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THE SYNTHESIS OF A-BISNORSTEROIDS

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A number of modified steroids are known in which one of the four rings is contracted by one carbon atom relative to the normal tetracyclic steroid nucleus.[1] We wish now to report the first examples of A-bisnorsteroids, which also represent the first steroids containing a doubly contracted ring.

Cholestan-1-one (I)[2] was nitrosated with n-butyl nitrite and potassium t-butoxide to give, in 70% yield, anti-2-oximino-cholestan-1-one (II), m.p. 198-201° (dec.); $[\alpha]_D^{31}$ +90.5° (c, 1.32); ν_{max} 1613 cm^{-1} (CN), 1715 cm^{-1} (CO), 3240 cm^{-1} (OH).[3] The anti configuration of oximinoketone II was indicated by the formation of colored complexes with divalent copper, nickel and cobalt ions,[4] as well as by the bathochromic shift of its ultraviolet spectrum which was observed in alkaline solution.[5]

Reaction of oximinoketone II with chloramine in aqueous ether gave, in 78% yield, 2-diazocholestan-1-one (III), m.p. 98-100°; $[\alpha]_D^{31}$ -0.2° (c, 0.63); ν_{max} 1620 cm^{-1} (CO), 2060 cm^{-1} (N_2). Irradiation of diazoketone III in aqueous tetrahydrofuran containing sodium bicarbonate gave, in 63% yield, 1β-carboxy-A-norcholestane (IV), m.p. 198-201°; $[\alpha]_D^{31}$ -22.6° (c, 1.06); ν_{max} 1710 cm^{-1} (CO), 2500-3200 cm^{-1} (OH). Treatment of the noracid (IV) with lithium aluminum hydride in tetrahydrofuran provided, in 60% yield, 1β-hydroxymethyl-A-norcholestane (V), m.p. 104-105°; $[\alpha]_D^{31}$ -9.7°(c, 1.35); ν_{max} 3290 cm^{-1} (OH).

The β-configuration of the carboxyl group of noracid IV was confirmed by conversion of IV, in 89% yield, via a Schmidt reaction (chloroform, sodium azide, sulfuric acid), into 1β-amino-A-norcholestane (VI), m.p. 89-91°; $[\alpha]_D^{29}$ -5.3° (c, 2.62); ν_{max} 3370 cm^{-1} (NH stretch), 1610 cm^{-1} (NH bend). Al-

though noramine VI has been previously reported and the β-configuration assigned to its amino group, it was described only as an oil.[6] Preparation of amine VI by the previously described procedure, i.e., lithium aluminum hydride reduction of 1-oximino-A-norcholestane (VIII) afforded, in our hands, crystalline noramine VI (61% yield), identical (mixed m.p., IR) with material obtained from acid IV.

Treatment of noramine VI with one equivalent of t-butyl hypochlorite in ether, followed by boiling with sodium ethoxide in ethanol and finally hydrolysis with 10% sulfuric acid gave, in 73% yield, the known A-norcholestan-1-one (VII), m.p. 73-74°.[7,8] It may be noted that our new synthesis of ketone VII is considerably more convenient than those previously reported.[6,7]

Treatment of norketone VII with n-butyl nitrite and potassium t-butoxide gave syn-2-oximino-A-norcholestan-1-one (IX) as an amorphous solid; ν_{max} 1660 cm^{-1} (CN), 1750 cm^{-1} (CO), 3180 cm^{-1} (OH). The syn configuration of the oximinoketone was assigned on the basis of its failure to form colored metal complexes[4] and from the failure of its ultraviolet spectrum to shift bathochromically upon addition of alkali.[5]

Reaction of noroximinoketone IX with chloramine in aqueous ether led, in 63% overall yield from the norketone, to 2-diazo-A-norcholestan-1-one (X), m.p. 102-104°; $[\alpha]_D^{28}$ +142.5° (c, 0.88); ν_{max} 1675 cm^{-1} (CO), 2075 cm^{-1} (N_2). Irradiation of diazoketone X in aqueous tetrahydrofuran containing sodium bicarbonate afforded, in 32% yield, 1β-carboxy-A-bisnorcholestane (XI), m.p. 165-167°; $[\alpha]_D^{31}$ -40.7° (c, 1.03); ν_{max} 1720 cm^{-1} (CO), 2500-3200 cm^{-1} (OH). The carboxyl group of acid XI is assumed to have the β-configuration on mechanistic grounds.[1d,9] Lithium aluminum hydride reduction of acid XI in tetrahydrofuran afforded, in 74% yield, 1β-hydroxymethyl-A-bisnorcholestane (XII), m.p. 104-105°; $[\alpha]_D^{31}$ -0.2° (c, 0.5); ν_{max} 3400 cm^{-1} (OH).

A study of bisnoracid XI is continuing, particularly with regard to the configuration of the carboxyl group and the degradation of the acid to A-bisnorcholestan-1-one.

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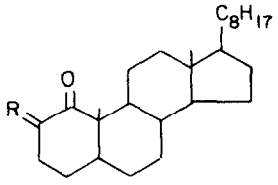
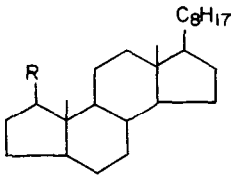
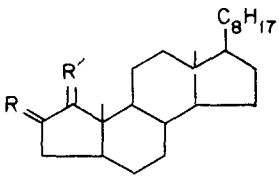


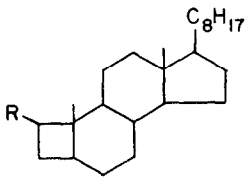
I: R = H, H
II: R = NOH
III: $R = N_2$



IV: $R = CO_2H$
V: $R = CH_2OH$
VI: $R = NH_2$



VII: R = H, H; R' = O
VIII: R = H, H; R' = NOH
IX: R = NOH; R' = O
X: $R = N_2$; R' = O



XI: $R = CO_2H$
XII: $R = CH_2OH$

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