APPLICATIONS OF 2-METHYL-2-CARBOXYMETHYL-3-OXOCYCLOPENTANECARBOXYLIC ACID DERIVATIVES IN STEROID SYNTHESES

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Abstract—A Friedel-Crafts condensation of 1,7-dimethoxynaphthalene with the anhydride IV gave a mixture of products from which, after esterification, the ketoesters IX and X could be isolated in 16 and 4.25% yield, respectively. These were hydrogenolysed with Pd-C to the desoxyesters XI and XII. Cyclodehydration of the latter with an acetic-hydrochloric acid mixture furnished the desired estrahexaene III. Reaction of the lithio derivative of 2-methoxynaphthalene with the dimethyl ester Vc yielded the hydroxyester XVb which was dehydrated to the unsaturated compound XVIII. Assignment of structures to the isomers IX and X by means of mass spectrometry is discussed.

REACTION of the 7-carbon β -methyltricarballylic acid anhydride (I) with 1,7-dimethoxynaphthalene was reported to render the tricyclic intermediate II, which was then converted¹ into the estrahexaene derivative III, utilizing the methyl acrylate reaction developed by Wilds and collaborators.² The latter Michael-type reaction serves, in effect, to introduce the carbon atoms 15 and 16 still missing in II.

We have now devised another method of synthesis of III by attaching a 9-carbon fragment comprising atoms 11, 12, 13, 14, 15, 16, 17, 18 and 20 of rings C and D to 1,7-dimethoxynaphthalene (Chart I). This fragment contains all the carbon atoms present in the anhydride I, *plus* the two carbon atoms derived from the acrylate reaction. The compound in question is 2-methyl-2(carboxymethyl)-3-oxocyclopentanecarboxylic acid anhydride (IV). A synthesis of the diethyl ester Vb, corresponding to this anhydride, has been described³ and involves condensation of ethyl acetoacetate with ethyl cyanoacetate, addition of hydrocyanic acid and cyanoethylation of the resulting dicyanoester VI (an intermediate in the synthesis of β -methyltricarballylic acid⁴). Hydrolysis and esterification furnished the tetramethyl ester VII which, on Dieckmann cyclization, yielded the β -ketoester VIII. Hydrolysis of VIII, decarboxylation and esterification furnished the ester Vb. Presently we have isolated the free acid Va and dehydrated it with acetic anhydride to the anhydride IV.

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¹ M. Harnik and E. V. Jensen, Israel J. Chem. 3, 173 (1965).

⁸ O. R. Rodig, N. A. Nelson, E. M. Gross, M. Harnik, and A. L. Wilds, *Abstracts*, 131st Meeting of the Amer. Chem. Soc. p. 32-0 April (1957).

⁸ G. Stork, U.S. Patents 2,793,233 (Chem. Abstr. 52, 441 (1958)) and 2,843,603 (Chem. Abstr. 53, 3180 (1959)).

⁴ M. Harnik, Israel J. Chem. 3, 1 (1965).



A Friedel-Crafts condensation of the anhydride IV with 1,7-dimethoxynaphthalene was expected to occur predominantly in position 4, in conformity with our previous finding¹ that acylations of 1,7-dimethoxynaphthalene occur preferentially in that position. It was also hoped that in this reaction the unsymmetrical anhydride IV would open in such a sense as to furnish the less crowded compound X, rather than the isomeric product IX⁴ (Chart II). In reality, however, the Friedel-Crafts reaction gave in 62% yield an acidic mixture from which it was possible to obtain, after esterification and a tedious isolation procedure, a 4.25% yield of the expected ester X, of m.p. 166–168°, and a 16% yield of the isomer IX, m.p. 92–95°, both having the expected UV spectra. In addition, there could be isolated in 1.8% yield a third isomeric compound, m.p. 185–187°, of unknown structure. Although it can be reasonably expected that an improved isolation technique might increase the yield of X, the ratio of the two isomers IX and X is unexplicably unfavourable. The assignment of structures to these two products was made on the basis of their mass spectra (*vide infra*) and was subsequently confirmed by further chemical conversions.

In one Friedel-Crafts condensation of the anhydride IV with benzene a broadmelting mixture was obtained which analysed for the ketoacids 2-methyl-2-(benzoylmethyl) 3-oxo-cyclopentanecarboxylic acid and 2-methyl-2(carboxymethyl)-3-benzoyl cyclopentanone. After esterification, a product m.p. 80-84° was obtained, whose mass spectrum showed it to be a mixture.



Hydrogenolysis of the ketoester IX in the presence of Pd and perchloric acid proceeded somewhat sluggishly, possibly due to the hindered nature of the carbonyl group. During the relatively long reaction time considerable reduction of the naphthalenic moiety took place, as evidenced by changes in the UV spectrum. The desoxyester XI, isolated in 6% yield, was subjected to several cyclodehydration reagents (hydrogen fluoride, hydrochloric-acetic acid, polyphosphoric acid), but no evidence for cyclization could be obtained.

In the desired series hydrogenolysis of the ester X afforded the desoxyester XII in 66% yield. The related compound XX has been previously obtained⁵ through a sequence of reactions identical with that depicted in Chart I, except that in the first step ethyl acetoacetate was replaced by the ketone XIIIa. Also Banerjee *et al.*⁶ independently followed a similar approach starting with the methoxy derivative XIIIb. Cyclization of the ester XII with an acetic-hydrochloric acid mixture⁵ afforded the desired compound III, identical in all respects with an authentical sample.¹

It is tentatively assumed that the carbomethoxy group in the isomer X still retains the " α " configuration derived from the anhydride IV and that inversion of

^{*} R. A. Barnes and R. Miller, J. Am. Chem. Soc. 82, 4960 (1960).

⁶ D. K. Banerjee, H. N. Khastgir, J. Dutta, E. J. Jacob, W. S. Johnson, C. F. Allen, B. K. Bhattacharyya, J. C. Collins, Jr., A. L. McCloskey, W. T. Tsatsos, W. A. Vredenburgh, and K. L. Williamson, *Tetrahedron Letters* 76 (1961).

configuration to the more stable 17β -isomer III occurs during the acid-catalysed cyclization reaction. However, partial isomerization during the Friedel-Crafts reaction cannot be excluded; in fact, this may be a reason for the low yield of X obtained.



Finally, we wish to mention briefly a synthetic application of the related dimethyl ester Vc of 2-methyl-2-carboxymethyl-3-oxocyclopentanecarboxylic acid (Chart III). Some years ago Newman *et al.* condensed the 6-lithio derivative of 2-methoxynaph-thalene with 2-methyl-2-carboisopropoxycyclopentanone (XIV) and obtained⁷ the hydroxyester XVa which was further transformed into 17-desoxyequilenin. In a related reaction, Buchta and Ziener⁸ reacted β -naphthylmagnesium bromide with the ketoesters XVI (R = H and Me) and isolated the corresponding lactones XVII. We have now condensed Newman's lithium compound with the dimethyl ester Vc and obtained the hydroxyester XVb. Dehydration with *p*-toluenesulfonic acid furnished the unsaturated ester XVIII. Although this aspect of our work was not pursued any further, the transformation of XVIII into the known⁶ ester XIX should be relatively facile employing published⁷ methods for the necessary ring closure.

Mass spectrometry

Since the compounds IX, X, XI and XII could not be identified on the basis of their NMR spectra, attention was turned to their mass spectra (Chart IV). The most abundant molecular ions in all four spectra were the base peaks (m/e 384 for IX and X, and m/e 370 for XI and XII), followed, in the case of IX and X, by ions m/e 215, formed by cleavage α to the carbonyl (Chart V). These may in turn lose CO (leading to m/e 187) and subsequently Me or MeO radicals, giving rise to the peaks

G. Eglinton, J. C. Nevenzel, A. I. Scott, and M. S. Newman, J. Am. Chem. Soc. 78, 2331 (1956).

^{*} E. Buchta and H. Ziener, Lieblgs Ann. 601, 155 (1956).

in the 130-200 mu range, all of which seem to contain the basic naphthalenic system. Thus the spectra of IX and X are almost identical up to and including m/e 215. In the upper mass region, however, the presence of a $-CH_2COOMe$ group in IX is indicated by the ions m/e 311 (M-73) formed by simple cleavage, and m/e 310 (M-74), arising by a McLafferty rearrangement involving the ester carbonyl group. These two ions are absent in the spectrum of X. Also the absence of fragment peaks arising from a similar rearrangement involving the aroyl carbonyl group corroborates the structure



IX, where cleavage of a bond β to this carbonyl does not lead to the rupture of the molecule. In contrast, the spectrum of X shows a very prominent peak at m/e 230, ascribed to ion *a* arising by this very rearrangement. Ion *a* may lose one MeO group



to give ion m/e 199, which, like its precursor a, is completely absent in the spectrum of IX. Furthermore, a McLafferty rearrangement involving the ester carbonyl of X would not cause fragmentation, but give the ion b, easily cleaved a to the carbonyl to yield ion c at m/e 283, which is again absent from the spectrum of IX.

The mass spectrum of the third Friedel-Crafts product (m.p. 185–187°) of the same mol wt (384) is remarkably similar to that of IX in the range above m/e 215 indicating an identical (or at most epimeric) structure for its aliphatic moiety. But in the range below m/e 215 there are marked differences from the spectra of IX and X.

This may mean that acylation of 1,7-dimethoxynaphthalene occurred here at a position other than 4.

The mass spectra of the pair of isomeric desoxyesters XI and XII confirm the structure assignments for the parent ketones. In both benzylic cleavage is responsible



CHART VI

for one of the major peaks at m/e 201. In XI this is accompanied by m/e 227 which must be formulated as d' or d'' (Chart VI). The former can arise much more readily from structure XI than from XII. Again, as in IX, the pair of peaks at m/e 297 (M⁺-73) and m/e 296 (M⁺-74) indicate the grouping—CH₂COOMe. In the spectrum of XII these two ions are completely absent. Here ion m/e 201 is accompanied by m/e 214, formulated as e' or e'', which can arise by a McLafferty process involving the 5-membered ring carbonyl, the positive charge being retained in the naphthalenic system. The second fragment can also retain the charge on ion $f(m/e \, 156)$.

The mass spectrum of the Friedel-Crafts condensation product of the anhydride IV with benzene, esterified with diazomethane, contains peaks for ions formed by fragmentation processes analogous to those of IX and X (m/e 105 from C₆H₅CO⁺; m/e 201 and 200 from the analogue of IX; m/e 173 analogous to ion c, and m/e 120 analogous to ion a, the last two arising only from the structure analogous to X), confirming our suspicion that the material m.p. 80–84° is a mixture of esters.

EXPERIMENTAL

2-Methyl-2-(carboxymethyl) 3-oxocyclopentanecarboxylic acid (Va). A Dieckmann condensation^{*} of 202 g of VII, b.p. 180–191°/2 mm, and decarboxylation of the resulting VIII was followed by distillation of HCl in vacuo. The dark solid cake was washed with cold cone HCl and then with cold ether to afford 69 g of the acid Va, m.p. 173–177°. Concentration of the combined washings gave additional 12 g, m.p. 170–175°. The analytical sample (from ether) melted at 176–178°. (Found: C, 53·83; H, 6·00. Calc. for $C_9H_{13}O_5$: C, 53·99; H, 6·04%.)

2-Methyl-2-(carboxymethyl) 3-oxocyclopentanecarboxylic acid anhydride (IV). The conditions for the preparation were rather critical. The acid Va (27 g) was added in one portion to 270 ml of boiling Ac₄O. Reflux was maintained for 2 min, whereupon the flask was cooled with tap-water. Distillation at 55° (bath temp) and 2 mm press for 3 hr with magnetic stirring gave a thick syrup which was treated with 30 ml benzene. Swirling for 5 min started cyrstallization which was completed by addition of 20 ml ether. After 10 min the solid was filtered off and washed twice with a 1:1 benzene-ether. The tan-colored anhydride IV (18 g) melted at 91-100° and was used directly in Friedel-Crafts reactions. It could be recrystallized from EtOAc-ether and it separated in a haphazard manner in one of 3 crystalline forms melting at 117°, 105-109° and 110°, respectively, each having a distinct IR spectrum. (Found: C, 59.71; H, 5.80. Calc. for C₆H₁₀O₄: C, 59.33; H, 5.53%.)

The main ether-benzene filtrate was taken to dryness and the gum heated on the steam bath with 50 ml water and 50 ml conc HCl until all dissolved. Distillation *in vacuo* to dryness and washing of the solid product with cold conc HCl furnished 7 g of the acid Va.

Friedel-Crafts reaction of anhydride IV with benzene. To a soln of 200 mg of IV in 20 ml CH₂Cl₂ was added 500 mg anhydr AlCl₂. After stirring for 20 min, 2 ml benzene was added and stirring was continued for 72 hr. The reaction mixture was decomposed with ice and HCl, the aqueous layer was reextracted with CH₂Cl₂ and the combined organic layers were washed with water and evaporated. The residual gum was taken up in ether and extracted with three 10 ml portions of 10% Na₂CO₂. The combined aqueous extracts were washed with ether and acidified with HCl. The mixture was twice extracted with ether, the combined extracts were washed with water and evaporated. Addition of ether precipitated 12 mg of a solid, m.p. above 270°, which was not investigated further. Dilution of the filtrate with pet. ether gave a total of 72 mg of crystals, m.p. 128-141°. Successive recrystalizations from pet ether-ether furnished wide-melting solids which probably are a mixture of 2-methyl-2-(benzoylmethyl) 3-oxo-cyclopentanecarboxylic acid and 2-methyl-2-(carboxymethyl) 3-benzoyl-cyclopentanenee. A sample m.p. 133-141° was analysed. (Found: C, 69.32; H, 6.07. Calc. for C₁₈H₁₈O₄: C, 69.21; H, 6.20%.)

Esterification of this sample with diazomethane and recrystallization from pet. ether afforded a product melting at 80-84°, the mass spectrum of which showed it to be a mixture. (Found: C, 69-83; H, 6-48. Calc. for $C_{16}H_{10}O_4$: C, 70-05; H, 6-61%.)

2-Methyl-2-[(4,6-dimethoxy-1-naphthoyl) methyl]-3-oxocyclopentanecarboxylic acid methyl ester (X) and 2-methyl-2-(carbomethoxymethyl) 3-(4,6-dimethoxy-1-naphthoyl) cyclopentanone (IX). A suspension of 45 g of anhydr AlCl, powder in 1.5 l. CH, Cl, was treated with 18 g of IV and stirred for 10 min. 1,7-Dimethoxynaphthalene (40 ml) was added and stirring was continued for 40 hr. The dark soln was poured into a mixture of ice and conc HCl and the aqueous phase was reextracted with CH₄Cl₄. The combined extracts were washed twice with water, the solvent was distilled and the residue taken up in 500 ml ether. The filtered ether soln was extracted with three 70 ml portions of 10% Na₄CO₄aq and the combined extracts were washed with ether and acidified with conc HCl. The precipitated gum was allowed to settle for 24 hr, the clear supernatant liquid was decanted and the gum washed by decantation with two portions of water. The aqueous soln was extracted twice with EtOAc and then twice with CHCl₄. The combined extracts were evaporated *in vacuo* to give a colorless solid, which after washing with a little ether weighed 2.4 g, melted at 170-175°, and was shown by IR spectroscopy to be the acid Va.

The gummy reaction product, which partially solidified on standing for 36 hr, was triturated with ether and the solid was filtered and washed with a small amount of ether to afford 12 g of a tan solid, m.p. 120-150°. The dried ether filtrates were evaporated and gave 8 g of an oil. Both the crude solid and the oil showed UV absorption characteristic of 1,7-dimethoxynaphthalene acylated in position 41, and were each esterified with diazomethane and purified by chromatography over Florisil. Elution with pet. ether-benzene mixtures, benzene and benzene-ether mixtures gave oily fractions which were diluted with a little ether. The "natural" ester X was usually obtained from the fractions eluted with the more polar mixtures of solvents, while the early eluates, and also the filtrates from X, slowly deposited several crops of the characteristic large transparent crystals of the isomer IX, which were washed with ether-pet. ether. If a mixture of the two solids crystallized out, the latter isomer could be dissolved in cold ether, leaving behind the ester X. When no further crops of the isomer IX could be obtained, the combined mother liquors were rechromatographed over Florisil, whereupon additional amounts of both isomers were obtained as above. The situation was further complicated by the fact that the relatively insoluble isomer X was sometimes admixed with a third isomeric compound ("C") of similar solubility. It could be separated from X either during the chromatographic purification or by trituration with hot MeOH in which it is somewhat more soluble than X.

The analytical sample of *isomer* "C" (from MeOH) melted at 185–187°. Its UV spectrum was different from that of IX and X: λ_{max}^{EOH} 222, 242, 294, 300, 330 and 340 m μ (e 37,000, 25,400, 4800, 4770, 3180 and 3500; λ_{max}^{EBT} 5.75 (wide) and 5.85 μ ; no OH in the 3 μ region nor an unsaturated carbonyl around 6 μ . (Found: C, 68.91; H, 6.31. Calc. for C₁₂H₃₄O₆: C, 68.73; H, 6.29%.)

The analytical sample of *isomer* IX (from ether-pet. ether) melted at 92-95°; λ_{max}^{moh} 250, 311 and 339 m μ (e 35,000, 8500 and 6500); λ_{max}^{max} 5.73, 5.78 and 6.00 μ . (Found: C, 68.69; H, 6.28. Calc. for C₃₃H₃₄O₆: C, 68.73; H, 6.29%.)

The analytical sample of *isomer* X (from MeOH) melted at 166–168°; λ_{max}^{HOH} 249, 315 and 338 mµ (e 36,000, 8700 and 6000); λ_{max}^{HBT} 5.73, and 6.00 µ. (Found: C, 68.59; H, 6.41. Calc. for C₃₃H₃₄O₆: C, 68.73; H, 6.29%.)

The 3 compounds were isolated in the following amounts: isomer "C", 0.60 g, m.p. 180-185°; isomer IX, 5.29 g, m.p. 80-90°; isomer X, 1.42 g, m.p. 161-165°.

2-Methyl-2[$\beta(4,6-dimethoxy-1-naphthyl)$ ethyl]-3-oxocyclopentanecarboxylic acid methyl ester XII. A soln of 580 mg of the ester X in 50 ml of AcOH containing 0.5 ml of 70% HClO₄ was shaken for 30 min with H₂ at 35 psi in the presence of 2 g of 5% Pd-C. The filtered soln was poured into 200 ml of water and the mixture extracted with three 100 ml portions of benzene. The combined extracts were washed with water, NaHCO₃aq and taken to dryness. The residual oil deposited overnight 145 mg of large prisms, m.p. 115-125°, which were washed with an ether-pet. ether mixture. Additional 235 mg, m.p. 120-125°, were obtained by chromatography of the filtrate over Florisil. Recrystallization from MeOH raised the m.p. to 123-125°; λ_{max}^{EOH} 218, 248, 287, 298, 323 and 338 mµ (e 42,000, 37,000, 5600, 5400, 2400 and 2800); λ_{max}^{EBF} 5.73 µ. (Found: C, 71.19; H, 7.00. Calc. for C₃₂H₃₄₀O₅: C, 71.33; H, 7.08%.)

2-Methyl-2-(carbomethoxymethyl) 3-[(4,6-dimethoxy-1-naphthyl) methyl] cyclopentanone (XI). Hydrogenation of a soln of 4.44 g ester IX in 200 ml of AcOH containing 2 ml of HClO₄ in the presence of 4 g of 5% Pd-C was carried out as described for isomer X, except that a 3.5 hr period was necessary to complete the hydrogenolysis. The resulting gum was chromatographed over 150 g of Florisil. The fractions eluted with benzene exhibited the required UV absorption and could be crystallized from MeOH to afford 284 mg of the ester XI, m.p. 117-119°. The analytical sample melted at 120-121°. UV absorption—like isomer XIV. $\lambda_{max}^{KBt} 5.70-5.82 \mu$. (Found: C, 71.52; H, 7.20. Calc. for C₂₃H₂₅O₅: C, 71.33; H, 7.08%.) 3,6-Dimethoxy-1,3,5(10),6,8,14-estrahexaene- 17β -carboxylic acid methyl ester (III). A soln of 123 mg of the ester XII in 11 ml of AcOH and 13 ml of conc HCl was refluxed for 10 hr. The soln was taken to dryness *in vacuo* and the residue was dried by azeotropic distillation with benzene. The green glass was dissolved in 5 ml of MeOH, treated overnight with an excess of ethereal diazomethane and the product was chromatographed on 4 g of Florisil. The fractions eluted with 5% benzene in pet. ether were crystallized from MeOH to afford 57 mg, m.p. 186–187° (reported¹ 188–189°), identical (IR, UV, TLC) with an authentic sample of III.

1-(6-Methoxy-2-naphthyl) 2-methyl-2-carbomethoxymethyl-3-carbomethoxycyclopentanol (XVb) To a soln of Vc (obtained by esterification of 20 g of the acid Va with diazomethane) in 50 ml of absolute ether kept at -10° was forced under N a soln of 1·18 equiv of 6-methoxy-2-naphthyllithium prepared as described.⁷ The stirred mixture was allowed to come to room temp, then stirred for additional 2 hr and finally cautiously treated with cooling with dil HCl. The organic layer was separated, washed with water, evaporated, and the residual oil refluxed for 3 hr with a soln of 50 g KOH in 700 ml of EtOH. The soln was taken to a low volume *in vacuo*, 300 ml water was added and the ppt was filtered off. It was further washed with 5% KOH, water, and was dried to furnish 10 g of a solid, m.p. 106°, shown to be the starting 2-bromo-6-methoxynaphthalene. The alkaline filtrate and washings were acidified with HCl and the precipitated oil was taken up in ether, washed with water and esterified with diazomethane. Chromatography over 300 g of Florisil gave, with pet. ether-benzene (1:1) and benzene, 2·3 g of the crude XVb, m.p. 120-123°. Recrystallization from ether afforded a sample m.p. 122-124°, $\lambda_{max}^{max} 2·90$, 5·73 and 5·78 μ . (Found: C, 68·29; H, 6·71. Calc. for C₁₂H₁₈₀O₈: C, 68·38; H, 6·78%.)

1-Methyl-1-carbomethoxymethyl-2-(6-methoxy-2-naphthyl) 5-carbomethoxycyclopent-2-ene (XVIII). A soln of 430 mg of XVb and of 1 g of p-toluenesulfonic acid in 85 ml benzene was refluxed for 1 hr. The cooled mixture was washed with water, dilute NaHCO₃aq and evaporated to afford an oil, which on trituration with a little MeOH deposited 130 mg of a solid, m.p. 108-109°. Chromatography of the filtrate over Florisil afforded (with 20% benzene in pet. ether) additional 120 mg of the same material. The analytical sample (MeOH) melted at 110-111°; λ_{mex}^{BED} 234, 286 and 330 m μ (e 57,500, 8,450 and 1470); λ_{max}^{BBT} 5.75 μ (broad). (Found: C, 71.75; H, 6.60; Calc. for C₃₅H₂₄O₅: C, 71.72; H, 6.57%.)

Fractions eluted with more polar mixtures of solvents consisted of oily material exhibiting lactone absorption at 5.60 μ .

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