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

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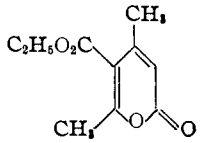
The reaction of methyl coumalate (methyl 2-pyrone-5-carboxylate) with a variety of amines is a useful method for preparing 2-pyridones.[1-4] Other 2-pyrones and 4-pyrones can also be converted to pyridones with the result that rather extensive generalizations to the effect that substantially all pyrones 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.



I

RNHCONHR

II

Pyridone formation from ammonia and ethyl isodehydroacetate is reported[6] to take place at 150° while at lower temperatures an adduct has been obtained.[7-9] The bromo derivative of the ester[10] and the diphenyl analog[11] 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 previously 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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Experimental[13]

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 $C_{17}H_{20}N_2O_3$: 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.

(1) R. H. Wiley, N. R. Smith and L. H. Knabeschuh, THIS JOURNAL, **75**, 4482 (1953).

(2) L. F. Cavalieri, *Chem. Revs.*, **41**, 575 (1947).

(3) J. Fried in R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, p. 356.

(4) H. S. Mosher, *ibid.*, p. 474.

(5) R. H. Wiley and N. R. Smith, THIS JOURNAL, **73**, 1383, 3531 (1951).

(6) R. Anschütz, P. Bendix and W. Kerp, *Ann.*, **259**, 151, 181 (1890).

(7) W. Kerp, *ibid.*, **274**, 280 (1893).

(8) A. Neime and H. V. Pechmann, *ibid.*, **261**, 199 (1891).

(9) A. Hantzsch, *ibid.*, **222**, 9 (1883).

(10) F. Feist, *Ber.*, **26**, 747 (1893).

(11) E. P. Kohler, THIS JOURNAL, **44**, 379 (1922).

(12) A. Sonn, *Ber.*, **47**, 2437 (1914).

(13) Analyses by Micro Tech Laboratories.

(14) L. W. Jones and E. S. Wallis, THIS JOURNAL, **48**, 179 (1926).

(15) A. F. McKay, W. Park and S. J. Veron, *ibid.*, **72**, 3659 (1950); R. Weerman and W. Jongkees, *Rec. trav. chim.*, **25**, 241 (1906); L. Mohunta and J. Ray, *J. Chem. Soc.*, 1263 (1934).

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On the Photoöxidation Products of Tryptophan

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It is well known that tryptophan is easily autoxidized under varying conditions. Kuiken and his co-workers[1] 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

(1) K. A. Kuiken, C. M. Lyman and F. Hale, *J. Biol. Chem.*, **171**, 551 (1947).

(2) J. Tabone, N. Mamounas and D. Robert, *Bull. soc. chim. biol.*, **33**, 1560 (1951).

that kynurenine as well as *o*-aminoacetophenone were formed in the alkaline solution. Irradiation of tryptophan as such or in proteins in the presence or absence of photosensitizers has also been studied.[3-7] It has been demonstrated that tryptophan is converted to 3-indoleacetic acid by the action of ultraviolet radiation.[8] However, autoxidation products other than the above three have rarely been found. Witkop, *et al.*,[9] have recently suggested that tryptophan might be oxidized to formylkynurenine in acidic (or neutral) solution.

We have studied the photoöxidation of tryptophan in slightly acidic aqueous solution in the following three cases: (1) in the absence of metal ions, (2) in the presence of ferrous ion and (3) in the presence of methylene blue as sensitizer. In every case kynurenine as well as 3-hydroxykynurenine were detected as photoöxidation products. On the contrary, only kynurenine was found in the dark autoxidation.

Experimental

L-Tryptophan (m.p. 289°) was dissolved in distilled water free of metal ions to give a 0.1% solution (*p*H 5.98). In a 20-cc. non-fluorescent test-tube, 5 cc. of the solution was exposed to sunlight (May) at 33 ± 2° for 10 hours. During the photoöxidation the *p*H of the solution increased from 5.98 to 6.67 in 10 hours. The photoöxidized solution was chromatographed on paper (developer: 4 *n*-butyl alcohol, 1 glacial acetic acid and 5 water) after 5 and 10 hours, respectively (22°). In both cases two fluorescent substances were found which gave a purple color with ninhydrin. One exhibited R_f 0.5 and the other R_f 0.45. The former fluoresced blue, the latter bluish-green under ultraviolet light (365 mμ). Both spots were respectively eluted with as little as possible warm water and the ultraviolet absorption spectrum of each was examined by means of a Beckman model DU spectrophotometer. The former had absorption maxima at 360 and 259 mμ and the latter at 273 and 235 mμ. These properties, respectively, were in accord with that of kynurenine and 3-hydroxykynurenine. The two solutions were also positive in Otani-Honda's reaction (kynurenine) and Ehrlich's diazotization reaction (3-hydroxykynurenine), respectively.

In an experiment done in the dark under the same conditions, only kynurenine was detected.

When ferrous sulfate ($FeSO_4 \cdot 7H_2O$) (10%) or methylene blue was added to the tryptophan solution and the photoöxidation carried out under the above conditions, the formation of 3-hydroxykynurenine was more or less enhanced. In the methylene blue-sensitized photoöxidation a 100-watt Mazda tungsten lump can be used in place of sunlight. With ferrous sulfate, 3-hydroxykynurenine was found even in the dark. The oxidation–reduction potential in each case was measured by means of the Shimazu model K-2 potentiometer every hour at 20° during the autoxidation. The results showed that more oxidation took place under illumination than in the dark, since in the illuminated reactions much more positive oxidation–reduction potentials were observed.

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(3) H. Gaffron, *Biochem. Z.*, **179**, 157 (1926).
(4) F. Lieben, *ibid.*, **184**, 453 (1927).
(5) A. W. Galston, *Science*, **111**, 619 (1950).
(6) L. Weil, W. G. Gordon and A. R. Buchert, *Arch. Biochem.*, **33**, 90 (1951).
(7) Y. Obata and S. Sakamura, *J. Chem. Soc. (Japan) Pure Chem. Section*, **73**, 811 (1952).
(8) A. Berthelot, *et al.*, *Compt. rend.*, **206**, 699 (1938).
(9) B. Witkop, *et al.*, *Experientia*, **8**, 36 (1952).

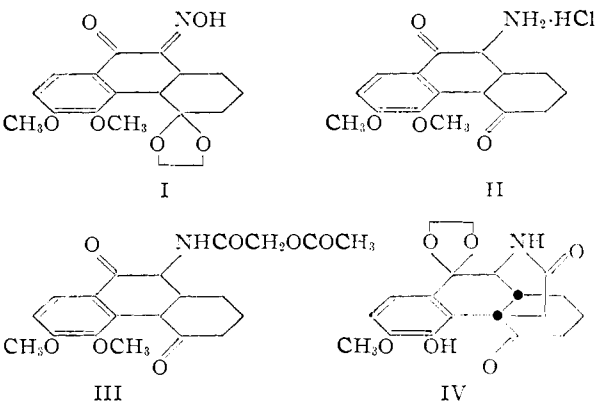
COMMUNICATIONS TO THE EDITOR

THE SYNTHESIS OF MORPHINE

Sir:

We wish to report the synthesis of dihydrothebainone and its resolution to the optically active base. This synthesis is equivalent to that of morphine since the steps involved in the conversion of dihydrothebainone to morphine have been accomplished by other investigators.[1]

The 4-ethylene glycol ketal of 1,2,3,4,4a,9,10,10a-octahydro-4,9-dioxo-5,6-dimethoxy-10-hydroxyiminophenanthrene (I)[2] was reduced catalytically to give the amine hydrochloride, II, m.p. 210–212° (dec.), found C, 58.0; H, 6.2; Cl, 10.9. Treatment with acetylglycolyl chloride in chloroform containing pyridine afforded the amide, III, m.p. 169–171°, found C, 61.8; H, 5.8; N, 3.6. This was cyclized under conditions similar to those described for the unmethoxylated analog,[2] to yield the lactam, IV, m.p. 244–246°, found C, 63.2; H, 5.7, N, 4.0; active hydrogen, 1.7. Demethylation of the C_5 methoxyl group occurs during the cyclization. Treatment with *n*-amyl nitrite in the presence of sodium ethoxide gave the hydroxyimino derivative, V,[3] m.p. 265–266° (dec.), found C, 58.6; H, 5.2; N, 7.1. Removal of the ketal blocking group with dilute acid afforded the mono-oxime diketone, VI, m.p. 212–214° (dec.), found C, 59.3; H, 4.5; N, 7.9.



(1) M. Gates and G. Tschudi, THIS JOURNAL, **74**, 1109 (1952); C. Schöpf and T. Pfeifer, *Ann.*, **483**, 157 (1930); H. Rapoport, C. H. Lovell and B. M. Tolbert, THIS JOURNAL, **73**, 5900 (1951).
(2) D. Ginsburg and R. Pappo, *J. Chem. Soc.*, 1624 (1953)
(3) *Cf.* D. Elad and D. Ginsburg, *J. Chem. Soc.*, 2664 (1953).