THE SYNTHESIS OF SOME ANALOGS OF $\Delta^{4,9}$-3-KETOSTEROIDS FROM 1-VINYL-$\Delta^{1(9),5(10)}$-6-HEXALONE

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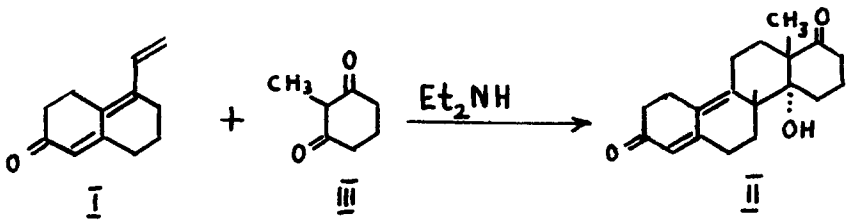
Abstract. The compounds $\Delta^{4,9}$-19-nor-D-homoandrostadiene-14α-ol-3,17a-dione (II), $\Delta^{4,9}$-19-nor-D-homoandrostatriene-3,17a-dione (IV), 2-methyl-1-(ε-carboxypropyl)-$\Delta^{1(10a),4a,8}$-octahydrophenanthrene-7-one (V) and $\Delta^{4,9}$-8,14-seco-19-nor-D-homoandrostadiene-3,14,17a-trione (VI) have been synthesized by condensation of 1-vinyl-$\Delta^{1(9),5(10)}$-6-hexalone (I) with methyldihydroresorcinol (III) under various conditions. In the presence of acids the triketone (VI) and $\Delta^{2,5(10),9(11)}$-3-methoxy-8,14-seco-19-nor-D-homoandrostatriene-14,17a-dione (VII) yield the diketol (II) and the diketone (IV). Reaction of the ketone (I) with 2-methylcyclopentane-1,3-dione leads to $\Delta^{4,9}$-8,14-seco-19-norandrostadiene-3,14,17-trione (IX).

Earlier[1] it was shown that condensation of 1-vinyl-$\Delta^{1(9),5(10)}$-6-hexalone (I) with methyldihydroresorcinol (III) in the presence of diethylamine affords $\Delta^{4,9}$-19-nor-D-homoandrostadiene-14-ol-3,17a-dione (II), which proved to be 14α-isomer*. We have now found that the course of the reaction is strongly dependent on the condensation agent. First of all it was found that the yield of the diketol (II) is determined by the quality of the diethylamine. Strange as it may seem, with pure,

* A paper on the configuration of diketol (II) will be soon published.



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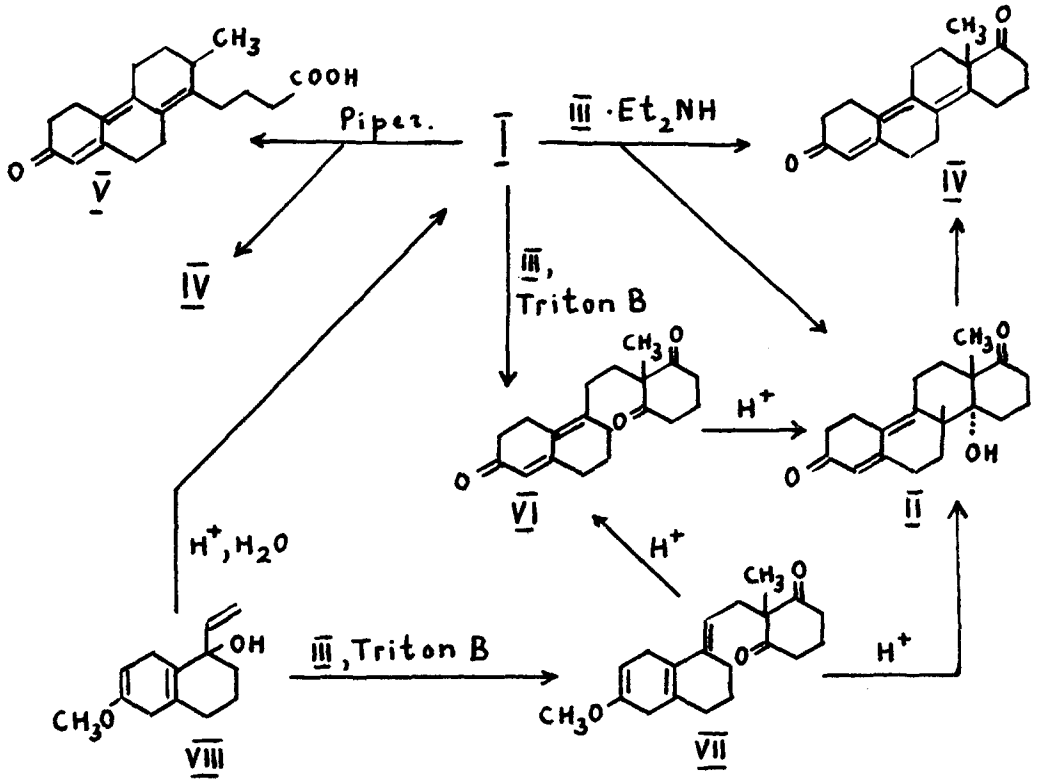
distilled diethylamine the reaction practically does not take place (97% of the methyldihydroresorcinol being returned), whereas ordinary diethylamine gives 20-24% of the diketol (II) and best yields are obtained on utilizing the residue from distillation of commercial diethylamine.

Of the impurities, triethylamine and diethylamine carbonate were tested as possible promoters of the action of diethylamine. On reaction of diethylamine carbonate with methyldihydroresorcinol /in the presence of the trienone (I)/ diethylamine methyldihydroresorcinate was formed. When this salt was heated with the trienone (I) in a mixture of tert.butanol and xylene, a mixture of compounds was formed of which only the diketone II and the known $\Delta^{4,9,8(14)}$-19-nor-D-homoandrostatriene-3, 17a-dione (IV)[2] could be isolated in 5 and 2,3% yields,respectively.

Triethylamine proved to be a weak condensation agent; in the presence of pyridine the reaction did not take place at all; with piperidine the reaction mixture yielded 10% of the diketol (II), 7% of the trienedione (IV) and 20% of an acidic product of the composition $C_{19}H_{24}O_3 \cdot H_2O$, apparently the hydrate of 2-methyl-1-(ε-carboxypropyl)-$\Delta^{1(10a),4a,8}$-octahydrophenanthrene-7-one (V). The ultraviolet spectrum of V

(λ_{max} 326 mμ) accords well with this formula.



The acid(V) is formed as the result of the hydrolytic cleavage of the diketone (IV), which may be regarded as the vinylog of the 2,2-disubstituted cyclohexanedione-1,3. Similar examples have been often described in the literature[3].

Condensation of the trienone (I) with methyldihydroresorcinol in the presence of Triton B in xylene at 110° gave $\Delta^{4,9}$-8,14-seco-19-nor-D-homoandrostadiene-3,14,17a-trione (VI) which was purified by rapid chromatography on plates using a non-fixed alumina layer. The same triketone (VI) is obtained on mild acid hydrolysis of the earlier described $\Delta^{2,5(10),9(11)}$-3-methoxy-8,14-seco-19-nor-D-homoandrostatriene-14,17a-dione (VII) a product of the condensation of the vi-

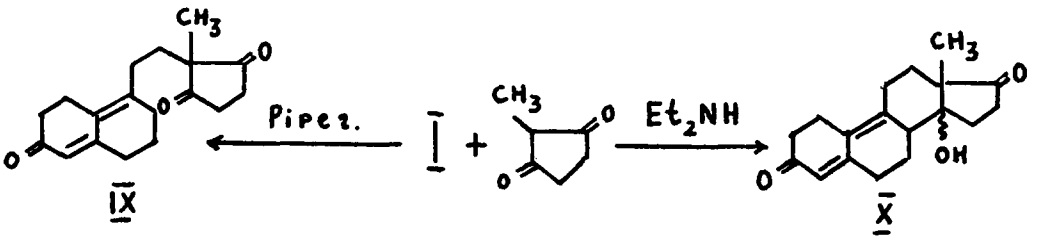
nyl carbinol (VIII) with methyldihydroresorcinol[1]. The first route to the triketone (VI) is the more feasible, since the yield of the diketone (VII) even in the improved variant could be raised from 10% to only 18-20% of the theoretical. It turned out that the triketone (VI) forms as an intermediate in the other above described methods of condensing the trienone (I) with methyldihydroresorcinol (III).

Cyclization of the diketone (VII) takes place under the action of p-toluenesulfonic acid in boiling benzene, the diketol (II) being obtained in 40% yield, together with a small amount of the diketone (IV). Similar cyclization of the triketone (VI), while giving a commensurate yield of the diketol (II), proceeds at a much slower rate than cyclization of the diketone (VII). It was therefore concluded that the diketone (VII) cyclizes to (II) without intermediate hydrolysis to (VI), but by an entirely different mechanism. The rate-determining stage of the process in both cases is most probably that of 3-enol formation. It is well known that α,β -unsaturated ketones enolize much slower than their β,γ -isomers[4], and that enolization of conjugated dienones (with shift of double bonds) proceeds slower than similar enolization of enones[5]. Hence the formation of the 3-enol from (VII) which does not require double bond shift should take place at a faster rate than its formation from the triketone (VI), thus explaining the sharp difference observed in cyclization rates.

Cyclization of the triketone (VI) in the presence of diethylamine (i.e. under conditions of direct formation of the di-

ketol (II) from the trienone (I) and methyldihydroresorcinol) practically does not take place.

We have also condensed the trienone (I) with 2-methylcyclopentane-1,3-dione. As in the case of methyldihydroresorcinol, pyridine does not catalyze the reaction, but in the presence of piperidine $\Delta^{4,9}$-8,14-seco-19-norandrostadiene-3,14,17-trione could be isolated, although in low yield.



In the presence of diethylamine* a small amount of a substance with melting point 237-240° could be isolated, which, judging from the UV and IR data, should be the diketol (X).

Experimental

The course of the reaction was followed by thin layer chromatography (1 mm layer of alumina; activity III, according to Brockmann). The UV spectra were taken in alcohol by means of an SF-4 spectrometer and the IR spectra in vaseline oil by means of UR-10 or IKS-14 instruments.

All reactions with the trienone (I) were carried out in the presence of pyrogallol in an atmosphere of nitrogen. All extracts were dried over magnesium sulfate and concentrated in vacuum.

* Recently[6] T.B.Windholz and others carried out a similar condensation, isolating dl-$\Delta^{4,9(10),8(14)}$-19-norandrostatriene-3,17-dione in 17% yield.

Condensation of the trienone (I) with methyldihydroresorcinol (III)

a) In the presence of diethylamine. A mixture of 2.5 g of freshly distilled trienone (I), 1.8 g of methyldihydroresorcinol (III), 1.8 g of diethylamine (residue after distillation of 90% commercial diethylamine), 3 ml abs.benzene and 3 ml abs. tert.-butanol was heated at 50° for 15 hrs., the methyldihydroresorcinol completely dissolving. To the reaction mixture was added 100 ml of methylene chloride and the brown solution was washed four times with saturated sodium bicarbonate, three times with 10% hydrochloric acid and once with water.

After the usual treatment, crystallization and chromatography of the mother liquors on alumina (elution with 1:1 benzene--chloroform mixture and with chloroform) 1.2 g of the diketol (II) of m.p.202-205° identical with authentic sample[1] was obtained.

b) In the presence of diethylamine methyldihydroresorcinate. To a vigorously stirred mixture of 2.8 g of methyldihydroresorcinol and 1 g of trienone (I) in 25 ml of p-xylene and 7 ml of tert.-butanol was added 2.5 g of freshly prepared diethylamine carbonate. A voluminous precipitate appeared after 1-2 min., which was filtered after an hour's standing and dried in air. Diethylamine methyldihydroresorcinate was obtained as a pale yellow amorphous powder, readily soluble in water and alcohol and insoluble in ether; yield 5.15 g (97%). The salt has a double m.p. at 148-154° and 203-206°. IR spectrum: 2691, 2510, 2431, 1643 and 1570 cm^{-1}.

Anal. Calcd. for $C_{11}H_{21}O_2N$:C,66.41; H,10.63; N,7.01. Found: C,66.45; H,10.65; N,6.82.

A mixture of 4.9 g of the salt, and 5 g of trienone (I) in 7 ml tert.-butanol and 6 ml benzene was heated for 16 hrs. at 50°. From the cooled mixture 600 mg of methyldihydroresorcinol separated out (m.p. 201-204°). The mother liquor was dissolved in methylene chloride and the solution was carefully washed with saturated sodium bicarbonate, 10% hydrochloric acid and

water. After evaporation in vacuum there was obtained 5.05 g of a brown oil which was chromatographed on alumina (activity II). Elution with benzene yielded 550 mg of trienone (I) rapidly polymerizing in air. On eluting with ether there were isolated 160 mg of trienedione (IV), m.p. 96-98° and 363 mg of diketol (II), m.p. 202-205.3°(identical with that obtained above). Subsequent elution with chloroform yielded 409 mg of a non-crystallizing (and non-distillable) dark yellow oil. The identity of the trienone (IV) with the authentic sample (kindly furnished by Dr. S.I.Zav'alov) was established by a mixed melting point determination and by comparison of the infrared spectra.

c) In the presence of piperidine. A mixture of 5 g of trienone (I), 3.52 g of methyldihydroresorcinol, 2.8 g of piperidine, 5 ml of abs. tert.-butanol and 8 ml of abs. benzene was heated at 90° for 20 hrs. After treatment as in the foregoing experiment the residual dark brown, thick oil (6.2 g) was dissolved in 100 ml of a 1:1 benzene-methylene chloride mixture and chromatographed on alumina. Elution with benzene gave 810 mg of crude trienedione (IV) as a slowly crystallizing oil. From the fraction eluted with the 1:1 benzene-methylene chloride mixture and methylene chloride was obtained 826 mg (10% theoret.) of the diketol (II), m.p. 204-206°, identical with that obtained above.

The bicarbonate solution (obtained after washing of reaction mixture by sodium bicarbonate) on acidification to pH 6 with hydrochloric acid and extraction with chloroform yielded a light brown thick mass which crystallized on adding ether. After crystallization from methylethylketone, 1.6 g (20% theoret.) of the keto acid (V), m.p. 195-198° (with decomp.) was obtained. λ_{max} 326 mμ (lgε 3.98).

Anal. Calcd. for $C_{19}H_{24}O_3 \cdot H_2O$: C,71.67; H,8.23; Found: C,71.50; H,8.84.

d) In the presence of Triton B. A solution of 3.44 g of trienone in 10 ml of p-xylene is added dropwise (in the course

of 20 min.) to a mixture, heated to 110°, of 2.52 g of methyldihydroresorcinol and 2.5 g of a 40% alcoholic solution of Triton B in 20 ml of p-xylene. The heating is continued for 2 hrs. at 100-105°. After the usual treatment from the reaction products (3.41 g) there was isolated (by preparative partition on alumina plates followed by elution with ether) 2.98 g (47% theoret.) of the triketone (VI) as a colourless oil, slowly crystallizing in needle-like crystals melting at 25-28°.
λ_{max} 301 mμ (lgε 4.26); IR spectrum: 1721, 1698 (β-diketone), 1661 (3-CO), 1622-(C=C), 1585 cm^{-1}.

Anal. Calcd. for $C_{19}H_{24}O_3$: C,75.97; H,8.05. Found: C,75.60; H,8.25.

Synthesis of the diketone (VII). A mixture of 3 g of methyldihydroresorcinol, 20 ml xylene and Triton B (from 2.8 g trimethylbenzylammonium chloride and 1.2 g potassium hydroxide) was heated at 170-175° (bath temperature), the residual alcohol was distilled off and to the boiling solution was added a solution of 4.8 g of 1-vinyl-6-methoxy-1,2,3,4,5,8-hexahydronaphthalene-1-ol (VIII) in 10 ml of xylene and the mixture was refluxed (with a water separator) for 6 hrs. (until water ceased to be eliminated). The reaction mixture was diluted with 25 ml of ether, the excess methyldihydroresorcinol was filtered off and the filtrate was evaporated to give 1.21 g of the diketone (VII)[1] with m.p. 127-129°(from alcohol).

λ_{max} 243 mμ (lgε 4.20).

Anal. Calcd. for $C_{20}H_{26}O_3$: C,76.49; H,8.31. Found: C,76.68; H,8.26.

Hydrolysis of the diketone (VII) to the triketone (VI). To a solution of 210 mg of the diketone (VII) in 20 ml of tetrahydrofuran was added 1 ml of 12% hydrochloric acid and the mixture was allowed to stand for 20 hours at 20°. Methylene chloride and a saturated solution of sodium bicarbonate were added to the reaction mixture and the organic layer was separated and evaporated. The triketone (VI), chromatographically identical with that obtained above, was isolated by prepara-

tive thin plate chromatography on alumina to the amount of 146 mg (73% theoret.).

Cyclization of the diketone (VII). To a solution of 90 mg of the diketone (VII) in 15 ml abs.benzene was added 17 mg of p-toluenesulfonic acid hydrate. The solution immediately assumed a bluish hue, which turned dark blue, then, on heating for 5 min., violet, crimson and finally a greenish light brown. After boiling for 12 min., and the usual treatment 34 mg (40%) of the diketone (II) m.p.202-205° was isolated. The mother liquor was almost pure trienedione (IV), chromatographically identical with that obtained above, which slowly crystallized on standing.

Cyclization of the triketone (VI). A mixture of 95 mg of the triketone (VI), 16 mg of p-toluenesulfonic acid and 8 ml abs. benzene was refluxed for 1 hr., another 16 mg of p-toluenesulfonic acid was added and the refluxing was carried out for another 2 hrs. After distilling off the benzene the residue was chromatographed (on plates) and (on elution with ether and ethyl acetate) 2 mg of chromatographically pure trienedione (IV), 24 mg of the initial diketone (VI) and 24 mg of the diketol (II), m.p. 192-197° were obtained.

Condensation of the trienone (I) with 2-methylcyclopentane-1,3-dione

a) In the presence of piperidine. A mixture of 800 mg of the trienone (I), 450 mg of methylcyclopentanedione, 0.5 g of piperidine, 2ml of abs. tert.-butanol and 3 ml of abs. benzene was heated with stirring for 21 hrs.at 60°. After the usual treatment and chromatography 40 mg of a light yellow oil was isolated from the methylene chloride fraction, the oil crystallizing on addition of ether. Crystallization from alcohol gave 21 mg of the triketone (IX), m.p.135-136°, λ_{max} 304 mμ (lg ε 4.20). IR spectrum 1768, 1726 (β-diketone), 1666 (3C0), 1621, 1587 cm^{-1}.

Anal. Calcd. for $C_{18}H_{22}O_3$: C,75.49; H,7.74. Found: C,75.11; H,7.8.

b) In the presence of diethylamine. A mixture of 5.1 g of trienone (I), 3.6 g of methylcyclopentanedione, 6 ml of abs. tert.-butanol, 7.5 ml of abs.benzene and 2.6 g of diethylamine was heated at 48° for 40 hours. On cooling 50 ml of ether was added and the unreacted methylcyclopentanedione (1.62 g) was separated. After the usual treatment and chromatography on alumina there were isolated 184 mg of the initial trienone (I) from the benzene fraction, 167 mg of a dark yellow non-crystallizing oil (from the benzene-chloroform 1:1) and 6 mg of colorless crystals of m.p. 237-240°, λ_{max} 306 mμ(lg ε 4.31), IR spectrum 3481 (OH), 1719, 1619, 1579 cm^{-1}, from the chloroform fraction. (Analysis of the substance could not be carried out). Further elution with alcohol gave 1.84 g of a tarry mass.

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