941. *Some Steroid Hydantoins*

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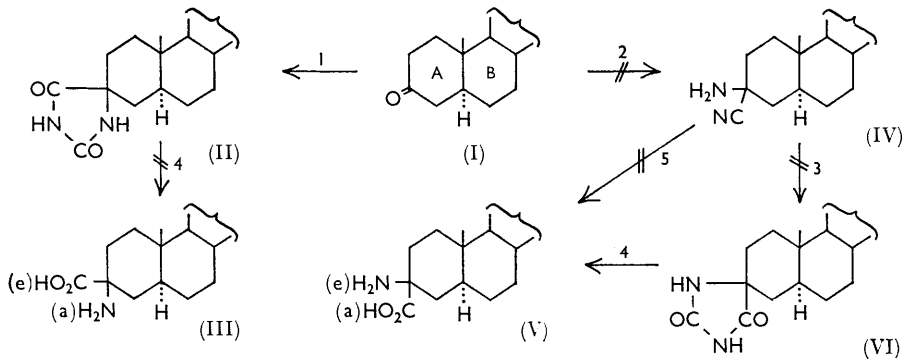
A wide range of 5-substituted hydantoins show anticonvulsant activity,[1] including several 5,5-spirohydantoins like 1,2,3,4-tetrahydronaphthalene-2-spiro-5′-hydantoin (tetrantoin).[2] We therefore attempted the preparation of some steroid spiro-5′-hydantoins in the hope that these might have useful biological properties. Also, the chemistry has some interesting features, since it has been recently demonstrated,[3,4] that substituted alicyclic ketones yield predominantly different stereoisomeric hydantoins depending on the method of preparation, and by alkaline hydrolysis these are converted into the corresponding isomeric amino-acids.[5] For simple substituted cyclohexane amino-acids Munday [3] has assigned configurations to the Strecker and hydantoin products based on the resistance of 1-amino-4-t-butylcyclohexanenitrile hydrochloride to hydrolysis, the infrared spectra, and dissociation constants of the amino-acids. By analogy, it was hoped to carry out a similar sequence of reactions in the steroid field, as shown, from cholestanone (I):



Reagents: 1, $KCN–(NH_4)_2CO_3$; 2, $KCN–NH_4Cl$; 3, $NaCNO–H^+$; 4, OH^-; 5, H^+

It was hoped, by investigation of the stereochemical course of the nitrous acid deamination of compounds (III) and (V), to confirm the conformation of the amino-group [6,7] and hence the configuration of the parent hydantoins (II) and (VI). We started by examining the application of the Bucherer hydantoin synthesis [8] to some steroid ketones, beginning with cholestanone, because here the keto-group is in a relatively unhindered position. Cholestanol has been prepared by pressure hydrogenation of cholesterol under various conditions.[9–11] The poor results obtained at ordinary temperature and pressure appeared to be due to the low solubility of cholesterol in the solvents used. We therefore investigated hydrogenation in dioxan, cellosolve, and tetrahydrofuran. The first two were unsatisfactory, but the last-named, in the presence of perchloric acid, gave a 90% yield of cholestanol. This is an improvement over existing methods, as it does not require either

[1] H. R. Henze and W. C. Craig, *J. Org. Chem.*, 1945, **10**, 2; H. R. Henze and W. B. Leslie, *ibid.*, 1950, **15**, 901.
[2] W. A. Sexton, "Chemical Constitution and Biological Activity," 3rd edn., E. and F. N. Spon Ltd., London, 1963, p. 440.
[3] L. Munday, *J.*, 1961, 4372.
[4] H. C. Brimelow, H. C. Carrington, C. H. Vasey, and W. S. Waring, *J.*, 1962, 2789.
[5] R. J. W. Cremlyn, *J.*, 1962, 3977.
[6] Cf. E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, 1962, p. 226.
[7] Cf. C. W. Shoppee, D. E. Evans, and G. H. R. Summers, *J.*, 1957, 97; C. W. Shoppee, R. J. W. Cremlyn, D. E. Evans, and G. H. R. Summers, *J.*, 1957, 4364.
[8] H. T. Bucherer and W. Steiner, *J. prakt. Chem.*, 1934, **140**, 291; H. T. Bucherer and V. A. Lieb, *ibid.*, **141**, 5.
[9] W. F. Bruce and J. O. Ralls, *Org. Synth.*, Coll. Vol. II, Wiley, New York, 1943, p. 191.
[10] R. Pavlic and H. Adkins, *J. Amer. Chem. Soc.*, 1946, **68**, 1471; H. R. Nace, *ibid.*, 1951, **73**, 2379.
[11] E. B. Hershberg, E. Oliveto, M. Rubin, H. Staeudle, and L. Kuhlen, *J. Amer. Chem. Soc.*, 1951, **73**, 1144.

heat or increased pressure. Cholestanol was readily oxidised to cholestanone by potassium dichromate under mild conditions.[12] The Bucherer synthesis is normally performed in warm aqueous ethanol [3,4,8] but when applied to cholestanone, under these conditions, the ketone was recovered unchanged, probably because of low solubility. The following solvents were, therefore, investigated for this reaction: tetrahydrofuran, dimethylformamide,[13] pyridine, and fused acetamide under pressure; [14] but only the last gave a good yield of the hydrantoin (II). Subsequently ethanol under pressure was found to be equally successful, and using these conditions, the spiro-5′-hydantoins from coprostanone and 6-oxocholestanol were also prepared.

Next we examined the alkaline hydrolysis of the cholestanespiro-5′-hydantoin (II) using similar conditions to those already described by one of us [5] for the preparation of substituted cyclohexane-α-amino-acids; but none of the amino-acid (III) was obtained. The other steroid hydantoins were similarly resistant to alkaline hydrolysis and to a number of different hydrolytic methods including boiling 60% sulphuric acid (cf. ref. 3), and "dimsyl sodium" [15] in dimethyl sulphoxide. The stability of these hydantoins may be compared with that shown by fluorenone spiro-5′-hydantoin [14] which required prolonged heating (75 hr. at 120°) with aqueous barium hydroxide, and even then only gave fluorenylidene amino-amide. Here steric hindrance affords a ready explanation, though with the cholestane spirohydantoin (II) it is probable that the main factors are the low solubility of the hydantoin in aqueous alkali, and the general lack of chemical reactivity. The latter was indicated by the failure to obtain *N*-acetyl or -benzoyl derivatives of the steroid hydantoins.[16]

Attempts to prepare the amino-nitrile (IV) by the Strecker reaction failed.[3,4,17]

Experimental.—Hydrogenation of cholesterol. Cholesterol (25 g.) was dissolved in tetrahydrofuran (150 c.c.); Adams catalyst (0·5 g.) and perchloric acid (2—3 drops) were added, and the mixture was shaken in hydrogen. Absorption of hydrogen was rapid (75% complete in ½ hr.), and had finished after 2 hr. The catalyst was removed and the solution concentrated *in vacuo*. Recrystallisation from ethanol gave cholestanol (23 g., 90%), m. p. 140—142°.

Cholestane-3-spiro-5′-hydantoin. Cholestanone [12] (3 g.) was dissolved in warm ethanol (50 c.c.), and a solution of potassium cyanide (1 g.) in water (5 c.c.) added, followed by solid ammonium carbonate (5 g.). The mixture was heated in a glass-lined steel vessel at 120° for 24 hr. After cooling, the mixture was acidified with hydrochloric acid, the precipitate collected and washed with water. Extraction with boiling ethanol in a Soxhlet apparatus gave *cholestane-3-spiro-5′-hydantoin* as a white solid (2·7 g., 90%) m. p. 316° (Found: C, 76·4; H, 10·4; N, 5·9. $C_{29}H_{48}N_2O_2$ requires C, 76·3; H, 10·6; N, 6·1%). The infrared spectrum showed characteristic double carbonyl bands [18] at 1721 and 1770 cm.$^{-1}$. The hydantoin was also prepared in similar yield using fused acetamide at 120° in a sealed vessel for 24 hr. (cf. ref. 14); and 12% was obtained using pyridine at 50—55° for 5 days at atmospheric pressure. When the Bucherer reaction was attempted in boiling dimethylformamide, the product was a white solid, m. p. 301° [Found: C, 75·7; H, 12·0; N, 3·1. Calc. for the *N*-formyl derivative of the amino-acid (cf. ref. 13), $C_{29}H_{49}NO_3$: C, 75·8; H, 10·7; N, 3·05%].

Coprostan-3-spiro-5′-hydantoin. This was prepared from coprostanone [19,20] by the Bucherer reaction in ethanol under identical conditions to those previously described. *The hydantoin* was a white solid (4 g., 80%), m. p. 314° after extraction with boiling ethanol (Found: C, 76·4; H, 10·0; N, 6·0. $C_{29}H_{48}N_2O_2$ requires C, 76·3; H, 10·6; N, 6·1%).* (Mixed m. p. with

* Trouble was experienced in obtaining good analytical data for the steroid hydantoins because of incomplete combustion (high m.p.s), and the difficulty of purification (low solubility).

[12] Cf. C. Djerassi, *J. Org. Chem.*, 1956, **21**, 1547.
[13] K. T. Potts, *J. Org. Chem.*, 1963, **28**, 543; G. R. Pettit and E. G. Thomas, *ibid.*, 1959, **24**, 895.
[14] W. H. McCown and H. R. Henze, *J. Amer. Chem. Soc.*, 1942, **64**, 689.
[15] G. G. Price and M. C. Whiting, *Chem. and Ind.*, 1963, **19**, 775.
[16] Cf. E. Ware, *Chem. Rev.*, 1950, **46**, 403.
[17] R. Gaudry, *Canad. J. Res.*, 1946, **24**, 301.
[18] L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd edn., Methuen, London, 1962, p. 221.
[19] R. J. Bridgwater, Ph.D. Thesis, London, 1951.
[20] L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, 1959, p. 28.

cholestan-3-spirohydantoin, 298—304°). Unsuccessful attempts were made to characterise these two steroid hydantoins by preparation of the *N*-acetyl and -benzoyl derivatives.

Cholestanol-6-spiro-5′-hydantoin. This was similarly obtained from 6-ketocholestanol.[21] This compound was rather more soluble than the other two steroid hydantoins, so it could be purified by normal recrystallisation from boiling butan-1-ol. The *hydantoin* separated as lustrous platelets (70%), m. p. 312° (Found: C, 73·6; H, 10·5; N, 5·8. $C_{29}H_{48}N_2O_3$ requires C, 73·7; H, 10·2; N, 5·9%).

Acetylation (boiling acetic anhyride–acetic acid) afforded *3-acetoxycholestane-6-spiro-hydantoin* as plates (from butan-1-ol), m. p. 270—271° (Found: C, 71·2; H, 9·8. $C_{31}H_{50}N_2O_4$ requires C, 72·3; H, 9·8%).

3β-Hydroxy-Δ⁵-pregnene-20-spiro-5′-hydantoin. This was similarly prepared from 3β-hydroxy-Δ⁵-pregnene-20-one. The *hydantoin* was a white solid (75%), m. p. 322° after extraction with boiling butan-1-ol (Found: C, 71·2; H, 8·9; N, 7·0. $C_{23}H_{34}N_2O_3$ requires C, 71·5; H, 8·9; N, 7·25%).

The authors' thanks are due to the Hertfordshire County Council for the award of a Research Assistantship (to M. C.), and to the Chemical Society for a Research Grant.

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Hatfield, Herts. [*Received, December 9th*, 1964.]

[21] C. W. Shoppee and G. H. R. Summers, *J.*, 1952, 3361.