$N^{2'}$-Acetyl-6-diacetoxymethylpterin

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Treatment of folic acid with bromine in 48% hydrobromic acid gives the hydrobromide salt of 6-formylpterin (**1**), and acetylation of **1** with recovered acetic anhydride leads to $N^{2'}$-acetyl-6-diacetoxymethylpterin (**3**).

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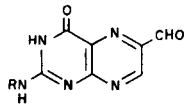
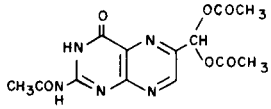
6-Formylpterin (**1**), usually in the form of its $N^{2'}$-acetyl derivative **2**, is a key starting material for the preparation of an important variety of pterin containing compounds, and for this reason an appreciable effort has been devoted to methods for its preparation [1-5]. Probably the most convenient method is from folic acid using a procedure described by Thijssen [2] involving treatment of folic acid with bromine in 40% hydrobromic acid. The resulting 6-formylpterin (**1**) may then be acetylated with acetic anhydride [3] to give **2**. We have repeated this two step method for the preparation of **2** but find that the results obtained depend critically upon the exact conditions used, and that apparently trivial variations from the published conditions lead to different results. Thus, when commercially available 48% hydrobromic acid was used instead of 40%, a yellow product was obtained as described [2]. This product was found to be highly insoluble in trifluoroacetic acid, however, was strongly acidic, and turned out to be the hydrobromide salt of **1** rather than the free base obtained by Thijssen [2]. When the hydrobromide was stirred with aqueous sodium bicarbonate solution it did not dissolve. Carbon dioxide was nevertheless released and the remaining yellow solid was identical with authentic **1**. It was soluble in trifluoroacetic acid, and an ^{1}H nmr spectrum measured in this solvent showed only two singlet resonances at δ 9.46 (H-7) and δ 10.21 (CHO). These chemical shifts agree with those obtained by Viscontini and Bieri [4], but differ from the values reported by other authors [1,2].

The 6-formylpterin (**1**) thus obtained could be converted to its acetyl derivative **2** by a published method [3] in which the pterin (1 g) is heated in acetic anhydride (1350 ml). Because of the inordinately large volume of acetic anhydride used in this procedure we recovered it from the reaction mixture and used the recovered anhydride, presumably containing a little acetic acid, as reagent for the acetylation of more 6-formylpterin (**1**). Under these conditions, however, a new product was obtained, which proved to be the acylal **3**. This was more tractable than **2**. It could be crystallised from methanol, and offers itself as a possible alternative to **2** for the preparation of 6-substituted pterins. When **3** was refluxed in 0.1*M* hydrochloric acid the acylal functionality was hydrolysed first, giving **2**. Further refluxing then hydrolysed the $N^{2'}$-acetyl group, regenerating **1**.



1 R = -H
2 R = -$COCH_3$



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EXPERIMENTAL

The ^{1}H nmr spectra were measured on a Bruker WP-80 instrument, and chemical shifts were determined relative to tetramethylsilane.

$N^{2'}$-Acetyl-6-diacetoxymethylpterin (**3**).

6-Formylpterin (**1**) (0.5 g) was heated under nitrogen at 130° in acetic anhydride (700 ml) recovered from a previous experiment, until all solid had dissolved (3 hours). The acetic anhydride was removed under reduced pressure and the solid residue was recrystallised from methanol with charcoal, giving white crystals of $N^{2'}$-acetyl-6-diacetoxymethylpterin (**3**), (0.3 g), mp 191°; nmr (deuteriotrifluoroacetic acid): δ 2.36 (6H, s), 2.57 (3H, s), 8.05 (1H, s) and 9.30 (1H, s).

Anal. Calcd. for $C_{13}H_{13}N_5O_6$: C, 46.57; H, 3.91; N, 20.89. Found: C, 46.75; H, 4.07; N, 21.09.

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REFERENCES AND NOTES

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