856. *Totally Synthetic Steroid Hormones. Part II.*[1] 13β-*Alkylgona*-1,3,5(10)-*trienes*, 13β-*Alkygon*-4-*en*-3-*ones*, *and Related Compounds.*

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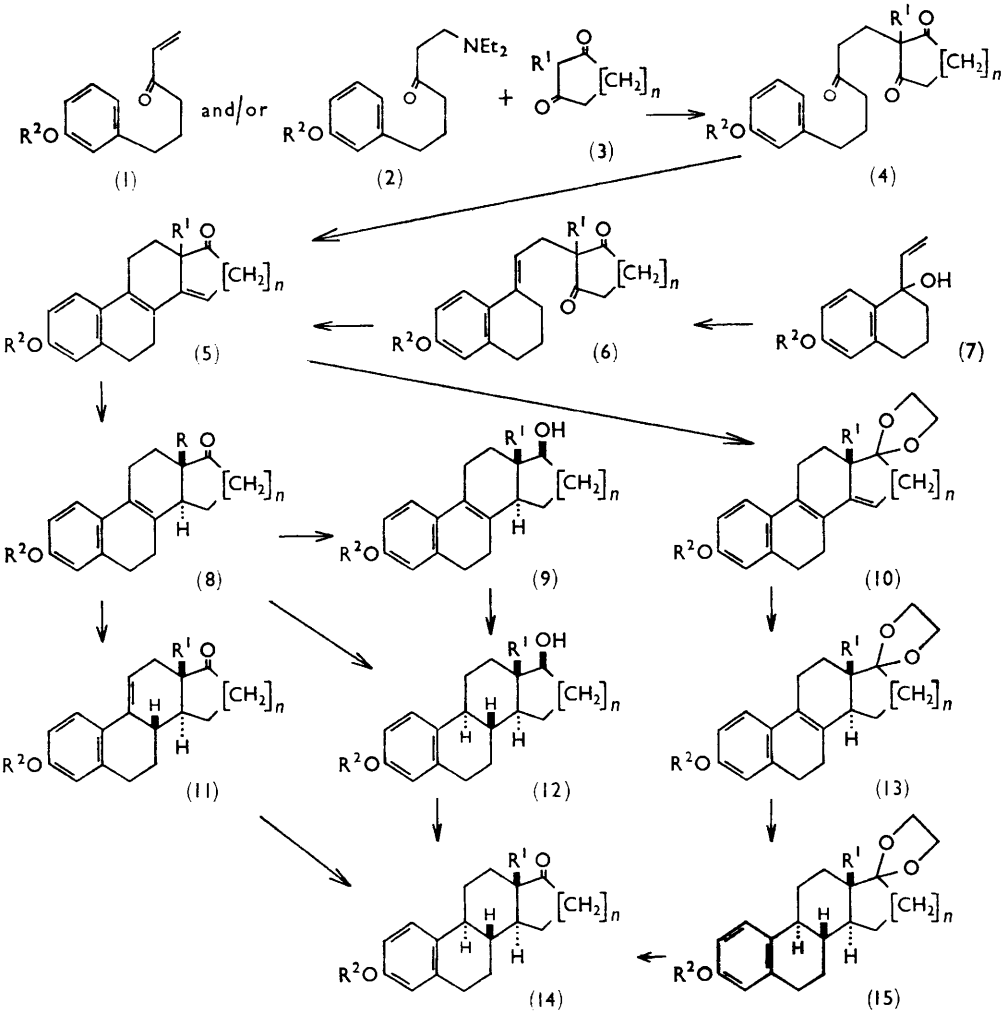
By using procedures previously developed for (±)-œstrone,[1] a variety of (±)-13β-alkylgona-1,3,5(10)-trienes and cognate compounds has been synthesised and converted into various (±)-13β-alkylgon-4-enes. Biological activities are given for several compounds and in some cases compared with those of the corresponding (+)- and (−)-enantiomers. A series of related (±)-œstranes has been totally synthesised for comparison in biological activities with these gonanes and the corresponding œstranes prepared from (+)-œstrone. Preliminary accounts[2,3] of some of this work have been given.

We[1] recently described a number of related total syntheses of œstrone by routes which are, in principle, capable of wide application. Here we record the use of the most efficient of these for the preparation of (±)-13β-alkylgonatrienes of the general structures (12), (14), and (15), and the conversion of appropriate members of the series into (±)-gonanes of the types (20), (21), (24), and (25). In these compounds the 13-alkyl group ranged from ethyl, n- and iso-propyl, and n- and iso-butyl to isopentyl, with ring D both five- and six-membered. The series thus provided an unprecedented opportunity for examining the effect of elongation and branching of the angular group on the biological activities of various œstrone and D-homoœstrone derivatives. The investigation, initially deemed worthwhile because of the importance in therapy of a number of œstrone derivatives as anabolic,[4] progestational,[5] and oral contraceptive agents,[6] has led to several compounds of pronounced clinical effectiveness.[7] In these studies biological testing has been routinely carried out on (±)-compounds in the belief that all of the biological activities would be derived from the enantiomers belonging to the same absolute configuration series as (+)-œstrone (the *d*-series as defined by Lardon *et al.*[8]). None of the data subsequently obtained for various *d*- and *l*-enantiomers, made available by microbiological[9] and chemical resolution procedures,[10] puts this belief in question (below). Throughout this Paper (±)-compounds and enantiomorphs are depicted by structural formulæ having the 13-alkyl group in the β-configuration. Subsequently, the (±)-prefix will be omitted and compounds are to be assumed racemic unless stated otherwise. The absolute configuration of enantiomorphs will be denoted by the previously mentioned convention.[8]

[1] Part I, Douglas, Graves, Hartley, Hughes, McLoughlin, Siddall, and H. Smith, *J.*, 1963, 5072.
[2] (*a*) H. Smith, Hughes, Douglas, Hartley, McLoughlin, Siddall, Wendt, Buzby, Herbst, Ledig, McMenamin, Pattison, Siuda, Tokolics, Edgren, Jansen, Gadsby, Phillips, and Watson, *Experientia*, 1963, **19**, 394; (*b*) Belg. P. 600,245, 600,759/1961; (*c*) 608,369, 608,370/1962.
[3] Edgren and H. Smith, *Excerpta Med.*, International Congress Series No. 51, 63; International Congress on Hormonal Steroids, Milan, 1962, Academic Press, New York, in the press; Edgren, H. Smith, Peterson, and Carter, *Steroids*, 1963, **2**, 319.
[4] (*a*) Colton, Nysted, Riegel, and Raymond, *J. Amer. Chem. Soc.*, 1957, **79**, 1123; (*b*) Overbeek and deVisser, *Acta Endocrinol.*, 1957, **24**, 209; 1960, **35**, 405.
[5] Ringold, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1956, **78**, 2477.
[6] (*a*) Pincus, Chang, Hafez, Zarrow, and Merrill, *Science*, 1956, **59**, 695; (*b*) Brown, Fotherby, and Loraine, *J. Endocrinol.*, 1962, **25**, 331.
[7] Private communications from Drs. J. A. Page and E. L. Rhodes, Medical Division, Wyeth Laboratories Inc.
[8] (*a*) Lardon, Schindler, and Reichstein, *Helv. Chim. Acta*, 1957, **40**, 676; (*b*) Fieser and Fieser, "Steroids," Reinhold, New York, 1959, p. 336.
[9] Foell, Greenspan, Rees, and L. L. Smith, unpublished work.
[10] Gadsby, Jansen, and H. Smith, unpublished work.

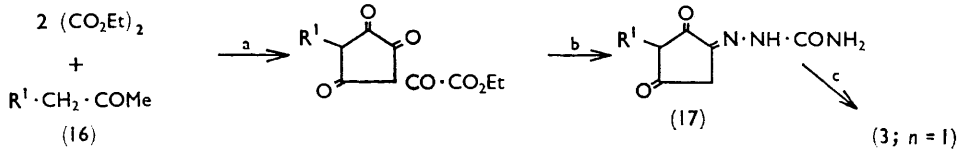
13β-*Alkylgona*-1,3,5(10)-*trien*-17β-*ols and Related Compounds*.—Key substances for the synthesis of the gonatrienes (12), (14), and (15) are the gonapentaenes (5). We record the synthesis of eleven of these substances *viz.* (5; R^1 = Et, Pr^n, Pr^i, Bu^n, Bu^i, isopentyl, n-hexadecyl, R^2 = Me, n = 1), (5; R^1 = Et, R^2 = CH_2Ph, n = 1), (5; R^1 = Et, R^2 = H, n = 1), and (5; R^1 = Et, Pr^n, R^2 = Me, n = 2) and the conversion of six of them into gona-1,3,5(10)-trienes by methods following those used in our œstrone syntheses.[1] The new 2-alkylcyclopentanediones (3; R^1 = Et, Pr^n, Pr^i, Bu^n, Bu^i, isopentyl, n-hexadecyl, n = 1) required for this work were made from the appropriate ketones (16) by an extension of the route previously developed for 2-methylcyclopentane-1,3-dione,[11] and shown in the annexed scheme. The first intermediates that needed to be isolated were the semicarbazones (17), which were smoothly converted without further purification into the diones (3; n = 1) by Wolff–Kishner reduction.



General methods for the synthesis of steroids of the types (5) and (14) will be exemplified for the 13-ethylgona-1,3,5(10)-triene series. Base-catalysed condensation of a mixture of the ketones (I and II; R^2 = Me) with 2-ethylcyclopentane-1,3-dione (3;

[11] Panouse and Sannié, *Bull. Soc. chim. France*, 1955, 1036.

$R^1 = Et, n = 1$) gave the trione (4; $R^1 = Et, R^2 = Me, n = 1$), which was cyclodehydrated with toluene-*p*-sulphonic or polyphosphoric acid in benzene to the gonapentaene (5; $R^1 = Et$, $R^2 = Me$, $n = 1$). The toluene-*p*-sulphonic acid reaction could be done at



Reagents: a, NaOMe; b, H^+, $H_2N{\cdot}NH{\cdot}CONH_2$; c, NaOMe.

reflux with continuous removal of the water formed,[1] or, preferably, at or below room temperature using 2·5 mol. of the anhydrous acid. In the second case the acid hydrate was precipitated as the reaction proceeded. For the gonapentaene (5; $R^1 = Et, R^2 = H, n = 1$), an excess of 2-ethylcyclopentane-1,3-dione was condensed with the ketone (2; $R^2 = H$) (cf. ref. 1) and the resulting trione was cyclodehydrated as before, although polyphosphoric acid was the preferred reagent. The gonapentaene (5; $R^1 = Et, R^2 = Me, n = 1$) was also prepared by the methanolic hydrochloric acid cyclisation of the seco-œstratetraene (6; $R^1 = Et, R^2 = Me, n = 1$) made from the base-catalysed condensation of 2-ethylcyclopentane-1,3-dione with the tetralol (7; $R^2 = Me$) (cf. refs. 1 and 12). A similar sequence from the tetralol (7; $R^2 = CH_2Ph$) gave the benzyl analogue (5; $R^1 = Et, R^2 = CH_2Ph, n = 1$).

Catalytic hydrogenation of the gonapentaenes (5; $R^1 = Et, R^2 = Me, H, n = 1$) gave the respective gonatetraenes (8; $R^1 = Et, R^2 = Me, H, n = 1$). A better overall yield of the phenol was obtained by hydrogenating the acetate (5; $R^1 = Et, R^2 = Ac, n = 1$) and hydrolysing the resulting gonatetraene. The ketone (8; $R^1 = Et, R^2 = Me, n = 1$) was converted into the corresponding alcohol (12) by metal–ammonia reduction, or preferably, by reduction, first with sodium borohydride, then with lithium–ammonia–aniline.[1,2] Chromium trioxide oxidation then gave the required gonatriene (14; $R^1 = Et, R^2 = Me, n = 1$). Another variant proceeded from the ketal (10; $R^1 = Et, R^2 = Me, n = 1$) through the gonatetraene (13; $R^1 = Et, R^2 = Me, n = 1$) and thence, by metal–ammonia reduction and acid hydrolysis to the corresponding gonatrienone (14). The same ketone was also obtained by catalytic hydrogenation of the gonatetraene (11; $R^1 = Et, R^2 = Me, n = 1$) made by methanolic hydrochloric acid isomerisation of the Δ^8-isomer (8; $R^1 = Et, R^2 = Me, n = 1$). The isomerisation indicates that the $\Delta^{9(11)}$-isomer is the more stable, as previously found for the pair of corresponding œstratetraenes.[1] A similar sequence, involving catalytic hydrogenation of the intermediate (11; $R^1 = Et, R^2 = H, n = 1$) gave the ketone (14; $R^1 = Et, R^2 = H, n = 1$) from the ketone (8; $R = Et, R^2 = H, n = 1$). It is the most convenient for this transformation since the styrenoid bonds in the last compound and its $\Delta^{9(11)}$-isomer resist reduction by metal–ammonia reagents (cf. refs. 1 and 2). An isomer formed in minor amount in the sequence may be formulated as the 9β-isomer of the gonatriene (14; $R^1 = Et, R^2 = H, n = 1$) since we have demonstrated appreciable formation of the 9β-œstra-1,3,5(10)-triene nucleus during the catalytic hydrogenation of the ethylene ketal of the œstratetraene (11; $R^1 = R^2 = Me, n = 1$).[1] The phenol (14; $R^1 = Et, R^2 = H, n = 1$) was also obtained by demethylating the corresponding methyl ether with pyridine hydrochloride.[13] The phenol (14; $R^1 = Pr^n, R^2 = H, n = 1$) was prepared from the ketal (15; $R^1 = Pr^n, R^2 = Me, n = 1$) by demethylation with sodamide in boiling piperidine[14] and acid hydrolysis. Velluz

[12] (*a*) Ananchenko and Torgov, *Doklady Akad. Nauk S.S.S.R.*, 1959, **127**, 553; (*b*) Ananchenko, Limanov, Leonov, Rzheznikov, and Torgov, *Tetrahedron*, 1962, **18**, 1355; (*c*) Crispin and Whitehurst, *Proc. Chem. Soc.*, 1963, 22.

[13] Prey, *Ber.*, 1941, **74**, 1219; 1942, **75**, 350, 445; Wilds and McCormack, *J. Amer. Chem. Soc.*, 1948, **70**, 4127.

[14] Brotherton and Bunnett, *Chem. and Ind.*, 1957, 80; Hodges and Raphael, *J.*, 1960, 50.

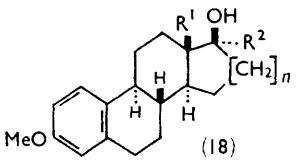
et al.[15] independently synthesised the (+)-gonatriene (12; $R^1 = Pr^n$, $R^2 = H$, $n = 1$).[13] The stereochemistry assigned to the structures of general types (8), (9), and (11—14) is based upon the stereochemical course demonstrated for the reactions described in Part I [1] and for the reduction of 17-keto-steroids and 17a-D-homo-keto-steroids with metal hydrides.[16] Strong supporting evidence is given in the sequel.

13β-*Alkylgon*-4- *and* -5(10)-*en*-3-*ones and Related Compounds.*—Birch reduction and acid hydrolysis of the group (12; $R^1 = Et$, Pr^n, Bu^n, Bu^i, $R^2 = Me$, $n = 1$, 2) gave, by way of gon-5(10)-enes of class (20; $R^2 = R^3 = H$), corresponding ketols of type (21; $R^2 = R^3 = H$). Sixteen were converted into a variety of esters for study as long-acting anabolic agents (see Experimental section). The formulation of the pair (21; $R^1 = Et$, Pr^n, $R^2 = R^3 = H$, $n = 1$) as 17β-ols is confirmed by their proton nuclear magnetic resonance spectra which show triplets centred about τ 3·31—3·32 (measured downfield from tetramethylsilane as standard). Shoolery and Rogers [17] report data which give, on conversion to our reference scale, τ 3·31 and 3·32 for the pseudo-axial 17α-protons of testosterone and 19-nortestosterone, respectively. The D-homo-alcohols (21; $R^1 = Et$, Pr^n, $R^2 = R^3 = H$, $n = 2$) exhibit similar multiplets at τ 6·77 and 6·78, respectively, which suggest axial character for the 17aα-protons and thus the equatorial β-configuration for the hydroxyl groups.

Ketols selected from the group (21; $R^1 = Et$, Pr^n, Bu^n, $R^2 = Me$, Et, or Pr^n, $R^3 = H$, $n = 1$, 2), required for evaluation as orally-active anabolic agents, were prepared from the corresponding gonatrienols of class (18) by the usual Birch reduction and acid hydrolysis. In some cases pyrrole was used as the proton donor in Birch reduction. Pyrrole (pK_a 16·5) [18] is about as strong an acid as methanol (pK_a 16) [18] and presumably can be effective because consumption of the metal with the production of molecular hydrogen is not a serious side reaction.[19,20] Pyrrole is an excellent solvent for the substrates, but tends to give highly coloured impurities and, being relatively involatile, is difficult to remove from the products. The required gonatrienols (18) can be made by a variety of routes which will be exemplified for the case (18; $R^1 = R^2 = Et$; $n = 1$). The ketone (14; $R^1 = Et$, $R^2 = Me$, $n = 1$), on treatment with acetylene and potassium t-butoxide in t-butanol–toluene [5] gave a low yield of an alcohol formulated as (18; $R^1 = Et$, $R^2 = C{:}CH$, $n = 1$). A reagent made by decomposing lithium aluminium hydride with acetylene in tetrahydrofuran, and evidently containing an acetylenic nucleophile, gave satisfactory yields of the alcohol, but better results were obtained with lithium acetylide in aniline or dimethylacetamide. Catalytic hydrogenation then gave the required alcohol (18; $R^1 = R^2 = Et$, $n = 1$). In a shorter and more efficient preparation, the ketone (8; $R^1 = Et$, $R^2 = Me$, $n = 1$) was converted as before into the alcohol (22; $R^1 = Et$, $R^2 = C{:}CH$, $n = 1$), the latter was selectively hydrogenated in benzene over palladised calcium carbonate to the alcohol (22; $R^1 = R^2 = Et$, $n = 1$), and a final reduction made with lithium in aniline–liquid ammonia. A similar process, involving the selective hydrogenation of the allyl side-chain in the alcohol (22; $R^1 = Et$, $R^2 = CH_2{\cdot}CH{:}CH_2$, $n = 1$) (formed from the corresponding 17-one with allylmagnesium bromide) gave the alcohol (18; $R^1 = Et$, $R^2 = Pr^n$, $n = 1$) which served as the precursor of the gonenone (21; $R^1 = Et$, $R^2 = Pr^n$, $R^3 = H$, $n = 1$). The gonatriene (18; $R^1 = R^2 = Et$, $n = 1$) was also prepared from the ketone (11; $R^1 = Et$, $R^2 = Me$, $n = 1$) by reaction with lithium acetylide and selective hydrogenation of the resulting ethynyl compound to the gonatetraene (23; $R^1 = R^2 = Et$, $n = 1$). Notably, the final stage could be done by catalytic hydrogenation over palladised charcoal

[15] Velluz, Nominé, Bucourt, Pierdet, and Dufay, *Tetrahedron Letters*, 1961, 127.
[16] (*a*) Ref. 8*b*, p. 467; (*b*) Clinton, Christiansen, Neumann, and Laskowski, *J. Amer. Chem. Soc.*, 1957, **79**, 6475.
[17] Shoolery and Rogers, *J. Amer. Chem. Soc.*, 1958, **80**, 5121.
[18] McEwen, *J. Amer. Chem. Soc.*, 1936, **58**, 1124.
[19] (*a*) Birch, *Quart. Rev.*, 1950, **4**, 69; (*b*) Birch and H. Smith, *ibid.*, 1958, **12**, 17; (*c*) H. Smith, "Organic Reactions in Liquid Ammonia," Vieweg und Sohn, Braunschweig, 1963, p. 237.
[20] Krapcho and Bothner-By, *J. Amer. Chem. Soc.*, 1959, **81**, 3658.

in ethanol, but the yield was only 35%. We found ketones of the series (8, 11, and 14; $R^1 \geqslant Et$, $R^2 = Me$, $n = 1$) to be considerably less reactive towards acetylenic nucleophiles than their 13-methyl counterparts, even though the α-face of the molecule is attacked



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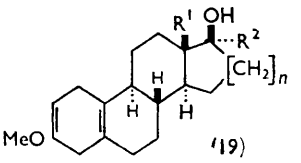

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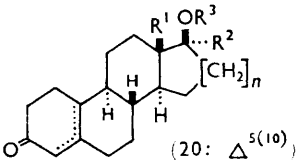
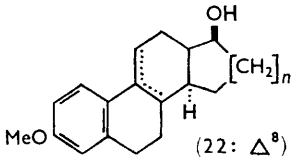
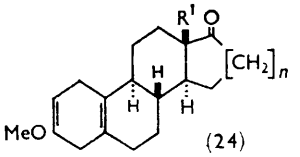


(20: $\Delta^{5(10)}$)
(21: Δ^4; 10β)



(22: Δ^8)
(23: $\Delta^{9(11)}$; 8β)



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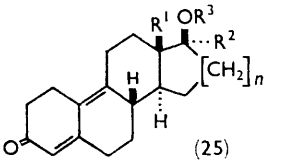

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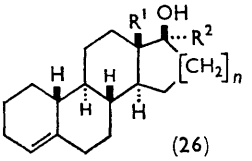

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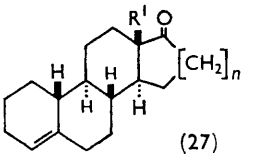


(27)

(below). The difference may be due to the extra steric hindrance provided by the ethyl and larger alkyl groups to the solvation of the transition states for addition.

Ketones of the types (20 and 21; $R^1 \geqslant Et$, R^2 = alkynyl, alkenyl, $R^3 = H$, $n = 1, 2$), required for evaluation as orally-active progestational and contraceptive agents, were made by processes involving, successively, Birch reduction and Oppenauer oxidation starting from alcohols of the class (12) (cf. ref. 4*a*). Reaction of the resulting ketones (24; $R^1 \geqslant Et$, $n = 1, 2$) with the appropriate alkali-metal acetylide or Grignard reagent, and acidic hydrolysis, gave the required gon-5(10)- or -4-en-3-ones, depending on whether methanolic oxalic or hydrochloric acid, respectively, was used. The stereochemical relationship between the gonenones (21; $R^1 = Et$, $R^2 = C{:}CH$, Et, $R^3 = H$, $n = 1$) was demonstrated by the selective hydrogenation of the first to the second over palladised strontium carbonate in benzene.

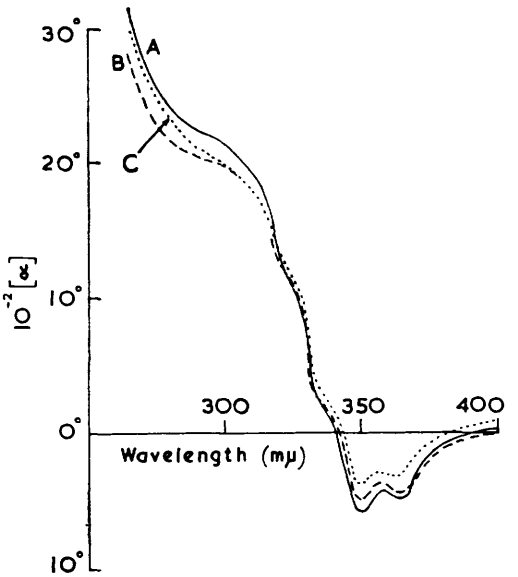
From the mode of reaction of Grignard reagents and alkali-metal acetylides with 17-oxo-steroids [16a] and of alkali-metal acetylides with 17a-oxo-D-homo-steroids,[21] we could formulate as 17β- or 17aβ-ols all appropriate members of the series (18—23) except those made by the interaction of a Grignard reagent with a 17a-oxo-D-homogonane derivative. Doubt as to the stereochemistry at the 17a-position arises in these cases from the reported formation of 17aβ-alkyl-17aα-ols from the interaction of methyl- and ethyl-magnesium halides with various 17a-oxo-D-homo-steroids.[12b,21] One example is the alcohol (21; $R^1 = Et$, $R^2 = Me$, $R^3 = H$, $n = 2$), made by a sequence involving interaction of the ketone (8; $R^1 = Et$, $R^2 = Me$, $n = 2$) with methylmagnesium bromide. This alcohol may be a 17aβ-ol from its appreciable androgenic–anabolic activity (below) and the reported [22] lack of such activity in 17α-hydroxy-19-norandrost-4-en-3-one, but the evidence is inconclusive. Ananchenko *et al.*[12b] observed the formation of both possible epimers in a similar Grignard reaction with the œstratetraene (8; $R^1 = R^2 = Me$, $n = 2$).

[21] (*a*) Clinton, Christiansen, Neumann, and Laskowski, *J. Amer. Chem. Soc.*, 1958, **80**, 3389; (*b*) Ruzicka, Wahba, Herzig, and Heusser, *Ber.*, 1952, **85**, 491.

[22] Robinson, Gnoj, and Oliveto, *J. Org. Chem.*, 1960, **25**, 2247.

The interesting biological properties demonstrated for various members of the series (21) (below) prompted the extension of our studies to the gona-4,9-diene and the gon-4-ene series (25) and (26), respectively. Compounds in the former series were made from appropriate gon-5(10)-en-3-ones of type (20) by the bromination–dehydrobromination sequence introduced by Perelman *et al.*[23] Those in the series (26) were made by interacting organometallic reagents with gonenones of type (27) [prepared from gonenones of type (21) by thioketalisation, metal–ammonia cleavage, and chromic acid oxidation (cf. ref. 24)], and by lithium–ethylamine cleavage[25] of the 3-acetoxy-analogue of the ketone (21; $R^1 = R^2 = Et$, $n = 1$).

(+)- and (−)-13β-*Alkylgonane Derivatives.*—The resolution studies previously noted led to the (+)- and (−)-enantiomers of the alcohols and ketones (12 and 14; $R^1 = Et$, Pr^n, $R^2 = H$, $n = 1$). Our sample of the (+)-alcohol (12; $R^1 = Pr^n$, $R^2 = H$, $n = 1$) agrees closely in optical rotation with that prepared by Velluz *et al.*[15] The (+)-ketones were convertible into the corresponding (+)-alcohols by sodium borohydride reduction



Optical rotatory dispersion curves of *d*-ketones (21; $R^2 = R^3 = H$, $n = 1$). A, $R^1 = Me$; B, $R^1 = Et$; C, $R^1 = Pr^n$.

and derivable from the latter by chromic acid oxidation. The derived (+)-ethers (12; $R^1 = Et$, Pr^n, $R^2 = Me$, $n = 1$) were transformed by Birch reduction and acid hydrolysis into the (+)-gonenones (21; $R^1 = Et$, Pr^n, $R^2 = R^3 = H$, $n = 1$) which were identical in infrared absorption spectra to the corresponding racemates. The similarity of the optical rotatory dispersion spectra of these enantiomers and of (+)-19-nortestosterone in general shape and magnitude (see Figure) leaves no doubt that all three compounds have the same absolute configuration, and incidentally supports the stereochemistry assigned to the series (8—15; $R^1 = Et$, Pr^n, $R^2 = H$, Me, $n = 1$) and (21; $R^1 = Et$, Pr^n, $R^2 = R^3 = H$, $n = 1$). By the same methods as were used in the (±)-series, the *d*-ketone (14; $R^1 = Et$, $R^2 = Me$, $n = 1$) was converted into the *d*-enantiomers (21; $R^1 = Et$, $R^2 = Et$, C:CH, $R^3 = H$, $n = 1$). Their optical rotatory dispersion spectra were practically superimposable on those of the corresponding *d*-œstrenones[4a,5] thereby confirming the stereochemistry assigned to the series (18—23; $R^1 = Et$, $R^2 = C{:}CH$, $R^3 = H$ in 20 and 21, $n = 1$). Interestingly, the (+)- and (−)-enantiomers of the ketone (21; $R^1 = R^2 = Et$, $R^3 = H$,

[23] Perelman, Farkas, Fornefeld, Kraay, and Rapala, *J. Amer. Chem. Soc.*, 1960, **82**, 2402.
[24] deWinter, Siegmann, and Szpilfogel, *Chem. and Ind.*, 1959, 905.
[25] Hallsworth, Henbest, and Wrigley, *J.*, 1957, 1969.

$n = 1$) (m. p. 175—176 and 172—175·5°, respectively) raise the m. p. of the (±)-compound (m. p. 144—145°), which is therefore shown to be a racemic mixture.

(±)-*Œstrane Derivatives*.—For comparison of their biological properties with those of the corresponding (+)-œstranes [4,5] and (±)-13-alkylgonanes, we also prepared the series (12; $R^1 = R^2 = Me$, $n = 1$), (18; $R^1 = Me$, $R^2 = C{:}CH$, $n = 1$), (21; $R^1 = Me$, $R^2 = H$, C:CH, Et, $R^3 = H$, $n = 1$), and (21; $R^1 = Me$, $R^2 = H$, $R^3 = CO{\cdot}[CH_2]_2{\cdot}Ph$, $n = 1$). These substances were made by methods identical with, or closely similar to, those used in the *d*-series (see Experimental). Notably, the ketone (21; $R^1 = Me$, $R^2 = R^3 = H$, $n = 1$), (±)-19-nortestosterone, previously obtained only as a gum,[26] has now been obtained crystalline in two polymorphic forms, m. p. 124 and 131°, the former being the more stable. The melting point of this polymorph is depressed on addition of the (+)-enantiomer,[27] m. p. 121°, thus showing it to be a racemic compound.

Biological Activities.—Biological studies of the compounds described in this Paper, although not complete, are sufficiently advanced to delineate tentatively some trends in structure–activity relationships. In experimental animals, compounds of types (12—14; $R^1 \geqslant Et$) generally have lower feminising potencies than their œstrane analogues whilst retaining, in lesser or greater degree, the characteristic effects upon blood lipids (cf. ref. 28). Thus, the diol (12; $R^1 = Et$, $R^2 = H$, $n = 1$), in a mouse uterine growth test,[29] had <1% of the œstrogenic activity of *d*-œstrone, and, in a 10-day rat blood-cholesterol depression test, was three times as potent as *d*-œstrone. In the same tests the diol (12; $R^1 = Pr^n$, $R^2 = H$, $n = 1$) had <1% of the œstrogenic, and 100% of the blood-cholesterol-depressing, activity of *d*-œstrone. Its (+)-enantiomer, in our hands, had <0·3—1% of the œstrogenic activity of (+)-œstrone. The same compound was reported [15] to have twice the physiologial hormonal potency of (+)-œstradiol although the biological test used was not disclosed. Separations of œstrogenic and blood lipid-mobilising activities have similarly been observed in the ketals (10; $R^1 = Et$, $R^2 = Me$, $n = 1$) and (15; $R^1 = Et$, $R^2 = Me$, $n = 1$), which had, respectively, 0·01 and 0·3% of the œstrogenic, and 80 and 200% of the blood-cholesterol-depressing, activities of *d*-œstrone. Compounds with this pattern of activities in man are of potential use in the treatment of atherosclerosis.[28]

We found compounds of the series (21, 25, and 26; $R^1 = Et$) to have higher anabolic and progestational, and comparably lower androgenic, potencies than similar œstranes, *e.g.*, the ester (21; $R^1 = Et$, $R^2 = H$, $R^3 = n\text{-}C_9H_{19}{\cdot}CO$), in a 5½-week study using a modified protocol [30] in the Hershberger [31] test, was more potent and had both a longer duration of anabolic activity and a better separation of anabolic and androgenic activities than (+)-19-nortestosterone β-phenylpropionate.[32] The ketone (21; $R^1 = R^2 = Et$, $R^3 = H$, $n = 1$), in the Hershberger test, was four times as potent a myotrophic agent as the corresponding œstrene [4a] with approximately three times the anabolic : androgenic ratio. Extensive clinical testing confirmed these findings.[7] The ketone (21; $R^1 = Et$, $R^2 =$ C:CH, $R^3 = H$, $n = 1$) had approximately 80 times the progestational activity of the 17α-ethynyl-17β-hydroxy-19-norandrost-4-en-3-one [5] in the Clauberg test.[33] The D-homogonenone (21; $R^1 = Et$, $R^2 = Me$, $R^3 = H$, $n = 2$), in the Hershberger test, had 20 and 5%, respectively, of the anabolic and androgenic activities of testosterone propionate.

The (−)-ketones (21; $R^1 = Et$, $R^2 = H$, Et, C:CH, $R^3 = H$) were devoid of biological activity in an anti-œstrogenic test.[34] No activity was observed in the Hershberger test

[26] Dryden and Chinn, *J. Org. Chem.*, 1961, **26**, 3904.
[27] Wilds and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 5366.
[28] Ref. 8*b*, p. 478.
[29] Edgren, *Proc. Soc. Exp. Biol. Med.*, 1956, **92**, 569.
[30] Edgren, unpublished work.
[31] Hershberger, Shipley, and Meyer, *Proc. Soc. Exp. Biol. Med.*, 1953, **83**, 175.
[32] B.P. 826,028.
[33] Elton and Edgren, *Endocrinology*, 1958, **63**, 464.
[34] Edgren, *Proc. Soc. Exp. Biol. Med.*, 1960, **105**, 252; Edgren, Weinberg, and Cochran, *Endocrinology*, 1963, **72**, 665.

with the first two, or in the Clauberg test with the last. In the same tests the biological responses of the corresponding (±)-compounds were not significantly different from those of the (+)-enantiomers at one half the dose. Preliminary data suggest a similar relationship between the biological activities of the (±)-œstrone derivatives described here and the corresponding (+)-enantiomers.

Experimental

Representative experiments are described chiefly for compounds of the 13β-ethylgonane series, other *compounds*, further details, and analyses are given in the Tables. Unless stated otherwise, it is to be assumed that the method of preparation of any 13-alkylgonane or 13-alkyl-D-homogonane derivative in Tables 2 and 3 follows closely upon that used for its precise 13-ethylgonane analogue. Where more than one preparation can apply, that used is denoted by the appropriate prefix (*a*), (*b*), etc.

All hydrogenations were at atmospheric pressure. Optical rotations were measured on 0·5—1% solutions in a 1 dm. tube at 25°. Light absorption spectra denoted (a) refer to ethanol solutions containing aqueous sodium hydroxide. Lithium acetylide–ethylenediamine complex was supplied by the Foote Mineral Company, Exton, Pennsylvania. All other general directions are as for Part I.[1]

Table 1.

2-Alkylcyclopentane-1,3-diones (3; $n = 1$).

R^1	M. p.	Cryst. from *	Yield † (%)	Found (%) C	Found (%) H	Formula	Reqd. (%) C	Reqd. (%) H	$\lambda_{max.}$ (mμ) (10^{-3} ε)	$\lambda_{max.}$ (a) (mμ) (10^{-3} ε)
Pr^n	175°	A–D	37·2	68·8	8·8	$C_8H_{12}O_2$	68·5	8·6	251 (17·0)	270 (25·0)
Pr^i	211—213	A–B	32·4	68·7	8·7	$C_8H_{12}O_2$	68·5	8·6	250 (19·0)	270 (25·15)
Bu^n	151—152	A–B; E	12·8	69·7	8·5	$C_9H_{14}O_2$	70·1	9·15	251 (17·1)	271 (25·7)
Bu^i	194—196	B	29·2	70·3	9·25	$C_9H_{14}O_2$	70·1	9·15	251 (16·4)	271 (26·35)
i-C_5H_{11}...	150—151	A; A–B	43·4	71·5	9·5	$C_{10}H_{16}O_2$	71·5	9·6	250 (15·0)	271 (22·1)
n-$C_{16}H_{33}$	128—130	A; D–F	43·3	78·5	12·1	$C_{21}H_{38}O_2$	78·2	11·9	252 (15·4)	267 (27·25)

* A, Water; B, ethanol; C, methanol; D, acetone; E, ethyl acetate; F, toluene; G, acetonitrile; H, hexane; I, ether; J, light petroleum; K, cyclohexane; L, chloroform. † Overall yield from the corresponding alkyl methyl ketone (16) using methods similar to that for 2-ethylcyclopentane-1,3-dione.

2-Ethylcyclopentane-1,3-dione (3; R^1 = Et; $n = 1$).—Pentan-2-one (172 g.) and diethyl oxalate (644·1 g.), both chilled to 0°, were added with vigorous stirring to sodium methoxide (244 g.) in ethanol (1·4 l.) at 0° (bath). The solution was kept at reflux for 1·5 hr., cooled, and sulphuric acid (292 c.c.)–water (1·46 l.) was added. After refluxing for a further 1·5 hr., the solution was cooled to 25° and basified with 10N-aqueous sodium hydroxide. The sodium sulphate was filtered off and washed with methanol. Glacial acetic acid was added to the combined filtrate and washings to pH 4·5 and semicarbazide hydrochloride (223 g.) and sodium acetate (196 g.) in water (860 c.c.) were added with stirring over 40 min. The semicarbazone (139 g.), obtained after filtration and washing with water and methanol, had m. p. 277°. It was added over 30 min. with stirring to sodium methoxide (140 g.) in n-decanol (817 c.c.) at 120°. The temperature was slowly raised to 200° to remove volatile solvents and then maintained at 205—215° for 3 hr. The mixture was cooled to 80°, and water (820 c.c.) and enough hydrochloric acid to bring the aqueous layer to pH 8 were added. The decanol layer was removed and extracted with water (2 × 150 c.c.) and the combined aqueous solutions were washed with toluene, acidified with hydrochloric acid to Congo Red, and kept at 10° for 16 hr. The crystals were filtered off and recrystallised from aqueous ethanol to give the *dione* (86 g.), m. p. 175—177°. The analytical sample had m. p. 180° (from ethyl acetate), $\lambda_{max.}$ 250 mμ (ε 17,400), $\lambda_{max.}$ (a) 270 mμ (ε 26,800) (Found: C, 66·3; H, 7·9. $C_7H_{10}O_2$ requires C, 66·6; H, 8·0%).

13-Ethyl-3-methoxygona-1,3,5(10),8,14-pentaen-17-one (5; R^1 = Et, R^2 = Me, $n = 1$).—(*a*) 1-Diethylamino-6-*m*-methoxyphenylhex-2-ynylamine was hydrated and the product distilled as previously described [1] to give a mixture of 6-*m*-methoxyphenylhex-1-en-3-one and 1-diethylamino-6-*m*-methoxyphenylhexan-3-one (1 and 2; R^2 = Me, respectively) (Found: N, 2·2%). This mixture (70 g.) was kept at reflux with 2-ethylcyclopentane-1,3-dione (44·5 g.)

TABLE 2.

13β-Alkylgonapolyenes and œstrapolyenes.

Compound							Yield †	Found (%)		Required (%)			$\lambda_{max.}$ (mμ)
Formula	R^1	R^2	n	M. p.	Cryst. from *	Method	(%)	C	H	Formula	C	H	(10^{-3} ε)
(5)	Et	Me	2 ‡	90—92°	B	(*b*)	48·3	81·6	7·7	$C_{21}H_{24}O_2$	81·8	7·8	311 (28·5)
(5)	Pr^n	Me	1	82—84	B	(*a*)	48·5	81·4	7·7	$C_{21}H_{24}O_2$	81·8	7·8	310 (24·7)
(5)	Pr^n	Me	2 §	86—89	B	(*b*)	36·4	82·1	8·2	$C_{22}H_{26}O_2$	81·95	8·1	312·5 (24·3)
(5)	Pr^i	Me	1	112—113	C	(*a*)	68·1	81·8	7·6	$C_{21}H_{24}O_2$	81·8	7·8	312 (28·0)
(5)	Bu^n	Me	1	53—55	B	(*a*)	32·4	82·1	8·0	$C_{22}H_{26}O_2$	81·95	8·1	312 (29·2)
(5)	Bu^i	Me	1	57—60	C–D	(*a*)	35·2	81·6	8·1	$C_{22}H_{26}O_2$	81·95	8·1	312 (25·2)
(5)	i-C_5H_{11}	Me	1 ¶			(*a*)	30·3	82·1	8·1	$C_{23}H_{28}O_2$	82·4	8·3	315 (18·4)
(5)	n-$C_{16}H_{33}$	Me	1	55—56·5	G	(*a*)	31·1	83·3	10·3	$C_{34}H_{50}O_2$	83·2	10·3	316 (24·0)
(8)	Et	Me	2 **	104—107	B		78·7	80·5	8·35	$C_{21}H_{26}O_2$	81·25	8·4	278 (15·7)
(8)	Pr^n	Me	1	126—128	C		70	81·0	8·3	$C_{21}H_{26}O_2$	81·25	8·4	280 (16·2)
(8)	Pr^n	Me	2 **	146—148	A–B		92·4	81·3	8·6	$C_{22}H_{28}O_2$	81·4	8·7	277 (16·1)
(8)	Bu^n	Me	1	105—108	C		73·9	81·3	8·8	$C_{22}H_{28}O_2$	81·4	8·7	278 (16·7)
(8)	Bu^i	Me	1	117—119	B		85	81·6	8·6	$C_{22}H_{28}O_2$	81·4	8·7	278 (14·6)
(9)	Et	Me	2 ††	115—116	B; A–B		84	80·5	8·9	$C_{21}H_{28}O_2$	80·7	9·0	
(9)	Pr^n	Me	1	134—138	E–H		88·6	80·5	9·0	$C_{21}H_{28}O_2$	80·7	9·0	278 (15·3)
(9)	Pr^n	Me	2	122—124	B		80	80·7	9·2	$C_{22}H_{30}O_2$	80·9	9·3	275 (16·3)
(9)	Bu^n	Me	1	90—100	H		74·3	81·0	9·0	$C_{22}H_{30}O_2$	80·9	9·3	279 (15·6)
(10)	Pr^n	Me	1	106—108	C–D		38·2	78·4	7·7	$C_{23}H_{28}O_2$	78·4	7·4	310 (29·2)
(11)	Bu^n	Me	1	109—114	C		31·25	81·2	8·2	$C_{22}H_{28}O_2$	81·4	8·7	264 (17·8)
(12)	Et	Me	2	103—105	C	(*b*)	75	80·5	9·4	$C_{21}H_{30}O_2$	80·2	9·6	280 (1·8)
(12)	Pr^n	Me	1	141—143	C; D–H	(*b*)	66·3	79·9	9·4	$C_{21}H_{30}O_2$	80·2	9·6	280 (2·0), 287 (1·9)
(12)	Pr^n	Me	2	123—125	C	(*b*)	81·3	80·3	9·9	$C_{22}H_{32}O_2$	80·4	9·8	280 (1·9)
(12)	Bu^n	Me	1	123—125	C	(*b*)	75	80·3	9·6	$C_{22}H_{32}O_2$	80·4	9·8	278 (2·1)
(12)	Bu^i	Me	1	103—104	I–J	(*b*)	76·4	80·4	9·8	$C_{22}H_{32}O_2$	80·45	9·8	278 (2·0)
(13)	Pr^n	Me	1	119—120	B		72	77·7	8·5	$C_{23}H_{30}O_3$	77·9	8·5	278 (15·3)
(14)	Et	Me	2	130—133	C	(*a*)	72·3	81·0	8·7	$C_{21}H_{26}O_2$	80·7	9·0	279 (3·2), 287 (2·45)
(14)	Pr^n	Me	1	120—122	C	(*a*)	80	80·7	9·0	$C_{21}H_{28}O_2$	80·7	9·0	278·5 (1·9)
(14)	Pr^n	H	1	221—223	C	(*b*)	49	80·3	8·9	$C_{20}H_{26}O_2$	80·5	8·8	280 (1·9)
(14)	Bu^n	Me	1	97—99	B	(*a*), (*b*)	79·4 (*a*)	80·8	9·0	$C_{22}H_{30}O_2$	80·9	9·3	278 (2·15)
(14)	Bu^n	H	1	174—176	E–J	(*b*)	25	80·3	8·8	$C_{21}H_{28}O_2$	80·7	9·0	
(15)	Pr^n	Me	1	113—114	B	(*a*), (*b*)	70·7 (*a*), 45 (*b*)	77·45	8·7	$C_{23}H_{32}O_3$	77·5	9·05	279 (2·0)
(18)	Me	C:CH	1	128—129	C		44·2	81·4	8·3	$C_{21}H_{26}O_2$	81·25	8·4	279 (2·05)
(18)	Pr^n	C:CH	1	125—130	D–H		52·7	81·6	8·6	$C_{23}H_{30}O_2$	81·6	8·9	280 (1·9)
(18)	Pr^n	Me	1	131—134	C		57·7	80·2	9·8	$C_{22}H_{32}O_2$	80·4	9·8	278 (2·3)
(18)	Pr^n	CH_2·CH:CH_2	1	86—89	H		97·3	81·0	9·1	$C_{24}H_{34}O_2$	81·3	9·1	280 (2·0)
(22)	Me	C:CH	1	133—137	C		83	81·6	7·6	$C_{21}H_{24}O_2$	81·8	7·8	
(22)	Me	Et	1	130—133	C		76·3	80·9	8·8	$C_{21}H_{24}O_2$	80·7	9·0	

* Solvents as in Table I. † Based on cycloalkanediones. ‡ From 2-ethylcyclohexane-1,3-dione (Stetter and Dierichs, *Ber.*, 1952, **85**, 1061; H. Smith, *J.*, 1953, 803). § From 2-n-propylcyclohexane-1,3-dione (Stetter and Dierichs, *loc. cit.*). ¶ B. p. 218—222°/0·008 mm. ** Prepared in tetrahydrofuran. †† Prepared by reduction with lithium aluminium hydride in tetrahydrofuran.

TABLE 3.

13-Alkyl-gonenes and -gonadienes, and œstrenes.

Compound								Found (%)			Required (%)		$\lambda_{max.}$ (mμ)
Formula	R^1	R^2	R^3	n	M. p.	Cryst. from [a]	Yield [b] (%)	C	H	Formula	C	H	(10^{-3} ε)
(20)	Me	C:CH	H	1	142—144°	I	20	80·6	8·8	$C_{20}H_{26}O_2$	80·5	8·7	
(20)	Et	C:CH	H	2	173—177	E	17·1	80·8	9·2	$C_{22}H_{30}O_2$	80·9	9·3	
(20)	Et	Et	H	2	116—123	E–H	53·9	79·5	10·2	$C_{22}H_{34}O_2$	79·95	10·4	
(20)	Pr^n	H	H	1 [c]	133—134	I	60·2	79·3	10·0	$C_{20}H_{30}O_2$	79·4	10·0	
(20)	Pr^n	C:CH	H	1	201—205	E	28·4	80·7	9·0	$C_{22}H_{30}O_2$	80·9	9·3	
(20)	Pr^n	C:CMe	H	1 [c]	147—150	E–H	56	80·8	9·4	$C_{23}H_{32}O_2$	81·1	9·5	
(20)	Bu^n	H	H	1	104—105	I	37·9	79·8	9·9	$C_{21}H_{32}O_2$	79·7	10·2	
(20)	Bu^n	C:CH	H	1	160—164	E–H	21·7	81·0	9·4	$C_{23}H_{32}O_2$	81·1	9·5	
(20)	Bu^i	H	H	1	133—135	K	41·3	80·0	10·2	$C_{21}H_{32}O_2$	79·7	10·2	
(21)	Me	H	H	1	123—124·5, 131—132 [d]	H–I	30·3	79·0	9·5	$C_{18}H_{26}O_2$	78·8	9·55	241 (16·6)
(21)	Me	H	Ac	1	113—114 [e]	I–J							
(21)	Me	Et	H	1	119—120	I–J	31·8 [f]	79·35	10·0	$C_{20}H_{30}O_2$	79·4	10·0	241 (15·6)
(21)	Me	C:CH	H	1	173—174·5	E–I	19·8	80·4	8·8	$C_{20}H_{26}O_2$	80·5	8·7	240 (17·5)
(21)	Me	C:CH	Ac	1	153—155	I–J	28 [g]	78·1	8·3	$C_{22}H_{28}O_3$	77·6	8·5	240 (16·4)
(21)	Et	H	H	2	144—146	E	46·4	79·2	9·9	$C_{20}H_{30}O_2$	79·4	10·0	240 (16·4)
(21)	Et	H	$CO[CH_2]_8Me$	2	48—52	H		78·6	10·5	$C_{30}H_{46}O_3$	78·9	10·6	240 (18·0)
(21)	Et	H	$CO[CH_2]_2Ph$	2	154—156	E		79·85	8·6	$C_{29}H_{38}O_3$	80·1	8·8	240 (17·1)
(21)	Et	C:CH	H	2	171—174	E	30·3	80·7	9·3	$C_{22}H_{30}O_2$	80·9	9·3	240 (17·4)
(21)	Et	Et	H	2	153—155	D–H	63·9	79·9	10·3	$C_{22}H_{34}O_2$	79·95	10·4	240 (16·3)
(21)	Pr^n	H	H	1	148—149	E–H	57·9	79·6	9·9	$C_{20}H_{30}O_2$	79·4	10·0	240 (15·6)
(21)	Pr^n	H	Bz	1	198—200	E		79·4	8·25	$C_{27}H_{34}O_3$	79·8	8·4	240 (25·0)
(21)	Pr^n	H	$CO[CH_2]_2Ph$	1	104—108	E–H		79·9	8·8	$C_{29}H_{36}O_3$	80·1	8·8	240 (16·0)
(21)	Pr^n	C:CH	H	1	149—150·5	K	19·1	81·0	9·3	$C_{22}H_{30}O_2$	80·9	9·3	240 (15·7)
(21)	Pr^n	$CH{:}CH_2$	H	1	102—105, 94—97 [h]	H–I	16·2	80·5	9·7	$C_{22}H_{32}O_2$	80·4	9·8	240 (15·6)
(21)	Pr^n	$CH_2{\cdot}CHMe{:}CH_2$	H	1	141·5—143·5	E	22·9	80·8	9·9	$C_{24}H_{36}O_2$	80·8	10·2	241 (16·7)
(21)	Pr^n	Me	H	1	134—135·5	E–H	24·7	79·7	10·4	$C_{21}H_{32}O_2$	79·7	10·2	240 (18·1)
(21)	Pr^n	Pr^n	H	1	147—149	E	18·9	80·3	10·5	$C_{23}H_{36}O_2$	80·2	10·5	241·5 (16·6)
(21)	Pr^n	H	H	2	150—152	E	52	79·6	10·1	$C_{21}H_{32}O_2$	79·7	10·2	242 (16·3)
(21)	Pr^n	H	$CO[CH_2]_8Me$	2	55—58	H		78·95	10·6	$C_{31}H_{50}O_3$	79·1	10·7	240 (15·25)
(21)	Pr^n	H	$CO[CH_2]_2Ph$	2	166—169	E–H		80·0	8·6	$C_{30}H_{40}O_2$	80·3	9·0	240 (16·9)
(21)	Pr^n	C:CH	H	2	165—168	E	11·1	81·1	9·5	$C_{23}H_{32}O_2$	81·1	9·5	240 (16·75)
(21)	Bu^n	H	H	1	168—170	E–I	54·2	79·5	10·3	$C_{21}H_{32}O_2$	79·7	10·2	240 (17·0)
(21)	Bu^n	C:CH	H	1	159—163	H–I	20·5	80·8	9·3	$C_{23}H_{32}O_2$	81·1	9·5	240 (15·9)
(21)	Bu^i	H	H	1	124—125·5	E	32·5	79·5	10·0	$C_{21}H_{32}O_2$	79·7	10·2	240 (18·2)
(25)	Et	Et	H	2	153	E		80·25	9·5	$C_{22}H_{32}O_2$	80·4	9·8	311 (19·9)
(25)	Et	$R^2 + R^3$ =	O	2 [i]	193—195	E		80·4	8·6	$C_{20}H_{26}O_2$	80·5	8·8	306 (20·9)
(25)	Pr^n	H	H	1	179—182	I–L	68·5	79·5	9·1	$C_{20}H_{28}O_2$	79·95	9·4	307 (20·3)
(25)	Pr^n	H	$CO[CH_2]_2Ph$	1	76—78	H–I		80·4	8·3	$C_{29}H_{36}O_3$	80·5	8·4	306 (21·4)
(25)	Pr^n	$R^2 + R^3$ =	O	1	180—181	E	46·2	80·4	8·55	$C_{20}H_{26}O_2$	80·5	8·8	305 (20·7)
(25)	Pr^n	C:CH	H	1	134—136	E–H	61·5	81·3	8·6	$C_{22}H_{28}O_2$	81·4	8·7	305 (21·3)
(25)	Pr^n	C:CMe	H	1	164—166	I–H		81·2	8·8	$C_{23}H_{30}O_2$	81·6	8·9	306 (20·65)
(25)	Bu^n	H	H	1	151—152	I–L	52·5	80·0	9·7	$C_{21}H_{30}O_2$	80·2	9·6	306 (20·4)
(26)	Pr^n	C:CH	—	1	118—119	H	34	84·8	10·4	$C_{22}H_{32}O$	84·55	10·3	
(26)	Pr^n	$CH_2{\cdot}CH{:}CH_2$	—	1	90—92	H	51·2	84·15	11·1	$C_{23}H_{36}O$	84·1	11·1	
(27)	Pr^n	—	—	1	89—90	I–H	58·1	83·9	10·6	$C_{20}H_{30}O$	83·9	10·5	

[a] Solvents as in Table 1. [b] Overall, from appropriate 13β-alkylgona-1,3,5(10)-triene precursors for classes (20) and (21). The reactions proceed by way of the gona-2,5(10)-dien-17β-ols, as in the synthesis of the analogous 13β-ethylgonenes. [c] Dioxan or tetrahydrofuran added at hydrolysis stage. [d] Polymorph. [e] Lit.,[26] 113—114°. [f] From 17α-ethyl-3-methoxyœstra-1,3,5(10),8-tetraen-17β-ol in three stages (without isolation of intermediates) as for the 13-ethyl homologue. [g] From the 17β-hydroxy-compound by the method used for the *d*-isomer (Iriarte, Djerassi, and Ringold, *J. Amer. Chem. Soc.*, 1959, **81**, 436). [h] After desolvation at 65°/0·005 mm. [i] Prepared by method (*b*).

in methanol (330 c.c.) containing potassium hydroxide (0·4 g.) for 18·5 hr. Evaporation of most of the methanol and isolation of the product with ether–hexane gave the crude trione (4; R^1 = Et, R^2 = Me; n = 1) (97·2 g.). A portion (7·1 g.) was refluxed for 5 hr. in benzene (150 c.c.) containing toluene-*p*-sulphonic acid [from the monohydrate (2 g.)] (Dean–Stark water-separator). Working up by the method used for the corresponding œstrapentaene [1] and distillation of the product gave a viscous oil (5·7 g.), b. p. 220° (bath)/0·01 mm. which was recrystallised from methanol–ethyl acetate to give the *ketone* (3·7 g.), m. p. 70—72°, $\lambda_{max.}$ 311 mμ (ε 28,000) (Found: C, 81·3; H, 7·3. $C_{20}H_{22}O_2$ requires C, 81·6; H, 7·5%).

(*b*) The crude trione (4; R^1 = Et, R^2 = Me, n = 1) (75 g.), prepared as in (*a*), in benzene (500 c.c.) was added with stirring to toluene-*p*-sulphonic acid [from the monohydrate (210 g.)] in benzene (2·5 l.) under nitrogen. After stirring at room temperature for 5 hr. the precipitate was filtered off and washed with benzene. The combined benzene solutions were washed successively with aqueous sodium carbonate, water, and brine, dried, and concentrated (charcoal). The product was recrystallised from methanol–ethyl acetate to give the ketone (38 g.), m. p. 69—71°, undepressed by material prepared as in (*a*) above.

(*c*) The crude trione (4; R^1 = Et, R^2 = Me, n = 1) (23 g.), prepared as in (*a*), in benzene (150 c.c.), was added with stirring to polyphosphoric acid at 65° under nitrogen. The mixture was stirred for 1·5 hr. at 70—80° then cooled to 60°, and crushed ice was slowly added. The crude product was dissolved in cyclohexane, percolated through Florisil, and recrystallised from methanol–ethyl acetate to give the ketone (12 g.), m. p. 71—73°, undepressed by the sample prepared by method (*a*) above.

(*d*) 6-Methoxy-1-vinyl-1-tetralol [35] (112 g.) and 2-ethylcyclopentane-1,3-dione (80 g.) were kept at reflux for 6 hr. in methanol (275 c.c.) containing potassium hydroxide (0·3 g.). Most of the methanol was evaporated, and ether–benzene (800 c.c.; 1 : 1) was added. The solution was washed successively with water, 5% aqueous sodium hydroxide, water, and brine, and dried. The product crystallised from methanol (180 c.c.) to give 13-*ethyl*-3-*methoxy*-8,14-*secogona*-1,3,5(10),9(11)-*tetraene*-14,17-*dione* (6; R^1 = Et, R^2 = Me, n = 1) (120 g.). The analytical sample had m. p. 65—67° (from methanol), $\lambda_{max.}$ 266 mμ (ε 17,000) (Found: C, 76·7; H, 7·6. $C_{20}H_{24}O_3$ requires C, 76·9; H, 7·7%). Concentrated hydrochloric acid (50 c.c.) was added with stirring over 1 min. to the foregoing dione (120 g.) in ethanol (750 c.c.) at 50°. After stirring for 5 min., warm (50°) cyclohexane (1 l.) was added followed by water (350 c.c.), and stirring continued for 5 min. The aqueous layer was extracted with cyclohexane and the combined organic solutions were washed, dried, and evaporated. The residue was dissolved in hot ethanol (200 c.c.) containing cyclohexane (20 c.c.) and kept at 0° for 16 hr. The precipitate was filtered off, dried, purified by percolation in cyclohexane–benzene (9 : 1) through Florisil, and recrystallised from ethanol–cyclohexane (10 : 1) to give the ketone (64·8 g.), m. p. 68—70°, undepressed by the sample prepared by method (*a*) above.

13-*Ethyl*-17,17-*ethylenedioxy*-3-*methoxygona*-1,3,5(10),8,14-*pentaene* (10; R^1 = Et, R^2 = Me, n = 1).—13-Ethyl-3-methoxygona-1,3,5(10),8, 14-pentaen-17-one (50 g.) was refluxed with ethylene glycol (345 c.c.) and toluene-*p*-sulphonic acid [from the monohydrate (16 g.)] in benzene (2·22 l.) for 20 hr. under nitrogen (Dean–Stark water-separator). Saturated aqueous sodium hydrogen carbonate was added to the cooled solution, the benzene layer was separated, washed, dried, and evaporated, and the residue distilled to give an oil, b. p. 210—220°/0·006 mm. which crystallised from ethanol to give the *ketal* (42·2 g.), m. p. 125—127°, $\lambda_{max.}$ 312 mμ (ε 31,200) (Found: C, 78·0; H, 7·75. $C_{22}H_{26}O_3$ requires C, 78·05; H, 7·75%).

13-*Ethyl*-3-*hydroxygona*-1,3,5(10),8,14-*pentaen*-17-*one* (5; R^1 = Et, R^2 = H, n = 1).—5-*m*-Acetoxyphenylpent-1-yne (193 g.) was kept at 70° for 24 hr. in dioxan (266 c.c.)–acetic acid (53·2 c.c.)–40% formalin (138 c.c.)–diethylamine (138 c.c.) containing trioxan (10·6 g.) and cuprous chloride (2·7 g.). The mixture was added with stirring to 2N-aqueous potassium hydrogen carbonate and extracted with ether. The ether solution was extracted with 2N-hydrochloric acid (850 c.c.). The aqueous solution was basified with 2N-aqueous potassium hydrogen carbonate and extracted with ether. The product was refluxed for 3 hr. in 2·25N-sulphuric acid (714 c.c.). Mercuric acetate (23 g.) in water (150 c.c.) was added to the cooled solution and the mixture kept at room temperature for 48 hr. Barium acetate (204 g.) in water (400 c.c.) was added with stirring and the mixture set aside for 16 hr. The clear solution was decanted and the remainder separated in the centrifuge. Evaporation of the aqueous solution at 40° (bath) gave an oil (275 g.). A portion (91 g.) was heated with 2-ethylcyclopentane-1,3-dione (99·5 g.)

[35] Nazarov, Torgov, and Verkholetova, *Doklady Akad. Nauk S.S.S.R.*, 1957, **112**, 1067.

in benzene (500 c.c.) and acetic acid (45 c.c.) at 100° for 2 hr. The cooled solution was diluted with water (2·5 l.) and extracted with ether–ethyl acetate. The organic solution was washed with aqueous potassium hydrogen carbonate, 2N-sulphuric acid, water, and brine, and dried. The resulting trione (48·4 g.) in benzene (123 c.c.) was added with stirring to polyphosphoric acid at 40—50° over 2 hr. The mixture was kept at 40° for 30 min., added to crushed ice, and worked up to give 13-*ethyl*-3-*hydroxygona*-1,3,5(10),8,14-*pentaen*-17-*one* (25·3 g.), m. p. 168—174° (decomp.) (from methanol), $\lambda_{max.}$ 311 mμ (ε 25,900) (Found: C, 81·0; H, 7·2. $C_{19}H_{20}O_2$ requires C, 81·4; H, 7·2%). The trione was also cyclodehydrated with toluene-*p*-sulphonic acid in refluxing benzene to give the same product.

The *acetate* had m. p. 129—130° (from ethanol), $\lambda_{max.}$ 306, 318 mμ (ε 21,400, 25,500) (Found: C, 78·4; H, 6·65. $C_{21}H_{22}O_3$ requires C, 78·2; H, 6·9%).

3-*Benzyloxy*-13-*ethylgona*-1,3,5(10),8,14-*pentaen*-17-*one* (5; R^1 = Et, R^2 = CH_2Ph, n = 1).—Benzyl chloride (3·1 g.) was added to 6-hydroxy-1-tetralone (4 g.) in water (10 c.c.)–methanol (1 c.c.) containing sodium hydroxide (1 g.). The mixture was refluxed for 2 hr., cooled, diluted with water, and extracted with ether–benzene. The organic solution was washed successively with 5% aqueous sodium hydroxide, water, and brine, and dried. The product, in benzene, was percolated through alumina and recrystallised from cyclohexane. The benzyl ether (3·2 g.), m. p. 96—99°, $\nu_{max.}$ (d), 1653, 1600, 1504 cm.$^{-1}$, was reacted with vinylmagnesium chloride (3·46 g.) in tetrahydrofuran (35 c.c.). The gummy product (3·2 g.), $\nu_{max.}$ (a) 3333, 1613, 1504 cm.$^{-1}$, was refluxed with 2-ethylcyclopentane-1,3-dione (1·5 g.) in methanol (25 c.c.) containing potassium hydroxide (0·03 g.) for 5 hr. The product was chromatographed on Florex and recrystallised from ether–methanol to give 3-*benzyloxy*-13-*ethyl*-8,14-*secogona*-1,3,5(10),9(11)-*tetraene*-14,17-*dione* (6; R^1 = Et, R^2 = CH_2Ph, n = 1) (0·8 g.), m. p. 64—67°, $\nu_{max.}$ (a) 1724, 1600, 1493 cm.$^{-1}$ (Found: C, 80·5; H, 7·2. $C_{26}H_{28}O_3$ requires C, 80·4; H, 7·3%). It was kept for 4 min. in ethanol (10 c.c.)–11N-hydrochloric acid (1 c.c.), then water (10 c.c.) and cyclohexane (30 c.c.) were added. The product was recrystallised from ethanol to give the *pentaene* (0·37 g.), m. p. 131—134°, $\lambda_{max.}$ 313 mμ (ε 28,000), $\nu_{max.}$ (d) 1739, 1600, 1504 cm.$^{-1}$ (Found: C, 84·3; H, 7·1. $C_{20}H_{26}O_2$ requires C, 84·3; H, 7·1%).

13β-*Ethyl*-3-*methoxygona*-1,3,5(10),8-*tetraen*-17-*one* (8; R^1 = Et, R^2 = Me, n = 1).—13-Ethyl-3-methoxygona-1,3,5(10),8,14-pentaen-17-one (670 g.) in benzene (2·15 l.) containing 2% palladised calcium carbonate (225 g.) was shaken with hydrogen until 57·64 l. had been absorbed (112 min.). Filtration and evaporation gave a residue which was recrystallised from methanol to give a product (561·1 g.), m. p. 110—119°, $\lambda_{max.}$ 278 mμ (ε 14,600). The *ketone* had m. p. 120—122·5° (from methanol), $\lambda_{max.}$ 280 mμ (ε 16,000) (Found: C, 81·2; H, 8·0. $C_{20}H_{24}O_2$ requires C, 81·0; H, 8·1%).

13β-*Ethyl*-3-*hydroxygona*-1,3,5(10),8-*tetraen*-17-*one* (8; R^1 = Et, R^2 = H, n = 1).—Hydrogenation of 3-acetoxy-13-ethylgona-1,3,5(10),8,14-pentaen-17-one (1·79 g.) in benzene (25 c.c.) containing 10% palladised charcoal (100 mg.) gave a product (1·37 g.), m. p. 132—135° (from ethanol) which, after chromatography on Florisil and recrystallisation from aqueous ethanol, gave 3-*acetoxy*-13β-*ethylgona*-1,3,5(10),8-*tetraen*-17-*one*, m. p. 132·5—134·5°, $\lambda_{infl.}$ 271, 287·5 mμ (ε 12,400, 8900), $\lambda_{max.}$ 277 mμ (ε 12,800) (Found: C, 77·3; H, 7·3. $C_{21}H_{24}O_3$ requires C, 77·75; H, 7·5%). The foregoing acetate (0·5 g.) was kept at 50° for 20 min. under nitrogen in methanol (30 c.c.)–water (10 c.c.) containing sodium hydroxide (1·2 g.). The product (0·348 g.), had m. p. 266—270° (decomp.), $\lambda_{max.}$ 278·5 mμ (ε 13,200). Recrystallisation from methanol gave the *tetraene*, m. p. 258—260° (decomp.), $\lambda_{max.}$ 279 mμ (ε 15,800) (Found: C, 80·4; H, 7·5. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·85%).

13β-*Ethyl*-3-*methoxygona*-1,3,5(10),8-*tetraen*-17β-*ol* (9; R^1 = Et, R^2 = Me, n = 1).—13β-Ethyl-3-methoxygona-1,3,5(10),8-tetraen-17-one (16·8 g.) was added portionwise with stirring to sodium borohydride (6 g.) in methanol (500 c.c.). The mixture boiled spontaneously. Acetic acid (15 c.c.) was added to the cooled solution, most of the solvent was evaporated, water was added, and the mixture was extracted with ether. The product was recrystallised from acetonitrile to give the *alcohol* (13·8 g.), m. p. 102—105°, $\lambda_{max.}$ 278 mμ (ε 13,700) (Found: C, 80·7; H, 8·8. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·8%).

13β-*Ethyl*-17,17-*ethylenedioxy*-3-*methoxygona*-1,3,5(10),8-*tetraene* (13; R^1 = Et, R^2 = Me, n = 1) (1·3 g.), prepared from 13β-ethyl-17,17-ethylenedioxy-3-methoxygona-1,3,5(10),8,14-pentaene (2 g.) by hydrogenation in benzene (70 c.c.) containing 2% palladised calcium carbonate (0·7 g.), had m. p. 135—137° (from aqueous ethanol), $\lambda_{max.}$ 278 mμ (ε 15,100) (Found: C, 77·5; H, 8·6. $C_{22}H_{28}O_3$ requires C, 77·6; H, 8·3%).

13β-*Ethyl*-3-*methoxygona*-1,3,5(10),9(11)-*tetraen*-17-*one* (11; R^1 = Et, R^2 = Me, n = 1).—13β-Ethyl-3-methoxygona-1,3,5(10),8-tetraen-17-one (7·8 g.) was kept at reflux for 45 min. in methanol (190 c.c.)–concentrated hydrochloric acid (38 c.c.). The mixture was cooled and the product filtered off and recrystallised from methanol–ethanol (1 : 1) (charcoal) to give the *tetraene* (4·5 g.), m. p. 140—143°, $\lambda_{max.}$ 264 mμ (ε 17,700) (Found: C, 80·95; H, 7·9. $C_{20}H_{24}O_2$ requires C, 81·0; H, 8·2%).

13β-*Ethyl*-3-*hydroxygona*-1,3,5(10),9(11)-*tetraen*-17-*one* (11; R^1 = Et, R^2 = H, n = 1) (3·14 g.), prepared from 3-acetoxy-13β-ethylgona-1,3,5(10),8-tetraen-17-one (5·1 g.) with methanolic hydrochloric acid, had m. p. 258° (decomp.) (from methanol), $\lambda_{max.}$ 266 mμ (ε 15,400) (Found: C, 80·5; H, 7·75. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·85%).

13β-*Ethyl*-3-*methoxygona*-1,3,5(10)-*trien*-17β-*ol* (12; R^1 = Et, R^2 = Me, n = 1).—(*a*) 13β-Ethyl-3-methoxygona-1,3,5(10),8-tetraen-17-one (1 g.) in tetrahydrofuran (100 c.c.) was added with stirring to potassium (1·4 g.) in liquid ammonia (150 c.c.). After stirring for 1 hr., ammonium acetate and water were added and the mixture was extracted with ether. After chromatography on alumina the product (0·8 g.) had m. p. 131—134°, $\lambda_{max.}$ 278 mμ (ε 1,900). Recrystallisation from benzene–hexane gave the *triene*, m. p. 136—137° (Found: C, 79·95; H, 9·6. $C_{20}H_{28}O_2$ requires C, 79·95; H, 9·4%).

(*b*) Lithium (6 g.) was added portionwise with stirring to 13β-ethyl-3-methoxygona-1,3,5(10),8-tetraen-17β-ol (16·8 g.) in liquid ammonia (400 c.c.)–aniline (150 c.c.)–tetrahydrofuran (50 c.c.). After stirring for 2 hr., ammonium chloride (50 g.) then water (600 c.c.) were added and the mixture was extracted with ether. The product was recrystallised from hexane to give the triene (14 g.), m. p. 126—130°, undepressed by material prepared by method (*a*) above.

(−)-13β-*Ethyl*-3-*methoxygona*-1,3,5(10)-*trien*-17β-*ol*, prepared by methylating [36] (−)-13β-ethylgona-1,3,5(10)-triene-3,17β-diol,[9,10] $[\alpha]_D$ −53·4°, had m. p. 107·5—109·5° (from methanol), $[\alpha]_D$ −51° ($CHCl_3$) (Found: C, 79·7; H, 9·1. $C_{20}H_{28}O_2$ requires C, 79·95; H, 9·4%).

(−)-3-*Methoxy*-13β-*n*-*propylgona*-1,3,5(10)-*trien*-17β-*ol* (12; R^1 = Pr^n, R^2 = Me, n = 1), prepared by methylating (−)-13β-n-propylgona-1,3,5(10)-triene-3,17β-diol,[9] $[\alpha]_D$ −51·3°, had m. p. 101—103° (from hexane), $[\alpha]_D$ −58·7° ($CHCl_3$) (Found: C, 80·1; H, 9·5. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%).

13β-*Ethylgona*-1,3,5(10)-*triene*-3,17β-*diol* (12; R^1 = Et, R^2 = H, n = 1), prepared from 13β-ethyl-3-hydroxygona-1,3,5(10)-trien-17-one with sodium borohydride in ethanol, had m. p. 199—201° (from methanol) (Found: C, 79·6; H, 8·9. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·15%).

(+)-13β-*n*-*Propylgona*-1,3,5(10)-*triene*-3,17β-*diol* (12; R^1 = Pr^n, R^2 = H, n = 1), prepared from (+)-13β-n-propylgona-1,3,5(10)-trien-17-one [9] with sodium borohydride in ethanol, had m. p. 109—113° (from acetone), $[\alpha]_D$ +58·1° (EtOH), $\lambda_{max.}$ 281, 288 mμ (ε 2300, 2100) (Found: C, 77·4; H, 9·4. $C_{20}H_{28}O_2,C_3H_6O$ requires C, 77·05; H, 9·6%). Velluz *et al.*[15] give, for the methylene chloride solvate, m. p. 110°, $[\alpha]_D$ +57° (EtOH).

13β-*Ethyl*-3-*methoxygona*-1,3,5(10)-*trien*-17-*one* (14; R^1 = Et, R^2 = Me, n = 1).—(*a*) 8N-Chromic acid [37] (60 c.c.) was added with stirring to 13β-ethyl-3-methoxygona-1,3,5(10)-trien-17β-ol (50 g.) in acetone (2 l.) containing anhydrous magnesium sulphate (60 g.). The mixture was stirred for 5 min. and propan-2-ol (200 c.c.) and sodium hydrogen carbonate (100 g.) were added. The solids were filtered off and washed with hot chloroform. Evaporation of the combined filtrate and washings gave a residue which was percolated in ether through a column of neutral alumina. Recrystallisation of the product from methanol gave the *ketone* (38·2 g.), m. p. 123—127°. The analytical sample, obtained after chromatography on neutral alumina and recrystallisation from methanol, had m. p. 128—130°, $\lambda_{max.}$ 279 mμ (ε 1900) (Found: C, 80·2; H, 8·9. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·8%).

(*b*) 13β-Ethyl-3-methoxygona-1,3,5(10),9(11)-tetraen-17-one (0·31 g.) was shaken with hydrogen in ethanol (15 c.c.) containing 10% palladised charcoal (0·3 g.) until hydrogen uptake ceased. The product was recrystallised from methanol to give the ketone (0·19 g.), m. p. 125—126·5°, undepressed on admixture with the sample prepared as in (*a*), $\lambda_{max.}$ 278 mμ (ε 2350).

13β-*Ethyl*-17,17-*ethylenedioxy*-3-*methoxygona*-1,3,5(10)-*triene* (15; R^1 = Et, R^2 = Me, n = 1) (2·4 g.), prepared by refluxing 13β-ethyl-3-methoxygona-1,3,5(10)-trien-17-one (3 g.) with ethylene glycol (3 c.c.) and toluene-*p*-sulphonic acid (0·3 g.) in toluene (105 c.c.), had m. p.

[36] Djerassi, Lippman, and Grossman, *J. Amer. Chem. Soc.*, 1956, **78**, 2479.
[37] Djerassi, Engle, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547.

88—90° (from ethanol), $\lambda_{max.}$ 278 mμ (ε 2000) (Found: C, 77·1; H, 8·7. $C_{22}H_{30}O_3$ requires C, 77·2; H, 8·8%).

The same compound was obtained (70%) by reduction of 13β-ethyl-17,17-ethylenedioxy-3-methoxy-1,3,5(10),8-tetraene with lithium and ammonium chloride in liquid ammonia.

(−)-13β-*Ethyl*-3-*methoxygona*-1,3,5(10)-*trien*-17-*one*, prepared from (−)-13β-ethyl-3-methoxygona-1,3,5(10)-trien-17β-ol with chromic acid in acetone, had m. p. 146—148° (from ethyl acetate–hexane), $[\alpha]_D$ −102·5° [MeOH–$CHCl_3$ (1 : 1)] (Found: C, 80·2; H, 8·5. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·8%).

13β-*Ethyl*-3-*hydroxygona*-1,3,5(10)-*trien*-17-*one* (14; R^1 = Et, R^2 = H, n = 1).—(*a*) 13β-Ethyl-3-hydroxygona-1,3,5(10),9(11)-tetraen-17-one (6 g.) was shaken with hydrogen in ethanol (800 c.c.) containing 10% palladised charcoal (2 g.) until hydrogen uptake ceased. Recrystallisation of the product from methanol gave the *ketone* (2·43 g.), m. p. 227·5—229°, $\lambda_{max.}$ 280 mμ (ε 2300). The analytical sample had m. p. 219—222° (from aqueous ethanol) (Found: C, 79·9; H, 8·1. $C_{19}H_{24}O_2$ requires C, 80·2; H, 8·5%). Evaporation of the mother-liquors gave a residue separated by chromatography on Florisil into this ketone and a second ketone formulated as 13β-*ethyl*-3-*hydroxy*-9β-*gona*-1,3,5(10)-*trien*-17-*one*. The analytical sample had m. p. 212—216° (from methanol), $\lambda_{max.}$ 279, 285 mμ (ε 1900, 1700) (Found: C, 80·2; H, 8·5%). In five replicate experiments the tetraene (total 12·93 g.) was converted into 13β-ethyl-3-hydroxygona-1,3,5(10)-trien-17-one (7·7 g.) and its 9β-isomer (0·88 g.).

(*b*) 13β-Ethyl-3-methoxygona-1,3,5(10)-trien-17-one (0·5 g.) was fused under nitrogen at 218° with pyridine hydrochloride (5 g.) for 40 min. After cooling, the mixture was dissolved in methanol (10 c.c.), poured into water (100 c.c.), and extracted with ether. Recrystallisation of the product from aqueous ethanol gave the phenol, m. p. 226—227° (Found: C, 79·9; H, 8·6%).

(−)-13β-*Ethyl*-3-*hydroxygona*-1,3,5(10)-*trien*-17-*one*, prepared from (−)-13β-ethylgona-1,3,5(10)-triene-3,17β-diol [9] with 8N-chromic acid in acetone, had m. p. 245—251° [after chromatography on silica gel and recrystallisation from benzene–ethyl acetate, (19 : 1)], $[\alpha]_D$ −103° (EtOAc) (Found: C, 80·2; H, 8·6%).

13β-*Ethyl*-17α-*ethynyl*-3-*methoxygona*-1,3,5(10),8-*tetraen*-17β-*ol* (22; R^1 = Et, R^2 = C:CH, n = 1).—13β-Ethyl-3-methoxygona-1,3,5(10),8-tetraen-17-one (66·6 g.) in dimethylacetamide (450 c.c.) was added with stirring under acetylene to lithium acetylide (42·4 g.) in dioxan (240 c.c.)–ethylenediamine (10 c.c.)–dimethylacetamide (250 c.c.). After stirring for 20 hr. the mixture was poured on to crushed ice (1·5 kg.) and extracted with benzene. The product was taken up in hot methanol (450 c.c.) (charcoal), concentrated, and diluted with water to precipitate the *alcohol* (62·4 g.). The analytical sample had m. p. 101—103° (from methanol), $\lambda_{max.}$ 278 mμ (ε 16,100) (Found: C, 82·0; H, 8·1. $C_{22}H_{26}O_2$ requires C, 82·3; H, 8·3%).

17α-*Allyl*-13β-*ethyl*-3-*methoxygona*-1,3,5(10),8-*tetraen*-17β-*ol* (22; R^1 = Et, R^2 = CH_2·CH:CH_2, n = 1).—13β-Ethyl-3-methoxygona-1,3,5(10),8-tetraen-17-one (50 g.) in tetrahydrofuran (1 l.)–allyl bromide (225 c.c.) was added with stirring over 45 min. to a slowly reacting mixture of magnesium (20 g.) and allyl bromide (11·8 g.) in tetrahydrofuran (225 c.c.). The mixture was refluxed for 3 hr., cooled to 5°, and 20% aqueous ammonium chloride was added with vigorous stirring. Recrystallisation of the product from hexane gave the *alcohol* (51 g.), m. p. 123—125°, $\lambda_{max.}$ 280 mμ (ε 18,300). The analytical sample had m. p. 124·5—126° (Found: C, 81·55; H, 8·8. $C_{23}H_{30}O_2$ requires C, 81·6; H, 8·9%).

13β,17α-*Diethyl*-3-*methoxygona*-1,3,5(10),8-*tetraen*-17β-*ol* (22; R^1 = R^2 = Et, n = 1).—13β-Ethyl-17α-ethynyl-3-methoxygona-1,3,5(10),8-tetraen-17β-ol (64·5 g.) in benzene (700 c.c.) containing 2% palladised calcium carbonate (20 g.) was shaken with hydrogen until uptake ceased. The product (58·9 g.), had m. p. 139—142° (from methanol). Further recrystallisation gave the *alcohol*, m. p. 141·5—143°, $\lambda_{max.}$ 278 mμ (ε 16,200) (Found: C, 80·7; H, 9·0. $C_{22}H_{30}O_2$ requires C, 80·9; H, 9·3%).

13β-*Ethyl*-3-*methoxy*-17α-*propylgona*-1,3,5(10),8-*tetraen*-17β-*ol* (22; R^1 = Et, R^2 = Pr^n, n = 1) (40 g.), prepared by hydrogenation of 17α-allyl-13β-ethyl-3-methoxygona-1,3,5(10),8-tetraen-17β-ol (50 g.) in benzene (500 c.c.) over 2% palladised calcium carbonate (25 g.), had m. p. 137—139° (from methanol), $\lambda_{max.}$ 278 mμ (ε 16,800) (Found: C, 81·0; H, 9·2. $C_{23}H_{32}O_2$ requires C, 81·1; H, 9·5%).

13β-*Ethyl*-17α-*ethynyl*-3-*methoxygona*-1,3,5(10),9(11)-*tetraen*-17β-*ol* (23; R^1 = Et, R^2 = C:CH, n = 1).—13β-Ethyl-3-methoxygona-1,3,5(10),9(11)-tetraen-17-one (3·5 g.) was stirred for 16 hr. under acetylene in dimethylacetamide (120 c.c.).–dioxan (10 c.c.)–ethylenediamine

(10 c.c.) containing lithium acetylide (3·5 g.). After chromatography on Florex and recrystallisation from aqueous methanol, the product (1·2 g.) had m. p. 109—110°. It was recrystallised from ethyl acetate–hexane to give the *alcohol*, m. p. 110—112°, $\lambda_{max.}$ 263 mμ (ε 20,400) (Found: C, 81·65; H, 7·9. $C_{22}H_{26}O_2$ requires C, 81·95; H, 8·1%).

13β,17α-*Diethyl*-3-*methoxygona*-1,3,5(10),9(11)-*tetraen*-17β-*ol* (23; $R^1 = R^2 = Et$, $n = 1$) (0·7 g.), prepared by hydrogenating the foregoing alcohol (1 g.) in benzene (15 c.c.) over 2% palladised calcium carbonate (0·3 g.), had m. p. 112—117° (from methanol), $\lambda_{max.}$ 265 mμ (ε 16,100) (Found: C, 80·7; H, 9·1. $C_{22}H_{30}O_2$ requires C, 80·9; H, 9·3%).

13β-*Ethyl*-17α-*ethynyl*-3-*methoxygona*-1,3,5(10)-*trien*-17β-*ol* (18; $R^1 = Et$, $R^2 = C{:}CH$, $n = 1$).—(*a*) 13β-Ethyl-3-methoxygona-1,3,5(10)-trien-17-one (3·5 g.) was stirred under acetylene for 4 hr., in dimethylacetamide (123 c.c.)–dioxan (20 c.c.)–ethylenediamine (2 c.c.) containing lithium acetylide (3·5 g.). The product was recrystallised from aqueous methanol to give the *alcohol* (2·7 g.) m. p. 156—158°. The analytical sample had m. p. 158—160°, $\lambda_{max.}$ 280 mμ (ε 2150) (Found: C, 81·2; H, 8·8. $C_{22}H_{28}O$ requires C, 81·4; H, 8·7%).

(*b*) 13β-Ethyl-3-methoxygona-1,3,5(10)-trien-17-one (0·6 g.) was added to a suspension made by passing acetylene into lithium aluminium hydride (1·2 g.) in tetrahydrofuran (15 c.c.) for 18 hr. The mixture was shaken for 5 min., kept for 20 hr. at room temperature, and poured into 2N-sulphuric acid containing crushed ice. The product was extracted with ether and purified by chromatography on alumina to give the alcohol (0·4 g.), m. p. 154—158°, undepressed by the sample prepared as in (*a*).

17α-*Allyl*-13β-*ethyl*-3-*methoxygona*-1,3,5(10)-*trien*-17β-*ol* (18; $R^1 = Et$, $R^2 = CH_2{\cdot}CH{:}CH_2$, $n = 1$).—13β-Ethyl-3-methoxygona-1,3,5(10)-trien-17-one (1·8 g.) in ether (80 c.c.)–allyl bromide (5·8 c.c.) was added with stirring to a slowly reacting mixture of magnesium (0·725 g.) and allyl bromide (0·3 c.c.) in ether (20 c.c.), and the mixture was refluxed for 3·5 hr. The product recrystallised from ether–methanol to give the *alcohol* (1·5 g.), m. p. 130—131·5°. The analytical sample had m. p. 131·5—132·5° (from n-hexane), $\lambda_{max.}$ 278·5 mμ (ε 2000) (Found: C, 80·85; H, 9·7. $C_{23}H_{32}O_2$ requires C, 81·1; H, 9·5%).

13β-*Ethyl*-3-*methoxy*-17α-*methylgona*-1,3,5(10)-*trien*-17β-*ol* (18; $R^1 = Et$, $R^2 = Me$, $n = 1$). Methylmagnesium bromide [from the metal (0·9 g.)] in ether (20 c.c.) was refluxed for 4 hr. under nitrogen with 13β-ethyl-3-methoxygona-1,3,5(10)-trien-17-one (1 g.) in benzene (50 c.c.)–ether (20 c.c.). The product was chromatographed on alumina and recrystallised from methanol to give the *alcohol* (0·9 g.), m. p. 142—145°, $\lambda_{max.}$ 279 mμ (ε 1950) (Found: C, 80·5; H, 9·4. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%).

13β,17α-*Diethyl*-3-*methoxygona*-1,3,5(10)-*trien*-17β-*ol* (18; $R^1 = R^2 = Et$, $n = 1$).—13β,17α-Diethyl-3-methoxygona-1,3,5(10),8-tetraen-17β-ol (13·3 g.) was reduced with lithium (5 g.) in liquid ammonia (400 c.c.; redistilled from sodium)–aniline (200 c.c.). The product (11·1 g.) was recrystallised from methanol to give the *triene*, m. p. 162—163°, $\lambda_{max.}$ 278 mμ (ε 2000) (Found: C, 80·3; H, 9·65. $C_{22}H_{30}O_2$ requires C, 80·4; H, 9·8%). The same compound was obtained by hydrogenation of 13β-ethyl-17α-ethynyl-3-methoxygona-1,3,5(10)-trien-17β-ol and of 13β,17α-diethyl-3-methoxygona-1,3,5(10),9(11)-tetraen-17β-ol over 10% palladised charcoal in ethanol.

13β-*Ethyl*-3-*methoxy*-17α-*n-propylgona*-1,3,5(10)-*trien*-17β-*ol* (18; $R^1 = Et$, $R^2 = Pr^n$, $n = 1$).—(*a*) 13β-Ethyl-3-methoxy-17α-n-propylgona-1,3,5(10),8-tetraen-17β-ol (40 g.) was reduced with lithium (1·68 g.) in liquid ammonia (1·1 l.)–tetrahydrofuran (580 c.c.)–aniline (45 c.c.). Recrystallisation of the product from ethyl acetate–hexane gave the *triene* (30 g.), m. p. 117—119°, $\lambda_{max.}$ 279 mμ (ε 2000) (Found: C, 80·7; H, 9·9. $C_{23}H_{34}O_2$ requires C, 80·65; H, 10·0%).

(*b*) 17α-Allyl-13β-ethyl-3-methoxygona-1,3,5(10)-trien-17β-ol (0·87 g.) was hydrogenated in ethanol (90 c.c.), containing 5% palladised charcoal (0·4 g.) to give the triene (0·745 g.), m. p. 123—125° (from hexane) undepressed by the sample prepared as in (*a*), $\lambda_{max.}$ 279 mμ (ε 1950).

13β,17aα-*Diethyl*-3-*methoxy*-D-*homogona*-1,3,5(10)-*trien*-17aβ-*ol* (18; $R^1 = R^2 = Et$, $n = 2$).—Reaction of 13β-ethyl-3-methoxy-D-homogona-1,3,5(10),8-tetraen-17a-one (20 g.) with lithium acetylide in dimethylacetamide–dioxan–ethylenediamine and recrystallisation of the product from methanol gave a solvated alcohol (16·2 g.), m. p. 80—90° (with desolvation), $\nu_{max.}$ (b) 3559, 3268 cm.$^{-1}$, which was shaken with hydrogen in benzene (300 c.c.) containing 2% palladised calcium carbonate (5 g.) until hydrogen uptake ceased. The product (13 g.), m. p. 165—170°, $\lambda_{max.}$ 278 mμ (ε 17,000), was reduced with lithium (0·5 g.) in liquid ammonia (500 c.c.)–tetrahydrofuran (270 c.c.)–aniline (20 c.c.) to give the *alcohol* (9 g.), m. p. 145—147° (from ethyl

acetate–hexane), $\lambda_{max.}$ 280 mμ (ε 1400) (Found: C, 80·5; H, 9·8. $C_{23}H_{34}O_2$ requires C, 80·65; H, 10·0%).

13β-*Ethyl*-17β-*hydroxygon*-5(10)-*en*-3-*one* (20; R^1 = Et, R^2 = R^3 = H, n = 1).—13β-Ethyl-3-methoxygona-1,3,5(10)-trien-17β-ol (223 g.) was reduced with lithium (122 g.) and ethanol (1·45 l.) in liquid ammonia (7 l., distilled from sodium)–tetrahydrofuran (4·46 l.). The crude product was triturated with hot methanol (500 c.c.), cooled, and filtered, to yield 13β-ethyl-3-methoxygona-2,5(10)-dien-17β-ol (19; R^1 = Et, R^2 = H, n = 1) (141 g.), m. p. 117—121°, $\nu_{max.}$ (d) 3205, 2833, 1695, 1667 cm.$^{-1}$, having no selective light absorption in the 220—300 mμ region. A portion (27·9 g.) was stirred with methanol (2 l.)–water (385 c.c.) containing oxalic acid [from the dihydrate (37 g.)] at room temperature until completely dissolved (1·5 hr.). The product (18·8 g.) was recrystallised from ethyl acetate to give the *ketone*, m. p. 147—149°, $\nu_{max.}$ (d) 3420, 1704, 1060 cm.$^{-1}$ (Found: C, 79·6; H, 9·6. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%).

13β-*Ethyl*-17α-*ethynyl*-17β-*hydroxygon*-5(10)-*en*-3-*one* (20; R^1 = Et, R^2 = C:CH, R^3 = H, n = 1).—13β-Ethyl-3-methoxygona-2,5(10)-dien-17β-ol (148 g.) was refluxed for 3 hr. under nitrogen in toluene (4·8 l.)–cyclohexane (1·35 l.) containing aluminium isopropoxide (67 g.). The solution was cooled to 26°, and water (192 c.c.) was added dropwise followed by sodium sulphate (280 g.). The filtrate was concentrated and the solid was filtered off and triturated with ice-cold methanol (300 c.c.) to yield 13β-ethyl-3-methoxygona-2,5(10)-dien-17-one (120 g.), m. p. 152—160°, having no selective light absorption in the 220—300 mμ region, $\nu_{max.}$ (d) 1742, 1701, 1669 cm.$^{-1}$. Lithium acetylide–ethylenediamine complex (122 g.) was added rapidly with stirring under acetylene to a suspension of the foregoing ketone (186 g.) in dimethylacetamide (6·1 l.). After stirring for 2 hr., the mixture was cooled to 10°, ice–water (12 l.) was added, and the mixture was extracted with benzene. The crude product was triturated with ice-cold methanol to afford, after filtration and drying, 13β-ethyl-17α-ethynyl-3-methoxygona-2,5(10)-dien-17β-ol (157 g.), m. p. 130—136°, no selective light absorption in the 220—300 mμ region, $\nu_{max.}$ (d) 3390, 3257, 1695, 1667 cm.$^{-1}$. The methanolic mother-liquors yielded a second crop (10 g.), m. p. 130—136°. The foregoing alcohol (30 g.) was hydrolysed with aqueous methanolic oxalic acid to give a product (22 g.) which, after recrystallisation from light petroleum–ethyl acetate, yielded the *ketone*, m. p. 182—190°, $\nu_{max.}$ (d) 3344, 1706 cm.$^{-1}$ (Found: C, 80·6; H, 9·2. $C_{21}H_{28}O_2$ requires C, 80·7; H, 9·0%).

13β-*Ethyl*-17β-*hydroxy*-17α-*propynylgon*-5(10)-*en*-3-*one* (20; R^1 = Et, R^2 = C:CMe, R^3 = H, n = 1).—13β-Ethyl-3-methoxygona-2,5(10)-dien-17-one (10 g.) was refluxed, with stirring, for 6 hr. in tetrahydrofuran (500 c.c.) containing propynylmagnesium bromide [from ethylmagnesium bromide (30·8 g.)]. Water and Celite were added to the cooled solution and the product was collected in ether. Digestion with boiling methanol, cooling, and filtration gave 13β-ethyl-3-methoxy-17α-propynylgona-2,5(10)-dien-17β-ol (9·5 g.), m. p. 158—161°, no selective light absorption in the 220—300 mμ region, $\nu_{max.}$ (d) 3448, 3247, 2222, 1701, 1667 cm.$^{-1}$. The foregoing alcohol (4 g.), after hydrolysis with aqueous methanolic oxalic acid and recrystallisation of the product from ethyl acetate–hexane, afforded the *ketone* (2·7 g.), m. p. 156—159°, $\nu_{max.}$ (c) 2899, 2198, 1715 cm.$^{-1}$ (Found: C, 81·05; H, 9·4. $C_{22}H_{30}O_2$ requires C, 80·9; H, 9·2%).

17α-*Allyl*-13β-*ethyl*-17β-*hydroxygon*-5(10)-*en*-3-*one* (20; R^1 = Et, R^2 = CH_2·CH:CH_2, R^3 = H, n = 1).—13β-Ethyl-3-methoxygona-2,5(10)-dien-17-one (4 g.) was reacted with allylmagnesium bromide as described for the corresponding gona-1,3,5(10)-trienone. Crystallisation of the product from methanol gave 17α-allyl-13β-ethyl-3-methoxygona-2,5(10)-dien-17β-ol (3·8 g.), $\nu_{max.}$ (d) 3300, 1695, 1664, 1639 cm.$^{-1}$. The alcohol, on hydrolysis with aqueous methanolic oxalic acid and recrystallisation of the product from ethyl acetate–hexane, gave the *ketone*, m. p. 115—118°, $\nu_{max.}$ (d) 3413, 1709, 1639 cm.$^{-1}$ (Found: C, 79·8; H, 9·7. $C_{22}H_{32}O_2$ requires C, 80·3; H, 9·6%).

13β-*Ethyl*-17β-*hydroxy*-17α-2′-*methylallylgon*-5(10)-*en*-3-*one* (20; R^1 = Et, R^2 = CH_2·CMe:CH_2, R^3 = H, n = 1).—13β-Ethyl-3-methoxygona-2,5(10)-dien-17-one (4 g.) in ether (500 c.c.) and methylallyl chloride (8 g.) were added to a reacting mixture of methylallyl chloride (8 g.) and magnesium (20 g.) in ether (100 c.c.), and the mixture was refluxed for 4 hr. The product was recrystallised from methanol to afford 13β-ethyl-17α-methylallyl-3-methoxygona-2,5(10)-dien-17β-ol (4 g.), $\nu_{max.}$ (d) 3497, 1701, 1664, 1639 cm.$^{-1}$. Hydrolysis with aqueous methanolic oxalic acid and recrystallisation from ethyl acetate–hexane gave the *ketone*, m. p. 135—137°, $\nu_{max.}$ (d) 3448, 1709, 1639, 870 cm.$^{-1}$ (Found: C, 80·85; H, 10·3. $C_{23}H_{34}O_2$ requires C, 80·7; H, 9·9%).

13β,17α-*Diethyl*-17β-*hydroxygon*-5(10)-*en*-3-*one* (20; $R^1 = R^2 = Et$, $R^3 = H$, $n = 1$).—13β,17α-Diethyl-3-methoxygona-1,3,5(10)-trien-17β-ol (200 g.) was reduced with lithium (82 g.) and ethanol (0·8 l.) in liquid ammonia (5 l.)–tetrahydrofuran (3 l.). Water (10 l.) was added and the product was filtered off, washed with water and dried *in vacuo*. Digestion with boiling tetrahydrofuran (500 c.c.), cooling, and filtration gave 13β,17α-diethyl-3-methoxygona-2,5(10)-dien-17β-ol (153·6 g.), m. p. 177—184°. A portion (5 g.) was hydrolysed in methanolic oxalic acid to a product (4·55 g.), m. p. 126—134°, which was recrystallised from ethyl acetate to give the *ketone*, m. p. 142—143°, $\nu_{max.}$ (d) 3448, 1709 cm.$^{-1}$ (Found: C, 79·6; H, 10·1. $C_{21}H_{32}O_2$ requires C, 79·9; 10·2%).

17β-*Hydroxy*-17α-*methyl*-13β-*n*-*propylgon*-5(10)-*en*-3-*one* (20; $R^1 = Pr^n$, $R^2 = Me$, $R^3 = H$, $n = 1$).—3-Methoxy-17α-methyl-13β-n-propylgona-1,3,5(10)-trien-17β-ol (1·7 g.) was reduced with lithium (2 g.) in liquid ammonia (170 c.c.)–pyrrole (85 c.c.). Recrystallisation of the product from methanol afforded 3-methoxy-17α-methyl-13β-n-propylgona-2,5(10)-dien-17β-ol (1·36 g.), m. p. 157—160°, $\nu_{max.}$ (d) 3257, 1695, 1667 cm.$^{-1}$. A portion (0·3 g.), hydrolysed in aqueous methanolic oxalic acid, gave the *ketone* (0·2 g.), m. p. 158—163° (from ether–hexane), $\nu_{max.}$ (d) 3425, 1709 cm.$^{-1}$ (Found: C, 79·4; H, 9·9. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%).

13β-*Ethyl*-17β-*hydroxygon*-4-*en*-3-*one* (21; $R^1 = Et$, $R^2 = R^3 = H$, $n = 1$).—13β-Ethyl-3-methoxygona-2,5(10)-dien-17β-ol (28·3 g.) was stirred in methanol (504 c.c.) containing 11N-hydrochloric acid (34 c.c.) and water (22 c.c.) until completely dissolved. The solution was kept at room temperature for 2 hr., then poured into brine and extracted with chloroform. The product was recrystallised from ethyl acetate to give the *ketone*, m. p. 149·5—150°, $\lambda_{max.}$ 238 mμ (ε 15,300) (Found: C, 79·25; H, 9·65. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%). The same compound was obtained (70%) from 13β-ethyl-17β-hydroxygon-5(10)-en-3-one by similar treatment with methanolic hydrochloric acid.

The *acetate* had m. p. 119—122° (from methanol), $\lambda_{max.}$ 240 mμ (ε 16,700) (Found: C, 76·0; H, 8·8. $C_{21}H_{31}O_3$ requires C, 76·4; H, 9·1%). The *isovalerate* had m. p. 82—89° (from hexane), $\lambda_{max.}$ 240 mμ (ε 15,650) (Found: C, 77·1; H, 9·7. $C_{24}H_{36}O_3$ requires C, 77·4; H, 9·7%). The *decanoate* had m. p. 97—97·5° (from benzene–hexane), $\lambda_{max.}$ 239 mμ (ε 16,500) (Found: C, 78·7; H, 10·5. $C_{29}H_{46}O_3$ requires C, 78·7; H, 10·5%). The *undec*-10-*enoate* had m. p. 87—88° (from methanol), $\lambda_{max.}$ 240 mμ (ε 17,000) (Found: C, 79·0; H, 10·0. $C_{30}H_{46}O_3$ requires C, 79·2; H, 10·2%). The *hydrogen succinate* had m. p. 179—182° (from chloroform–ether), $\lambda_{max.}$ 239 mμ (ε 15,600) (Found: C, 71·0; H, 8·2. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%). The γ-*cyclopentylpropionate* had m. p. 88—89° (from methanol), $\lambda_{max.}$ 241 mμ (ε 17,000) (Found: C, 78·5; H, 9·65. $C_{27}H_{39}O_3$ requires C, 78·8; H, 9·55%). The *benzoate* had m. p. 141—149° (from ethyl acetate–hexane), $\lambda_{max.}$ 237 mμ (ε 27,300) (Found: C, 79·3; H, 8·0. $C_{26}H_{32}O_3$ requires C, 79·55; H, 8·2%). The *phenylacetate* had m. p. 143—145° (from methanol), $\lambda_{max.}$ 240 mμ (ε 16,300) (Found: C, 79·6; H, 8·4. $C_{27}H_{34}O_3$ requires C, 79·8; H, 8·4%). The γ-*phenylpropionate* had m. p. 146—148° (from ethyl acetate), $\lambda_{max.}$ 240 mμ (ε 15,600) (Found: C, 79·9; H, 8·7. $C_{28}H_{36}O_3$ requires C, 79·95; H, 8·6%). The *nicotinate* had m. p. 154—155° (from ethyl acetate), $\lambda_{max.}$ 239 mμ (ε 20,000) (Found: C, 76·1; H, 7·9; N, 3·7. $C_{25}H_{31}NO_3$ requires C, 76·3; H, 7·9; N, 3·6%).

(−)-13β-*Ethyl*-17β-*hydroxygon*-4-*en*-3-*one*, prepared from (−)-13β-ethyl-3-methoxygona-1,3,5(10)-trien-17β-ol by Birch reduction and acid hydrolysis, had m. p. 158—160°, $[\alpha]_D$ −54·5° ($CHCl_3$) (Found: C, 79·4; H, 9·7. $C_{19}H_{28}O_2$ requires C, 79·1; H, 9·8%). The *acetate* had m. p. 83—85° (from aqueous acetone), $[\alpha]_D$ −44·5°, $\lambda_{max.}$ 240 mμ (ε 16,800) (Found: C, 76·1; H, 8·8. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·15%).

(+)-13β-*Ethyl*-17β-*hydroxygon*-4-*en*-3-*one*, prepared from (+)-13β-ethyl-3-hydroxygona-1,3,5(10)-trien-17-one [9] by methylation,[36] successive reduction with sodium borohydride, and lithium and 1-methoxypropan-2-ol in liquid ammonia, and acid hydrolysis, had m. p. 154—157°, $[\alpha]_D$ +52·4° ($CHCl_3$), optical rotatory dispersion measurements in dioxan (*c* 0·0464) 26°, $[\alpha]_{400}$ −17·3°, $[\alpha]_{363}$ −462°, $[\alpha]_{357}$ −379°, $[\alpha]_{350}$ −505°, $[\alpha]_{335}$ +220°, $[\alpha]_{325}$ +1135°, $[\alpha]_{313}$ +1750°, $[\alpha]_{300}$ +1970°, $[\alpha]_{265}$ +2750° (Found: C, 78·8; H, 9·6%).

(−)-17β-*Hydroxy*-13β-*n*-*propylgon*-4-*en*-3-*one*, prepared from (−)-3-methoxy-13β-n-propylgona-1,3,5(10)-trien-17β-ol by Birch reduction and acid hydrolysis, had m. p. 155—157°, $[\alpha]_D$ −76·4° ($CHCl_3$) (Found: C, 79·4; H, 9·9. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%).

(+)-17β-*Hydroxy*-13β-*n*-*propylgon*-4-*en*-3-*one*, prepared from (+)-3-hydroxy-13β-n-propylgona-1,3,5(10)-trien-17-one by methylation,[36] reduction, and acid hydrolysis, had m. p. 162—164°, $[\alpha]_D$ +69° ($CHCl_3$), optical rotatory dispersion measurements in dioxan (*c* 0·0441) 24°;

$[\alpha]_{400}$ +68°, $[\alpha]_{363}$ −345°, $[\alpha]_{357}$ −304°, $[\alpha]_{349}$ −413°, $[\alpha]_{335}$ +268°, $[\alpha]_{325}$ +1115°, $[\alpha]_{315}$ +1680°, $[\alpha]_{300}$ +2000°, $[\alpha]_{265}$ +3000° (Found: C, 79·4; H, 9·85%).

13β-*Ethyl*-17α-*ethynyl*-17β-*hydroxygon*-4-*en*-3-*one* (21; R^1 = Et, R^2 = C:CH, R^3 = H, n = 1).—13β-Ethyl-17α-ethynyl-3-methoxygona-2,5(10)-dien-17β-ol (167 g.) was hydrolysed with methanolic hydrochloric acid and the product was recrystallised from methanol (charcoal) to give the *alcohol* (101 g.), m. p. 205—207°, $\lambda_{max.}$ 241 mμ (ε 16,700) (Found: C, 80·5; H, 9·0. $C_{21}H_{28}O_2$ requires C, 80·7; H, 9·0%). The same compound was obtained by similar treatment with acid of 13β-ethyl-17α-ethynyl-17α-hydroxygon-5(10)-en-3-one.

(−)-13β-*Ethyl*-17α-*ethynyl*-17β-*hydroxygon*-4-*en*-3-*one*, prepared from (−)-13β-ethyl-3-hydroxygona-1,3,5(10)-trien-17-one by methylation, sodium borohydride reduction, Birch reduction, Oppenauer oxidation, reaction with lithium acetylide, and acid hydrolysis as described for the racemic compound, had m. p. 238—242°, $[\alpha]_D$ +40·7° ($CHCl_3$), optical rotatory dispersion measurements in dioxan (*c* 0·0482) 28°; $[\alpha]_{400}$ −237°, $[\alpha]_{362}$ −707°, $[\alpha]_{357}$ −685°, $[\alpha]_{349}$ −815°, $[\alpha]_{335}$ −262°, $[\alpha]_{325}$ +403°, $[\alpha]_{300}$ +1195° $[\alpha]_{280}$ +1105°, $[\alpha]_{265}$ +1170° (Found: C, 80·5; H, 8·8%).

(+)-13β-*Ethyl*-17α-*ethynyl*-17β-*hydroxygon*-4-*en*-3-*one*, prepared from (+)-13β-ethyl-3-methoxygona-1,3,5(10)-trien-17β-ol as for the (+)-enantiomer, had m. p. 239—241° (from methanol–chloroform), $[\alpha]_D$ −42·5° ($CHCl_3$) (Found: C, 80·55; H, 9·25%).

17β-*Hydroxy*-13β-*n*-*propyl*-17α-*propynylgon*-4-*en*-3-*one* (21; R^1 = Pr^n, R^2 = C:CMe, R^3 = H, n = 1).—Reduction of 3-methoxy-13β-n-propylgona-1,3,5(10)-trien-17β-ol (85·5 g.) with lithium (35·7 g.) and ethanol (500 c.c.) in liquid ammonia (2·5 l.) gave 3-methoxy-13β-n-propylgona-2,5(10)-dien-17β-ol (70·2 g.), m. p. 147—155°. Oxidation of a portion (39·7 g.) with aluminium isopropoxide (25 g.) and cyclohexanone (284 g.) in toluene (500 c.c.) gave 3-methoxy-13β-n-propylgona-2,5(10)-dien-17-one (31·7 g.), m. p. 127—132°. This ketone (5 g.) with propynylmagnesium bromide [from ethylmagnesium bromide (37 g.)] in tetrahydrofuran gave 3-methoxy-13β-n-propyl-17α-propylnylgona-2,5(10)-dien-17β-ol (5 g.), m. p. 111—118°. Hydrolysis with methanolic hydrochloric acid and chromatography of the product on Florex gave the *ketone* (2·9 g.), m. p. 182—184° (from ethyl acetate–hexane), $\lambda_{max.}$ 240 mμ (ε 16,700) (Found: C, 80·9; H, 9·4. $C_{23}H_{32}O_2$ requires C, 81·1; H, 9·5%).

13β-*Ethyl*-17β-*hydroxy*-17α-*vinylgon*-4-*en*-3-*one* (21; R^1 = Et, R^2 = CH:CH_2, R^3 = H, n = 1).—13β-Ethyl-17α-ethynyl-17β-hydroxygon-4-en-3-one (0·5 g.) in pyridine (20 c.c.) was shaken with 2% palladised calcium carbonate (0·15 g.) in an atmosphere of hydrogen until 1 mol. had been absorbed. Recrystallisation of the product twice from ether–hexane gave a solvate (0·49 g.), m. p. 84—87°, which was dried at 65°/0·005 mm. to give the *alcohol*, m. p. 108—111°, $\lambda_{max.}$ 240 mμ (ε 15,200) (Found: C, 80·4; H, 9·7. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%).

13β-*Ethyl*-17β-*hydroxy*-17α-2′-*methylallylgon*-4-*en*-3-*one* (21; R^1 = Et, R^2 = CH_2CMe:CH_2, R^3 = H, n = 1).—13β-Ethyl-3-methoxy-17α-2′-methylallylgona-2,5(10)-dien-17β-ol (1·5 g.) was stirred with concentrated hydrochloric acid (2·4 c.c.)–methanol (36 c.c.)–water (1·6 c.c.)–dioxan (10 c.c.) until 20 min. after it had completely dissolved. The solution was diluted with water, the precipitate filtered off, washed with water, dried, and crystallised from ethyl acetate–hexane and then acetonitrile to yield the *ketone* (1·2 g.), m. p. 135—138°, $\lambda_{max.}$ 240 mμ (ε 16,800) (Found: C, 80·6; H, 9·7. $C_{23}H_{34}O_2$ requires C, 80·7; H, 9·9%).

17α-*Allyl*-17β-*hydroxy*-13β-*n*-*propylgon*-4-*en*-3-*one* (21; R^1 = Pr^n, R^2 = CH_2CH:CH_2, R^3 = H, n = 1).—3-Methoxy-13β-n-propylgona-2,5(10)-dien-17-one (2 g.) was refluxed for 3 hr. with stirring in ether (110 c.c.)–allyl bromide (2·5 c.c.) containing magnesium turnings (1·7 g.), and aqueous sodium potassium tartrate was added to the cooled solution. The product (0·77 g.) was stirred under nitrogen with concentrated hydrochloric acid (2·4 c.c.)–water (1·6 c.c.)–propan-2-ol (25 c.c.) for 2·5 hr. Chromatography of the product on Florex and recrystallisation from ethyl acetate gave the *alcohol* (0·79 g.), m. p. 135—137°, $\lambda_{max.}$ 241·5 mμ (ε 17,500) (Found: C, 80·4; H, 9·8. $C_{23}H_{34}O_2$ requires C, 80·6; H, 10·0%).

13β-*Ethyl*-17β-*hydroxy*-17α-*methylgon*-4-*en*-3-*one* (21; R^1 = Et, R^2 = Me, R^3 = H, n = 1).—13β-Ethyl-3-methoxy-17α-methylgona-1,3,5(10)-trien-17β-ol (1·2 g.) was reduced with lithium (1·2 g.) and 1-methoxypropan-2-ol (100 c.c.) in liquid ammonia (200 c.c.)–tetrahydrofuran (250 c.c.). The product, on recrystallisation from methanol, gave 13β-ethyl-3-methoxy-17α-methylgona-2,5(10)-dien-17β-ol (0·59 g.), m. p. 151—155°, $\nu_{max.}$ (d) 3344, 1695, 1656 $cm.^{-1}$. 3N-Hydrochloric acid (0·6 c.c.) was added to the alcohol (0·5 g.) in boiling methanol (55 c.c.) and the solution was allowed to cool to room temperature. Recrystallisation of the product

successively from ether–hexane and benzene gave a benzene solvate which, after drying *in vacuo*, afforded the *alcohol* (0·2 g.), m. p. 128—129°, $\lambda_{max.}$ 240 mμ (ε 16,200) (Found: C, 79·2; H, 10·2. $C_{20}H_{30}O_2$ requires C, 79·4; H, 10·0%).

13β,17α-*Diethyl*-17β-*hydroxygon*-4-*en*-3-*one* (21; $R^1 = R^2 =$ Et, $R^3 =$ H, $n = 1$).—13β,17α-Diethyl-3-methoxygona-2,5(10)-dien-17β-ol (242·9 g.) was stirred under nitrogen with methanol (9·2 l.)–water (433 c.c.)–10N-hydrochloric acid (595 c.c.). After 2 hr. charcoal (38 g.) was added, and the mixture stirred for 30 min. and filtered. The filtrate was diluted with water (13 l.) and kept overnight at 5° to give a product (146·8 g.), m. p. 143·5—145·5° (from acetone). Recrystallisation gave the *alcohol*, m. p. 144—145°, $\lambda_{max.}$ 241 mμ (ε 16,500) (Found: C, 79·9; H, 10·2. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%). The same compound was obtained (70%) by treating 13β,17α-diethyl-17β-hydroxygon-5(10)-en-3-one with methanolic hydrochloric acid.

(−)-13β,17α-*Diethyl*-17β-*hydroxygon*-4-*en*-3-*one*, prepared from (−)-13β-ethyl-3-methoxygona-1,3,5(10)-trien-17-one by reaction with lithium acetylide, hydrogenation, Birch reduction, and hydrolysis as described for the racemic compound, had m. p. 172—175·5° (from acetone–hexane), $[\alpha]_D$ −18·1° ($CHCl_3$) (Found: C, 79·8; H, 10·1%).

(+)-13β,17α-*Diethyl*-17β-*hydroxygon*-4-*en*-3-*one*, prepared from (+)-13β-ethyl-3-hydroxygona-1,3,5(10)-trien-17-one, as for the (−)-enantiomer, had m. p. 175—176° (from acetone–hexane), $[\alpha]_D$ +20·7° ($CHCl_3$), optical rotatory dispersion measurements in dioxan (*c* 0·0474) 25°; $[\alpha]_{400}$ −105°, $[\alpha]_{363}$ −510°, $[\alpha]_{356}$ −456°, $[\alpha]_{350}$ −603°, $[\alpha]_{334}$ +29·6°, $[\alpha]_{326}$ +667°, $[\alpha]_{312}$ +1450°, $[\alpha]_{300}$ +1710°, $[\alpha]_{265}$ +216° (Found: C, 79·6; H, 10·3%).

13β-*Ethyl*-17β-*hydroxy*-17α-*n-propylgon*-4-*en*-3-*one* (21; $R^1 =$ Et, $R^2 =$ Pr^n, $R^3 =$ H, $n = 1$).—13β-Ethyl-3-methoxy-17α-n-propylgona-1,3,5(10)-trien-17β-ol (0·74 g.) was reduced with lithium (0·75 g.) and ethanol (20 c.c.) in liquid ammonia (100 c.c.)–ether (100 c.c.) to give, from methanol, 13β-ethyl-3-methoxy-17α-n-propylgona-2,5(10)-dien-17β-ol (0·575 g.), m. p. 127—133°, $\nu_{max.}$ (d) 3333, 1698, 1664 cm.$^{-1}$. This alcohol, on hydrolysis with aqueous methanolic hydrochloric acid gave the *ketone* (0·23 g.), m. p. 132—134·5° (from ethyl acetate), $\lambda_{max.}$ 240 mμ (ε 15,900) (Found: C, 79·8; H, 10·2. $C_{22}H_{34}O_2$ requires C, 79·5; H, 10·4%).

13β-*Ethyl*-D-*homo*-17aβ-*hydroxy*-17aα-*methylgon*-4-*en*-3-*one* (21; $R^1 =$ Et, $R^2 =$ Me, $R^3 =$ H, $n = 2$).—13β-Ethyl-D-homo-3-methoxygona-1,3,5(10),8-tetraen-17a-one (13·3 g.) was kept at reflux for 8 hr. in benzene (350 c.c.)–ether (200 c.c.) containing methylmagnesium bromide (71 g.). The product, on recrystallisation from methanol, gave an alcohol (9·2 g.), m. p. 117—123°, $\lambda_{max.}$ 276 mμ (ε 15,500), $\nu_{max.}$ (d) 3448 cm.$^{-1}$, which was reduced with lithium (1·5 g.) and aniline (40 c.c.) in liquid ammonia (450 c.c.)–tetrahydrofuran (100 c.c.). The product (8 g.), m. p. 153—163°, $\lambda_{max.}$ 280 mμ (ε 1,300), was reduced with lithium (3 g.) and ethanol in liquid ammonia (500 c.c.)–tetrahydrofuran (240 c.c.). The alcohol (7·2 g.), m. p. 175—180°, $\nu_{max.}$ (d) 3413, 1695, 1667 cm.$^{-1}$, was hydrolysed with methanolic hydrochloric acid to give a product which was chromatographed on neutral alumina and recrystallised from ethyl acetate–hexane to yield the *ketone* (3·35 g.), m. p. 129·5—130·5° $\lambda_{max.}$ 242 mμ (ε 17,100) (Found: C, 80·0; H, 10·1. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%).

13β-*Ethyl*-17β-*hydroxygona*-4,9-*dien*-3-*one* (25; $R^1 =$ Et, $R^2 = R^3 =$ H, $n = 1$).—13β-Ethyl-17β-hydroxygon-5(10)-en-3-one (2·16 g.) in pyridine (7·5 c.c.) was added with stirring to perbromopyridine hydrobromide (2·4 g.) in pyridine (22·5 c.c.) under nitrogen. The mixture was stirred for 30 min. at room temperature and 30 min. at 100°, cooled, and added to crushed ice and hydrochloric acid. The *ketone* (1·55 g.), obtained by extraction with ether and recrystallisation from ether, had m. p. 152—154·5° (from ethyl acetate–benzene), $\lambda_{max.}$ 303 mμ (ε 19,200), $\nu_{max.}$ (d) 3400, 1640, 1612, 1578 cm.$^{-1}$ (Found: C, 79·8; H, 9·3. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·15%). The *γ-phenylpropionate* had m. p. 127—129°, $\lambda_{max.}$ 305 mμ (ε 21,600); $\nu_{max.}$ (d) 1725, 1650, 1605 cm.$^{-1}$ (Found: C, 80·65; H, 8·2. $C_{28}H_{34}O_3$ requires C, 80·3; H, 8·2%).

13β-*Ethylgona*-4,9-*diene*-3,17-*dione*.—(*a*) 13β-Ethyl-3-methoxygona-2,5(10)-dien-17-one was hydrolysed with aqueous methanolic oxalic acid to 13β-*ethylgon*-5(10)-*ene*-3,17-*dione*, m. p. 127—128°, having no selective absorption in the 200—280 mμ region (Found: C, 79·7; H, 9·15. $C_{19}H_{24}O_2$ requires C, 79·9; H, 9·15%). On treatment with perbromopyridine hydrobromide and dehydrobromination, the ketone (1·5 g.) gave the *dione* (0·85 g.), m. p. 126—128° (from ethyl acetate–hexane), $\lambda_{max.}$ 303 mμ (ε 20,200) $\nu_{max.}$ (d) 1733, 1645, 1597, 1575 cm.$^{-1}$ (Found: C, 80·3; H, 8·4. $C_{19}H_{26}O_2$ requires C, 80·3; H, 8·45%).

(*b*) Oxidation of 13β-ethyl-17β-hydroxygona-4,9-dien-3-one with 8N-chromic acid acid in acetone [37] gave the dione, m. p. 126—128°.

13β-*Ethyl*-17aβ-*hydroxy*-D-*homogona*-4,9-*dien*-3-*one* (25; R^1 = Et, R^2 = R^3 = H, n = 2).—13β-Ethyl-3-methoxy-D-homogona-2,5(10)-dien-17aβ-ol was hydrolysed with aqueous methanolic oxalic acid to 13β-ethyl-17aβ-hydroxy-D-homogona-5(10)-en-3-one, m. p. 110—115° (from ethyl acetate–hexane), $\nu_{max.}$ (d) 1709 cm.$^{-1}$. The ketone (3·3 g.) on treatment with perbromopyridine hydrobromide gave the *homodienone* (1·76 g.), m. p. 156—158° (from ethyl acetate), $\lambda_{max.}$ 306 mμ (ε 21,900) (Found: C, 79·9; H, 9·3. $C_{20}H_{28}O_2$ requires C, 79·95; H, 9·4%).

13β,17α-*Diethyl*-17β-*hydroxygona*-4,9-*dien*-3-*one* (25; R^1 = R^2 = Et, R^3 = H, n = 1), prepared from 13β,17α-diethyl-17β-hydroxygon-5(10)-en-3-one, had m. p. 182·5—195·5° (from chloroform–hexane), $\lambda_{max.}$ 306 mμ (ε 20,000), $\nu_{max.}$ (d) 3390, 1640, 1640, 1600 cm.$^{-1}$ (Found: C, 81·0; H, 8·3. $C_{21}H_{26}O_2$ requires C, 81·25; H, 8·4%).

17β-*Hydroxy*-17α-*methyl*-13β-*n*-*propylgona*-4,9-*dien*-3-*one* (25; R^1 = Pr^n, R^2 = Me, R^3 = H, n = 1), prepared from 17β-hydroxy-17α-methyl-13β-n-propylgon-5(10)-en-3-one, had m. p. 153—156° (from ether–hexane), $\lambda_{max.}$ 307 mμ (ε 21,300), $\nu_{max.}$ (d) 3415, 1640, 1605 cm.$^{-1}$ (Found: C, 80·0; H, 9·4. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%).

13β-*Ethyl*-17α-*ethynyl*-17β-*hydroxygona*-4,9-*dien*-3-*one* (25; R^1 = Et, R^2 = C:CH, R^3 = H, n = 1), prepared from 13β-ethyl-17α-ethynyl-17β-hydroxygon-5(10)-en-3-one, had m. p. 121—122° (from ethyl acetate), $\lambda_{max.}$ 307 mμ (ε 21,200), $\nu_{max.}$ (d) 3320, 3220, 2170, 1638, 1600 cm.$^{-1}$ (Found: C, 80·3; H, 9·4. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%).

13β-*Ethyl*-17β-*hydroxy*-17α-*propynylgona*-4,9-*dien*-3-*one* (25; R^1 = Et, R^2 = C:CMe, R^3 = H, n = 1), prepared from 13β-ethyl-17β-hydroxy-17α-propynylgon-5(10)-en-3-one, had m. p. 160—163° (from ethyl acetate–hexane), $\lambda_{max.}$ 306 mμ (ε 19,600) $\nu_{max.}$ (d) 3400, 1630, 1600 cm.$^{-1}$ (Found: C, 81·5; H, 8·7. $C_{22}H_{32}O_2$ requires C, 82·1; H, 8·7%).

13β-*Ethylgon*-4-*en*-17-*one* (27; R^1 = Et, n = 1).—13β-Ethyl-17β-hydroxygon-4-en-3-one (0·46 g.) was kept for 15 min. at room temperature in methanol (5 c.c.) containing ethane-1,2-dithiol (0·25 c.c.) and boron trifluoride etherate (0·25 c.c.). The product was recrystallised from ethyl acetate–light petroleum to give 13β-*ethyl*-3,3-*ethylenedithio*-17β-*hydroxygon*-4-*ene* (0·38 g.), m. p. 167—169°, $\nu_{max.}$ (e) 3490, 3340, 1645 cm.$^{-1}$ (Found: C, 69·1; H, 8·9%. $C_{21}H_{32}OS_2$ requires C, 69·2; H, 8·85%). Sodium (0·5 g.) was added to the dithioketal (0·34 g.) in liquid ammonia (50 c.c.)–ether (5 c.c.)–tetrahydrofuran (2 c.c.) followed by sufficient ethanol to discharge the blue colour. The crude alcohol, m. p. 118—120°, was oxidised in acetone (40 c.c.) with 8N-chromic acid. The *product* (0·242 g.) had m. p. 88—90° (from ethanol), $\nu_{max.}$ (e) 1732, 1655 cm.$^{-1}$ (Found: C, 83·55; H, 10·7. $C_{19}H_{28}O$ requires C, 83·8; H, 10·4%).

13β-*Ethyl*-17α-*ethynyl*-17β-*hydroxygon*-4-*ene* (26; R^1 = Et, R^2 = C:CH, n = 1), prepared from 13β-ethylgon-4-en-17-one by treatment with lithium acetylide–ethylenediamine complex in dimethylacetamide, had m. p. 107—108° (from methanol) (Found: C, 80·2; H, 10·0. $C_{21}H_{30}O$,MeOH requires C, 79·95; H, 10·4%).

17α-*Allyl*-13β-*ethyl*-17β-*hydroxygon*-4-*ene* (26; R^1 = Et, R^2 = CH_2·CH:CH_2, n = 1), prepared by treating 13β-ethylgon-4-en-17-one with allylmagnesium bromide in ether, had m. p. 92—94° (from methanol) (Found: C, 84·4; H, 10·9. $C_{22}H_{34}O$ requires C, 84·0; H, 10·9%).

13β,17α-*Diethyl*-17β-*hydroxygon*-4-*ene* (26; R^1 = R^2 = Et, n = 1).—13β,17α-Diethyl-17β-hydroxygon-4-en-3-one (10 g.) in tetrahydrofuran (100 c.c.)–ether (100 c.c.) was added with stirring to lithium aluminium hydride (5 g.) in ether (1 l.). The product (10 g.) had m. p. 110—122°. A portion (3 g.) was kept for 12 hr. at 0° in pyridine (30 c.c.)–acetic anhydride (3 c.c.). The acetate (2·43 g.) had m. p. 85—100°. A portion (1·35 g.) in ether (50 c.c.) was added with stirring to lithium (0·5 g.) in ethylamine (100 c.c.), stirring was continued for 15 min., and the blue colour was discharged with sodium nitrite. After evaporation of the ethylamine, sodium sulphate (10 g.) and ether were added and the mixture was filtered. After recrystallisation from ether-hexane, chromatography on neutral alumina and recrystallisation from ether, the *product* (0·36 g.) had m. p. 117·5—118·5° (Found: C, 83·4; H, 11·3. $C_{21}H_{34}O$ requires C, 83·4; H, 11·3%).

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