A Potential Synthetic Intermediate of *dl*-Carnosic Acid

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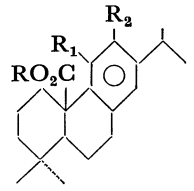
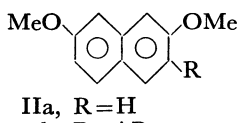
The Birch reduction of 2,7-dimethoxy-3-isopropylnaphthalene (IIb), which itself was made from IIa in five steps, followed by acid hydrolysis yielded the tetralone IIIa and the latter was carboxymethylated to IIIb by reaction with dimethyl carbonate and sodium hydride. Michael condensation of IIIb with methyl vinyl ketone yielded the unsaturated ketone IV. The tricyclic ketone IV on methylation followed by thioketalisation gave the thioketal IXa and the latter on Raney nickel desulfurisation yielded Ic.

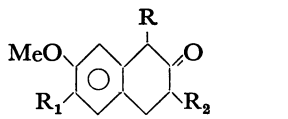
Ever since Wenkert[1] established the structure of the naturally occuring oxygenated diterpene carnosic acid (Ia) the synthesis of this material with a rare C–20 carboxylic acid function presented great challenge. While the present work[2] was in progress Meyer and Schindler[3] reported the total synthesis of ethyl *dl*-carnosate dimethyl ether (Ib) following an A→B→C sequence. Later Mayer and Shew[4] developed a new method of constructing the 11,12-dihydroxylated C-ring of carnosic acid.



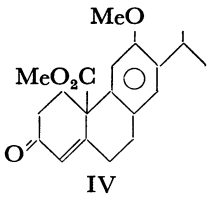
Ia, R=H, R_1=R_2=OH
b, R=Et, R_1=R_2=OMe
c, R=Me, R_1=H, R_2=OMe



IIa, R=H
b, R=*i*-Pr
c, R=CO_2H
d, R=CO_2Me
e, R=$CMe_2(OH)$
f, R=C(=CH_2)Me



IIIa, R=R_2=H, R_1=*i*-Pr
b, R=CO_2Me, R_1=*i*-Pr, R_2=H
c, R=R_1=H, R_2=*i*-Pr



IV

Results and Discussion

The present work[2] is centred around the total synthesis of Ic following a C→B→A sequence. The known 2,7-dimethoxynaphthalene (IIa) was converted to IIb in five steps. This conversion involved (i) lithiation of IIa with butyl lithium and carbonation[5] of the lithiation product using Dry Ice, (ii) esterification of IIc, (iii) reaction of IId with methyl magnesium iodide, (iv) dehydration of the tertiary alcohol IIe and (v) hydrogenation of IIf. The procedure employed in the above reaction sequence was similar to Bergmann's method[6] of converting 2-acetylnaphthalene to 2-isopropylnaphthalene.

The next aim was to selectively reduce the less substituted ring and functionalise C–1 of the resultant tetralone. Thus the Birch reduction[7] of IIb using 2.45 equivalents of sodium in liquid ammonia followed by acid hydrolysis yielded the 2-tetralone IIIa. It is possible that some amount of reduction of the more substituted ring might have taken place at the same time resulting in the tetralone IIIc. Since the carbonyl group of IIIc is sterically hindered it cannot be expected to form a bisulfite adduct and hence this reaction can be used to separate IIIc from IIIa. The tetralone IIIa was carboxymethylated at the 1-position with dimethyl carbonate and sodium hydride in 80% yield by a modification of the procedure of Rhoads.[8,9] It is interesting to note that the reaction of methyl magnesium carbonate with 5-methoxy-2-tetralone has been reported[10] to result in carboxymethylation at the 3-position only. The highly enolic nature of the keto-ester IIIb obtained above implies that the steric interaction between the C–1 ester group and C–8 hydrogen was not sufficient to destabilise its enolic form.

To construct the tricyclic skeleton the Michael addition[11] of the keto-ester IIIb to methyl vinyl ketone was carried out in the presence of triton B methoxide and this resulted in the tricyclic ketone IV in 41.5% yield. The unsaturated ketone IV was methylated with methyl iodide and potassium tertiary butoxide according to the general procedure of Barton.[12] This procedure has been applied to systems similar to the one under study by Meyer[13] and by Stork.[14] The crude methylation product contained in addition to V, minor quantities of poly-methylation products as evidenced by the mass spectrum. Attempts to hydrogenate the crude methylation product at atmospheric pressure in the presence of 5% palladium-on-charcoal in glacial acetic acid resulted in a complex mixture of compounds containing products of reduction of the 5,6-double bond and/or the 3-keto group. Hydrogenation at high pressures yielded the saturated lactone VI. In hydrogenation of similar bicyclic ketone VII Meyer[13] obtained the lactone VIII.

In order to avoid the complicating effects of the 3-keto group during hydrogenation, the methylation product V was converted to the thioketal IXa by treatment with ethane-1,2-dithiol and boron trifluoride etherate in acetic acid. The procedure adopted was that of Stork.[14,15] Thioketalisation was accompanied by partial demethylation of the C–20 ester group. The thioketal acid (IXb)–thioketal ester (IXa) mixture on treatment with diazomethane in ether afforded the thioketal ester (IXa) in a pure form. The reaction proceeded in an overall yield of 80.4% from the unsaturated ketone IV. Desulfurisation of the thioketal IXa was effected by refluxing an alcoholic solution of

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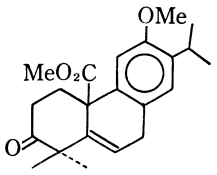
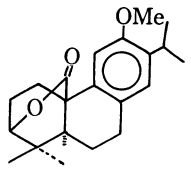
IXa with an active variety of Raney nickel prepared by the method of Burgstahler.[16] Desulfurisation was accompanied by partial reduction of the 5,6-double bond. In similar tricyclic compounds with a C–20 methyl group the reduction of the 5,6-double bond has been found[14,15] to occur concomitantly with desulfurisation of the thioketal group. The rationalisation of the resistance of the 5,6-double bond to reduction in compounds with C–20 ester functions is rather difficult. The reduction of the 5,6-double bond was completed by refluxing the mixture obtained from the previous treatment with a large excess of the same active variety of Raney nickel in a current of hydrogen. Methyl *O*-methyl-11-desoxycarnosate (**1c**) was thus obtained in 62.4% yield from the thioketal IXa. An authentic sample of Ic was not available for comparison. But the authenticity of the synthetic sample was proved by the results of microanalysis, NMR and mass spectral data.

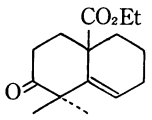
Since oxygenation of the C–11 position[3] of 11-desoxycarnosate has been achieved and demethylation of the C–20 ester[3] and the C–12 methyl ether[1] have been carried out, the total synthesis of Ic completes the synthesis of a potential synthetic intermediate of *dl*-carnosic acid.



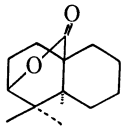
V



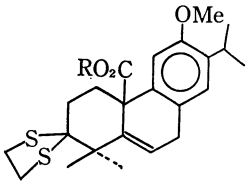
VI



VII



VIII



IXa R=Me
b R=H

Experimental

2,7-Dimethoxy-3-naphthoic acid (IIc). The preparation of 2,7-dimethoxynaphthalene (IIa) was effected by the reaction of 2,7-dihydroxynaphthalene with dimethyl sulfate and sodium hydroxide. The naphthoic acid IIc was obtained by carboxylation of IIa by the procedure of Gilman.[5] The reaction proceeded in 64.2% yield. Two crystallisations from 1: 1 benzene–ethanol afforded an analytical sample, mp 185—186 °C; reported[5] mp 185.5 °C.

2,7-Dimethoxy-3-carbomethoxynaphthalene (IId). The esterification of the naphthoic acid IIc was carried out by the method of Fisher.[17] Refluxing a solution of the acid IIc in absolute methanol containing catalytic amounts of concentrated sulfuric acid gave the ester IId in 93% yield. Two crystallisations from 1: 1 benzene–hexane yielded an analytical sample of IId, m.p. 101—102 °C; IR ($CHCl_3$) 1627, 1722 cm^{-1} (ester carbonyl); PMR δ ($CDCl_3$) 3.83 (s, C–7 methoxyl), 3.87 (s, C–2 methoxyl), 3.92 (s, C–3 ester methyl), 6.94 (q, C–6 H, $J_{5,6}$=9.5 Hz, $J_{6,8}$=2 Hz), 6.95 (d, C–8 H, $J_{5,8}$=2 Hz), 7.03 (s, C–1 H), 7.62 (d, C–5 H, $J_{5,6}$=9.5Hz), 8.19 (s, C–4H); Found: C, 68.32; H, 5.77%. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73%.

2,7-Dimethoxy-3-(2'-hydroxy-2'-propyl) naphthalene (IIe). A solution of 17.5 g of methyl 2,7-dimethoxynaphthalene-3-carboxylate (IId) in about 700 ml of anhydrous ether was added to 100 ml of a stirred solution of methyl magnesium bromide in ether containing 0.43 g of the reagent per ml. As the reaction progressed a white precipitate separated out. When all the ester was added the reaction mixture was refluxed for 1 h. The mixture was allowed to cool to room temperature and decomposed with 10% acetic acid. The reaction product was extracted with ether and the ether solution on evaporation yielded 17.3 g (99%) of naphthalene alcohol IIe, which was sufficiently pure for further reaction. A small portion of IIe was dissolved in hexane and filtered through a small column of alumina. The filtrate on evaporation yielded IIe as colourless crystals and two crystallisations from hexane and one from hexane–ether (3: 1) mixture gave an analytical sample, mp 104.5—106 °C; IR ($CHCl_3$) 1630, 3533 (broad, intramolecularly hydrogen bonded OH), 3650 cm^{-1} (sharp, free OH); PMR δ ($CDCl_3$) 1.68 (s, isopropanol methyls), 3.77 (3H, s) and 3.81 (3H, s) (C–2 and C–7 methoxyl groups), 4.1 (1H, s, OH, $W^{h/2}$=7.5 Hz), 6.95 (q, C–6 H, $J_{5,6}$=9.5 Hz, $J_{6,8}$=2.5 Hz), 6.97 (d, C–8 H, $J_{6,8}$=2.5 Hz), 6.99 (s, C–1 H), 7.57 (d, C–5 H, $J_{5,6}$= 9.5 Hz), 7.69 (s, C–4 H); Found: C, 73.21; H, 7.45%. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37%.

2,7-Dimethoxy-3-isopropylnaphthalene (IIb). A solution of the naphthalene alcohol IIe (17 g) in 150 ml of glacial acetic acid was refluxed for 30 min and the volume of the solution was reduced to about 25 ml by evaporation. The isopropenylnaphthalene IIf was not isolated and was hydrogenated in the presence of 1.8 g of 5% palladium on charcoal at 60 psi pressure for 24 h. The catalyst was removed by filtration and the filtrate evaporated to dryness. The residue on work up gave 16.3 g of IIb. A benzene solution of IIb was filtered through a column containing 60—65 g of alumina and this treatment resulted in 15.62 g (98.5%) of pure isopropylnaphthalene. Three crystallizations from hexane–petroleum ether, 30—60°C (3: 1) gave an analytical sample, mp 95—96°C; IR ($CHCl_3$) 1602, 1623 cm^{-1}, PMR δ ($CDCl_3$) 1.28 (6H, C–3 isopropyl CH_3, d, J=7 Hz), 3.52 (1H, m, C–3 isopropyl methine H, J=7 Hz), 3.7 (3H) and 3.74 (3H) (s, C–2 and C–7 methoxyl groups), 6.85 (s, C–1 H), 6.88 (d, C–8 H, $J_{6,8}$=2.5 Hz), 6.89 (q, C–6 H, $J_{5,6}$=9.5 Hz, $J_{6,8}$=2.5 Hz), 7.43 (s, C–4 H), 7.51 (d, C–5 H, $J_{5,6}$=9.5 Hz); Found: C, 78.35; H, 7.86%. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88%.

1,2,3,4-Tetrahydro-7-methoxy-6-isopropylnaphthalen-2-one (IIIa). The 2-tetralone IIIa was prepared by the reduction of the naphthalene IIb using sodium in liquid ammonia solution. To a solution of the naphthalene IIb (6.4346 g) in a solvent mixture of 25 ml of absolute ethanol, 30 ml of tetrahydrofuran, 150 ml of anhydrous ether and 500 ml of liquid ammonia was added clean metallic sodium (1.572 g) in small pieces at a time. The reaction mixture was left overnight and the residue was acidified to pH 5 and extracted with ether. The

crude dihydronaphthalene (6.5 g) was hydrolysed by boiling with 30 ml of acetone and 6 ml of 3 M hydrochloric acid. The resultant solution was diluted with water, extracted with ether and the ether solution evaporated to dryness to yield 4.336 g of the crude tetralone IIIa. The crude product was purified by conversion to its bisulfite adduct and regeneration of the tetralone with sodium bicarbonate solution. Finally fractional distillation under reduced pressure afforded 4.0961 g (67.1%) of IIIa as a colorless liquid, bp 120—125 °C (0.33 mmHg); IR ($CHCl_3$) 1711 cm^{-1}; PMR δ ($CDCl_3$) 1.16 (6H, d, isopropyl methyls, J=6.5 Hz), 2.4 (t, C-3 H, $J_{3,4}$=6.5 Hz), 2.92 (t, C-4 H, $J_{3,4}$=6.5 Hz), 3.22 (m, isopropyl methine H, J=6.5 Hz), 3.38 (s, C-1 H), 3.75 (s, C-7 methoxyl), 6.46 (s, C-8 H), 6.88 (s, C-5 H); Found: C, 76.87; H, 8.19%. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31%.

1,2,3,4-Tetrahydro-7-methoxy-6-isopropyl-1-carbomethoxynaphthalen-2-one (IIIb). To a solution of 5.45 g of the 2-tetralone IIIa in 50 ml of dimethyl carbonate was added sodium hydride derived from 1.32 g of a sample of sodium hydride in mineral oil (51%) made free from mineral oil by washing with anhydrous ether. The reaction mixture was kept at ice-bath temperature for 15 min and at room temperature for 48 h in an atmosphere of nitrogen. It was then refluxed for 30 min, cooled to room temperature and the excess sodium hydride destroyed by pouring the reaction mixture in to ice-cold 10% hydrochloric acid. The organic material was extracted with ether and the solvents evaporated off. The residue on vacuum distillation afforded 5.52 g (80%) of the keto-ester IIIb as a colorless liquid, bp 150—160 °C (0.03 mmHg); IR ($CHCl_3$) 1587, 1629 (hydrogen bonded ester carbonyl), 1700 (weak), 1723 (weak) cm^{-1}; UV (MeOH) max. 212 (ε, 47200), 248 (ε, 15000), 255 (ε, 12400), 292 (ε, 6300), 300 (ε, 6200), 315 nm (ε, 3700); PMR δ ($CDCl_3$) 1.17 (6H, d, isopropyl methyls, J=7 Hz), 2.55 (m, C-3 and C-4 H, A_2B_2 system), 3.31 (m, isopropyl methine H, J=7 Hz), 3.75 (s, C-7 methoxyl), 3.85 (s, ester methyl), 6.81 (s, C-8 H), 7.17 (s, C-5 H), 12.96 (s, C-2 enolic H); Found: C, 69.66; H, 7.20%. Calcd for $C_{17}H_{20}O_4$: C, 69.54; H, 7.20%.

2,3,4,4a,9,10-Hexahydro-4a-methoxycarbonyl-6-methoxy-7-isopropylphenanthren-2-one (IV). To a solution of 5.52 g of the keto-ester IIIb in 200 ml of ice-cold absolute methanol under an atmosphere of nitrogen was added dropwise 1.68 g of methyl vinyl ketone. Triton B methoxide (470 mg) (40% solution of benzyl trimethyl ammonium methoxide in methanol) was then added and the reaction mixture cooled for a further 15 minutes and then left at room temperature for 24 h. The progress of the reaction was followed by periodic testing with ferric chloride. After 20—24 h a negative test was obtained. The reaction was stopped by addition of a few drops of 10% acetic acid until the solution was neutral. The methanol was evaporated under reduced pressure and the residue diluted with water and extracted with ether. The solution was evaporated to dryness and the IR and PMR spectra of the product indicated that it was a hydroxy ester.

It was, without further purification, refluxed with *p*-toluene sulfonic acid (5% by weight) in toluene solution using a Dean-Stark water separator. After 16 h the reaction mixture was evaporated to dryness and the residue chromatographed on alumina. In this way 2.722 g (41.5%) of the unsaturated ketone IV was obtained. Three crystallisations from hexane-ether (8: 1) mixture yielded an analytical sample, mp 94—95 °C: IR ($CHCl_3$) max. 1661, 1722 cm^{-1}; UV (MeOH) max. 230 (ε, 23000), 282 nm (ε, 3000); PMR δ ($CDCl_3$) 1.18 (6H, d, isopropyl CH_3, J=7 Hz), 3.23 (m, isopropyl methine H, J=7 Hz), 3.65 (s, C-6 methoxyl), 3.78 (s, ester methyl), 5.99 (s, C-1 H), 6.87 (s, C-5 H), 6.89 (s, C-8 H); Found: C, 73.17; H, 7.46%. Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37%.

Methyl O-Methyl-3-keto-11-desoxy-Δ^5-carnosate (V). To a solution of 656 mg of the unsaturated ketone IV in 20 ml of anhydrous *t*-butanol was added a solution of 672 mg of potassium *t*-butoxide with stirring. During the addition of the butoxide the pale yellow solution turned deep orange in coloru. Methyl iodide (0.78 ml, 1.704 g) was then added and after a short interval the solution became turbid due to precipitated potassium iodide. The reaction mixture was left at room temperature under a nitrogen atmosphere for 48 h and the reaction was stopped by addition of 10% hydrochloric acid. The bulk of *t*-butanol was evaporated off under reduced pressure, and the residue extracted with ether after mixing with 50 ml of water. The ether solution on evaporation yielded 680 mg of an unstable dark brown liquid which was used directly to prepare IXa. *Thioketal IXa.* To a well-stirred solution of the methylation product V (680 mg) in 7 ml of glacial acetic acid kept at 5°C in an atmosphere of nitrogen was added 2 ml of ethane-1,2-dithiol and then dropwise 2 ml of boron trifluoride etherate over a 10 min period. The reaction mixture developed deep orange colour and the thioketal derivative separated out. Stirring was continued at 5 °C for 30 min and at room temperature for 1 h. The mixture was again cooled to 5°C and filtered under suction. The product was dissolved in 20 ml of ether and treated with excess of diazomethane solution in ether for 5 min and the ether evaporated off and this resulted in 695 mg (80.4%) of the thioletal IXa as colourless crystals. Three recrystallisations from acetone afforded an analytical sample of IXa, mp 206—207.5 °C; UV (MeOH) max. 238 (ε, 1850), 280 (ε, 1240), 285 nm (ε, 1240); PMR δ ($CDCl_3$) 1.18 (6H, d, C-16 and C-17 methyls, $J_{15,16}$=6.5 Hz), 1.22 (s, C-4 axial CH_3), 1.51 (s, C-4 equatorial CH_3), 3.2 (4H, m, C-3 thioketal $-CH_2-CH_2-$ group), 3.53 (C-20 ester CH_3), 3.77 (s, C-12 $-OCH_3$), 6.12 (m, C-6 H), 6.73 (s, C-11 H), 6.93 (s, C-14 H); Found: C, 66.52; H, 7.34; S, 14.82%. Calcd for $C_{24}H_{32}S_2O_3$: C, 66.65; H, 7.46; S, 14.80%.

Methyl O-Methyl-11-desoxycarnosate (Ic). A solution of 57.6 mg of the thioketal IXa in 20 ml of ethanol (absolute) was heated to reflux in an atmosphere of nitrogen. To the boiling solution was added 5 g of active Raney nickel prepared according to the procedure of Burgstahler.[16] The reaction mixture was refluxed for 30 min, cooled to room temperature and the catalyst filtered off under suction in an atmosphere of carbon dioxide. The filtrate was evaporated to dryness and a PMR spectrum of the product indicated partial reduction of 5,6-double bond. The material was dissolved in 20 ml of ethanol and refluxed with 5 g of active Raney nickel for a further 5 h in an atmosphere of hydrogen. The reaction mixture was cooled to room temperature, the catalyst filtered off and the filtrate evaporated to dryness. The residue on crystallisation from ethanol afforded 28.6 mg (62.4%) of methyl *O*-methyl-11-desoxycarnosate (Ic). Two crystallisations from ethanol yielded an analytical sample of Ic, mp 108—109.5 °C; IR ($CHCl_3$) max. 1605, 1707 cm^{-1}; UV (MeOH) max. 230 (ε, 5730), 280 (ε, 2400), 287 nm (ε, 2350); PMR δ ($CDCl_3$) 0.8 (s, C-4 axial CH_3), 0.98 (s, C-4 equatorial CH_3), 1.18 (6H, d, C-16 and C-17 methyls, J=6.5 Hz), 3.2 (1H, heptet, C-15 H, J=6.5 Hz), 3.55 (s, C-20 ester methyl), 3.75 (s, C-12 methoxyl), 6.72 (s, C-11 H), 6.86 (s, C-14 H); mass spectrum, mol wt calcd for $C_{22}H_{32}O_3$, 344.235; observed, 344.236; mass calcd for $C_{22}H_{31}O_3$, $(M-1)^+$ ion, 343.227; observed, 343.226; mass calcd for $C_{21}H_{29}O_3$, $(M-15)^+$ ion, 329.212; observed, 329.213. Found: C, 76.80; H, 9.43%. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36%.

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