 9·75. $C_{27}H_{43}NO_4,0{\cdot}5H_2O$ requires C, 71·4; H, 9·8. Found, in material sublimed at 270—290°/0·01 mm.: C, 72·8; H, 8·25; N, 3·6. $C_{27}H_{43}NO_4$ requires C, 72·8; H, 9·75; N, 3·15%). The sublimed amorphous anhydrous material, on crystallisation from aqueous methanol, gave back the hydrate, m. p. (140—150°) 200—202°. Mazur [6] records that this compound melted over the range 145—215° and gave no analysis.

Action of Nitrous Acid on Hecololactam Acetate.—Hecololactam acetate (1·9 g.) in acetic anhydride (40 ml.) and acetic acid (8 ml.) was cooled to 0° and treated with sodium nitrite (12 g.) for 22 hr. Water was added and the organic material isolated by ether-extraction. This was a syrup which on addition of methanol afforded crystals (140 mg.), m. p. 270—279°. These, after crystallisation from methylene chloride–methanol, gave hecololactone acetate, m. p. 298—301°, $[\alpha]_D$ −63° (*c* 0·79), which did not depress the m. p. of an authentic sample and had an identical infrared spectrum.

The material in the mother-liquors was not crystalline and was refluxed with 5% methanolic potassium hydroxide (50 ml.) for 1 hr. Addition of water caused, on one occasion only, the precipitation of hecololactam, m. p. (145°) 200—205°. In other cases a clear solution was obtained which on acidification with 6N-hydrochloric acid gave crystals (2·1 g.), m. p. 205—215°, $[\alpha]_D$ −37°. Recrystallisation from aqueous acetone gave 3β-*hydroxy*-12,13-*seco*-5α,25D-*spirost*-13-*en*-12-*oic acid* (*anhydrohecolic acid*) (XI), m. p. 220—223°, $[\alpha]_D$ −39° (*c* 1·0) (Found: C, 72·8; H, 9·4. $C_{27}H_{42}O_5$ requires C, 72·6; H, 9·5%), $\lambda_{max.}$ 208 mμ (ε 4450), giving a yellow colour with tetranitromethane in chloroform.

Anhydrohecolyl Alcohol.—(*a*) Anhydrohecolic acid (310 mg.) was treated with lithium aluminium hydride (220 mg.) in refluxing tetrahydrofuran (80 ml.) for 3·25 hr. After decomposition of the excess of reagent and addition of dilute mineral acid the product was isolated by ether. The product (340 mg.), on crystallisation from acetone, gave 12,13-seco-5α,25D-spirost-13-ene-3β,12-diol (anhydrohecolyl alcohol) (XII), m. p. 176—178°, $[\alpha]_D$ −43° (*c* 1·05) (Found: C, 75·25; H, 10·5. Calc. for $C_{27}H_{44}O_4$: C, 74·95; H, 10·25%), $\lambda_{max.}$ 205 mμ (ε 4400).

(*b*) Hecolyl alcohol, prepared by reduction of methyl hecolate with lithium aluminium

hydride in tetrahydrofuran,[2] had m. p. 140—142°, $[\alpha]_D$ −65° (*c* 0·8 in acetone). Rothman *et al.*[2] record m. p. 141°, $[\alpha]_D$ −71·4°.

This material (100 mg.) was dissolved in methanol (5 ml.) and treated with 60% aqueous perchloric acid (0·1 ml.) at 20° for 17 hr. Addition of water precipitated anhydrohecolyl alcohol, m. p. 178—181° undepressed by admixture with material prepared by method (*a*) and having an identical infrared spectrum. Rothman *et al.*[2] record m. p. 174—176°, $[\alpha]_D$ −46·1°.

9(11)-*Dehydrohecogenin Acetate Oxime*.—9(11)-Dehydrohecogenin acetate [10] was converted into its oxime (XIII; R = Ac, R′ = H) by the method used for hecogenin acetate. It had m. p. 286—289°, $[\alpha]_D$ +26°, $\lambda_{max.}$ 238 mμ (ε 11,000). Mazur [6] records m. p. 282—284°, $[\alpha]_D$ +36°, $\lambda_{max.}$ 238 mμ (ε 13,600).

Beckmann Rearrangement of 9(11)-*Dehydrohecogenin Acetate Oxime*.—The oxime (5·18 g.) in pyridine (80 ml.) was treated with toluene-*p*-sulphonyl chloride (4 g.) at 20° for 64 hr. Water (1 l.) was added and the precipitated pink solid filtered off (m. p. 168—175°; 3·55 g., 52%). Crystallisation from aqueous acetone gave needles of 12-*toluene*-p-*sulphonyloxyimino*-5α,25D-*spirost*-9(11)-*en*-3β-*yl acetate* (XIII; R = Ac, R′ = *p*-$C_6H_4Me{\cdot}SO_2$), m. p. 184—186°, $[\alpha]_D$ −46° (*c* 1·46) (Found: C, 67·1; H, 7·4; N, 2·3; S, 5·1. $C_{36}H_{49}NO_7S$ requires C, 67·6; H, 7·7; N, 2·2; S, 5·0%), $\lambda_{max.}$ 204 (ε 21,000), 227 mμ (ε 21,600), $\nu_{max.}$ (KCl disc) 3422, 1736, 1666, 1629, 1600, 1250 cm.$^{-1}$.

The aqueous pyridine filtrates were acidified to pH 3 with hydrochloric acid, and the precipitate filtered off (m. p. 220—227°; 2·2 g., 40%). Recrystallisation from aqueous acetone gave 3β-acetoxy-12a-aza-c-homo-5α,25D-spirost-9(11)-en-12-one (dehydrohecololactam acetate), m. p. 230—232°. From acetone–light petroleum (b. p. 60—80°) it separated as prisms, m. p. 255—258°, $[\alpha]_D$ −69·4° (*c* 1·19) (Found: C, 71·5; H, 9·2; N, 3·0. Calc. for $C_{29}H_{43}NO_5$: C, 71·7; H, 8·9; N, 2·9%), $\lambda_{max.}$ 220 mμ (ε 17,200). There was no loss in weight at 100°/0·01 mm. The two forms of this substance had identical infrared spectra. Mazur [6] records m. p. 228—231°, $[\alpha]_D$ −72°, $\lambda_{max.}$ 220 mμ (ε 15,800).

Treatment of Dehydrohecololactam Acetate with Nitrous Acid.—The lactam acetate (206 mg.) in acetic anhydride (4 ml.) and acetic acid (0·8 ml.) was treated with sodium nitrite (1·1 g.) at 0° for 68 hr. Addition of water and extraction with ether gave neutral material (200 mg.). Crystallisation from acetone–light petroleum gave the starting material, m. p. and mixed m. p. 254—257° (60 mg.). Further crops (total 120 mg.) had m. p. 252—255°.

Formation of Dehydrohecololactam Acetate from the Oxime Toluene-p-*sulphonate* (XIII; R = Ac, R′ = *p*-$C_6H_4Me{\cdot}SO_2$).—(*a*) The oxime toluene-*p*-sulphonate (160 mg.) in ethanol (8 ml.), acetic acid (4 ml.), and a few drops of water was refluxed for 30 min. Addition of water precipitated the lactam acetate which after crystallisation from acetone–light petroleum had m. p. 252—255°.

(*b*) On attempted recrystallisation of the oxime toluene-*p*-sulphonate (3·5 g.) from chloroform–methanol, a syrup was obtained. Prolonged storage of this in ether–isopentane gave the low-melting form of the lactam acetate (1·5 g.), m. p. 222—226°.

The authors are indebted to Mr. Wm. McCorkindale for the microanalyses, Miss E. Bell and Miss M. Black for the ultraviolet spectra, and Miss J. Goldie for the infrared spectra. They also thank Dr. F. S. Spring, F.R.S., for advice.

THE ROYAL COLLEGE OF SCIENCE AND TECHNOLOGY,
GLASGOW, C.1.

[*Received, February 22nd*, 1961.]