STEROIDS. PART II[1]

Preparation of 6-dehydro-pregnane derivatives

By M. HALMOS, J. SZABÓ and Ö. KOVÁCS
Institute of Organic Chemistry, József Attila University, Szeged

(Received May 3, 1965)

Dehydrogenation by means of different dehydrogenation agents of acylated derivatives and 3-enolethers of 3β,17α-dihydroxy-Δ_5-pregnene-20-one and 3β-hydroxy-17α-acetoxy-Δ_5-pregnene-20-one as well as of 17α-hydroxy-progesterone has been studied.

At synthetical steroids with strong biological effect, which have been prepared in recent time and especially in case of different hormones, unsaturated bonds introduced in different parts of the steroids play a decisive role in forming the extent of the effect. Of these the more important are the Δ_1 and Δ_6 double-bonds, the latter increasing the effect of the compounds in question first of all in case of simultaneous introduction of 6 alkyl or halide functions. *E. g.* the effect of 17α-acetoxy-progesterone (oral Clauberg assay) is 15 times increased by the introduction of 6 chlorine function, and the simultaneously introduced double bond increases it 250 times [1, 9]. Besides profilactic anticancer compounds have recently been found among 6-dehydro-pregnane derivatives [2, 3].

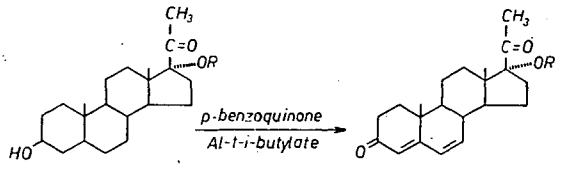
The usual methods to form Δ_6-unsaturated bond are eliminations of hydrogen halide or water from the compound substituted in the required place [4—11] and rearrangement of a known unsaturated bond from 6-methylene derivatives [12]. More recently the most widespread method is the dehydrogenation by different quinones, what may lead to Δ_1- and Δ_6-unsaturated steroids, depending on the solvent, temperature and the quinone applied. As it is well known, Δ_1-double bond can be introduced even by means of selene dioxide [11, 13a, 13b]. WETTSTEIN [14] has applied benzoquinone as hydrogen acceptor together with aluminum alcoholates in case of 3-hydroxy-Δ_5-androstene- and pregnene-derivatives, and under such conditions $\Delta_{4,6}$-diene-3-onebond systems were formed, that is the oxidation of the hydroxyl group is accompanied by a dehydrogenation process in the B-ring. Chloranil (tetrachloro-p-benzoquinone) was first used for dehydrogenation of hydrocortisone acetate. The products of the reactions are 6-dehydro derivatives in xylene solution, 1,6-bis-dehydro derivatives in n-amylalcohol. This method became fairly widespread for synthesizing Δ_6 unsaturated steroids. [1b, 7, 9, 10, 13a, 13b, 16—24]. Dehydrogenation can be well performed if the diene system is already preformed in form of 3-enolester or enolether [11, 23, 25, 36]. For preparation of 3-enol systems in the case of Δ_4-3 oxo derivatives ethyl orthoformate [26, 33] or 2,2-diethoxypropane [34] are used. Tetrachloro-o-benzoquinone and often 2,3-dicyano-5,6-dichloro-1,4-benzoquinone (DDQ) are used as dehydrogenation

[1] Part I — Acta Chim. Hung. (1965). in press.

agents [9, 24, 35, 36]. JACKMANN [37] reviewed on dehydrogenations caused by quinones, further AGNELLO and LAUBACH [38] and RINGOLD and his coworkers [24, 39, 40] dealt with the reaction mechanism.

For synthetic purposes we have studied the dehydrogenation of some pregnane derivatives by means of chloranil and by WETTSTEIN's method, respectively [14].

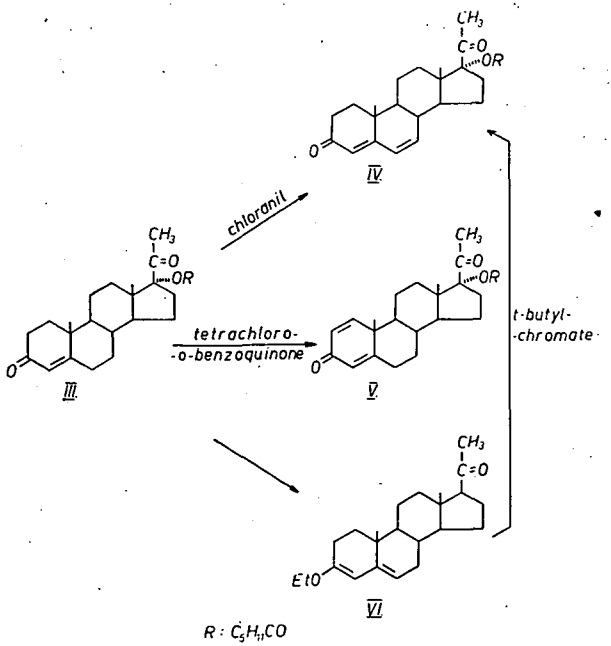
3β,17α-dihydroxy-Δ_5-pregnene-20-one (Ia) and 3β-hydroxy-17α-acetoxy-Δ_5-pregnene-20-one (Ib) were treated in presence of p-benzoquinone with aluminum isobutoxide in toluene and the desired 17α-hydroxy-Δ_6-progesterone (IIa) and 17α-acetoxy-Δ_6-progesterone, resp., have been obtained [42]. In the case of Ib during the process the hydrolysis of 17α-acetoxy-group does not take place. It was possible to prepare IIb by acetylation of IIa with acetic anhydride in presence of p-toluenesulphonic acid.



I
a, R:H
b, R:OAc

II
a, R:H
b, R:OAc

The dehydrogenation of 17α-caproyloxy-progesterone (III) with chloranil in tetrahydrofurane yields 17α-caproyloxy-Δ_6-progesterone (IV) [42].



III IV V VI

R: $C_5H_{11}CO$

III being treated with tetrachloro-ortho-benzoquinone und erconditions similar to that of dehydrogenation by chloranil, the product obtained is not identical with IV. On the basis of physical constants of the compound and of the IR spectra, dehydrogenation likely proceeds in $\Delta_{1(2)}$ position and 17α-caproyloxy-Δ_1-progesterone was formed (V) [44]. A broad band found in the infrared spectra at 1660 cm^{-1} as well as an olefin band found at 800 cm^{-1} indicates $\Delta_{1,4}$-diene-3-one-structure. 17α-caproyloxy-progesterone (III) was treated with ethyl orthoformate in presence of hydrochloric acid [26], sulphuric acid [27] and p-toluene sulphonic acid [28] to give the enolether (VI). The latter was treated by the method of KIKUO, JASUDA and their coworkers [43] with t-butylchromate in carbon tetrachloride. We isolated 17α-caproyloxy-Δ_6-progesterone (IV) from the reaction product by chromatography on silicagel.

According to our experiences best yield was reached with dehydrogenation by chloranil in the preparation of 6-dehydro derivatives. Concerning the different suppositions on the mechanisms we do not think it necessary to suppose the cyclic intermediate, as it has been done by MANDELL [40], dehydrogenation through enolization appears to be more probable. It had been proved by RINGOLD and TURNER [24] in the course of their experiments. They found that the rate of dehydrogenation is depending on the enolization and on the concentration of reactants promoting enolization. We have to note that the rate of dehydrogenations carried out with different quinones are independent of the redox potentials of different quinones, that is, depends on other factors [37].

Experimental

17α-*hydroxy*-Δ_6-*progesterone* (17α-*hydroxy*-$\Delta_{4,6}$-*pregnadiene*-3,20-*dione*) (*IIa*)

To 3 g of 3β,17α-dihydroxy-Δ_5-pregnene-20-one (Ia) dissolved in 180 ml of anhydrous toluene, 18 g of p-benzoquinone was added and 30 ml of toluene distilled from the solution. After addition of 3 g of aluminum-t-isobutoxide the mixture was refluxed for an hour, then it was steam-distilled for three hours the cooled residue acidified with 10 ml of 1 N sulphuric acid and was extracted with 5 × 100 ml of ether. The extracts were washed with 1 N Na_2CO_3 solution until negative $FeCl_3$ test. The solution was then washed with water, dried (Na_2SO_4 sicc.) and evaporated to 50 ml, filtered on a short Al_2O_3 column (80 g, act.: II), washed with 50 ml of ether and evaporated. 1,2 g of oil was obtained and it was chromatographed on silica gel (60 g) with ethyl acetate. The crystalline substance obtained (622 mg) was recrystallized from acetone-ether. Yield: 452 mg of 17α-hydroxy-Δ_6-progesterone (IIa). Mp.: 239—241°; $(\alpha)_D^{20}$: +22° (c: 1, $CHCl_3$); IR $\lambda_{max}^{CCl_4}$: 3660 cm^{-1} (OH free), 3540 cm^{-1} (OH assoc), 1690 cm^{-1} (20-ketone) 1660 cm^{-1} (conjugated-3-ketone), 1617, 1586 cm^{-1} (conjugated olefin), 1015 cm^{-1} (OH).

Anal.: Calcd. $C_{21}H_{28}O_3$ C 76,79 H 8,59 Found C 76,68 H 8,63%.

17α-*acetoxy*-Δ_6-*progesterone* (17α-*acetoxy*-$\Delta_{4,6}$-*pregnadiene*-3,20-*dione*) (*IIb*).

A) 1,5 g of 3β-hydroxy-17α-acetoxy-Δ_5-pregnene-20-one (Ib) was dissolved in 90 ml of anhydrous toluene, 9 g p-benzoquinone was added and 15 ml toluene

distilled from the solution. 1,5 g aluminum-t-isobutoxide was added to the solution and boiled for an hour. After steam distilling for two hours the cooled residue was acidified with 1 N sulphuric acid and extracted with 5×50 ml of ether. The extract was washed with cool saturated $NaHCO_3$ solution until negative $FeCl_3$ test. Then the solution was washed with water, dried (Na_2SO_4 sicc.) and evaporated. The residue was chromatographed on silica gel (50 g) with ethyl acetate and 350 mg of crystalline substance was obtained and crystallized from acetone-ether. Yield: 228 mg 17α-acetoxy-Δ_6-progesterone (IIb). Mp.: 218—220°; $(\alpha)_{20}^{D}$: +18° (c: 1, $CHCl_3$). IR $\lambda_{max}^{CCl_4}$: 1720, 1240 cm_{-}^{-1} (ester), 1690 cm^{-1} (20-ketone), 1660 (conjugated-3-ketone), 1617, 1586 cm^{-1} (conjugated olefin).

Anal.: Calcd.: $C_{23}H_{30}O_4$ C 74,54 H 8,16 Found: C 74,32 H 8,09%.

B) 300 mg of 17α-hydroxy-Δ_6-progresterone (IIa) was dissolved in 10 ml anhydrous toluene, 10 ml of p-toluenesulphonic acid and 1 ml of acetic anhydride were added, then the solution boiled for 3 hours and 4 ml of solvent was distilled off. 1 ml of pyridine was added and the solution distilled under reduced pressure till it became dry. The residue was recrystallized from aceton-ether. 152 mg of 17α-acetoxy-Δ_6-progesterone was obtained (IIb). Mp.: 219—220 °; $(\alpha)_D^{20}$: +18°: (c: 1, $CHCl_3$). IR spectra were identical with those of A.

Anal.: Found: C 74,28 H 8,12%.

17α-caproyloxy-Δ_6-progesterone (17α-caproyloxy-$\Delta_{4,6}$-pregnadiene-3,20-dione (IV)

A) 2 g of 17α-caproyloxy-progesterone (III) was disseolve in 60 ml of anhydrous tetrahydrofurane. 1,6 g chloranil was added and the solution refluxed for 20 hours. The cooled mixture was diluted with water for five times of its original volume, then extracted with 2×60 ml of ethyl acetate. The extract was washed with 1 N NaOH solution until the disappearance of $FeCl_3$ reaction, then with water and dried (Na_2SO_4 sicc.). The solution was filtered on a short Al_2O_3 column (30 g, act: II) and evaporated at reduced pressure. The residue was recrystallized from acetone. 782 mg of 17α-caproyloxy-Δ_6-progresterone (IV) was obtained. Mp.: 108—110 °C; $(\alpha)_D^{20}$: +10° (c: 1, $CHCl_3$). IR $\lambda_{max}^{CCl_4}$: 1718 cm^{-1}(ester), 1690 cm^{-1} (20-ketone), 1660 cm^{-1} (conjugated-3-ketone), 1608, 1552 cm^{-1} (olefin).

Anal.: Calcd.: $C_{27}H_{38}O_4$ C 76,02 H,8,98 Found: C 76,00 H 8,87%.

B) 1 g of 3-ethoxy-17α-caproyloxy-$\Delta_{3,5}$-pregnadiene 20-one (VI) was dissolved in 50 ml carbon tetrachloride and 10 ml t-butylchromate solution [43] was added, the solution was boiled on water-bath for three hours at constant stirring. Then 100 ml of 10% aqueous oxalic acid and 5 g oxalic acid were added and then the solution was stirred for two hours at room temperature. It was extracted with 3×100 ml ethyl acetate, the extract washed with 1 N sodium hydroxide solution then with water and dried (Na_2SO_4 sicc.) and distilled under reduced pressure. The residue is dissolved in 50 ml acetone and filtered through 20 g Al_2O_3, evaporated and recrystallized from acetone. 222 mg of 17α-caproyloxy-Δ_6-progesterone (IV) was obtained. Mp.: 109—110°; $(\alpha)_D^{20}$: +11° (c: 1, $CHCl_3$). IR $\lambda_{max}^{CCl_4}$: 1720 cm^{-1} (ester), 1690 cm^{-1} (20-ketone), 1658 cm^{-1} (conjugated-3-ketone), 1608, 1550 cm^{-1} (olefin).

Anal.: Found C 76,05 H 8,96%.

3-ethoxy-17α-caproyloxy-$\Delta_{3,5}$-pregnadiene-20-one (VI)

A) 2,5 g of 17α-caproyloxy-progesterone (III) was dissolved in anhydrous benzene, 1,25 ml of freshly distilled ethyl orthoformate, 1 ml of dry ethanol and 1 drop 22% hydrochloric acid in anhydrous ethanol were added, then the mixture boiled for two hours. After cooling it was made alkaline with 1 N NaOH solution then the mixture was washed with water. The organic layer was distilled under reduced pressure, then it was chromatographed with benzene on Al_2O_3-column (80 g, act.: II). The obtained crystalline substance was recrystallized from methanol: 1,22 g of 3-ethoxy-17α-caproyloxy-$\Delta_{3,5}$-pregnadiene-20-one (VI) was obtained. Mp.: 138—140 $(\alpha)_D^{20}$: +11° (c: 1, $CHCl_3$). IR $\lambda_{max}^{CCl_4}$: 1708 cm^{-1} (ester), 1660, 1608 cm^{-1} (olefin).

Anal.: Calcd.: $C_{29}H_{44}O_4$ C 76,27 H 9,71 Found C 76,18 H 9,68%.

B) 2 g of 17α-caproyloxy-progesterone (III) was dissolved in 25 ml of anhydrous tetrahydrofurane, then 1 ml of anhydrous ethanol, 1,9 ml of ethyl orthoformate and 30 mg of p-toluenesulphonic acid were added. After shaking for 30 min 1,5 ml of anhydrous pyridine was added and the solution distilled under reduced pressure to dryness. Residue was recrystallized from methanol. 1,01 g of 3-ethoxy-17α-caproyloxy-$\Delta_{3,5}$-pregnadiene-20-one (VI) was obtained. M. p: 137—140°; $(\alpha)_D^{20}$: +10° (c: 1, $CHCl_3$). IR spectra proved to be identical with that of compounds described in A.

Anal.: Found C 76,22 H 9,69.

C) 1 g of 17α-caproyloxy-progesterone (III) was dissolved in 15 ml of anhydrous dioxane, 1 ml of ethyl orthoformate, 0,1 ml of anhydrous ethanol and 0,04 ml of cc. H_2SO_4 dissolved in 1 ml anhydrous dioxane were added. The reaction mixture was shaken for 30 min., then 1 ml of pyridine added. Then it was diluted with water and the obtained crystalline solid filtered, dried and recrystallized from methanol. 0,42 g of 3-ethoxy-17α-caproyloxy-$\Delta_{3,5}$-pregnadiene-20-one was obtained. Mp.: 137—139°; $(\alpha)_D^{20}$: +10° (c: 1, $CHCl_3$). The IR spectra was identical with of product described in A. Anal.: Found: C 76,12 H 9,79%.

Dehydrogenation of 17α-caproyloxy-progesterone (III) with tetrachloro-benzoquinone

1 g of 17α-caproyloxy-progesterone (III) was dissolved in 30 ml of anhydrous tetrahydrofurane, 1 g of tetrachloro-o-benzoquinone was added and the solution boiled for 18 hours. The cooled mixture was diluted with water up to five volume then extracted with 3×40 ml of ethyl acetate. The extract was washed with 1 N NaOH solution until negative $FeCl_3$ test, then with water and dried (Na_2SO_4 sicc.). The resulting solution was evaporated under reduced pressure and the residue chromatographed on a silica gel column (40 g) with ethyl acetate. A crystalline substance (303 mg) was obtained which after recrystallization from acetone-ether yields 201 mg of 17α-caproyloxy-$\Delta_{1,4}$-pregnadiene-3,20-dione [44]. Mp.: 100—101°; $(\alpha)_D^{20}$: +2°. (c: 1, $CHCl_3$). IR $\lambda_{max}^{CCl_4}$: 1720 cm^{-1} (ester), 1660 cm^{-1} (conjugated ketone), 1620, 1558 cm^{-1} (olefin), 800 cm^{-1} (olefin).

Anal.: Calcd.: $C_{27}H_{38}O_4$ C 6,02 H 8,98 Found C 75,98 H 8,75%.

* * *

The authors wish to thank to Gedeon Richter Ltd for their support of this work, to L. CORNELIA LÁNG and B. GIZELLA BOZÓKI for carrying out the mycro-analysis and to EVA BARABÁS for her technical assistance.

References

[1] a) *Applezweig N.:* Steroid Drugs. (McGraw-Hill Book Co. New York 1962.) p. 340, 341.; b) *Ringold H. J., E. Batres, A. Bowers, J. Edwards and J. Zderic:* J. Amer. Chem. Soc. **81,** 3485 (1959).
[2] Cancer Research at B. D. H. Chem. and Ind. **1963,** 1733.
[3] *Wilson A. J.:* J. Amer. med. Ass. **182,** 327 (1962).
[4] *Dean J. W. and R. G. Christiansen:* J. Org. Chem. **28,** 2110 (1963).
[5] *Huang Minlon and Han Kuang Tieng:* Acta Chim. Sinica **29,** 99 (1963).
[6] *Brückner K.:* a) Ger 1,075.114 (1960) Chem. Abstr. **55,** 12458a (1961). b) Ger. 1,156.407 (1964); Chem. Abstr. **60,** 3070a (1964).
[7] *Brückner K., B. Hampel und U. Johnsen:* Chem. Ber. **94,** 1225 (1961).
[8] *Sciaky R.:* Gazz. Chim. Ital. **91,** 545 (1961).
[9] *Weiss M. J., R. E. Schaub, J. F. Poletto, G. R. Allen and Ch. C. Pidacks:* Steroids **1,** 608 (1963).
[10] *Deghenghi R., Y. Leffebvre, P. Mitchell, P. F. Morand and R. Gaudry:* Tetrahedron **19,** 289 (1963).
[11] *Knox L. H., J. A. Zderic, J. P. Ruelas, C. Djerassi and H. J. Ringold:* J. Amer. Chem. Soc. **82,** 1230 (1960).
[12] *Petrow V.:* U. S. 3,117,966 (1964); Chem. abstr. **60,** 9336b (1964).
[13] a) *Ringold H. J., J. P. Ruelas, E. Batres and C. Djerassi:* J. Amer. Chem. Soc. **81,** 3712 (1959). b) *Bowers A., Laura C. Ibánez and H. J. Ringold:* J Amer. Chem. Soc. **81,** 5991 (1959).
[14] *Wettstein A.:* Helv. Chim. Acta **23,** 388 (1940).
[15] *Agnello E. J. and G. D. Laubach:* J. Amer. Chem. Soc. **79,** 1258 (1957).
[16] Brit. 890, 315.
[17] *Graber R. P., M. B. Meyers, Le Roy G. Hickmann, E. H. Borochoff and A. D. Odell:* J. Med. Chem. **7,** 540 (1964).
[18] *Syhora K.:* Czech: 104,667 (1962); Chem. Abstr. **60,** 8100f (1964).
[19] *Syhora K.:* Czech. 110.406 (1964); Chem. Abstr. **62,** 17260 (1965).
[20] *Syhora K., R. Mazác:* Coll. Czech. Chem. Comm. **29,** 2351 (1964).
[21] Brit. 932, 153 (1963), Brit. 935,116 (1963).
[22] Ger. 1,158,968 (1963), Ger. 1,159,954 (1963).
[23] *Ringold H. J. and. E. Batres:* Fr. M. 1201 (1962); Chem. Abstr. **58,** 10281 g.
[24] *Ringold H. J. and A. Turner:* Chem. and Ind. **1962,** 211.
[25] *Campbell and J. C. Babcoek:* J. Amer. Chem. Soc. **81,** 4069 (1959).
[26] *Vargha L., M. Rados and L. Szpornyi:* Hung. 151,037 (1963) Chem. Abstr. 9335 g (1964).
[27] *Julian P. L., E. W. Meyer, W. J. Karpel and W. Cole:* J. Amer. Chem. Soc. **73,** 1982 (1951).
[28] *Gardi R., R. Vitali, A. Ercoli:* J. Org. Chem. **27,** 668 (1962).
[29] Ger. 1,158,506 (Merck); Chem. Abstr. **60,** 5602 g (1964).
[30] *Dusza J. P.:* J. Org. Chem. **28,** 92 (1963).
[31] *Sermi A. and H. Köster:* Chem. Ber. **71,** 1766 (1938).
[32] *Riegel B.:* J. Org. Chem. **16,** 1610 (1951).
[33] Ger. 1,158,506 (1963), Chem. Abstr. **60,** 5602 (1964).
[34] *Nussbaum A. L., E. Yuan, D. Dincer and E. P. Oliveto:* J. Org. Chem. **26,** 3925 (1961).
[35] *Burn D., D. N. Kirk and W. Petrow:* Proc. Chem. Soc. **1960,** 14.
[36] *Pradhan S. K. and H. J. Ringold:* J. Org. Chem. **29,** 601 (1964).
[37] *Jackmann L. M.:* Advances in Org. Chem. (R. A. Raphael et al.) New York (1960), Vol. II. 329. 333.
[38] *Agnello E. J. and G. D. Laubach:* J. Amer. Chem. Soc. **82,** 4293 (1960).
[39] *Burstein S. H. and H. J. Ringold:* J. Amer. Chem. Soc. **86,** 4952 (1964).
[40] *Mandell L.:* J. Amer. Chem. Soc. **78,** 3199 (1956).
[41] *Sondheimer F., C. Amendolla and G. Rosenkranz:* J. Amer. Chem. Soc. **75,** 5932 (1953).
[42] *Kerb K., E. Kasper, M. Schenk:* Ger. 1,122,950 (1962); Chem. Abstr. **57,** 5989ab (1963).

[43] *Kihno Yosuda, Noji Yamada, Hiroshi Mori and Hiroaki Tajima:* Japan, 230 (64) (1960); Chem. Abstr. **60**, 10760b (1964).
[44] *Shungo Wada:* Yakugaku Zasshi **79**, 120 (1959); Chem. Abstr. **53**, 10296b. (1959).

СТЕРОИДЫ. II

Изготовление 6-дегидропрегнен-производных

М. Гальмош, Й. Сабо и Ё. Ковач

Авторы изучали дегидрогенацию ацилированных производных и 3-энолового эфира 3β-17α-дигидрокси-Δ_5-прегнен-20-он, 3β-гидрокси-17α-ацетокси-Δ_5-прегнен-он, и 17α-гидрокси-прогестерона различными реагентами дегидрогенации.