Tetrahedron. Vol 24, pp 5421 to 5424 Pergamon Press 1968 Printed in Great Britain

THE SYNTHESIS OF METHYL 5-HYDROXY-2-METHYL-3-OXO-1-CYCLOPENTENE-1-CARBOXYLATE

THE METHYL ESTER OF A PICROTOXININ DEGRADATION PRODUCT

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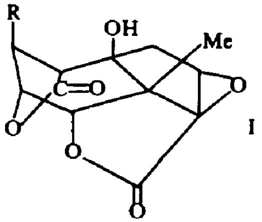
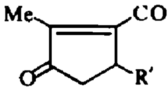
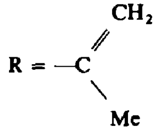
(*Received in USA* 9 *February* 1968; *received in the UK for publication* 21 *March* 1968)

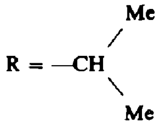
Abstract—The known methyl 2-methyl-3-oxo-1-cyclopentene carboxylate was acetoxylated by reaction with N-bromosuccinimide and subsequent treatment with silver acetate. Methanolysis of this acetoxy compound yielded methyl 5-hydroxy-2-methyl-3-oxo-1-cyclopentene carboxylate. Reaction of silver 3,5-dinitrobenzoate with the intermediate bromo compound yielded the corresponding 3,5-dinitrobenzoate, which was identical with that derived from a picrotoxinin degradation product.

PICROTOXININ (Ia) occurs naturally as a difficulty separable molecular complex with picrotin. This complex, picrotoxin, has been shown to be a powerful analeptic.[1] The pharmacological properties of picrotoxin are associated with picrotoxinin (Ia) as picrotin is inactive. Understandably, the chemistry of picrotoxin in (Ia) has been the subject of several investigations.[2-4]

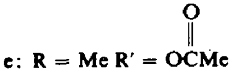

I

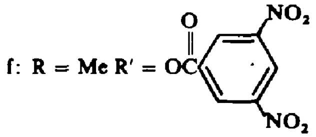

II

a:

$R = -C(=CH_2)Me$

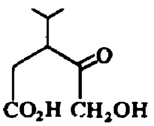
b:

$R = -CH(Me)_2$

a: R = H R′ = OH
b: R = R′ = H
c: R = Me R′ = H
d: R = Me R′ = Br


e: $R = Me\ R' = OC(=O)Me$


f: $R = Me\ R' = OC(=O)C_6H_3(NO_2)_2$

g: R = Me R′ = OH


III

One of the key experiments which led to the structural elucidation of picrotoxinin (Ia)[4,5] was the base catalyzed degradation of dihydro-α-picrotoxinin[6] (Ib) which yielded a pair of acids IIa and III thus accounting for all the C atoms of picrotoxinin and providing important clues for the positions of oxygenation. The structural proposals by Conroy[4,5] have received additional support by an X-ray structure analysis of α-bromopicrotoxinin.[7]

The structure of acid IIa can thus be considered to be secure in view of its derivation from the natural product by a very reasonable mechanism.[8] Earlier attempts,[9] before the structure of picrotoxinin was elucidated, to establish the structure of acid IIa by synthesis were unsuccessful. Subsequently, a method for the allylic acetoxylation of cyclopentenones has been described.[10] As one of us has developed an interest in the chemistry of 4-hydroxycyclopentenones, it was decided to reinvestigate the synthesis of acid IIa.

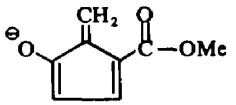
The synthesis of 2-methyl-3-oxo-1-cyclopentene carboxylic acid (IIb) also obtained as a picrotoxinin degradation product[6] has already been described.[11] Reaction of its methyl ester (IIc) with N-bromosuccinimide in refluxing carbon tetrachloride proceeded well. The intermediate bromo compound IId was used without purification. Reflux in acetic acid containing silver acetate converted it to beautifully crystalline acetoxy compound IIe. Remarkably large crystals can be obtained by slow evaporation of pentane solutions containing this compound. Methanolysis by methanolic hydrochloric acid yielded the desired methyl 5-hydroxy-2-methyl-3-oxo-1-cyclopentene carboxylate (IIg) as an oil. This was characterized as its semicarbazone. Acylation of this hydroxy ester (IIg) by 3,5-dinitrobenzoyl chloride yielded a crystalline 3,5-dinitrobenzoate (IIf) identical with that derived from the degradation acid methyl ester.[12,*]

This same 3,5-dinitrobenzoate (IIf) could also be obtained, albeit in low yield, by the direct reaction of the intermediate bromo compound (IId) with silver 3,5-dinitrobenzoate.

As the structure of the degradation acid IIa rests upon the securely established structure of picrotoxinin, the identity of the synthetic and naturally derived compounds assures us that acetoxylation of the Newman ester IIc has occurred allylically.[†]

The NMR spectrum of the acetoxy ester (IIe) is quite simple, a single peak for the methyl ester (3·90 δ, 3) and acetate (2·08 δ), with the Me doublet (2·12 δ $J = 2$ c/s) partly overlapping the acetate. The Me signal doublet is due to long range splitting by the single allylic proton. This provides additional support for the allylic position of the acetoxy group. The remainder of the spectrum can be described as an ABX, the X proton being centered at 6·15 δ.

One unusual reaction of both IIe and IIf, not observed with the hydroxy cyclo-



IV

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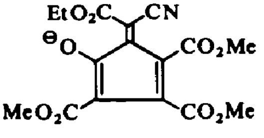
[*] We are grateful to Dr. M. Sutter, CIBA Ltd., Basel, for providing us with this and the other comparison samples.

[†] In contradistinction to a related cyclopentenone under investigation at this time. (N. Finch, unpublished observations).

pentenone (IIg) is the immediate formation of a deep red color on treatment of a methanolic solution with base. Spectroscopically this corresponds to a change from λ_{max} 240 mμ to λ_{max} 252 mμ and λ_{max} 412 mμ. Most probably this represents the formation of a cyclopentadienone enolate (IV). Cyclopentadienone enolates of a related type V have intense color[13] [λ_{max} 625 mμ (ε = 1660)].



V

EXPERIMENTAL

M.ps are uncorrected. NMR spectra were determined in $CDCl_3$ with TMS as an internal standard on a Varian A60 apparatus.

Methyl 2-methyl-3-oxo-1-cyclopentenecarboxylate (IIc) was prepared as described by Newman, by reesterification of the crystalline acid and redistillation of the resultant product; b.p. 80–82° at 1·5 mm.

Methyl 4-acetoxy-2-methyl-3-oxo-1-cyclopentanecarboxylate (IIe). Methyl 2-methyl-3-oxo-1-cyclopentenecarboxylate (3·350 g, 21·8 mmoles) was dissolved in CCl_4 (60 ml) and N-bromosuccinimide (4·82 g, 27·1 mmoles) added. The mixture was brought to reflux and a few crystals of initiator (azo-*bis*-butyronitrile) added. The soln darkened slowly and then suddenly, after about 15 min reflux, it cleared rapidly. Heating was discontinued and the floating succinimide (2·30 g, 24·1 mmoles) removed by filtration. Removal of the CCl_4 from the filtrate gave an oil (6·2 g), which moved slightly faster than the starting material on silica gel plates eluted by $CHCl_3$.

This crude bromo compound was refluxed in AcOH (20 ml) with AgOAc (7 g) for 45 min. The reaction mixture was poured into excess cold 10% $KHCO_3$aq and extracted with ether. Removal of the ether gave an oil (3·10 g). This was distilled to yield a main fraction; (1·77 g) b.p. 100° at 0·15 mm. This water-white oil crystallized on standing. Recrystallization from petrol ether gave 1·18 g, m.p. 67–69°.

An additional crystallization yielded an analytical sample: m.p. 70–71°, $\nu_{max}^{CHCl_3}$ 1726 cm^{-1} (s, ester C═O); 1230 cm^{-1} (s, acetate C—O). λ_{max}^{MeOH} 240 mμ (ε = 9160). NMR 6·15 δ (m, 1H), 3·90 δ (s, 3H), 2·12 δ (d, J = 2 c/s, 3H), 2·08 δ (s, 3H). (Found: C, 56·60; H, 5·74. Calc. for $C_{10}H_{12}O_5$: C, 56·60; H, 5·70%).

Methyl 4-hydroxy-2-methyl-3-oxo-1-cyclopentanecarboxylate (IIg). The ester IIe (500 mg, 2·36 mmole) was dissolved in MeOH (7 ml) and conc. HCl (7 ml) was added. The mixture was allowed to stand at room temp for 18 hr. Salt soln was added and the mixture was extracted continuously by ether. Removal of the ether gave an oil (380 mg, 2·24 mmoles) slower moving than the starting material on silica gel plates eluted by $CHCl_3$, ν_{max}^{film} 3450 cm^{-1} (m, broad, OH); 1720 cm^{-1} (s, ester C═O); 1650 cm^{-1} (w, C═C). We were unable to obtain a satisfactory elemental analysis on this oil.

It was however, readily characterized as the semicarbazone: m.p. 240° (dec); ν_{max}^{Nujol} 3400 cm^{-1} (m, OH); 1700 cm^{-1} (s, broad, ester C═O and semicarbazone C═O); λ_{max}^{MeOH} 291 mμ (ε = 24,390). (Found: C, 47·77; H, 6·12. Calc. for $C_9H_{13}N_3O_4$: C, 47·57; H, 5·77%).

Acylation by 3,5-dinitrobenzoyl chloride and pyridine[13] gave a crystalline 3,5-dinitrobenzoate, m.p. 98–100°, which did not depress the m.p. of a sample from Dr. Sutter.[*] Identity was verified by comparison of the IR spectra ($CHCl_3$ solns).

Methyl 4-3,5-dinitrobenzoyloxy-2-methyl-3-oxo-1-cyclopentenecarboxylate (IIf). 3,5-Dinitrobenzoic acid (3·234 g) was dissolved in acetonitrile (50 ml) and Ag_2O (3·536 g) added. The mixture was warmed on a steam bath; slowly the bulk of the oxide dissolved (30 min). The soln was filtered. The filtrate on cooling deposited crystals of silver 3,5-dinitrobenzoate, m.p. 325°.

A portion of the crude IId (1·618 g) from reacting NBS with the keto ester IIc was added to a hot soln of the above Ag salt (2·50 g) and 3,5-dinitrobenzoic acid (3 g) in acetonitrile (60 ml). The reaction was refluxed for 1 hr. The reaction was filtered to remove the ppt (845 mg); the filtrate was taken to dryness and extracted by ether. The total ether was washed by 10% $KHCO_3$aq. Removal of the ether gave a gum

[*] In our apparatus Dr. Sutter's sample had a m.p. 99–101°, reported[12] 106°.

(1·60 g). A portion of this material (108 mg) was put onto four 5 × 8 cm plates coated with 1 mm of silica gel HF. The plates were eluted by $CHCl_3$ and the central UV visible band cut out and eluted by CH_2Cl_2 containing 10% MeOH. The material obtained this way (27 mg) was crystallized from hexane–$CHCl_3$; the first crop was discarded. From the mother liquors were obtained beautiful crystals, m.p. 93–98°. Recrystallization gave 3 mg, m.p. 98–100°, identical with that obtained by 3,5-dinitrobenzoylation of IIg and the sample obtained from Dr. Sutter (IR and mixed m.p.).

Acknowledgements—We thank Mr. L. Dorfman for helpful advice and his staff for Microanalyses and spectra. We would like to acknowledge help from Mr. John Nebzydoski with the preparation of 2-methyl-3-oxo-1-cyclopentene carboxylic acid.

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