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Short Communications

Naturally Occurring Lactones and Lactames. IV. Friedel-Crafts Acylation of the Tetronic Acid Nucleus and Synthesis of (*S*)-Carolic Acid

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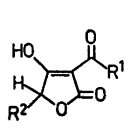
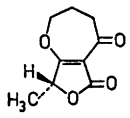
This note is concerned with the Friedel-Crafts acylation of the tetronic acid nucleus as part of our attempt to develop general methods for the synthesis of the more complex mold tetronic acids. The application of this reaction has previously been reported by Haynes and Jamieson,[1] who found that only 3,3-substituted tetronic acids and 3-phenyltetronic acid (in 20 % yield) could be acylated, whereas 5-methyltetronic acid, which is naturally occurring and a possible precursor to some mold tetronic acids, underwent no acylation. Recently Bloomer and Kappler [2] reported the acylation of 5-methyltetronic acid to 3-butyryl-5-methyltetronic acid and to (*RS*)-carolic acid, just as they have synthesized (*R*)-carolic acid by acylating (*R*)-5-methyltetronic acid obtained by degradation of naturally occurring (*R*)-carolic acid.[3]



(1)



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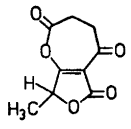

(3)

By modifying the acylation procedure of Haynes and Jamieson [1] we were able to acylate the tetronic acids (*1*) listed in Table 1. Furthermore, acylating (*S*)-5-methyltetronic acid, synthesized from ethyl (*S*)-lactate,[4] with 4-chlorobutyryl chloride, we obtained (*S*)-carolic acid identical in all respects with authentic carolic acid (*3*) isolated from *Penicillium charlesii* except for the specific rotation, which was of opposite sign.

It should be mentioned that in accordance with Haynes and Jamieson [1] cyclohexane-spiro-5-tetronic acid appeared not to undergo acylation.

Attempts to synthesize (*R,S*)-carolinic acid (*3*) from 5-methyltetronic acid by acylating with β-carbomethoxypropionyl chloride was not met with success. On working up the reaction mixture only succinic anhydride could be isolated.

Experimental. Standard acylation procedure. To 2.0 mmol tetronic acid and 2.2 mmol of the appropriate acid chloride was added 3 mmol of tin (IV) chloride. The solution was kept at room temperature for about 2 min to allow the

Table 1.

Compound	R^1	R^2	M.p.	M.p. lit. val.	Yield %
3-Acetyltetronic acid (*1*)	CH_3	H	78.0 – 80.2	79.5 – 80.5[7]	39
3-Propionyltetronic acid (*1*)	CH_3CH_2	H	94.0 – 96.0		64
3-Acetyl-5-methyltetronic acid (*1*)	CH_3	CH_3	56.0 – 57.5		44
3-Propionyl-5-methyltetronic acid (*1*)	CH_3CH_2	CH_3	64.5 – 65.5		75
3-Butyryl-5-methyltetronic acid (*1*)	$CH_3CH_2CH_2$	CH_3	40.0 – 42.0		93
3-Isobutyryl-5-methyltetronic acid (*1*)	$(CH_3)_2CH$	CH_3	50.0 – 51.5		70
3-Phenylacetyl-5-methyltetronic acid (*1*)	$C_6H_5CH_2$	CH_3	78.5 – 80.5		49
3-Propionyl-5-ethyltetronic acid (*1*)	CH_3CH_2	CH_3	55.0 – 57.5		68
3-Acetyl-5-phenyltetronic acid (*1*)	CH_3	C_6H_5	100 – 103	102 – 104[1]	86
(*RS*)-Carolic acid			116 – 118	117[5]	5
(*S*)-Carolic acid			130 – 132	132[6]	14

formation of an enol ester and was then heated to 110° and maintained at this temperature for 3 h. After cooling, the mixture was poured into ice-cold 4 N hydrochloric acid and extracted repeatedly with chloroform, and the extract was shaken with concentrated aqueous sodium hydrogen carbonate. The aqueous layer was acidified with conc. hydrochloric acid and extracted with chloroform. The dried chloroform extract gave on evaporation the pure 3-acylated tetronic acid. Only 3-acetyl- and 3-propionyl-tetronic acid had to be recrystallized from petrol ether.

(R,S)-*Carolic acid.* 5-Methyltetronic acid (4.38 mmol) was acetylated with 500 mmol of 4-chlorobutyryl chloride to give 0.47 g of dark red oil, which solidified when treated with ether. Four recrystallizations from ethyl acetate-light petrol gave 50 mg (5 %) of amber coloured crystals, m.p. 112.5–115.2°. Sublimation rised the m.p. to 116–118°. ^{1}H NMR in $CDCl_3$: 1.46 d (CH_3), 4.64 q (H), 3.45 t ($COCH_2$), 2.28 m ($CH_2CH_2CH_3$), 4.80 t (CH_2O). M_{MS} = 182.05843; M_{calc} = 182.0579 (Lit. [5] m.p. 117°).

(S)-*Carolic acid.* Acylation of 2 mmol of synthetic (*S*)-5-methyltetronic acid [4] resulted in the isolation of 70 mg (14 %) colourless crystals m.p. 130–132° (Lit.[6] 132°). $[\alpha]_{546}^{25}$ −70.8° (c = 0.49, H_2O) (Lit. val. for the enantiomeric form +84°) ^{1}H NMR as above.

Attempted synthesis of (R,S)-*carolinic acid (3).* 5-Methyltetronic acid (4.38 mmol), 5.0 mmol of β-carbethoxypropionyl chloride and 6.50 mmol of tin(IV) chloride reacted very slowly and did not become homogeneous. On working up about 100 mg of a yellow syrupy reaction product was obtained. On acid hydrolysis and extraction with a small amount of chloroform, the chloroform extract contained only succinic anhydride.

1. Haynes, L. J. and Jamieson, J. W. M. *J. Chem. Soc.* (1958) 4123.
2. Bloomer, J. L. and Kappler, F. E. *Tetrahedron Lett.* (1973) 163.
3. Bloomer, J. L. and Kappler, F. E. *Personal communication.*
4. Boll, P. M., Sørensen, E. and Balieu, E. *Acta Chem. Scand. 22* (1968) 3251.
5. Haynes, L. J., Plimmer, J. R. and Stanners, A. H. *J. Chem. Soc.* (1956) 4661.
6. Clutterbuck, P. W., Raistrick, H. and Reuter, F. *Biochem. J. 29* (1935) 300.
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Tobacco Chemistry. 26. Synthesis of 14,15-Bisnor-8-hydroxylabd-11*E*-en-13-one, A New Tobacco Constituent

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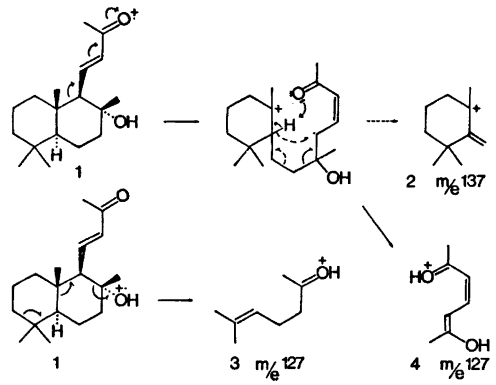
Current research in this laboratory has revealed that tobacco flavour comprises a large number of norisoprenoid constituents.[1,2] The present report deals with the identification and synthesis of a probable diterpenoid degradation product isolated from a medium-volatile, neutral fraction [3] of an extract [4] of sun-cured Greek *Nicotiana tabacum* L.

The elemental composition of this new tobacco compound, $C_{18}H_{30}O_2$, was established by high resolution mass spectrometry. The two oxygen atoms were accomodated by a *3E*-penten-2-oxo-1-ylidene moiety, >CH−CH=CH−CO−CH_3, [978 and 1661 cm^{-1}, 230 nm, δ 2.24 (3H, s), δ 6.16 (1 H, d, J 16 Hz), δ 6.82 (1 H, dd, J 10 and 16 Hz)], and a tertiary hydroxyl group (3450 cm^{-1}) attached to a methyl substituted [δ 1.26, (3 H, s)] carbon atom, >C(OH)−CH_3, respectively. Based on this evidence, the presence of three quaternary methyl groups (singlets at δ 0.83, 0.89, 0.99), its electron-impact induced fragmentation pattern being characteristic of labdane-type diterpenoids devoid of oxygen-substituents on ring A (*cf.* Scheme 1),[5] and no indication of further double bonds, 14,15-bisnor-8-hydroxy-labd-11*E*-en-13-one (*1*)** appeared likely as the structure for this new tobacco compound. This structure, including the stereochemistry inferred in *1*, was confirmed by total synthesis using drimenol [6] (*5*) as starting material.



Scheme 1.

**Nomenclature according to J. W. Rowe, Oct., 1968; personal communication.