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PARTIAL SYNTHESIS OF ALDOSTERONE*

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SEVERAL methods of partial synthesis of aldosterone (1), the most potential mineral corticoid, have been reported.[1] This paper presents a synthesis of this compound in which our method[2] of hydrocyanation was applied to the enone (6) for introduction of the 18-functionated group.

Adrenosterone was converted, via its $\Delta^{3,5}$-dienolether[3], into the 17-monooxim (2), m.p. 250.5~252° (d.), $[\alpha]_D^{33}$ +159°, in a yield of 75%. Beckmann rearrangement[4,5] of (2) afforded the lactam (3), m.p. 299~302°, $[\alpha]_D^{31}$ +172°, as a main product. (3) was transformed

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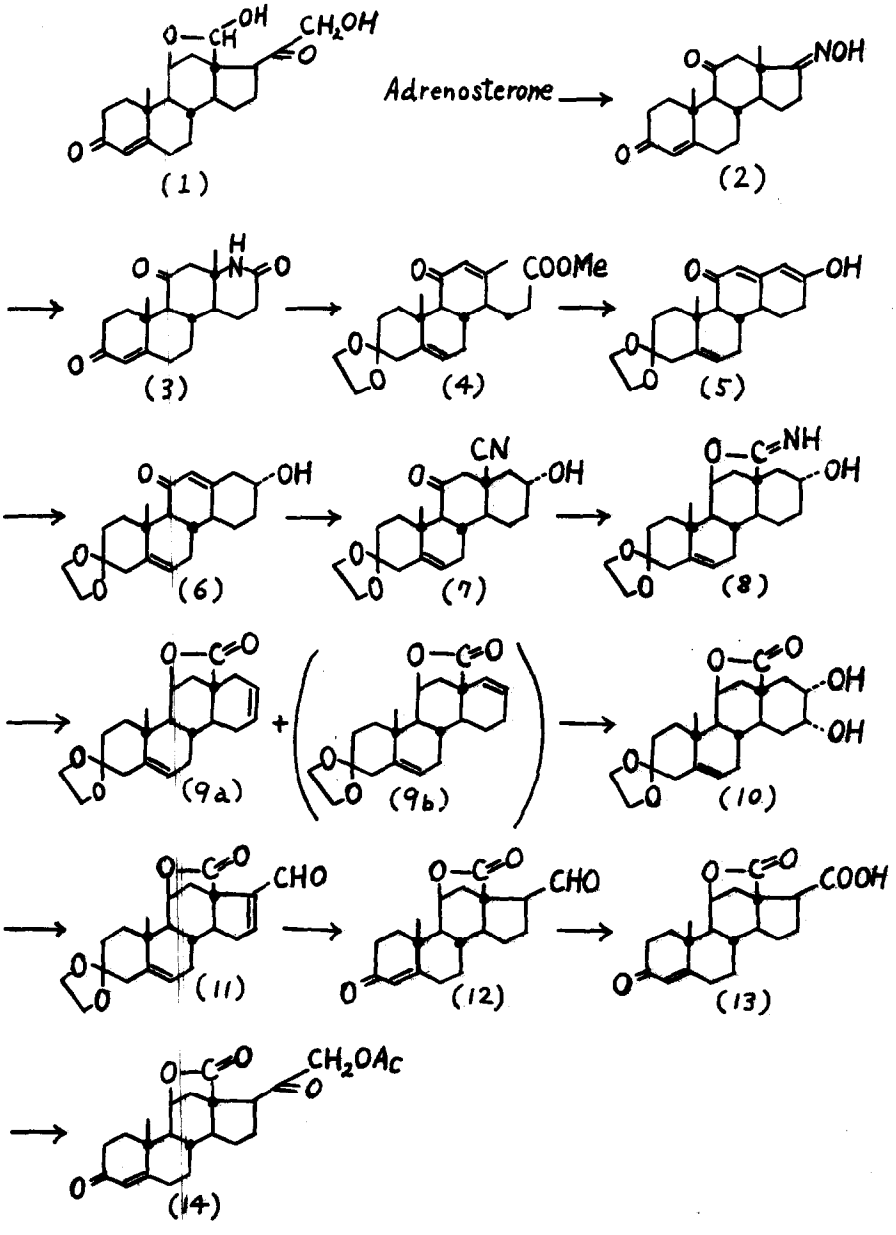
* Angularly Substituted Polycyclic Compounds IX.

1a K. Heusler, J. Kalvoda, Ch. Meystre, P. Wieland, G. Anner, A. Wettstein, G. Cainell, D. Arigoni and O. Jeger, Exper. 16, 21 (1960); Helv. Chim. Acta 44, 502 (1961); b L. Velluz, G. Muller, R. Bardoneshi and A. Poittevin, Compt. rend. 250, 725 (1960); c D.H.R. Barton and J.M. Beaton, J. Am. Chem. Soc. 82, 2641 (1960); 83, 750 (1961); 83, 4083 (1961); d M.E. Wolff, J.F. Kerwin, F.F. Owings, B. Blank, A. Maganani and V. Georgian, J. Am. Chem. Soc. 82, 4117 (1960); e Ch. Meystre, K. Heusler, J. Kolvoda, P. Wieland, G. Anner and A. Wettstein, Exper. 17, 475 (1961); K. Heusler, P. Wieland and A. Wettstein, Helv. Chim. Acta 44, 1374 (1961).

2a W. Nagata, S. Hirai, H. Itazaki and K. Takeda, J. Org. Chem. 26, 2413 (1961); b W. Nagata, M. Yoshioka and S. Hirai, Tetrahedron Letters in press.

3a S. Bernstein, R.H. Lenhard and J.W. Williams, J. Org. Chem. 18, 1166 (1953); b C. A. 51, P 10602b (1957), Brit. 757950, Sept. 26, 1956.


Adrenosterone
(1)
(2)
(3)
(4)
(5)
(6)
(7)
(8)
(9a)
(9b)
(10)
(11)
(12)
(13)
(14)

into the 3-ethyleneketal, which on hydrolysis with sodium hydroxide in refluxing aqueous n-butanol[6] and subsequent esterification gave an oily seco-ester (4), $[\alpha]_D^{26}$ -20°. UV λ_{max}^{EtOH} 237 mμ (ε 13,000). Cyclization[7] of (4) with potassium t-buthoxide yielded a dienolone (5), m.p. 219-221° (d.), $[\alpha]_D^{21}$ -67°, UV λ_{max}^{EtOH} 325 mμ (ε 26,400) and 387 mμ (ε 8,890), $\lambda_{max}^{EtOH-NaOH}$ 387 mμ (ε 79,700), which on partial reduction[7] with sodium borhydride gave the enone (6), m.p. 219-221°, $[\alpha]_D^{23}$ -84°. UV λ_{max}^{EtOH} 240 mμ (ε 14,200). Hydrocyanation of (6) with potassium cyanide and ammonium chloride in dimethylformamide[2a] or with hydrocyanic acid and triethylaluminum in tetrahydrofuran[2b] afforded exclusively the 13β-cyanoketone (7), m.p. 239-241°, $[\alpha]_D^{21}$ -5°. Reduction of the 11-keto group of (7) with sodium borhydride gave the imidolactone (8), m.p. 263-264.5°, $[\alpha]_D^{25}$ +15°, IR ν_{max}^{Nujol} 1683 cm^{-1}, where simultaneous cyclization occurred. (8) was smoothly transformed into its diacetyl, ditosyl or dimesyl derivative. Diacetyl: m.p. 255-257°, $[\alpha]_D^{21}$ -18°. Ditosyl: m.p. 179-180° (d.), $[\alpha]_D^{24}$ -35°. Dimesyl: m.p. 171.5-172.5° (d.), $[\alpha]_D^{29}$ -65°. Solvolysis of the dimesyl (or the ditosyl) derivative with K_2CO_3 in dimethylformamide gave a mixture of two isomeric unsaturated lactones (9a and 9b). The mixture was treated with osmium tetroxide to give the glycol (10) as a main product, m.p. 280-282.5°, $[\alpha]_D^{29}$ -16°. Cleavage of (10) with periodic acid-pyridine and cyclization[8] of the result-

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4 Cf. St. Kaufmann, J. Am. Chem. Soc. 73, 1779 (1951).

5 Cf. R. Anliker, M. Müller, J. Wohlfahrt and H. Heusser, Helv. Chim. Acta 38, 1404 (1955).

6 Cf. J. Schmidt-Thomé and W. Fritsch, C. A. 53, P 1290e (1959): Ger. 919532, Oct. 25, 1954.

7 Cf. L. Velluz, G. Amiard, R. Heymes and B. Goffinet, Compt. rend. 250, 371 (1960).

8 Cf. W.J. van der Burg, D.A. van Dorp, O. Schindler, C.M. Siegmann and S.A. Szpilfogel, Rec. trav. 77, 171 (1958).

ing crude seco-dialdehyde with triethylamine acetate afforded the conjugated aldehyde (11), m.p. 268~272°, $[\alpha]_D^{28}$ +23°. (11) was obtained also either by ozonolysis of the mixture (9a and 9b) or by oxidative cleavage[9] of it with periodic acid-pyridine in the presence of a trace of osmium tetroxide and by following cyclization of the resulting seco-dialdehydes. (11) was hydrogenated over palladium-charcoal and deketalized to give the aldehyde (12), m.p. 230~236°, which was treated with sodium dichromate in acetic acid to give the acid (13), m.p. above 320°. IR ν_{max}^{Nujol} (cm^{-1}): 3178, 1773, 1739, 1636 and 1614. Methyl ester: m.p. 224~230°. Physical constants of this acid and its methyl ester agree with those[10] of the degradation product of aldosterone. The ketolacetate (14) was synthesized by the known method,[11] via the acid chloride of (13) and the diazoketone. The ketolacetate (14), m.p. 203~205°, $[\alpha]_D^{28}$ +121°, was proved to be identical with the authentic specimen,[10a,12] the degradation product of aldosterone, by mixed melting point and by comparison of infrared spectra.[13] Transformation of this lactone to aldosterone has been reported[14] already.

9a Cf. R. Pappo, D.S. Allen, R.U. Lemieux and W.S. Johnson, J. Org. Chem. 21, 478 (1956); b Cf. P. Wieland, K. Heusler, H. Ueberwasser and A. Wettstein, Helv. Chim. Acta 41, 74 (1958).

10a S.A. Simpson, J.F. Tait, A. Wettstein, R. Neher, J. von Euw, O. Schindler and T. Reichstein, Helv. Chim. Acta 37, 1200 (1954); b E.A. Ham, R.E. Herman, N.G. Brink and L.H. Sarett, J. Am. Chem. Soc. 77, 1637 (1955).

11a T. Reichstein and J. von Euw, Helv. Chim. Acta 23, 136 (1940); b A.L. Wilds and C.H. Shunk, J. Am. Chem. Soc. 70, 2427 (1948).

12 The authors wish to express their heartful thanks to Prof. T. Reichstein for his kindness of supplying us his valuable sample.

13 Cf. J. Schmidlin, G. Anner, J.R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland and A. Wettstein, Helv. Chim. Acta 40, 1295 (1957).

14 J. von Euw, R. Neher and T. Reichstein, Helv. Chim. Acta 38 1423 (1955).

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