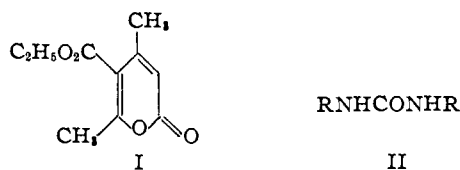


2-Pyrones. VI. Pyridones from Pyrones. The Anomalous Formation of 1,3-Bis-ureas from Ethyl Iso-dehydroacetate and Amines

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The reaction of methyl coumalate (methyl 2-pyrone-5-carboxylate) with a variety of amines is a useful method for preparing 2-pyridones.¹⁻⁴ Other 2-pyrones and 4-pyrones can also be converted to pyridones with the result that rather extensive generalizations to the effect that substantially all pyrones undergo this reaction can be found in the literature.^{3,4} It is the purpose of this discussion to present evidence that ethyl isodehydroacetate (I), a readily available 2-pyrone,⁵ does not form a 2-pyridone when treated with alkaryl amines, under conditions successfully used with methyl coumalate, but does under drastic conditions decompose with the formation of a symmetrical, 1,3-bis-urea of the amine II.



Pyridone formation from ammonia and ethyl isodehydroacetate is reported⁶ to take place at 150° while at lower temperatures an adduct has been obtained.⁷⁻⁹ The bromo derivative of the ester¹⁰ and the diphenyl analog¹¹ also have been converted to pyridones. We have studied the reaction of ethyl isodehydroacetate with five different amines, benzylamine, *p*-methoxybenzylamine, β -phenylethylamine, β -(3,4-dimethoxyphenyl)-ethylamine and benzedrine. Under a variety of conditions, these amines either do not react at all with ethyl isodehydroacetate or form the bis-urea in up to 93% yields.

In order to bring about any reaction between the amine and ester, it is necessary to heat the two reactants together at 200°. Attempts to combine the two at lower temperatures with or without solvents results in recovery of the ester and amine unchanged. This behavior is in marked contrast to that of methyl coumalate which reacts readily at room temperature in methanol with all of these amines. On cooling the reaction mixtures, white crystals, characterized as the 1,3-bis-urea, separate. All of the bis-ureas obtained, with the exception of that from *p*-methoxybenzylamine, have been pre-

viously described. They were characterized by identity of melting point and absence of depression of the melting point of mixtures with authentic samples. The comparison samples were prepared from urea and the amine by a procedure previously used with other amines.¹² The bis-(β -phenylethyl)-urea was also identified by carbon-hydrogen and nitrogen analyses. The reaction with tyramine and *p*-hydroxybenzedrine gave no identifiable products.

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Experimental¹³

The ethyl isodehydroacetate was prepared as previously described.⁵ All of the amines were obtained commercially except benzedrine and *p*-hydroxybenzedrine which were generously supplied by Dr. G. E. Ullyot of Smith, Kline and French Laboratories. Typical experimental details are given for two reactions.

1,3-Bis-(α -methyl- β -phenylethyl)-urea.—To 5.0 g. (0.037 mole) of benzedrine in a small round-bottom flask fitted with a reflux condenser and a calcium oxide-filled drying tube, was added 1.0 g. (0.0051 mole) of ethyl isodehydroacetate. The mixture was heated on an oil-bath at 210–220° for 6 hours. After sitting at room temperature for two days, 1.36 g. (93.1% of the theoretical amount) of yellow, needle-like crystals of 1,3-bis-(α -methyl- β -phenylethyl)-urea were obtained. The compound was recrystallized twice from benzene and once from an ethanol-water mixture to give white crystals, melting at 204–205°; reported m.p. 199°.¹⁴

1,3-Bis-(*p*-methoxybenzyl)-urea.—To 4.0 g. (0.029 mole) of *p*-methoxybenzylamine and 5.0 g. of glacial acetic acid in a small distilling flask was added 1.0 g. of urea. A small amount (2 ml.) of the acetic acid was distilled off and the residue taken up in methanol. The addition of water deposited 1.4 g. of a white crystalline compound, which was recrystallized from benzene and from an ethanol-water mixture, and dried *in vacuo* to give 1.4 g. (28% the theoretical amount) of 1,3-bis-(*p*-methoxybenzyl)-urea, melting at 178–179.5°.

Anal. Calcd. for C₁₇H₂₀N₂O₃: N, 9.33. Found: N, 9.05, 9.11.

1,3-Bis-ureas were prepared by both of these reactions from benzylamine, *p*-methoxybenzylamine, β -phenylethylamine, β -(3,4-dimethoxyphenyl)-ethylamine and benzedrine. The melting points corresponded to those reported in the literature.^{14,15} Mixtures of samples from both preparations showed no depression of melting point.

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On the Photooxidation Products of Tryptophan

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It is well known that tryptophan is easily autoxidized under varying conditions. Kuiken and his co-workers¹ have found that the reaction is catalyzed by base as well as by heavy metal ions (especially cupric ion). Tabone, *et al.*,² have reported

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