SYNTHESIS OF 1,3-OXAZINE DERIVATIVES BASED ON DIKETENE

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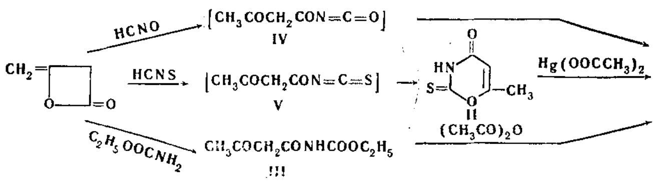
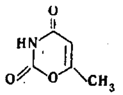
Reaction of diketene with potassium cyanate in acetic acid gives 6-methyl-2, 3-dihydro-2, 4-diketo-1, 3-oxazine, also formed by cyclizing acetoacetylurethane, or by treating ammonium thiocyanate with diketene in the presence of mercuric acetate. Acetylation of N-trisubstituted ureas with ketene in acetic acid gives N-alkyl derivatives of 6-methyl-2, 3-dihydro-2, 4-diketo-1, 3-oxazine.

We previously showed [1] that diketene reacts with N,N-dimethylurea and ammonium thiocyanate, to give 6-methyl-2,3-dihydro-2,4-diketo-1,3-oxazine (I), and its 2-thio derivative (II). In the present work it was found that I can be prepared by cyclizing acetoacetylurethane (III) with acetic anhydride, by the action of diketene on potassium cyanate in acetic acid, or by desulfurizing II with $Hg(OAc)_2$. Preparation of II and its desulfurization can be effected in a single operation, if the reaction of diketene with NH_4CNS is carried out in the presence of $Hg(OAc)_2$.

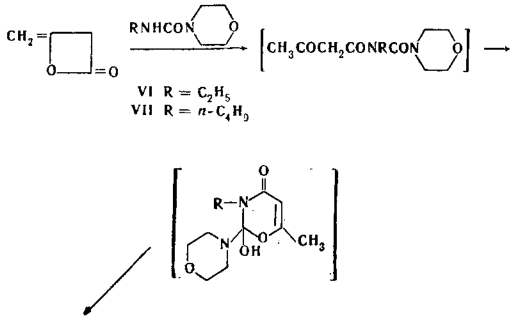
Conversion of diketene into I and II evidently involves acetoacetylation of the iso forms of HCNS, followed by cyclization of the isocyanate (IV) or isothiocyanate (V), the equations being

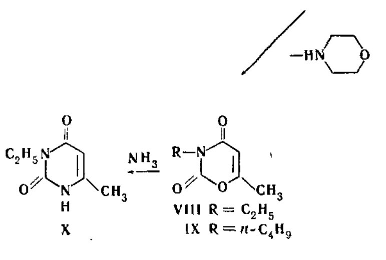




I

Heating of diketene with the morpholides of ethyl- and n-butylcarbamicoacids VI and VII in acetic acid, leads to the isolation of N-alkyl substituted oxazines VIII and IX, whose formations can be regarded as involving a multistage process, proceeding through the intermediate steps of acetoacetylation, cyclization, and deamination:

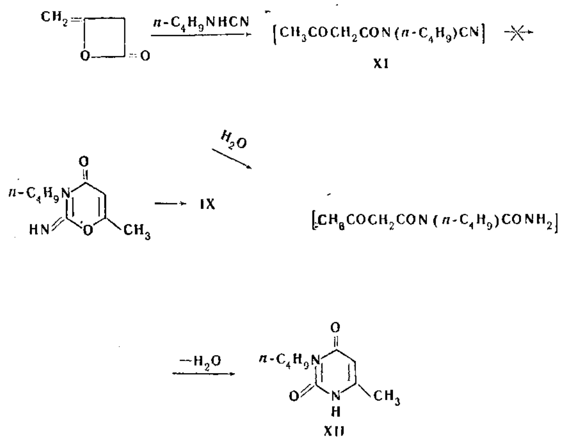




The 3-ethyl-6-methyl-2,3-dihydro-2,3-diketo-1,3-oxazine (VIII) obtained in that way has the same melting point at the oxazine synthesized from diketene and diethylcarbodiimide [2].

Aqueous ammonia causes VIII to undergo ammonolysis, giving the known 3-ethyl-6-methyluracil (X) [3].

Acetylation of butylcyanamide in acetic acid in the presence of $Hg(OAc)_2$ gives an oily mixture of products which does not contain the expected IX.



On treatment with hydrochloric acid it gives a small yield of the known 3-n-butyl-6-methyluracil (XIII) [3], apparently by hydrolysis of the intermediate acetoacetylbutylcyanamide (XI).

EXPERIMENTAL

6-Methyl-2, 3-dihydro-2, 4-diketo-1, 3-oxazine (I). a) A mixture of 6.5 g (about 0.38 mole) acetoacetylurethane and 20 ml acetic anhydride was refluxed for 6 hr, cooled, and the crystals that precipitated filtered off. Yield 1.5 g (31%) I, mp 230–231°, undepressed mixed mp with an authentic sample (mp 230–231°) [1]. I was identified in the same way in experiments (b), (c), and (d) below.

b) 1.5 ml (0.014 mole) diketene was added to 0.81 g (0.01 mole) KCNO in 5 ml acetic acid, when an exothermic reaction took place, and the temperature rose to 60°. When the evloution of heat ceased, the products were treated with water, and the crystals precipitated filtered off: the yield of I was 0.5 g (40%), mp 230–231°.

c) 8.4 g (0.025 mole) $Hg(OAc)_2$ was added to 4 g (0.05 mole) NH_4CNS in 20 ml AcOH, when heat was evolved, and the temperature rose to 35°. The mixture was cooled to 20° and 9.7 ml (0.1 mole) diketene added gradually. The products were held at 20° for 1 hr after the vigorous exothermic reaction had ceased, and the black precipitate extracted with hot water (3 × 100 ml). The aqueous solution was vacuum evaporated to dryness, and the residue recrystallized from water, with the addition of decolorizing charcoal. Yield 1.9 g (28%) I, mp 230–232°.

d) A mixture of 1 g (0.007 mole) II, 1.1 g (0.0035 mole) $Hg(OAc)_2$, and 5 ml acetic acid was refluxed for 15 min. The black precipitate formed was filtered off, and washed with hot water (3 × 10 ml). The aqueous filtrate was vacuum evaporated to dryness, and the residue recrystallized from water, using decolorizing charcoal. Yield 0.25 g (28%) I mp 229–231°.

3-Ethyl-6-methyl-2, 3-dihydro-2, 4-diketo-1, 3-oxazine (VIII). The morpholide of ethylcarbamic acid (IV) was prepared from propionyl chloride, sodium azide, and morpholine [4, 5], yield 45%, mp 118–119° (ex Pr_2O). Found: N 18.02; 18.23%. Calculated for $C_7H_{14}O_2N_2$: N 17.71%. A mixture of the morpholide of ethylcarbamic acid (VI), 2 ml (0.02 mole) diketene in 20 ml acetic acid was refluxed for 2 hr, then vacuum evaporated for 10 min with bath temperature 70°, the residue treated with ether, and the crystals which separated filtered off, yield of VIII 0.25 g. The filtrate was diluted with methanol and cooled with dry ice, when another 0.5 g VIII separated, the total yield being 48%, mp 69–70° (ex heptane), λ_{max} 234 mμ, ε 6270 (in EtOH). The literature gives [2] mp 69–70° and λ_{max} 227 mμ, ε 7900 (in EtOH).

A solution of 0.31 g VIII in 50 ml 20% ammonia was kept for 48 hr at room temperature, then vacuum evaporated to dryness, and the residue washed with water to give 0.2 g (65%) 3-methyl-6-methyluracil (X), mp 187–190°, undepressed mixed up with an authentic specimen (197–198°) [3].

3-n-Butyl-6-methyl-2, 3-dihydro-2, 4-diketo-1, 3-oxazine (IX). The morpholide of n-butylcarbamic acid (VII) was prepared from butyryl chloride, sodium azide, and morpholine [4, 5], yield 50%, mp 73–75° (ex ether). Found N 15.16, 14.91%. Calculated for $C_9H_{18}O_2N_2$: N 15.04%. A solution of 2.8 g of the morpholide of n-butylcarbamic acid (VII) and 3 ml (0.03 mole) diketene, in 20 ml acetic acid was refluxed for 4 hr, then vacuum-evaporated to dryness, the residue treated with boiling water, the solution cooled, and the precipitate filtered off. Yield 1.55 g (55%) IX mp 66–67° (ex heptane), λ_{max} 229 mμ ε 7800 (in ethanol). Found: N 7.60; 7.57%. Calculated for $C_9H_{13}O_3N$: N 7.65%.

Reaction of n-butylcyanamide with diketene in acetic acid. A mixture of 5.6 g crude n-butylcyanamide [6], 8.6 g diketene, and 0.1 g $Hg(OAc)_2$, was kept at room temperature for 2 days, then vacuum evaporated and the oily residue heated at 100° for 4 hr with dilute HCl (1:1), the whole again evaporated to dryness, and the residue chromatographed on Al_2O_3, activity grade II. Chloroform eluted 0.42 g (5%) 3-n-butyl-6-methyluracil (XII), mp 176–177°, undepressed mixed mp with an authentic specimen (179–180°) [3].

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