Tetrahedron, 1963, Vol. 19, pp. 1259 to 1263. Pergamon Press Ltd. Printed in Northern Ireland

SIMPLE SYNTHETIC ANALOGS OF NATURAL STEROIDS

SYNTHESIS OF 6,7-BENZHYDRINDAN-1-HYDROXYMETHYL KETONE AND ITS ACETATE

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(*Received* 27 *February* 1963)

Abstract—The half esters, resulting from the Stobbe condensation of α-tetralone with succinic esters, on cyclization give the keto-ester "ethyl 3-keto-Δ^8-6,7-benzhydrindan-l-carboxylate". This on Clemmensen reduction yields the corresponding αβ-unsaturated ester, from which 6,7-benzhydrindan-l-carboxylic acid was prepared by catalytic reduction and hydrolysis and from this acid 6,7-benzhydrindan-l-hydroxymethyl ketone and its acetate were prepared.

The route chosen for the preparation of the intermediate, 6,7-benzhydrindan-1-carboxylic acid (VII; R = H) involved a modified Stobbe condensation of diethyl succinate with a cyclic ketone.

α-Tetralone was condensed with dimethyl succinate in the presence of potassium t-butoxide, to give β-carbmethoxy-β-(3,4-dihydro-1-naphthyl)-propionic acid (I; R = CH_3), m.p. 110–111° in 80% yield. When diethyl succinate was used, the half-ester[1] (I; R = C_2H_5) was obtained.

Catalytic reduction of both ethyl and methyl half-esters (I; R = C_2H_5 and CH_3) using platinum oxide, gave the corresponding saturated half-esters (II; R = C_2H_5 and CH_3), which on alkaline hydrolysis yielded 1,2,3,4-tetrahydro-1-naphthylsuccinic acid (II; R = H), m.p. 160–160·5°.

Cyclization of the half-ester (I; R = C_2H_5) using acetic anhydride and anhydrous zinc chloride in acetic acid gave a mixture of the paraconic ester (IV; R = C_2H_5) m.p. 86–87°, and the keto-ester (III; R = C_2H_5) as a viscous oil (2,4-dinitro-phenylhydrazone, m.p. 203–205°). Alkaline hydrolysis of the paraconic ester gave the known dibasic acid[1] (I; R = H), while acid hydrolysis and decarboxylation of the keto-ester gave the known ketone (V).[1,2]

The light absorption of the keto-ester, its semicarbazone and its dinitrophenylhydrazone confirms the presence of an αβ-unsaturated ketone grouping, the values recorded agreeing with those for 6,7-dihydro-4,5-benzindanone (V)[2] and 1-carbethoxy-Δ^8-octahydro-5,6-benzindan-3-one (IX),[3] if the bathochromic shift (about 50 mμ) for the extra conjugation with the aromatic nucleus is taken into account.[4]

Clemmensen reduction of the keto-ester (III) yielded an oily mixture of neutral (main product) and acid fractions. The neutral fraction consisted chiefly of the unsaturated ester (VI; R = C_2H_5), which on alkaline hydrolysis, gave the αβ-unsaturated acid (VI; R = H), m.p. 127–129° (*p*-toluidide derivative, m.p. 230–231°)

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[1] W. S. Johnson, H. C. E. Johnson and J. W. Petersen, *J. Amer Chem. Soc.* **67**, 1360 (1945).

[2] D. W. Mathieson, *J. Chem. Soc.* 3248 (1953).

[3] A. M. El-Abbady, *J. Amer. Chem. Soc.* **79**, 1757 (1957).

[4] A. L. Wilds, L. W. Beck, W. J. Close, C. Djerassi, J. A. Johnson, Jr. Thomas, L. Johnson and C. H. Shunk, *J. Amer. Chem. Soc.* **69**, 1985 (1947).

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Clemmensen reduction of the keto-ester (III) yielded an oily mixture of neutral (main product) and acid fractions. The neutral fraction consisted chiefly of the unsaturated ester (VI; R = C_2H_5), which on alkaline hydrolysis, gave the αβ-unsaturated acid (VI; R = H), m.p. 127–129° (*p*-toluidide derivative, m.p. 230–231°)

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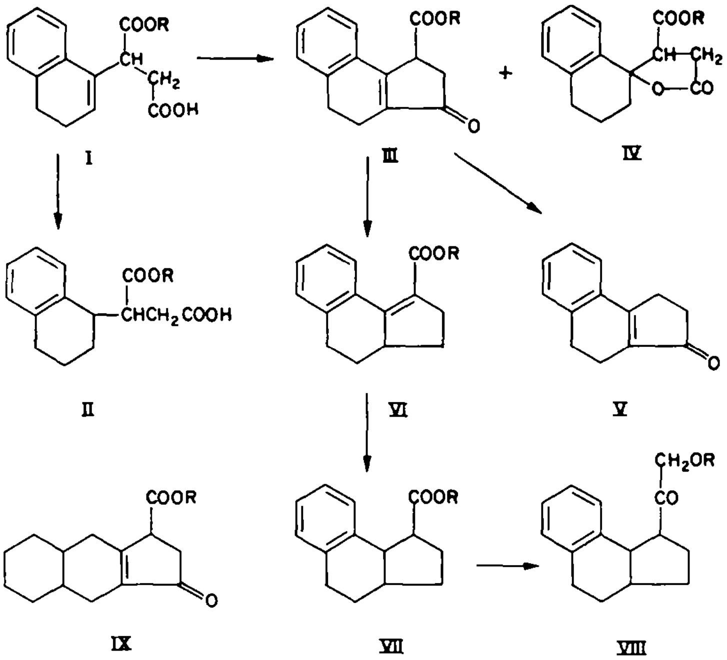
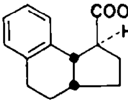


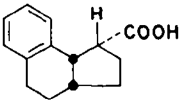
and a smaller amount of oil the structure of which is under investigation. The structure of the ester (VI; R = C_2H_5) and its acid (VI; R = H) was inferred from the U.V. spectra which are characteristic of *αβ*-unsaturated esters and acids.[5]

This shows that the double bond in the keto-ester (III) shifted during the Clemmensen reduction and is in conjugation with the carbethoxyl group. The acid fraction of the Clemmensen reduction was found to be the *αβ*-unsaturated acid (VI; R = H), identified as its *p*-toluidide.

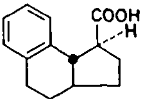
Hydrogenation of the neutral fraction gave after alkaline hydrolysis an oily mixture of the saturated acids (VII; R = H), theoretically capable of existing in the following four isomeric forms:



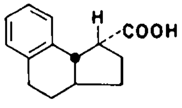
Cis-*β*



Cis-*α*



Trans-*β*



Trans-*α*

This oily mixture on standing partly solidified, yielding one of the isomeric saturated acids, m.p. 68·5–70°, the configuration of which is not yet established.

6,7-Benzhydrindan-1-carboxylic acid (VII; R = H) on treatment with thionyl chloride,[6] yielded the corresponding acid chloride which with diazomethane[7] gave the corresponding diazomethyl ketone. This when treated with glacial acetic or with 2*N* sulphuric acid yielded 6,7-benzhydrindan-1-acetoxymethyl ketone (VIII; R = CH_3CO) or 6,7-benzhydrindan-1-hydroxymethyl ketone (VIII, R = H), respectively.

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[5] H. E. Ungnade and I. Ortega, *J. Amer. Chem. Soc.* **73**, 1564 (1951).
[6] W. S. Knowles, J. A. Kuck and R. C. Elderfield, *J. Org. Chem.* **7**, 374 (1942).
[7] M. Steiger and T. Reichstein, *Helv. Chim. Acta* **20**, 1164 (1937).

Both these compounds (VIII; R = CH_3CO and H) reduce ammoniacal silver nitrate solution. They are being tested for cortical activity and the results may be available at a later date.

TABLE 1. COMPARISON OF THE U.V. SPECTRA OF THE KETO-ESTER AND ITS DERIVATIVES WITH RELATED COMPOUNDS

Compound	Ketone		Semicarbazone		2,4-Dinitrophenylhydrazone	
	$\lambda_{max}^{Ethanol}$	log ε	$\lambda_{max}^{Chloroform}$	log ε	$\lambda_{max}^{Chloroform}$	log ε
III	227·5 234·5 296	4·15 4·17 4·15	326	4·59	402·5	4·54
V	234 297	4·06 4·22	326	4·51	410	4·54
IX	239	4·00	286	4·42	388	4·52

EXPERIMENTAL[*]

Condensation of α-tetralone with succinic esters

A solution of α-tetralone (7 g) and methyl succinate (11 g) in t-butanol (10 ml) was added to a chilled solution of potassium t-butoxide (from potassium, 2·1 g, in dry t-butanol 40 ml) during 35 min, and then refluxed under nitrogen for 40 min at 110°. The cold mixture was acidified with ice-cold dil. hydrochloric acid. Removal of the t-butanol *in vacuo* left a brownish semi-solid which was extracted with ether. The acid fraction was isolated with cold saturated sodium bicarbonate solution and the resulting viscous oil (about 10 g; 80%) solidified on keeping, m.p. 102–103° and was identified as *β-carbmethoxy-β-*(3,4-*dihydro*-1-*naphthyl*) *propionic acid* (I; R = CH_3), m.p. 110–111° (from aqueous methanol). (Found: C, 69·74; H, 6·15. $C_{15}H_{16}O_4$ requires: C, 69·23, H, 6·15%).

Condensation of α-tetralone (7 g) with ethyl succinate (13 g) yielded the ethyl half-ester (I; R = C_2H_5) (12 g; 91%) which crystallized from aqueous ethanol, m.p. 89–91° (cf. ref. 1). U.V. spectrum, $\lambda_{max}^{Ethanol}$ 218, 225, 260, 295 mμ (log ε 4·19, 4·06, 3·88, 2·84).

β-Carbethoxy-β-(1,2,3,4-*tetrahedro*-1-*naphthyl*)-*propionic acid* (II; R = C_2H_5)

The ethyl half-ester (1 g) dissolved in absolute ethanol (20 ml) was shaken with hydrogen in presence of 5% Pd/C (0·5 g) until uptake of H_2 was complete (3 hr). The oily product (1 g) solidified in pet. ether (b.p. 40–60°) and recrystallized from the same solvent yielding the reduced half-ester (II; R = C_2H_5) as colourless crystals, m.p. 95·5–96·5°. (Found: C, 69·54; H, 7·35. $C_{16}H_{20}O_4$ requires: C, 69·54; H, 7·30%).

β-Carbmethoxy-β-(1,2,3,4-*tetrahydro*-1-*naphthyl*)-*propionic acid* (II; R = CH_3)

Repeating the above experiment with the methyl half-ester, gave β-carbmethoxy-β-(1,2,3,4-tetrahydro-1-naphthyl)-propionic acid (II; R = CH_3) as colourless crystals from pet. ether (b.p. 40–60°), m.p. 100–101°. (Found: C, 68·85; H, 6·76. $C_{15}H_{18}O_4$ requires; C, 68·68; H, 6·92%).

1,2,3,4-*Tetrahydro*-1-*naphthylsuccinic acid* (II; R = H)

The reduced methyl half-ester (II; R = CH_3; 0·2 g) was refluxed in 10% NaOH solution (10 ml) for 3 hr. The reaction mixture after extraction with ether, was cooled and acidified. The precipitated dibasic acid (II; R = H); 0·15 g; 79%) was crystallized from water, m.p. 160–160·5°. (Found: C, 68·52; H, 6·49. $C_{14}H_{16}O_4$ requires: C, 67·73; H, 6·50%).

Cyclization of the ethyl half-ester

A mixture of the ethyl half-ester (10 g), a 2% solution of fused zinc chloride in redistilled glacial acetic acid (50 ml) and distilled acetic anhydride (100 ml), was refluxed for 3½ hr under nitrogen. The acetic acid and acetic anhydride were removed *in vacuo*, and the dark brown residue poured into

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[*] All m.ps and b.ps are uncorrected.

cold water (100 g) and made alkaline with sodium bicarbonate. Ether extraction yielded a dark brown viscous oil (8 g) which partly solidified on standing giving:

(a) A colourless solid (4 g) which crystallized from ether, m.p. 86–87° and analysed for *spiro tetrahydro-naphthalene*-1-2′(3′-*carbethoxy*-5′-*ketotetrahydrofuran*). (IV, R = C_2H_5). (Found: C, 70·46; H, 7·06. $C_{16}H_{18}O_4$ requires: C, 70·07; H, 6·49%).

Refluxing the paraconic ester (IV; R = C_2H_5; 0·3 g) with 5% sodium hydroxide solution (50 ml) for 1 hr, afforded a solid (0·15 g) which crystallized from dil. methanol, m.p. 185–186° identical by mixed m.p. with a sample of 3,4-dihydro-1-naphthylsuccinic acid[1] (I; R = H, m.p. 186–187° obtained by the alkaline hydrolysis of the half-ester).

(b) A brown viscous oil (4 g) which after washing with 5% sodium hydroxide solution and distillation yielded *ethyl* 3-*keto*-Δ^8-6,7-*benzhydrindan*-1-*carboxylate* (III; R = C_2H_5) as a pale yellow heavy oil, b.p. 182°/1·7 mm; U.V. spectrum $\lambda_{\max}^{\text{Ethanol}}$ 227·5, 234·5, 296 mμ (log ε 4·15, 4·17, 4·15). (Found: C, 74·8; H, 6·5. $C_{16}H_{16}O_3$ requires: C, 75·0; H, 6·3%).

The *semicarbazone* crystallized from ethanol in colourless crystals changing to golden yellow, m.p. 225–227° (cf. ref. 1), U.V. spectrum: $\lambda_{\max}^{\text{Ethanol}}$ 326 mμ (log ε 4·59). (Found: C, 65·17; H, 5·83; N, 13·39, Calc. for $C_{17}H_{18}N_3O_3$: C, 65·38; H, 5·75; N, 13·46%).

The 2,4-*dinitrophenylhydrazone* crystallized from glacial acetic acid in crimson crystals, m.p. 203–205°, U.V. spectrum: $\lambda_{\max}^{\text{Chloroform}}$ 402·5 mμ (log ε 4·54). (Found: C, 59·99; H, 4·71; N, 12·74. $C_{22}H_{20}O_6N_4$ requires: C, 60·54; H, 4·62; N, 12·84%).

The cyclization of the ethyl half-ester (4 g) using polyphosphoric acid (40 g syrupy phosphoric acid and 50 g phosphorous pentoxide) and heating on a water-bath for 6 hr, yielded only the keto-ester.

Hydrolysis of the ethyl keto-ester (2·7 g) with conc. hydrochloric acid (40 ml) for 1 hr afforded after dilution with water and extraction with ether 6,7-dihydro-4,5-benzindanone (V; 1·8 g; 92·7%, m.p. 75–78°; 2,4-dinitrophenylhydrazone, m.p. 277–278°) (cf. ref. 1 & 2).

$\Delta^{1(8)}$-*Tetrahydro*-6,7-*benzindan*-1-*carboxylic acid* (VI; R = H)

To amalgamated zinc wool (40 g) in water (34 ml) and conc. hydrochloric acid (80 ml) was added the ethyl keto-ester (10 g) in toluene (70 ml). The mixture was refluxed for 30 hr with addition of hydrochloric acid (15 ml) every 6 hr. The colour on heating changed from brown to orange to yellow. After cooling, the toluene layer was separated and the aqueous layer extracted with ether and then the ether and toluene solutions extracted with sodium bicarbonate solution to remove any acid present. The organic layer after washing with water and drying afforded mainly the unsaturated ester (VI; R = C_2H_5) as a fluorescent pale yellow liquid (7 g), b.p. 115°/0·45 mm U.V. spectrum $\lambda_{\max}^{\text{Ethanol}}$ 220·5, 227, 266, 273 mμ (log ε 4·13, 4·09, 3·83, 3·81).

A mixture of this liquid (1·5 g) and 5% sodium hydroxide solution (30 ml) was refluxed for 2 hr. The alkaline solution after extraction with ether was cooled and acidified. The resulting yellow viscous oil (0·9 g), b.p. 160–170°/0·25 mm solidified in pet. ether (b.p. 40–60°) and crystallized from the same solvent as $\Delta^{1(8)}$-tetrahydro-6,7-benzindan-1-carboxylic acid (VI; R = H), colourless crystals m.p. 127–9° U.V. spectrum: $\lambda_{\max}^{\text{Ethanol}}$ 220·5, 227, 267, 275 mμ (log ε 4·15, 4·07, 3·92, 3·93). (Found: C, 78·33; H, 6·43. $C_{14}H_{14}O_2$ requires: C, 78·48; H, 6·59%).

A sample of the acid was converted through its acid chloride to the p-*toluidide*, which crystallized from chloroform in colourless crystals, m.p. 230–231°. (Found: N, 4·37. $C_{21}H_{21}ON$ requires: N, 4·62%).

The ethereal solution from the hydrolysis experiment afforded a neutral colourless oil (0·4 g), b.p. 130–135°/0·4 mm. The structure of the substance is under investigation.

The carbonate solution from the Clemmensen reduction experiment after extraction with ether and acidification, afforded an acid (1·2 g) as an oil which gave a p-toluidide derivative, m.p. 229–230° (from chloroform). The mixed m.p. of this *p*-toluidide with that of $\Delta^{1(8)}$-tetrahydro-6,7-benzindan-1-carboxylic acid (VI; R = H) obtained from the hydrolysis experiment, gave no depression.

6,7-*Benzhydrindan*-1-*carboxylic acid* (VII, R = H)

A solution of the neutral oily fraction (distilled) of the Clemmensen experiment (1·3 g) in glacial acetic acid (20 ml) was shaken with hydrogen in presence of Adams platinum oxide (0·15 g), until the absorption of hydrogen ceased. The oily product, b.p. 170°/0·7 mm, was refluxed for 6 hr with 10% sodium hydroxide solution (15 ml) and ethanol (10 ml). After removal of alcohol *in vacuo* the mixture was ether extracted and acidified. Extraction with ether afforded the saturated acid as a liquid (0·8 g; 73%), which partly solidified on keeping. Recrystallization from pet. ether (b.p. 40–60°) gave colourless crystals, m.p. 68·5–70°. (Found: C, 78·53; H, 7·73. $C_{14}H_{16}O_2$ requires: C, 77·75; H, 7·46%).

6,7-*Benzhydrindan*-1-*acetoxymethyl ketone* (VIII; R = CH_3CO)

6,7-Benzhydrindan-1-carboxylic acid (VII; R = H; 1 g) in dry benzene (10 ml) was allowed to stand 48 hr at room temp. with redistilled thionyl chloride (10 ml). Excess thionyl chloride and benzene were removed *in vacuo* and the final traces of thionyl chloride removed by addition and subsequent removal of 2 × 10 ml dry benzene. The dry residue was then dissolved in ether (15 ml) and added to an ethereal solution of diazomethane (250 ml from 10 g of N-nitrosomethyl urea) at 0°; after standing for ½ hr at 0° and then overnight at room temp, removal of ether and excess diazomethane *in vacuo* left the corresponding diazo-ketone as a residual oil. This was dissolved in glacial acetic acid (30 ml); and gradually heated on a water-bath. After 40 min (nitrogen evolution complete), the contents of the flask were diluted with water and ether extracted. The ether solution after washing with 5% sodium carbonate then water, was dried (Na_2SO_4) and evaporated to give a yellow oil (0·9 g; 75%), b.p. 160–165°/0·2 mm which reduced ammoniacal silver nitrate. (Found: C, 74·67; H, 7·20. $C_{17}H_{20}O_3$ requires: C, 74·97; H, 7·40%).

6,7-*Benzhydrindan*-1-*hydroxymethyl ketone* (VIII, R = H)

The diazoketone from 0·85 g 6,7-benzhydrindan-1-carboxylic acid chloride, as in the previous experiment, was dissolved in 20 ml pure dry dioxan and 10 ml 2N sulfuric acid added. The evolution of nitrogen started when the mixture was warmed on a water-bath and ceased after 40 min. The mixture was then diluted with water and thoroughly extracted with ether. The ethereal solution was washed with small amounts of 5% sodium bicarbonate solution, then with water. After drying, the ether was removed *in vacuo* and the residue (0·7 g; 77%) distilled as yellow oil, b.p. 140–150°/0·09 mm which reduced ammoniacal silver nitrate. (Found: C, 77·9; H, 8·32. $C_{15}H_{18}O_2$ requires: C, 78·23; H, 7·88%).

Acknowledgement—The authors thank Dr. F. G. Baddar, Professor of Organic Chemistry, Faculty of Science, Ain Shams University, for U.V. spectral determinations.