β-DICARBONYL COMPOUNDS

COMMUNICATION 26. CHEMICAL PROPERTIES AND BIOLOGICAL ACTIVITY OF ENAMINES DERIVED FROM β-DICARBONYL COMPOUNDS

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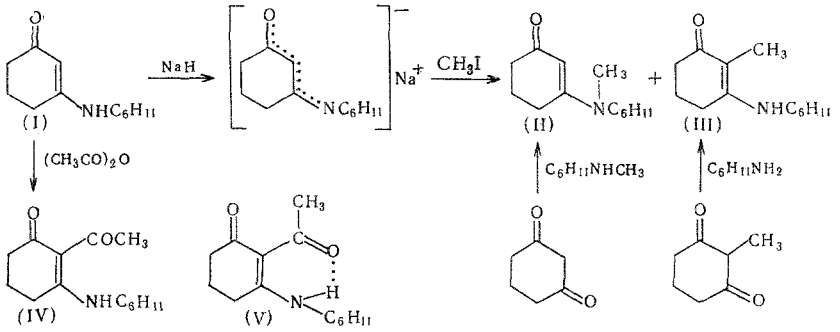
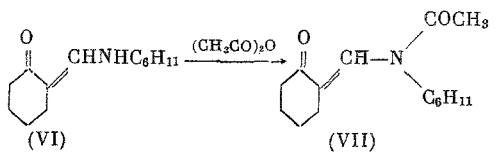
In continuation of our investigation on the chemistry of enamines [1] we have studied the alkylation and acylation of an enamine derived from 1,3-cyclohexanedione – 3-(cyclohexylamino)-2-cyclohexen-1-one (I), examined the possibility of using it in the synthesis of heterocyclic compounds, and found a new method for the preparation of the 2H-pyran-2-ones (XIV) and (XV) and internal N-acyl enamines of the 2(1H)-pyridone series (XVI) and (XVII).



The enamine (I) is not alkylated when treated for 6 h with methyl iodide in boiling methanol or t-butyl alcohol whether in absence or in presence of an alkoxide. This behavior of the enamine (I) indicates its weak nucleophilic character and low acidity, which does not allow the establishment of an adequate concentration of the metal derivative in alcoholic solution. Reaction can be brought about only by the action of methyl iodide on the sodium derivative prepared with sodium hydride in tetrahydrofuran, and it leads to the N- and C-methylation products (II) and (III). Their structures were proved by independent syntheses: by the reactions of 1,3-cyclohexanedione and of 2-methyl-1,3-cyclohexanedione with N-methylcyclohexylamine and with cyclohexylamine respectively. When boiled with acetic anhydride-3-(cyclohexylamino)-2-cyclohexen-1-one is converted smoothly into the C-acetyl derivative (IV), whose structure was confirmed by its characteristic reaction with ferric chloride. The low NH frequency in its IR spectrum



(3020 cm^{-1}) is probably determined by its chelate structure (V). A different course of reaction is observed in the acetylation of the enamine 2-[(cyclohexylamino)methylene]cyclohexanone (VI), which by treatment

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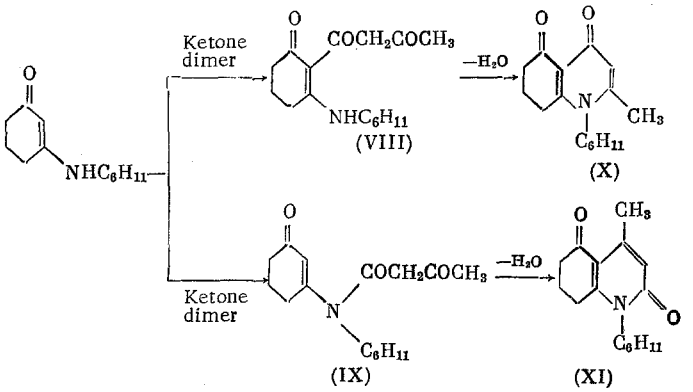
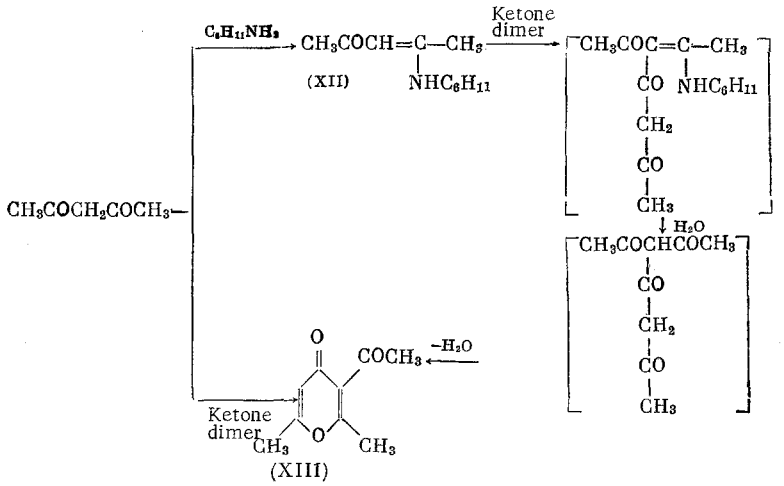
with acetic anhydride forms the N-acetyl derivative (VII), which in keeping with its structure does not give a reaction with ferric chloride and breaks down on acid hydrolysis to cyclohexanone and N-cyclohexylacetamide. The possibility of the direct acylation of enamines derived from cyclic β-diketones prompted us to try ketene dimer as an acylating agent and effect the cyclization of the intermediate C- and N-acetoacetyl derivatives (VIII) and (IX) into the pyridones (X) and (XI).

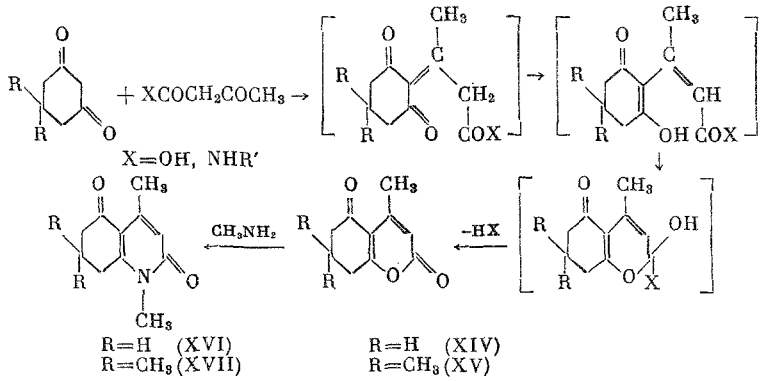


It was found, however, that in reaction with ketene dimer in boiling acetic acid 3-(cyclohexylamino)-2-cyclohexen-1-one gives an unidentified colored substance of m.p. 208-210°, which differed appreciably in elemental composition from the pyridones (X) and (XI). Under the same conditions 4-(cyclohexylamino)-3-penten-2-one (XII) forms 3-acetyl-2,6-dimethyl-4H-pyran-4-one (XIII), which has been prepared previously by the condensation of ketene dimer with 2,4-pentanedione in presence of concentrated H_2SO_4 [2].



Since 2,4-pentanedione itself does not react with ketene dimer in boiling acetic acid in presence or absence of cyclohexylamine, we may assert that the formation of the 4H-pyran-4-one (XIII) from the enamine (XII) goes through the intermediate stages of C-acetoacetylation and hydrolysis. The unexpected possibility of the synthesis of 2(1H)-pyridones of type (XI) was revealed in a study of the reactions of cyclic β-diketones with acetoacetamides, which are readily prepared by the action of amines on ketene dimer. When 1,3-cyclohexanedione and 5,5-dimethyl-1,3-cyclohexanedione (dimedon) are treated with acetoacetamide or an N-alkylacetoacetamide in boiling toluene with an addition of pyridine as catalyst, 7,8-dihydro-4-methyl-2H-1-benzopyran-2,5(6H)-dione (XIV) and 7,8-dihydro-4,7,7-trimethyl-2H-1-benzopyran-2,5(6H)-dione (XV) are formed respectively. The reaction of dimedon with acetoacetic ester in presence of N,N-diethylaniline at 170-180° goes analogously, but in lower yield. These interesting transformations probably include intermediate stages of crotonic condensation and cyclization with elimination of an amine or alcohol (see scheme on following page).

The structures of the 2H-pyran-2-ones (XIV) and (XV) were confirmed by their IR spectra (presence of carbonyl frequencies in the region 1730-1750 cm^{-1}) and their conversion into the 2(1H)-pyridones (XVI) and (XVII) on treatment with methylamine in aqueous solution. We were unable to cause 2,4-pentanedione to react with acetoacetamides in boiling toluene in presence of pyridine.



For use in biological tests we prepared a number of enamines derived from 2,4-pentanedione, dimedon, 1,3-cyclohexanedione, and 2-substituted 1,2-cyclohexanediones by the usual method, i.e., the action of amines on the β-diketones (see Table 1).

The enamines (I), (XXIV), (XXV), (XXVII), and (XXVIII) show weak activity in vitro against ascarids (Ascaris lumbricoides var. suum). In a dilution of 1:1000 the enamines (XVIII), (XXV), (XXVI), and (XXVIII) proved to be toxic to mollusks (Physastra proteus) and fish (Lebistes reticulatus), and the enamines (XVIII), (XXVI), and (XXVIII) were also toxic to infusorians (Paramecium candatum). The enamines (XVIII), (XXIV), and (XXVII) are active against cestodes (Hymenolepis nana) in vitro at low dilutions. Also, all the enamines obtained show weak bacteriostatic and fungistatic activity in vitro (Prof. G. N. Pershin, S. Ordzhonikidze All-Union Chemical and Pharmaceutical Research Institute).

EXPERIMENTAL

Methylation of 3-(Cyclohexylamino-2-cyclohexen-1-one (I). 0.9 ml of methyl iodide was added to a solution of the sodium derivative prepared from 1.9 g of (I) and 0.3 g of sodium hydride in 15 ml of dry tetrahydrofuran, and when the exothermic reaction had subsided the mixture was boiled for 1.5 h. It was then vacuum-evaporated, and the residue was treated with water and extracted with benzene and ether. After removal of solvents and vacuum distillation of the reaction products we obtained 1.3 g of an oil, b.p. 210-222° (3 mm). On treatment of this with ether 0.2 g of the original enamine (I), m.p. 151-153°, came down. The residual mixture was dissolved in ether and cooled to −78°, when we isolated 0.3 g (14%) of 3-(cyclohexylmethylamino)-2-cyclohexen-1-one (II), m.p. 77-79°. By means of thin-layer chromatography on Stahl silica gel we showed that the mother liquor contained 3-(cyclohexylamino)-2-methyl-2-cyclohexen-1-one (III) (R_f 0.28 in 1:9 heptane−acetone).

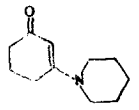
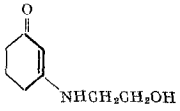
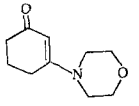
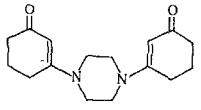
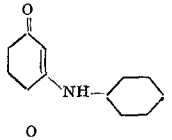
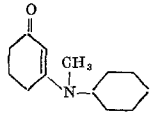
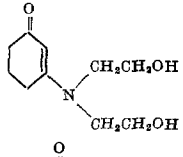
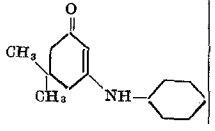
Acetylation of 3-(Cyclohexylamino)-2-cyclohexen-1-one (I). A solution of 10 g of (I) in 50 ml of acetic anhydride was boiled for 1.5 h. Excess of acetic anhydride was removed, and the residue was vacuum-distilled. We obtained 7.6 g (62%) of 2-acetyl-3-(cyclohexylamino)-2-cyclohexen-1-one (IV); b.p. 186-189° (2 mm); m.p. 78-79° (benzene−heptane). IR spectrum (ν, cm^{-1}, $CHCl_3$): 3020, 2950, 2400, 1635, 1575, 1465. Found %: N 5.87, 5.83. $C_{14}H_{22}O_2N$. Calculated %: N 5.92.

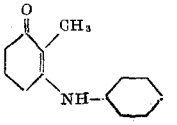
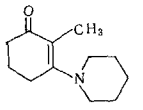
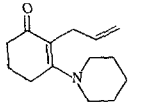
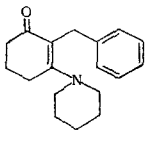
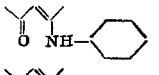
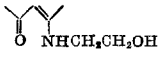
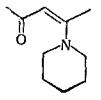
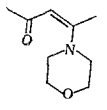
Acetylation of 2-[(Cyclohexylamino)methylene]cyclohexanone (VI). A solution of 15 g of the enamine (VI) [3] in 100 ml of acetic anhydride was heated for 3 h at 100°. After the removal of excess of acetic anhydride the residue was vacuum-distilled. We obtained 13 g (72%) of the N-acetyl enamine (VII), b.p. 135-137° (0.1 mm); m.p. 65-67°. Found %: N 5.82, 5.84. $C_{15}H_{23}O_2N$. Calculated %: N 5.61.

When heated with dilute NaOH (100°, 6 h), the N-acetyl anamine (VII) decomposed into cyclohexanone and N-cyclohexylacetamide.

Reaction of 3-(Cyclohexylamino)-2-cyclohexen-1-one with Ketene Dimer. A mixture of 1.9 g of (I) and 1 ml of ketene dimer in 25 ml of glacial acetic acid was boiled for 3 h and then vacuum-evaporated. The oily residue was dissolved in benzene and passed through a column containing 50 g of alumina of activity II. From the first fraction we isolated 0.4 g of yellow crystals, m.p. 200-201°, raised by recrystallization from a mixture of methanol and chloroform to 208-210°; λ_{max} (alcohol) 220, 268, 328, 370 and 440 mμ. Found %: C 75.82, 75.80; H 8.43, 8.35; N 5.76, 5.76. $C_{16}H_{21}O_2N$. Calculated %: C 74.10; H 8.16; N 5.40.

TABLE 1. Enamines Derived from β-Diketones

No.	Formula of enamine	Yield, %	B.p., °C (p, mm)	B.p., °C	n_D^{20}	Molecular formula	Found N, %	Calc. N, %
XVIII		77	166—167 (1)	—	1,5965	$C_{11}H_{17}ON$	8,03 7,90	7,81
XIX		57	—	103—105 (ethyl acetate)	—	$C_8H_{13}O_2N$	9,23 9,08	9,03
XX		57	—	93—94 (ethyl acetate)	—	$C_{10}H_{15}O_2N$	7,73 7,97	7,74
XXI		24	—	210—212 (ethyl acetate)	—	$C_{16}H_{22}O_2N_2$	10,19 10,05	10,21
I		91	—	152—154 (ethyl acetate)	—	$C_{12}H_{19}ON$	7,06 7,18	7,24
II		54	—	80—82	—	$C_{13}H_{21}ON$	6,73 6,45	6,75
XXII		—	—	98—99 (ethyl acetate)	—	$C_{10}H_{17}O_2N$	7,06 7,05	7,05
XXIII		47	—	166—168 (benzene)	—	$C_{14}H_{23}ON$	6,52 6,45	6,32

No.	Formula of enamine	Yield, %	B.p., °C (p, mm)	B.p., °C	n_D^{20}	Molecular formula	Found N, %	Calc. N, %
III		65	—	94—95	—	$C_{13}H_{21}ON$	6,80 6,78	6,75
XXIV		76	144—146 (1)	—	1,5795	$C_{12}H_{19}ON$	7,33 7,29	7,25
XXV		35	160—170 (1)	—	1,5640	$C_{14}H_{21}ON$	6,42 6,28	6,39
XXVI		60	204—203 (1)	—	1,6080	$C_{18}H_{23}ON$	5,36 5,07	5,20
XII		82	114—115 (2)	—	—	$C_{11}H_{19}ON$	7,82 7,87	7,72
XXVII		74	—	68—70 (ether)	—	$C_{17}H_{15}O_2N$	10,03 9,83	9,78
XXVIII		61	—	45—46 (hexane)	—	$C_{10}N_{17}ON$	8,35 8,28	8,38
XXIX		83	—	43—44 (hexane)	—	$C_9H_{15}O_2N$	8,40 8,20	8,28

Reaction of 4-(Cyclohexylamino)-3-penten-2-one (XII) with Ketene Dimer. A solution of 1.8 g of (XII) and 1.3 ml of ketene dimer in 20 ml of glacial acetic acid was boiled for 3 h and then evaporated; the residue was vacuum-distilled. We obtained 1.2 g of a fraction of b.p. 121-123° (3 mm), which crystallized on standing. By cooling of its ethereal solution at −78° we isolated 0.4 g (24%) of the 4H-pyran-4-one (XIII), m.p. 56-57° (heptane). IR spectrum (ν, cm^{-1}, $CHCl_3$): 1696, 1668, 1616. The 4H-pyran-4-one obtained melted without depression in admixture with a known sample prepared by the action of ketene dimer on 2,4-pentanedione in presence of concentrated H_2SO_4 [2].

Reaction of 5,5-Dimethyl-1,3-cyclohexanedione (Dimedon) with N-Methylacetoacetamide. A solution of 10 ml of ketene dimer in 30 ml of dry benzene was added in portions to a solution of 4 g of methylamine in 40 ml of dry benzene at 0-5°, and the mixture was left for 12 h at room temperature. Solvent was removed, and we obtained 11 g of oily N-methylacetoacetamide, which was used in reactions with cyclic β-diketones without further purification.

A mixture of 1.4 g of dimedon, 3 g of unpurified N-methylacetoacetamide, and 1.5 ml of pyridine in 20 ml of dry toluene was boiled with a water separator for 3 h. The solution was vacuum-evaporated to dryness, and the solid residue was treated with dilute sodium carbonate solution and washed with water. We obtained 1.3 g (62%) of 7,8-dihydro-4,7,7-trimethyl-2H-1-benzopyran-2,5(6H)-dione (XV), m.p. 109-110° (aqueous methanol); λ_{max} (alcohol) 261 mμ (ε 13600). IR spectrum (ν, cm^{-1}, $CHCl_3$): 1750, 1735, 1685, 1623, 1547. Found %: C 69.60, 69.82; H 6.82, 6.87. $C_{12}H_{14}O_3$. Calculated %: C 69.89; H 6.84.

Analogous results were obtained in the reactions of dimedon with acetoacetamide and with N-hexylacetoacetamide.

Reaction of 1,3-Cyclohexanedione with N-Methylacetoacetamide. The procedure was as described above. The yield of the 7,8-dihydro-4-methyl-2H-1-benzopyran-2,5(6H)-dione (XIV) obtained was 55%; m.p. 95-96° (aqueous methanol); λ_{max} (alcohol) 261.5 mμ (ε 11750). Found %: C 67.30, 67.11; H 5.85, 5.90. $C_{10}H_{10}O_3$. Calculated %: C 67.39; H 5.65.

When dissolved in hot NaOH solution with subsequent acidification with hydrochloric acid, the 2H-pyran-2-one (XIV) was recovered unchanged.

Reaction of Dimedon with Acetoacetic Ester. A mixture of 1.4 g of dimedon, 1.3 g of acetoacetic ester, and 1.5 g of N,N-diethylaniline was heated at 170-180° for 20 min and then cooled to room temperature, treated with excess of dilute hydrochloric acid, and extracted with ether. Most of the solvent was removed, the residue was cooled to −78°, and the crystals which came down were filtered off. We obtained 0.2 g (10%) of 7,8-dihydro-4,7,7-trimethyl-2H-1-benzopyran-2,5(6H)-dione (XV), m.p. 108-110°.

Reaction of 7,8-Dihydro-4,7,7-trimethyl-2H-1-benzopyran-2,5(6H)-dione (XV) with Methylamine. A mixture of 0.3 g of (XV) and 5 ml of 25% aqueous methylamine solution was heated for 1.5 h at 100° and then vacuum-evaporated to dryness. The residue was recrystallized from aqueous methanol. We isolated 0.2 g (62%) of 7,8-dihydro-1,4,7,7-tetramethyl-1,5(2H,6H)-quinolinedione (XVII), m.p. 111-112°; λ_{max} (alcohol) 219 and 282.5 mμ (ε 10400 and 16650). Found %: C 70.77, 70.77; H 7.89, 7.92; N 6.53, 6.52. $C_{13}H_{17}O_2N$. Calculated %: C 71.20; H 7.80; N 6.39.

Reaction of 7,8-Dihydro-4-methyl-2H-1-benzopyran-2,5(6H)-dione (XIV) with Methylamine. In the action of an aqueous solution of methylamine on (XIV), as described above, we obtained a 53% of 7,8-dihydro-1,4-dimethyl-2,5(1H,6H)-quinolinedione (XVI), m.p. 116-117° (benzene–heptane). Found %: C 69.01, 69.06; H 6.57, 6.46; N 7.27, 7.50. $C_{11}H_{13}O_2N$. Calculated %: C 69.09; H 6.85; N 7.32.

We are deeply indebted to G. A. Kogan for carrying out the spectral investigations.

CONCLUSIONS

1. When treated with methyl iodide in tetrahydrofuran, the sodium derivative of 3-(cyclohexylamino)-2-cyclohexen-1-one undergoes C- and N-methylation.

2. When heated with acetic anhydride, 3-(cyclohexylamino)-2-cyclohexen-1-one and 2-[(cyclohexylamino)methylene]cyclohexanone form C- and N-acetyl derivatives respectively.

3. 1,3-Cyclohexanedione and its 5,5-dimethyl derivative react with acetoacetamides with formation of 7,8-dihydro-4-methyl- and 7,8-dihydro-4,7,7-trimethyl-2H-1-benzopyran-2,5(6H)-diones respectively.

4. Enamines derived from β-diketones have a weak toxic action in vitro toward some species of infusorians, mollusks, fish, and ascarids.

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