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SYNTHESIS OF DIMETHYL THAMNOLATE AND DIMETHYL HYPOTHAMNOLATE

K. AGHORAMURTHY, T. R. SESHADRI and G. B. VENKATASUBRAMANIAN
Department of Chemistry, University of Delhi, Delhi 8, India

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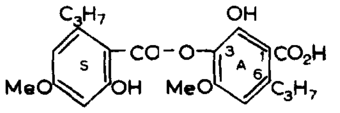
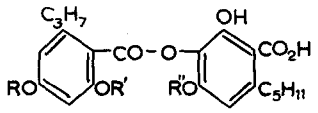
Abstract—Methyl 5-hydroxyhaematommate (XIX) and methyl 5-hydroxy-β-orcinolcarboxylate (XII) are conveniently made by the application of paranuclear oxidation using methyl haematommate and methyl β-orcinol carboxylate respectively. These undergo preferential acylation of the hydroxyl in the *meta* (5) position and by employing this property, syntheses of dimethyl thamnolate (XVIII) and dimethyl hypothamnolate (VII) have been accomplished.

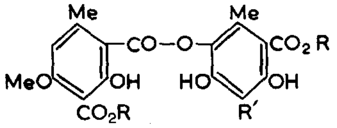
IN an earlier paper[1] on the biogenesis of lichen depsides and depsidones, it was pointed out that *meta* depsides were invariably produced when the orcinol unit forming the right half (A of formula I) had undergone nuclear oxidation involving the 3 or the 5 position. Both types are known. Sekikaic acid (I), homosekikaic acid (II), ramalinolic adid (III) and boninic acid (IV) are examples of the first type, and the orcinol unit forming the A part provides a *meta* hydroxyl group in the 3 position. Thamnolic acid (V) and hypothamnolic acid (VI) belong to the second type, where the *meta* hydroxyl group is in the 5 position; the unit involved is a β-orcinol derivative and hence only the 5 position can undergo oxidation.



I



II, R=R''=OMe; R'=H
III, R=OMe; R'=R''=H
IV, R=R'=R''=OMe



V, R=H; R'=CHO VI, R=H; R'=Me
VII, R=R'=Me XVIII, R=Me; R'=CHO

After a consideration of the reactivity of the concerned positions, the view was expressed that nuclear oxidation takes place in the C_8 (orsellinic) unit prior to the depside formation and since a *meta* hydroxyl group is thus rendered available, a *meta* depside results. It was definitely implied that a *meta* depside is more favoured as compared with a *para* depside and that it is formed directly from the C_8 components. The correctness of the above view was supported by the war-time publication, which came to our notice much later, describing the laboratory synthesis of ramalinolic acid (III)[2] and dimethyl hypothamnolate (VII),[3] in which use was made of the preferential *meta* acylation.

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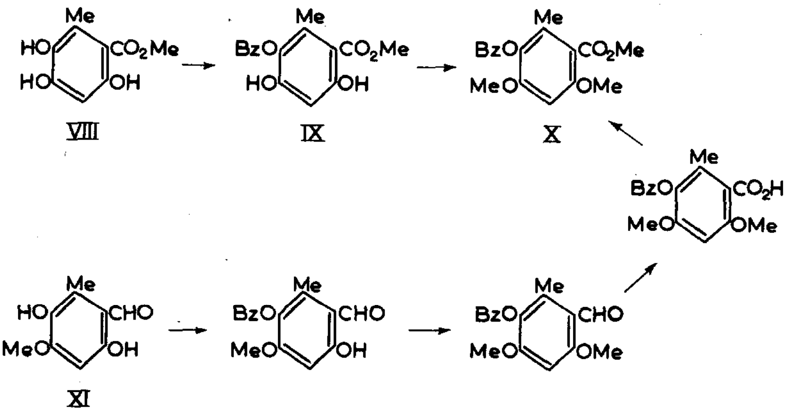
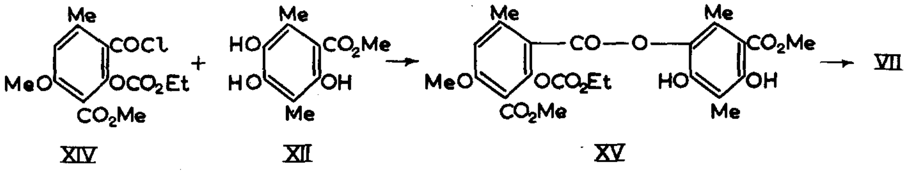
[1] T. R. Seshadri *Proc. Indian Acad. Sci.* A **19**, 1 (1944).
[2] Y. Asahina and T. Kusaka *Ber. Dtsch. Chem. Ges.* **69**, 1896 (1936).
[3] Y. Asahina, F. Fuzikawa and H. Aoki *Ber. Dtsch. Chem. Ges.* **74**, 824 (1941).

In continuation of our earlier paper on the role of nuclear oxidation in the biogenesis of lichen acids,[4] the synthesis of dimethyl hypothamnolate (VII) has now been re-examined with the result that considerable simplification has been effected. Further by these means, the synthesis of a more complex *meta* depside viz., thamnolic acid (V) as its dimethyl ester (XVIII) has also been accomplished.

In exploratory experiments, a simpler case studied was the monobenzoylation of methyl 5-hydroxyorsellinate (VIII). The product obtained contained the benzoyl group linked to the 5-hydroxyl group (IX), since on complete methylation, it yielded a dimethyl ether which agreed with methyl 2 : 4-dimethoxy-5-benzoyloxy-6-methylbenzoate (X) prepared earlier by Asahina and Kusaka[5] by a different and unambiguous route. They started from 2 : 5-dihydroxy-4-methoxy-6-methylbenzaldehyde (XI) and proceeded through the stages indicated below.



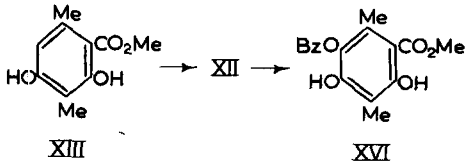
The next example studied was the mono-acylation of methyl 5-hydroxy-β-orcinolcarboxylate (XII). This compound has now been readily obtained by the nuclear oxidation of methyl β-orcinolcarboxylate (XIII) with alkaline potassium persulphate. The earlier synthesis of this compound was made starting from *p*-xyloquinone and passing through a large number of steps.[3] Condensation of (XII) with one mole of 2-ethylcarbonato-3-carbomethoxy-4-methoxy-6-methylbenzoyl chloride (XIV), prepared by the method of Asahina *et al.*,[3] gave the carboethoxy derivative of dimethyl hypothamnolate (XV), which on decarboethoxylation gave dimethyl hypothamnolate (VII).



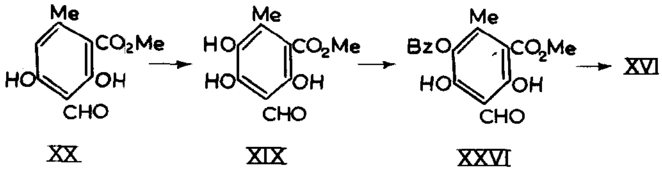
The monobenzoylation of methyl 5-hydroxy-β-orcinolcarboxylate (XII) has also been carried out and on the basis of the above analogy, the benzoyl group has been considered to be linked in the 5 position (XVI). This has been used later as a reference compound.

[4] K. Aghoramurthy and T. R. Seshadri *Proc. Indian Acad. Sci.* A **35**, 327 (1952).

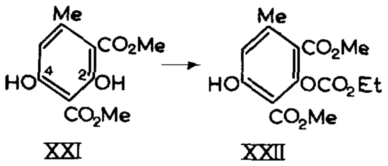
[5] Y. Asahina and T. Kusaka *Bull. Chem. Soc. Japan* **17**, 158 (1942).



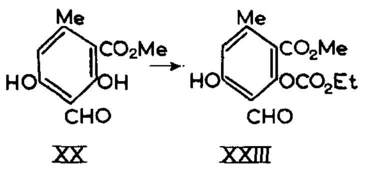
For the synthesis of dimethyl thamnolate (XVIII), in which the part A contains an aldehydic group instead of the methyl group, two points had to be worked out: (i) the preparation of methyl 5-hydroxyhaematommate (XIX), and (ii) the depside condensation with this compound. The preparation of (XIX) has been achieved in a simple manner by the nuclear oxidation of methyl haematommate (XX).

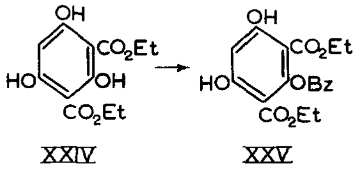


Some difficulty was expected in the second step owing to the influence of the carbonyl of the aldehyde group, which in certain cases has been considered to activate the hydroxyl group in the 2 position over that in the 4 position. Thus, Asahina and Yanagita[6] and Asahina and Sakurai[7] have found that the monocarboethoxylation of dimethyl orcinol-2 : 4-dicarboxylate (XXI) yields the 2-carboethoxy derivative (XXII).



Similarly, the monocarboethoxylation of methyl haematommate (XX) has been shown to yield the 2-monocarboethoxy derivative (XXIII).[7] The monobenzoylation of ethyl phloroglucinoldicarboxylate (XXIV) has also been reported to yield the 2-mono benzoyl derivative (XXV).





In order to make sure of the position of partial acylation, the monobenzoylation of methyl 5-hydroxyhaematommate (XIX) was first effected. The monobenzoyl derivative, when subjected to the Clemmensen reduction yielded a compound identical with the one obtained by the partial benzoylation of methyl 5-hydroxy-β-orcinolcarboxylate viz., (XVI). Hence, in the case of methyl 5-hydroxyhaematommate also, the benzoyl group should have entered the 5 position (XXVI), and the projected synthesis of

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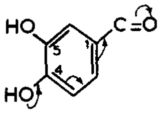
[6] Y. Asahina and M. Yanagita *Ber. Dtsch. Chem. Ges.* **66**, 393 (1933).

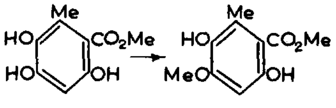
[7] Y. Asahina and Y. Sakurai *Ber. Dtsch. Chem. Ges.* **71**, 2561 (1938).

dimethyl thamnolate seemed to be feasible. Condensation of the acid chloride (XIV) with methyl 5-hydroxyhaematommate (XIX) yielded a carboethoxy derivative which on decarboethoxylation yielded dimethyl thamnolate (XVIII) identical in every respect with a specimen prepared by the controlled esterification of naturally occurring thamnolic acid (V) with diazomethane, according to the method of Asahina *et al.*[3]

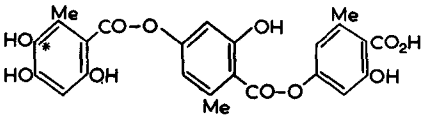
Besides what has been mentioned above regarding the preferential formation and greater stability of *meta* depsides, may be mentioned the earlier work of Fischer and co-workers[9] on the formation of gallic acid *meta* depsides by the transformation of the *para* isomers. Recently, Critchlow, Haworth, and Pauson[10] observed a similar transformation in the case of 4-benzoylpyrogallolcarboxylic acid also. No satisfactory explanation seems to have been offered so far for the preferential formation of the *meta* depsides or for their greater stability. The following tentative explanation is now suggested. As a result of the electromeric polarisation initiated by the C═O group in the structure (XXVII), the hydroxyl group in the *para* (4) position will become more acidic whereas the one in the *meta* (5) position will be unaffected. Consequently an ester involving the *para* hydroxyl will have part of the instability of an anhydride, whereas the one involving the *meta* hydroxyl will be more akin to an ester and thus be more stable. The reactivity of these hydroxyl groups towards methylation supports the above views. A *para* hydroxyl group, being more acidic, should be methylated with greater ease, whereas the *meta* one should be less reactive. This is actually found to be the case, Thus methyl 5-hydroxyorsellinate (VIII) on partial methylation has now been found to give the 4-methyl ether (XXVIII). A similar case is hiascinic acid (XXIX). It has been reported that the *meta* hydroxyl group marked with an asterisk in (XXIX) is resistant to methylation.[5] The behaviour of aesculetin (XXX) towards partial methylation and partial benzoylation also follows a similar course. Partial methylation gives the 7-monomethyl ether[11] (XXXI) whereas partial benzoylation gives the 6-benzoyl derivative[12] (XXXII). In this case the influence of the C═O group is transmitted to the benzene ring through the ethylenic link present in conjugation.



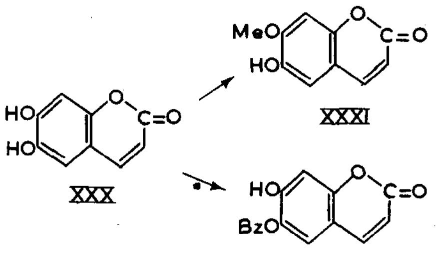
XXVII



VIII XXVIII



XXIX



XXX XXXI XXXII

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[8] H. Leuchs and I. Waldorf *Ann.* **460**, 1 (1928).
[9] E. Fischer, M. Bergmann and W. Lipschitz *Ber. Dtsch. Chem. Ges.* **51**, 45 (1918).
[10] A. Critchlow, R. D. Haworth and L. Pauson *J. Chem. Soc.* 1321 (1951).
[11] G. Bargellini and L. Monti *Gazzetta* **45**, 97 (1915).
[12] F. S. H. Head and A. Robertson *J. Chem. Soc.* 1266 (1939).

EXPERIMENTAL

Methyl 5-benzoyloxyorsellinate (IX)

A mixture of methyl 2 : 4 : 5-trihydroxy-6-methylbenzoate[4] (2 g), benzoyl chloride (1·4 cm^3) and pyridine (2 cm^3) in dry ether (100 cm^3) was left at room temperature for 18 hr. The ether solution was washed successively with dilute hydrochloric acid, water, and saturated sodium hydrogen carbonate solution and dried. Evaporation of ether gave the *benzoate* as a solid which crystallised from methanol as colourless prisms and needles, m.p. 212–213° (2 g) (Found: C, 63·9; H, 4·6. $C_{16}H_{14}O_6$ requires C, 63·6; H, 4·6 per cent). It produced a blue colour with ferric chloride and a yellow solution with aqueous sodium hydroxide.

Methyl 2 : 4-dimethoxy-5-benzoyloxy-6-methylbenzoate (X)

Methylation of the above ester with dimethyl sulphate by the acetone–potassium carbonate method for 12 hr gave the dimethyl ether, which crystallised from alcohol as rectangular tablets, m.p. 156–57°. It did not give any colour with ferric chloride or aqueous sodium hydroxide. Asahina and Kusaka[5] gave the same m.p.

Methyl 5-hydroxy-β-orcinolcarboxylate (XII)

A solution of methyl β-orcinolcarboxylate[13] (5 g) in aqueous sodium hydroxide (10 per cent; 40 cm^3) was treated at 0° with stirring for 2 hr with aqueous potassium persulphate (6 per cent; 100 cm^3); the mixture was kept at room temperature for 24 hr, acidified to Congo-red with concentrated hydrochloric acid, and extracted with ether (5 × 100 cm^3). The ethereal extracts were dried and evaporated to yield the unchanged ester (1 g). The aqueous solution was treated with more concentrated hydrochloric acid (30 cm^3) and sodium sulphite (2 g), heated at 80° for 1 hr, cooled, saturated with sodium chloride, and extracted with ether (5 × 200 cm^3). The ether extracts were dried and evaporated and the solid residue was crystallised from ethyl acetate–light petroleum (40–60°). The *hydroxy ester* was obtained as colourless needles, m.p. 151–152°. Asahina *et al.* gave the same m.p. It gave a red-brown colour with ferric chloride and a purple colour with traces of alkali. The triacetate formed colourless needles from ethyl acetate–light petroleum (40–60°) m.p. 197–198°. Asahina *et al.* (*loc. cit*) gave the same m.p.

Dimethyl hypothamnolate (VII)

A mixture of 2-ethylcarbonato-3-carbomethoxy-4-methoxy-6-methylbenzoyl chloride[3] (0·55 g), methyl 5-hydroxy-β-orcinolcarboxylate (0·35 g) and pyridine (5 cm^3) in dry ether (100 cm^3) was left at room temperature for 20 hr. The ether solution was washed successively with dilute hydrochloric acid, water and saturated sodium hydrogen carbonate solution. The residue obtained on evaporation of the ether was dissolved in acetone (10 cm^3), treated with N sodium hydroxide (20 cm^3) and kept at room temperature in a hydrogen atmosphere for 1 hr. Acidification with dilute hydrochloric acid gave dimethyl hypothamnolate which crystallised from benzene as colourless prismatic needles, m.p. 200° (Found: C, 57·8; H, 5·3. Calc. for $C_{21}H_{22}O_{10}$, C, 58·1; H, 5·1 per cent). It gave a purple colour with ferric chloride and a purple

[13] W. B. Whalley *J. Chem. Soc.* 3278 (1949).

solution with alkalis. Asahina *et al.*[3] gave the m.p. 197–198° and reported similar colour reactions.

Methyl 5-benzoyloxy-β-orcinolcarboxylate (XVI)

The condensation of benzoyl chloride with methyl 5-hydroxy-β-orcinolcarboxylate was carried out as described previously using equimolar quantities of reactants. The *monobenzoate* crystallised from benzene as colourless needles, m.p. 176–177° (Found: C, 64·3; H, 5·2. $C_{17}H_{16}O_6$ requires, C, 64·6; H, 5·1 per cent). It gave a transient purple colour with ferric chloride and a purple solution with alkalis.

Methyl 5-hydroxyhaematommate (XIX)

The experimental procedure was similar to that described for methyl 5-hydroxy-β-orcinolcarboxylate. Methyl haematommate[14] (6 g) yielded unchanged material (1 g) and *methyl 5-hydroxyhaematommate* (1·5 g), yellow prisms (from ethyl acetate), m.p. 150–152° (Found: C, 53·7; H, 5·0. $C_{10}H_{10}O_6$ requires C, 53·1; H, 4·4 per cent). It gave an intense green colour with alcoholic ferric chloride and a yellow solution with alkalis.

Methyl 5-benzoyloxyhaematommate (XXVI)

The condensation of benzoyl chloride and methyl 5-hydroxyhaematommate was carried out using equimolar quantities as described before. The *benzoate* crystallised from alcohol as colourless flat needles, m.p. 152–154° (Found: C, 62·2; H, 4·5. $C_{17}H_{14}O_7$ requires, C, 61·8; H, 4·3 per cent). It gave wine-red colour with alcoholic ferric chloride and a yellow solution with alkalis.

Methyl 5-benzoyloxy-β-orcinolcarboxylate (XVI) *by Clemmensen Reduction*

To a mixture of the above benzoate (1 g) and zinc amalgam (20 g) in alcohol (25 cm^3), was added dilute hydrochloric acid (2 : 1; 30 cm^3), and the contents were refluxed for ½ hr. The amalgam was removed by filtration. The filtrate on cooling gave *methyl 5-benzoyloxy-β-orcinolcarboxylate* which crystallised from benzene as shiny thin needles, m.p. 176–177° alone or on admixture with the sample described previously.

Dimethyl thamnolate (XVIII)

The condensation of 2-ethylcarbonato-3-carbomethoxy-4-methoxy-6-methylbenzoyl chloride (0·75g) with methyl 5-hydroxyhaematommate (0·5 g) was carried out as described in the case of dimethyl hypothamnolate. Dimethyl thamnolate was obtained as colourless prisms from benzene–light petroleum, m.p. 160° (Found: C, 56·4; H, 4·9. Calc. for $C_{21}H_{20}O_{11}$, C, 56·3; H, 4·5 per cent). It gave a wine-red colour with ferric chloride and a yellow solution with alkalis. A mixed m.p. with an authentic specimen of dimethyl thamnolate, m.p. 158° prepared from thamnolic acid by esterification with diazomethane according to the method of Asahina *et al.*[3] showed no depression. The infra-red spectra in chloroform solution of the natural and synthetic specimens were identical in the 5–7 μ region.

Methyl 2:5-dihydroxy-4-methoxy-6-methylbenzoate (XXVIII)

A solution of methyl 5-hydroxyorsellinate (0·6 g; 1 mol.) and dimethyl sulphate (0·3 cm^3; 1 mol.) in dry acetone (50 cm^3) was refluxed with anhydrous potassium

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[14] V. V. K. Sastri and T. R. Seshadri *Proc. Indian Acad. Sci.* A **12**, 502 (1940).

carbonate (2 g) for 12 hr. The acetone solution on evaporation yielded the methyl ether as a solid which crystallised from alcohol as colourless needles, m.p. 154°. A mixed m.p. with an authentic specimen of (XXVIII) described in an earlier paper[4] showed no depression. It gave a transient blue colour with ferric chloride which changed into green.

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