Tetra-acetylcaffeoylputrescine: an Acetyl–Cinnamoyl Diacylamine. Nuclear Magnetic Resonance Studies of Acetyl Groups

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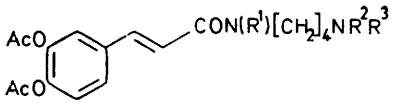
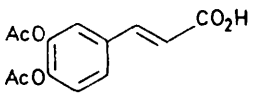
Comparison of the n.m.r. spectra of *NN'*-diacetylputrescine (6), *NNN'N'*-tetra-acetylputrescine (7), *OO'*-diacetylcaffeic acid (5), and the title compound indicate the last to have structure (4). Preparation conditions and stabilities support this conclusion.

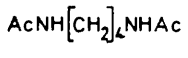
In 1894, Merck [1] reported an alkaloid from pauco nuts (*Pentaclethra macrophylla* Benth.) which he named paucine. Hollerbach and Spiteller [2,3] showed by mass spectrometry that Merck's original preparations contained caffeoylputrescine. This has since been isolated from tobacco and synthesised,[4,5] and its presence demonstrated in fresh seeds of *P. macrophylla*.[6]



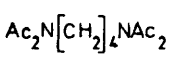
(1) $R^1 = R^2 = R^3 = Ac$
(2) $R^1 = R^2 = H$, $R^3 = Ac$
(3) $R^1 = H$, $R^2 = R^3 = Ac$
(4) $R^1 = R^2 = Ac$, $R^3 = H$



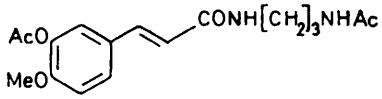
(5)



(6)



(7)



(8)

By acetylating caffeoylputrescine in acetic anhydride–pyridine we obtained a tetra-acetyl derivative agreeing with that described by Hollerbach and Spiteller.[2,3] These authors also described an unstable penta-acetyl and a triacetyl derivative, which presumably have structures (1) and (2) respectively. However, the tetra-acetyl derivative could have structure (3) or (4).

The present work was undertaken to settle this question, and has provided some additions to the scanty knowledge concerning the formation, physical properties, and stability of diacylamines. An attempt to locate the unsubstituted position in the tetra-acetyl derivative by permethylation was ineffective, because three of the four acetyl groups were replaced by methyl groups.[7]

The study of acylation of amides, pioneered by Titherley,[8] has not progressed far and there is not general agreement on reagents that promote specific substitutions.[9] Thompson [10] found that, under varying experimental conditions, he obtained either mono- or di-acylamides, or complete dehydration of the amide giving the nitrile. Using pyridine and different acid chlorides, he showed that the course of the reaction was affected by the presence of substituents on the acyl–chlorine bond, the structure of the amide, and the experimental conditions employed. Titherley [8] prepared dibenzamide in quantitative yield by the benzoylation of benzamide in pyridine solution with benzoyl chloride. Inch and Fletcher,[11] in their studies with glucosamine derivatives found benzoyl chloride in pyridine to be an effective reagent for producing *N*-benzoylation in acetamidocyclohexyl derivatives and acetamidodeoxyglucopyranoses. The same authors found isopropenyl acetate–toluene-*p*-sulphonic acid to be an effective *N*-acetylating reagent for both acetamides and benzamides. McCluer and Evans,[12] working on cerebrosides, showed that benzoyl chloride produced amide acylation which benzoic anhydride tended to avoid.

Our approach to the study of the structure of tetra-acetylcaffeoylputrescine has involved a comparison of its n.m.r. spectrum with those of the model compounds *OO'*-diacetylcaffeic acid (5), *NN'*-diacetylputrescine (6), and *NNN'N'*-tetra-acetylputrescine (7). The position of absorption of the two acetyl methyl groups in the n.m.r. spectrum of (5) should enable identification of the absorption signals due to the two corresponding groups in the n.m.r. spectrum of tetra-acetylcaffeoylputrescine. If tetra-acetylcaffeoylputrescine has structure (4), the absorption position of the NHAc methyl group should be comparable with that of the *N*-acetyl methyl groups in (6); if it has structure (3), the absorption positions of the two acetyl methyl groups in the NAc_2 fragment should

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be comparable with those of the *N*-acetyl methyl groups in (7).

RESULTS AND DISCUSSION

The data from the n.m.r. spectra of (5)—(7) and tetra-acetylcaffeoylputrescine are given in the Table. We

N.m.r. spectra of compounds (4)—(7) (90 MHz; [$^2H_6$]DMSO solution; Me_4Si internal standard)

	τ		
(4)	2.40—2.75	(m,	4H)
	3.38	(d,	1 H, *J* 16 Hz)
	6.55—7.05	(m)	*
	7.70	(s,	6 H)
	8.20	(s,	3 H)
	8.53	(m,	4 H)
(5)	2.28—2.72	(m,	4 H)
	3.45	(d,	1 H, *J* 16 Hz)
	7.70	(s,	6 H)
(6)	6.96	(t,	4 H)
	8.22	(s,	6 H)
	8.61	(quintet,	4 H)
(7)	6.37	(t,	4 H)
	7.65	(s,	12 H)
	8.50	(quintet,	4 H)

* Signal partially obscured by that due to solvent; integration unreliable.

assign the singlet at τ 7.70 (6 H) in the spectrum of tetra-acetylcaffeoylputrescine, to the two *O*-acetyl groups, by comparison with the spectrum of (5). Weinges and Piretti [13] also found, for (5) in $CDCl_3$, that these two groups absorb coincidentally at τ 7.70. The spectrum of tetra-acetylcaffeoylputrescine also shows a singlet at τ 8.20 (3 H) due to an *N*-acetyl methyl group. The similarity between this absorption and that due to the *N*-acetyl methyl groups in (6) suggests that the amino-group is monoacetylated.

We are unable to observe in the spectrum recorded in [$^2H_6$]DMSO the absorption due to the remaining *N*-acetyl methyl group. That this group is present is clearly demonstrated by the mass spectrum of the compound.[3] We conclude that this acetyl group exists in several different conformations, giving rise to several small peaks or even a broad absorption, instead of a sharp singlet. A molecular model of structure (4) shows this to be a reasonable explanation. A similar effect has been observed with the *N*-acetyl methyl signal in the n.m.r. spectrum of the *N*(2)-methyl derivative of the alkaloid chaenorhine.[14]

The absorption signals due to this remaining *N*-acetyl methyl group are obscured by the absorptions due to the α-methylene protons of the putrescine residue, and to the residual hydrogen in the solvent, thus preventing their detection by integration. Attempts to overcome this by recording the spectrum in non-interfering solvents ($CDCl_3$, [$^2H_5$]pyridine, and D_2O) were unsuccessful due to solubility problems.

Consideration of the results of the n.m.r. studies leads to the conclusion that (4) is the correct structure for tetra-acetylcaffeoylputrescine. The published spectrum of compound (8) [15] appears to support this conclusion.

Thus when the unstable penta-acetylcaffeoylputrescine obtained by Hollerbach and Spiteller [2,3] decomposes to the tetra-acetyl derivative, the acetyl group lost is from the *NN*-diacetyl group rather than from the *N*-cinnamoyl-*N*-acetyl group. The stability of diacylamines has been the subject of little study. It is recognised that, when two acyl groups are attached directly to one central atom, they render each other mutually more susceptible to attack by nucleophilic reagents. However, in such reactions involving mixed diacylamines, a mixture of products often results,[11] and there appears at present to be no explanation why one type of acyl group should be lost in preference to another.

The fact that, under the conditions we employed in the acetylation of caffeoylputrescine, putrescine itself gives the diacetyl derivative, and is converted into the tetra-acetyl only under forcing conditions, led us *a priori* to expect tetra-acetylcaffeoylputrescine to have structure (4) rather than (3). Our conclusion is further supported by Hollerbach's [3] observation that tetra-acetylputrescine is converted to diacetylputrescine by recrystallization from aqueous alcohol, whereas tetra-acetylcaffeoyl-putrescine is stable to this treatment.

EXPERIMENTAL

Preparation of Tetra-acetylcaffeoylputrescine using Pyridine–Acetic Anhydride.—To caffeoylputrescine hydrochloride (15 mg), a cooled (5°) 1 : 1 (v/v) mixture of acetic anhydride–pyridine (7 ml) was added with vigorous shaking until all the hydrochloride dissolved. The reaction flask was left at room temperature overnight, when a wine-red solution resulted. Ice-cold water (7 ml) was added with cooling and the flask was left at room temperature for 1 h to decompose the excess of acetic anhydride. It was then repeatedly evaporated with water additions (40° *in vacuo*) until pyridine was absent. The aqueous product (10 ml) was extracted with portions (4 × 10 ml) of chloroform. The evaporated residue from the pooled chloroform extracts was dried (H_2SO_4–NaOH) in a vacuum and crystallized from aqueous ethanol, m.p. 188—192° (uncorr.), yield 80%. The low-resolution mass spectrum agreed with that published by Hollerbach.[3]

Tetra-acetylputrescine (7).—This was prepared according to ref. 16 (*cf.* ref. 3), m.p. 110—111° (lit.,[16] 114°).

Diacetylputrescine (6).—This was made by acetylation of putrescine with acetic anhydride and pyridine,[3,17-21] m.p. 138° (lit.,[3] 136°).

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Diacetylcaffeic Acid (5).—This was prepared by the method of Tiemann and Nagai,[22] m.p. 197—198° (lit.,[22] 190—191°).

We thank Professor R. L. M. Synge for valuable discussion, Professor G. Spiteller for making available A. Hollerbach's thesis,[3] Mrs. B. Howard for the n.m.r. spectra, Mr. J. Eagles for the mass spectra, and the Federal Nigerian Government for a Research Scholarship to E. I. M.

5/1453 *Received*, 23*rd July*, 1975]

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