4-Acetyl-3-benzylidenepiperazine-2,5-diones

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Cyclisation of (*N*-acetyldidehydrophenylalanyl)sarcosine with acetic anhydride at 75° has furnished the hitherto unknown 4-acetyl-3-*trans*-benzylidene-1-methylpiperazine-2,5-dione (IV), which readily undergoes deacetylation on treatment with morpholine.

EVIDENCE in the literature suggests that a 4-acetyl group in a 3-benzylidenepiperazine-2,5-dione may be subject to so much steric strain that deacetylation is extremely easy, and that, as a result, the 4-acetyl derivative may not even be isolable. We describe here the synthesis and properties of 4-acetyl-3-benzylidene-1-methylpiperazine-2,5-dione (IV).

In 1969, Dominy and Lawton [1] reported the cyclisation of (*N*-acetyldidehydrophenylalanyl)glycine (I) with acetic anhydride at 100° to give a product with just one acetyl group; they assumed that this was the expected 4-acetyl-3-benzylidenepiperazine-2,5-dione (III). However, in 1970, Porter and Sammes [2] proved that this product was in fact the 1-acetyl isomer (V). The same monoacetyl compound was subsequently obtained by Gallina and Liberatori [3] from the diacetylpiperazinedione (VIII) by base-catalysed condensation with benzaldehyde; n.m.r. studies by these authors indicated that it was the 4-acetyl group that was lost during the reaction. There was no evidence for the formation of the diacetyl derivative (VII).

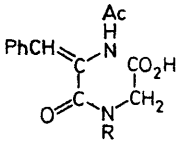
During their model studies, Porter and Sammes cyclised (*N*-acetyldidehydrophenylalanyl)sarcosine (II) with acetic anhydride at 100° and obtained the product (VI), m.p. 142—143°, lacking an acetyl group. They suggested that 'the loss of the *N*-acetyl group from position 4, either during the reaction or during isolation' may be a consequence of steric strain. We have now discovered that if less drastic conditions are employed during this cyclisation (75°; 8 h under nitrogen), the

[1] B. W. Dominy and R. G. Lawton, *J. Org. Chem.*, 1969, **34**, 2013.

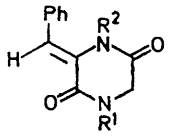
[2] A. E. A. Porter and P. G. Sammes, *J. Chem. Soc.* (*C*), 1970, 2530.

[3] C. Gallina and A. Liberatori, *Tetrahedron Letters*, 1973, 1135; *Tetrahedron*, 1974, **30**, 667.

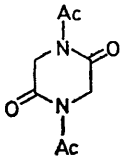
expected 4-acetyl derivative (IV) is obtained in good yield. The identification rests on analytical and spectral data, and smooth deacetylation to give compound (VI).



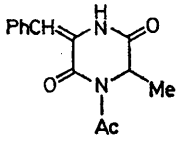
(I) R = H
(II) R = Me



(III) R^1 = H, R^2 = Ac
(IV) R^1 = Me, R^2 = Ac
(V) R^1 = Ac, R^2 = H
(VI) R^1 = Me, R^2 = H
(VII) R^1 = R^2 = Ac



(VIII)



(IX)

The mass spectrum shows the molecular ion at *m/e* 258 (*ca.* 5%) and the base peak at *m/e* 216 (M — CH_2:C:O). The ^{1}H n.m.r. spectra of the acetyl (IV) and deacetyl (VI) derivatives (see Table) show only one significant

^{1}H N.m.r. bands of compounds (IV) and (VI) in $CDCl_3$ (δ values)

	(IV)	(VI)[2]		(IV)	(VI)[2]
C=CH	7·43	70·6	NMe	3·03	3·08
P	7·35	7·38	Ac	2·38	
CH_2	4·13	4·14	NH		8·0

difference apart from the acetyl proton signal: the signal due to the olefinic proton is further downfield in the spectrum of the acetyl derivative (IV) by *ca.* 0·35 p.p.m. The i.r. spectrum (Nujol) of the 4-acetyl derivative (IV) exhibits bands at 1742, 1715, 1665, and 1642 cm^{-1}. These values may be compared with those of the 1-acetyl-3-benzylidene derivative (IX)[4] at 1700, 1690, 1680, and 1635 cm^{-1}. The unusually high carbonyl frequency in the 4-acetyl-3-benzylidene derivative (IV) may perhaps be due to inefficient overlap between the lone pair on N-4 and the adjoining carbonyl groups, as a result of steric crowding. The u.v. spectrum of 4-acetyl-3-benzylidene-1-methylpiperazine-2,5-dione (IV) [$\lambda_{max.}$ 247·5br and 282·5br nm (ε 12,400 and 13,300)] also seems to suggest some conformational change due to overcrowding; it shows a flattened appearance in comparison with that of the deacetyl derivative (VI).

Compound (IV) is reasonably stable to heat; it is recovered unchanged after being refluxed in toluene for 6 h. As expected, it is easily attacked by nucleophiles. Treatment with aqueous potassium hydroxide at room temperature results in ring opening to give the starting acid (II). However, smooth deacetylation to 3-benzylidene-1-methylpiperazine-2,5-dione (VI) is achieved by treatment with morpholine in benzene at room temperature. Porter and Sammes have already established[2] that this deacetyl derivative (VI) possesses the *trans*-configuration about the double bond. We believe, therefore, that our 4-acetyl derivative (IV) has the same configuration. The downfield shift of the olefinic proton signal already mentioned is perhaps to be ascribed to the decreased electron density at the olefinic carbon atom in the *NN*-diacyl enamine (IV) as opposed to the *N*-monoacyl enamine (VI).

In the hope of obtaining the 1,4-diacetyl derivative (VII), we heated (*N*-acetyldidehydrophenylalanyl)-glycine (I) in acetic anhydride at 70° for 10 h under nitrogen and obtained a product melting at *ca.* 150—155° [the previously reported[1] monoacetyl compound (V) melts at 200—202°]. However, the ^{1}H n.m.r. spectrum ($CDCl_3$) showed that the product was probably a *ca.* 1 : 1 mixture of the diacetyl (VII) and monoacetyl (V) derivatives δ: 8·13br (NH), 7·55 (s, C:CH), 7·17 (s, C:CH), 7·37 (s, Ph), 7·42 (s, Ph), 4·62 (s, CH_2), 4·47 (s, CH_2), 2·62 (s, Ac), 2·58 (s, Ac), and 2·47 (s, Ac). We have so far been unable to obtain the pure diacetyl derivative (VII) from this mixture by crystallisation.

A series of 4-acetyl-3-arylidene derivatives of glycyl-L-proline anhydride has been reported recently;[5] no spectral data were provided.

EXPERIMENTAL

N.m.r. spectra were taken with a Varian A-60 instrument, with Me_4Si as internal standard.

4-Acetyl-3-trans-benzylidene-1-methylpiperazine-2,5-dione (IV).—(*N*-Acetyldidehydrophenylalanyl)sarcosine (16 g) in acetic anhydride (80 ml) was heated on an oil-bath at 75° under nitrogen, with stirring, for 8 h. The acetic anhydride was then distilled off under vacuum and the residue digested with benzene. The solid was filtered off and recrystallised from benzene–hexane to give the *product* (IV) (7·5 g), m.p. 160—163° (Found: C, 65·5; H, 5·7; N, 10·65. $C_{14}H_{14}N_2O_3$ requires C, 65·1; H, 5·45; N, 10·85%).

Deacetylation of Compound (IV).—A solution of compound (IV) (3·3 g) in benzene (100 ml) was treated with morpholine (1·1 g), left at room temperature for 2½ h, then evaporated *in vacuo*. The residue crystallised from ethyl acetate–hexane to give 3-*trans*-benzylidene-1-methylpiperazine-2,5-dione (VI) (2·2 g), m.p. and mixed m.p.[2] 140—143° (Found: C, 66·65; H, 5·9; N, 12·7. Calc. for $C_{12}H_{12}N_2O_2$: C, 66·65; H, 5·6; N, 12·95%).

Ring-opening of Compound (IV).—A solution of compound (IV) (0·3 g) in methanol (5 ml) was treated with potassium hydroxide (0·1 g) in water (2 ml), left at room temperature for 3 h, and then evaporated *in vacuo*. The residue was treated with water (5 ml) and the mixture filtered. The filtrate was acidified and the solid filtered off. Recrystallisation from methanol–propan-2-ol gave the dipeptide (II) (0·15 g), m.p. and mixed m.p. 216—218°, identical (i.r. spectrum) with authentic material (Found: C, 60·75; H, 6·25; N, 10·05. Calc. for $C_{14}H_{16}N_2O_4$: C, 60·85; H, 5·85; N, 10·15%).

We thank Professor T. R. Govindachari for his interest in this work, and Dr. S. Selvavinayakam and his associates for the microanalytical and spectral data.

[4/1883 *Received*, 16*th September*, 1974]

[4] K. W. Blake and P. G. Sammes, *J. Chem. Soc.* (*C*), 1970, 980.
[5] H. Poisel and U. Schmidt, *Chem. Ber.*, 1973, **106**, 3408.