BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 41 165—167 (1968)

The Cyclization of Ethyl Acetoacetate and Ketones by Ammonium Acetate

Akio SAKURAI and Hiroshi MIDORIKAWA

The Institute of Physical and Chemical Research, Komagome, Bunkyo-ku, Tokyo

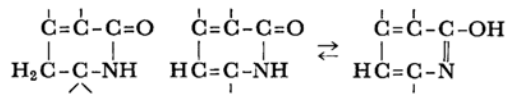
(Received June 16, 1967)

The reactions of ethyl acetoacetate with cyclic ketones and aromatic methyl ketones by using excessive ammonium acetate gave some heterocyclic compounds, such as 2-hydroxy-4-methyl-5, 6, 7, 8-tetrahydroquinoline (III), 2-hydroxy-4-methyl-6, 7-dihydro-5*H*-1-pyrindine (IV), and 2-hydroxy-4-methyl-6-alkyl-pyridines (VI). The structures of these compounds were investigated by means of their infrared and NMR spectra.

In a previous paper,[1] the synthesis of pyridone derivatives and related heterocyclic compounds by the condensation of ethyl cyanoacetate with various ketones in the presence of excessive ammonium acetate was reported.

The present paper will deal with the synthesis of hydroxyquinoline and hydroxypyridine derivatives by the reactions of ethyl acetoacetate and aromatic ketones or cyclic ketones with ammonium acetate. The cyclizations between ethyl acetoacetate and the ketones were quite limited compared with the case of ethyl cyanoacetate previously reported.

The cyclization reactions with a number of ketones were attempted; cyclic ketones, such as cyclohexanone and cyclopentanone, and aromatic methyl ketones, such as acetophenone and methyl α-naphthyl ketone, could be involved in this reaction, the hydroxyquinoline derivative (III) and the hydroxypyridine derivatives (IV) and (VI) being products. However, attempts to prepare the hydroxypyridine derivatives by reaction with aliphatic methyl ketones, such as acetone and methyl ethyl ketone, were unsuccessful under similar conditions. The infrared spectra of the dihydro-2-pyridone derivatives (I) described in the previous paper showed sharp bands at 3200 cm^{-1} and 1660 cm^{-1} attributed to the imino group and the carbonyl group of pyridone ring respectively. The NMR spectra of these compounds revealed a signal at 7.8—8.6 ppm due to the imino proton of the pyridone ring.



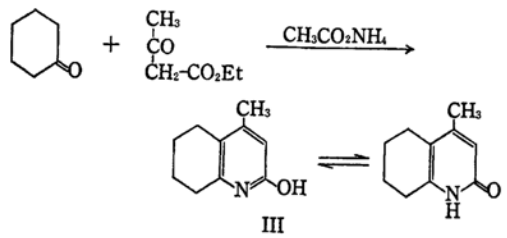
I II

On the other hand, 2-pyridone derivatives (II) gave no signal at 7.8—8.6 ppm and no infrared absorption band at 3200 cm^{-1}. The carbonyl band always appeared in the 1640—1660 cm^{-1} region. None of the infrared spectra of the compounds, III, IV and VI, in the present study exhibited a band at 3200 cm^{-1}, only a broad and weak band at 3370—3440 cm^{-1} and a strong band at 1640—1650 $cm.^{-1}$ Furthermore, the NMR

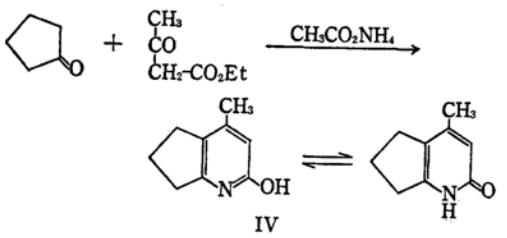
1) A. Sakurai and H. Midorikawa, This Bulletin, **40**, 1680 (1967).

spectra of these compounds showed no signal in the 7.8—8.6 ppm region, but they did show a signal at 10—12.5 ppm corresponding to one proton. Presumably, the infrared absorption at 3370—3440 cm^{-1} and the NMR signal at 10—12.5 ppm are due to the hydroxy group; dihydro-2-pyridone derivatives are predominantly in the -NH-CO- form, but the 2-quinolone derivatives (III) and the 2-pyridone derivatives (IV and VI) in both the -NH-CO- and -N=C(OH)- forms, as in the structure II. However, the NMR spectra seem to indicate that the -N-C(OH)- form rather than the -NH-CO- form is predominant.

The condensation between ethyl acetoacetate and cyclic ketones in a 1 : 1 molar ratio took place. The corresponding tetrahydroquinoline derivative (III) or dihydropyrindine derivative (IV) were obtained with the elimination of water and alcohol. The scheme of these reactions is



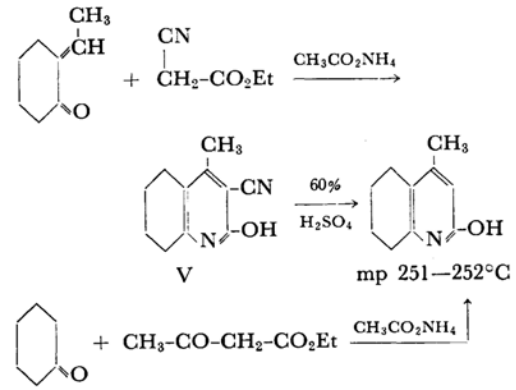
III



IV

indicated as follows. The dehydration takes place between the carbonyl group of ethyl acetoacetate and the methylene group adjacent to the carbonyl group of ketones.

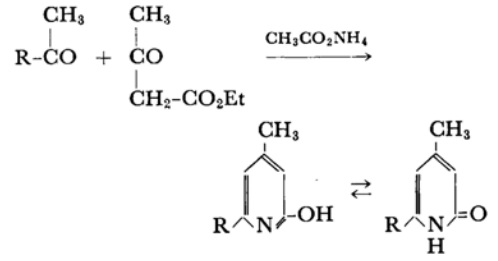
The condensation of ethyl cyanoacetate with ethylidenecyclohexanone[1] proceeds through a



Michael reaction; 2-hydroxy-3-cyano-4-methyl-5, 6, 7, 8-tetrahydroquinoline (V) is thus obtained. On hydrolysis, the cyano group of V gave 2-hydroxy-4-methyl-5,6,7,8-tetrahydroquinoline (mp 251—252°C), as is illustrated below:

The compound III was identical with this tetrahydroquinoline (mp 251—252°C) in its melting point, infrared spectrum, and NMR spectrum. Therefore, the condensation products obtained from ethyl acetoacetate and cyclic ketones can be relied upon to have the structures indicated in the scheme A.

The condensations of aromatic methyl ketones with ethyl acetoacetate are considered to proceed similarly to those of cyclic ketones (molar ratio 1 : 1). The dehydration between the carbonyl group of ethyl acetoacetate and the methyl group of the ketones and the elimination of alcohol took place to form hydroxypyridine derivatives. The



VI

a $R=C_6H_5$
b $R=C_{10}H_7$

compound VIa was identical with the known 6-phenyl-4-methyl-2-pyridone[2] in its melting point.

All the compounds (III, IV, VIa, and VIb) were colored a reddish orange by alcoholic ferric chloride.

Experimental

All the melting points are uncorrected.

The infrared spectra were determined by means of pressed potassium bromide disks.

The NMR spectra were determined in deuteriochloroform or trifluoroacetic acid at a frequency of 60 Mc, using tetramethylsilane as the internal standard. The chemical shifts are given as ppm downfield from tetramethylsilane.

2-Hydroxy-4-methyl-5, 6, 7, 8-tetrahydroquinoline (III). A mixture of ethyl acetoacetate (13 g, 0.1 mol), cyclohexanone (9.8 g, 0.1 mol), and ammonium acetate (7.7 g, 0.1 mol) was refluxed for 12 hr. After cooling, and after water had been added the reaction mixture was allowed to stand overnight; a crystalline matter was thus precipitated. Recrystallization from alcohol gave colorless needles, mp 252—253°C (lit[3] mp 217—218°C and lit[4] mp 240—241°C); yield 1.9 g (12%).

2) J. C. Bardhan, *J. Chem. Soc.*, **1929**, 2223.
3) A. Dornow and E. Neuse, *Arch. Pharm.*, **287**, 361 (1954).
4) A. I. Meyers and G. Garcia-Munonz, *J. Org. Chem.*, **29**, 1435 (1964).

Found: C, 73.64; H, 7.66; N, 8.60%. Calcd for $C_{10}H_{13}ON$: C, 73.59; H, 8.03; N, 8.58%.

IR: 3370 (broad, ν OH), 1645 (ν C=O), 1620 (ν C=C).

NMR: 2.5 (CH_3, singlet), 2.0, 2.8 (ring CH_2, broad), 7.04 (=CH–, singlet), 11.7—12 (OH, broad).

2-Hydroxy-4-methyl-6, 7-dihydro-5*H*-1-pyrindine (IV). A mixture of ethyl acetoacetate (13 g, 0.1 mol), cyclopentanone (8.4 g, 0.1 mol), and ammonium acetate (7.7 g, 0.1 mol) was refluxed for 8 hr. After the reaction mixture had then stood overnight, a crystalline matter was precipitated. Recrystallization from glacial acetic acid afforded colorless needles, mp 243—244°C; yield 3.5 g (23.5%).

Found: C, 72.47; H, 7.27; N, 9.36%. Calcd for $C_9H_{11}ON$: C, 72.45; H, 7.43; N, 9.39%.

IR: 3440 (broad, ν OH), 1650 (ν C=O), 1620, 1580 (ν C=C), 1450, 1375 (δ CH_3).

NMR: 2.5 (CH_3, singlet), 2—2.8 (ring CH_2, multiplet), 2.85—3.5 (ring CH_2, multiplet), 7.0 (=CH–, singlet), 12—12.5 (OH, broad).

2-Hydroxy-4-methyl-6-phenylpyridine (VIa). A mixture of ethyl acetoacetate (26 g, 0.2 mol), acetophenone (24 g, 0.2 mol), and ammonium acetate (15.4 g, 0.2 mol) was refluxed for 15 hr. After the reaction mixture had then stood several days, a crystalline compound separated. Recrystallization from alcohol gave colorless needles, mp 181—182°C;[2] yield 2.3 g (6%).

Found: C, 77.87; H, 5.84; N, 7.64%. Calcd for $C_{12}H_{11}ON$: C, 77.81; H, 5.99; N, 7.56%.

IR: 3420 (broad and weak, ν OH), 1645 (ν C=O), 1600 (ν C=C).

NMR: 2.26 (CH_3, singlet), 6.36 (=CH–, singlet), 7.55 (C_6H_5, multiplet), 10—10.5 (OH, broad).

2-Hydroxy-4-methyl-6-(α-naphthyl)pyridine (VIb). A mixture of ethyl acetoacetate (13 g, 0.1 mol), methyl α-naphthyl ketone (17g, 0.1mol), and ammonium acetate (7.7 g, 0.1 mol) was refluxed for 12 hr. After the reaction mixture had then been cooled, it was washed with water and extracted with benzene. After the solvent had been removed, the residue was allowed to stand more than three days. A pale yellow powder was thus obtained. Recrystallization from methanol and benzene gave colorless crystals, mp 204—206°C; yield 2 g (8.5%).

Found: C, 81.93; H, 6.11; N, 5.78%. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95%.

IR: 1640 (ν C=O), 1600, 1580, 1550, 1510 (ν C=C).

NMR: 2.2 (CH_3, singlet), 6.2 (=CH–, singlet), 7.3—8.0 ($C_{10}H_7$, multiplet), 11.3—11.8 (OH, broad).

The authors wish to express their hearty thanks to Dr. Taro Hayashi and Dr. Tatsuo Takeshima for their kind advice. Thanks are also to Dr. Haruo Homma and his staff for their microanalyses.