Some Terpene and Steroid Hydantoins

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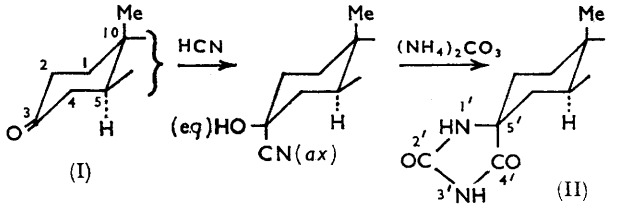
3β-Hydroxy-5α-androstan-17-one, (+)-camphor, and (−)-menthone have been converted into the corresponding spiro-hydantoins by the Bucherer synthesis. The reaction failed with cholestan-7-one, cholest-4-en-3-one, and 17α,21-dihydroxy-5α-pregnane-3,11,20-tri-one 3,20-disemicarbazone. Efforts to obtain steroid dihydantoins were unsuccessful. Deamination of camphane and menthane amino-acids provides evidence of their configurations.

In a previous Publication [1] we described the preparation of some steroid spiro-5′-hydantoins by the Bucherer synthesis.[2] This method has been extended to the preparation of 3β-hydroxy-5α-androstane-17-spiro-5′-hydantoin. However, the reaction was unsuccessful with cholestan-7-one, 17α,21-dihydroxy-5α-pregnane-3,11,20-trione 3,20-disemicarbazone, and cholest-4-en-3-one. The Bucherer synthesis has also been applied to certain steroid diones: 5α-androstane-3,17-dione, 5α-pregnane-3,20-dione, and 21-acetoxy-17α-hydroxy-5α-pregnane-3,11,20-trione (which reacts as a 3,20-dione). The products were mainly mixtures of the monohydantoins, probably because the relatively insoluble monohydantoins are precipitated from solution as they are formed, so protecting them from further attack. A recent claim [3] that several steroid ketones, including 5α-cholestan-3-one, can be converted into the corresponding spiro-5′-hydantoins by the Bucherer reaction in 80% ethanol under mild conditions could not be substantiated. Reasonable yields were only obtainable by heating at 120° under pressure for 24 hr. (cf. ref. 1). The low reactivity of relatively unhindered steroid ketones, like 5α-cholestan-3-one, is largely due to their low aqueous solubility. When the carbonyl group is in a sterically hindered position (*e.g.*, at 7 or 11) the additional unfavourable steric factor completely inhibits the Bucherer reaction, even under drastic conditions. Since the isomeric Strecker steroid spiro-hydantoins and the related amino-acids were unobtainable,[1] it was decided to prepare some optically active terpene spiro-hydantoins principally for o.r.d. measurements which might assist in establishing the configuration around the spiro-atom. With (+)-camphor the Bucherer synthesis required drastic conditions for even a moderate yield of the hydantoins (cf. ref. 4). This illustrates the importance of steric factors, since camphor is readily soluble in ethanol, but the carbonyl group is seriously hindered by the *gem*-dimethyl group. Hoyer [4] reported a 1 : 1 ratio of the two isomeric camphor spiro-hydantoins, but our results were 88% of the α- and 12% of the β-isomer; this ratio is to be expected since the Bucherer synthesis is well known [5,6] to be largely stereospecific. With (−)-menthone the Bucherer reaction goes under mild conditions, as would be expected since the carbonyl group is unhindered. The camphane and menthane α-spiro-hydantoins have been hydrolysed to the corresponding α-amino-acids. Deamination gave a relatively small amount of unsaturated material indicative of an equatorial amino-group (by comparison with the deamination of the decalin amino-acids).[7] O.r.d. curves were determined by Professor W. Klyne for the camphane and menthane spiro-hydantoins, but did not give definitive information regarding structure. All efforts [1] to hydrolyse the steroid spiro-hydantoins directly to the corresponding amino-acids failed; accordingly 5α-cholestanespiro-5′-hydantoin was converted into the 3′-amino-derivative with boiling hydrazine hydrate,[8] but the 3′-compound also proved resistant to hydrolysis. Steroid spiro-hydantoins generally showed a remarkable lack of chemical reactivity, as illustrated by their resistance to hydrolysis and the failure to obtain *N*-acetyl

[1] R. J. W. Cremlyn and M. C. Chisholm, *J. Chem. Soc.*, 1965, 5117.
[2] H. T. Bucherer and W. Steiner, *J. prakt. Chem.*, 1934, **140**, 291; H. T. Bucherer and V. A. Lieb, *ibid.*, 1934, **141**, 5.
[3] K. Tanabe and K. Sakai, Jap.P. 4066 (*Chem. Abs.*, 1963, **59**, 11,625).
[4] H. L. Hoyer, *Chem. Ber.*, 1950, **83**, 491.
[5] L. Munday, *J. Chem. Soc.*, 1961, 4372.
[6] H. C. Brimelow, H. C. Carrington, C. H. Vasey, and W. S. Waring, *J. Chem. Soc.*, 1962, 2789.
[7] R. J. W. Cremlyn and M. C. Chisholm, *J. Chem. Soc.* (*C*), 1967, in the press; R. J. W. Cremlyn, M. C. Chisholm, and P. J. Taylor, *Tetrahedron Letters*, 1967, 1373.
[8] J. S. Davidson, *J. Chem. Soc.*, 1964, 4646.

or *N*-benzoyl derivatives;[1] also they were not reduced by lithium aluminium hydride (cf. ref. 9). The preferred orientation of hydrogen cyanide addition to substituted cyclohexanones is known[7] to involve axial attack by the cyanide anion. Steroid ketones, like 5α-cholestan-3-one (I), may be regarded as trisubstituted cyclohexanones, and in nucleophilic additions to the carbonyl group there is almost exclusive α-attack, suggesting that the Bucherer spiro-5′-hydantoin has the configuration (II):



(I) (II)

This is supported by analogy with the configuration of the Bucherer *trans*-decalin spiro-hydantoins, obtained from the n.m.r. spectra of the isomeric spiro-hydantoins, and deamination studies and p*K* values of the corresponding decalin amino-acids.[7]

EXPERIMENTAL

Infrared spectra were determined in Nujol mulls with a Perkin-Elmer 237 spectrophotometer.

3′-Aminocholestane-3-spiro-5′-hydantoin.— Cholestane-3-spiro-5′-hydantoin (2·0 g.) was boiled under reflux with hydrazine hydrate (20 c.c., 64%) then butan-1-ol (50 c.c.) was added (to obtain complete solution), and heating continued for 5 hr. The solution was diluted with water, and the solid product recrystallised from ethanol yielding the *3′-amino-hydantoin* as plates (0·8 g.), m. p. 296—300° (decomp.) (Found:* C, 72·6; H, 10·6; N, 8·8. $C_{29}H_{49}N_3O_2$ requires C, 73·8; H, 10·5; N, 8·8%), $\nu_{max.}$ 3320, 3260, and 3210 (N–H stretching bands), and 1625 cm.$^{-1}$ (N–H deformation band). The amino-hydantoin was not altered by boiling for 5 days with hydrazine hydrate, and no carbohydrazide was isolated (cf. ref. 8); it could not be characterised as the benzylidene derivative.

Attempted Reduction of Cholestane-3-spiro-5′-hydantoin with Lithium Aluminium Hydride.—The hydantoin (1 g.) dissolved in tetrahydrofuran (100 c.c.) was treated with a solution of lithium aluminium hydride (1 g.) in tetrahydrofuran (20 c.c.), and the mixture boiled under reflux for 5 hr. The usual working up gave the unchanged hydantoin (0·9 g.), m. p. and mixed m. p. 315—316°.

3β-Acetoxypregn-5-ene-20-hydantoin.— The hydantoin (m. p. 322°) was acetylated with boiling acetic anhydride–acetic acid giving *3β-acetoxypregn-5-ene-20-hydantoin* as plates from aqueous ethanol, m. p. 301—303° (Found: C, 70·3; H, 8·8; N, 6·2. $C_{25}H_{36}N_2O_4$ requires C, 70·1; H, 8·5; N, 6·5%).

3β-Hydroxy-5α-androstane-17-spiro-5′-hydantoin.— This was obtained from 3β-hydroxy-5α-androstan-17-one (3 g.) by the Bucherer reaction as previously described. The hydantoin separated as needles from methanol (2·2 g., 62%), m. p. 275° (lit.,[10] >350°) (Found: C, 69·6; H, 9·2; N, 7·7. Calc. for $C_{21}H_{32}N_2O_3$: C, 70·0; H, 9·0; N, 7·8%), $\nu_{max.}$ 3385, 1768, and 1735 cm.$^{-1}$. Acetylation (boiling acetic anhydride–acetic acid) gave *3β-acetoxy-5α-androstane-17-spiro-5′-hydantoin* as needles from ethanol, m. p. 245° (Found: C, 69·1; H, 8·5; N, 6·5. $C_{23}H_{34}N_2O_4$ requires C, 68·6; H, 8·5; N, 7·0%).

Attempted Preparation of 5α-pregnane-3,20-dihydantoin.— 5α-Pregnane-3,20-dione (3 g.) was heated with potassium cyanide (3 g.) and ammonium carbonate (8 g.) in ethanol at 120° for 48 hr. under pressure. The brownish product was boiled with activated charcoal in ethanol and recrystallised from ethanol–tetrahydrofuran as a white solid (1·2 g.), m. p. 285° (Found: N, 10·5. Calc. for the monohydantoin, $C_{23}H_{34}N_2O_3$: N, 7·25; for the dihydantoin, $C_{25}H_{36}N_4O_4$: N, 12·3%), $\nu_{max.}$ 3205, 1780, and 1740 cm.$^{-1}$ (diffuse, poorly resolved, carbonyl bands).[11]

A similar Bucherer reaction on 5α-androstane-3,17-dione (3 g.) gave white needles from ethanol (2·1 g., 60%), m. p. 241—245° (Found: N, 7·3. Calc. for the monohydantoin, $C_{21}H_{30}N_2O_3$: N, 7·8%).

(+)-Camphane-2-spiro-5′-hydantoin.— (+)-Camphor (76 g.) was treated with an excess of sodium cyanide and 10 atmospheres of carbon dioxide in a sealed tube as described by Hoyer.[4] The dark brown product was suspended in water, acidified with concentrated hydrochloric acid, and extracted with ether (2 × 50 c.c.), to remove unchanged camphor. The solid was then dissolved in hot 20% aqueous sodium hydroxide solution (3 × 100 c.c.), and acidified with hydrochloric acid. The brown precipitate was collected and recrystallised from boiling ethanol in the presence of activated charcoal (5 g.) giving colourless plates (48 g., 47%), m. p. 266° (lit.,[4] 265°). Fractional recrystallisation from ethanol afforded the less soluble α-hydantoin as platelets (88%),† m. p. 266°, $[\alpha]_D^{25}$ +26·3° (*c* 1·95 in ethanol) (lit.,[4] $[\alpha]_D^{20}$ +14·8°) (Found: C, 64·7; H, 8·1; N, 12·7. Calc. for $C_{12}H_{18}N_2O_2$: C, 64·8; H, 8·2; N, 12·6%), $\nu_{max.}$ 3225, 1768, and 1720 cm.$^{-1}$. Concentration of the ethanolic mother-liquor gave the more soluble β-isomer as cubes (12%),† m. p. 260—262°, $[\alpha]_D^{25}$ +34·7° (*c* 1·64 in ethanol) (lit.,[4] m. p. 255—256°, $[\alpha]_D^{20}$ +35·0°) (Found: C, 65·1; H, 8·2; N, 12·7%), $\nu_{max.}$ 3225, 1765, and 1715 cm.$^{-1}$. (The Bucherer synthesis with camphor, under the conditions used[1] for the preparation of cholestane-3-spiro-5′-hydantoin gave a poor yield (10%) of the camphor hydantoin.)

(−)-Menthane-3-spiro-5′-hydantoin.—(−)-Menthone (25 g.) was stirred with potassium cyanide (12 g.) and ammonium carbonate (32 g.) in aqueous ethanol (300 c.c.) as described by Munday.[5] The product, a mixture of the isomeric hydantoins, formed a white solid from ethanol (16 g., 51%), m. p. 232—234° (lit.,[12] 228—229°). Fractional recrystallisation afforded the less soluble α-isomer as platelets (96%),† m. p. 232°, $[\alpha]_D^{20}$ +12·1° (*c* 0·2 in ethanol) (lit.,[12] m. p. 228°, $[\alpha]_D^{20}$ +11·7°) (Found: C, 64·3; H, 8·7; N, 12·6. Calc. for $C_{12}H_{20}N_2O_2$: C, 64·3; H, 9·0; N, 12·5%), $\nu_{max.}$ 3280, 1750, and 1735 cm.$^{-1}$. The ethanolic mother-liquor, by concentration, gave the more soluble β-isomer as cubes (4%),† m. p. 283°, $[\alpha]_D^{20}$ +4·0° (*c* 0·1 in ethanol) (lit.,[12]

* Repeat analyses gave persistently low carbon figures, the steroid hydantoins generally have been troublesome in this respect (cf. ref. 1).

† Figures expressed as a percentage of the yield of the spiro-hydantoin mixture.

[9] E. Ware, *Chem. Rev.*, 1950, **46**, 403.

[10] G. G. Nathansohn, G. F. Odasso, C. R. Pasqualucci, and E. Testa, *Steroids*, 1965, **5**, 263.

[11] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 2nd edn., 1962, p. 221.

[12] E. S. Rothman and A. R. Day, *J. Amer. Chem. Soc.*, 1954, **76**, 111.

m. p. 235—238°, $[\alpha]_D^{20}$ +5·85°) (Found: C, 64·3; H, 8·6; N, 12·6%), $\nu_{max.}$ 3220, 1760, and 1715 cm.$^{-1}$.

2-Aminocamphane-2-carboxylic Acid.—The α-hydantoin (1 g.) was heated in an autoclave with barium hydroxide octahydrate (2·1 g.) in water (50 c.c.) at 120° for 24 hr. The hot reaction mixture was filtered, and treated with an excess of ammonium carbonate (to remove excess barium as the carbonate). It was then boiled, until no more ammonia was evolved, and filtered; the filtrate on concentration *in vacuo* gave 2-aminocamphane-2-carboxylic acid (α-isomer) as cubes (0·7 g., 78%), m. p. 277° (lit.,[4] m. p. 278°).

3-Aminomenthane-3-carboxylic Acid.— α-Menthane-3-spiro-5′-hydantoin (1·0 g.) was similarly hydrolysed with barium hydroxide (2·0 g.) giving 3-aminomenthane-3-carboxylic acid as a white powder from aqueous ethanol (0·65 g., 73%), m. p. 338° (lit.,[13] m. p. 330° decomp.) (Found: C, 65·9; H, 10·4; N, 7·1. Calc. for $C_{11}H_{21}NO_2$: C, 66·3; H, 10·6; N, 7·0%).

Deamination of 2-Aminocamphane-2-carboxylic Acid (α-Isomer).—The amino-acid (1 g.) was dissolved in acetic acid (50 c.c.). Sodium nitrite (4 g.) in 50% acetic acid (10 c.c.) was gradually added, and the mixture shaken for 24 hr. at room temperature. The product was isolated by extracting with ether and washing well with water. The oily solid was dissolved in ethyl acetate and was quantitatively hydrogenated when 30 c.c. of H_2 were absorbed ≡25% unsaturated material. A similar experiment with 3-aminomenthane-3-carboxylic acid indicated 35% of unsaturated material.

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[13] L. Munday, *Chem. and Ind.*, 1960, 1057.