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The Cyclization of Benzoylacetonitrile and Ketones by Ammonium Acetate

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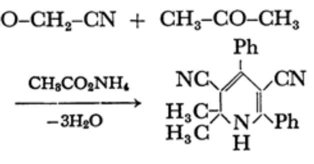
Several heterocyclic compounds, such as dihydropyridine, pyridine, tetrahydroquinoline and hexahydroquinoline derivatives, were prepared by the reaction of benzoylacetonitrile with such ketones as acetone, cyclopentanone, cyclohexanone, alkylcyclohexanone, alkylidenecyclohexanone, and aromatic α,β-unsaturated ketone in the presence of ammonium acetate.

In previous paper,[1–3] the syntheses of various nitrogen heterocyclic compounds by means of cyclization between active methylene compounds (ethyl cyanoacetate, ethyl acetoacetate, and malononitrile) and ketones in the presence of ammonium acetate have been reported.

The present paper will deal with the syntheses of similar heterocyclic compounds containing nitrogen by means of the reaction of benzoylacetonitrile with ketones in the presence of ammonium acetate.

Benzoylacetonitrile and acetone in the presence of ammonium acetate reacted in a 2 : 1 molar ratio to give 3,5-dicyano-2,2-dimethyl-4,6-diphenyl-1,2-dihydropyridine (I), with the elimination of three moles of water, as is indicated in the following scheme:

$$2\ \mathrm{Ph{-}CO{-}CH_2{-}CN} + \mathrm{CH_3{-}CO{-}CH_3}$$



I

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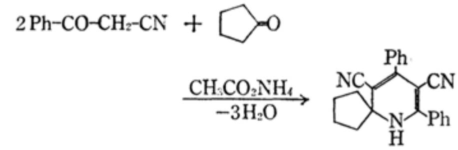
[1] A. Sakurai and H. Midorikawa, This Bulletin, **40**, 1680 (1967).

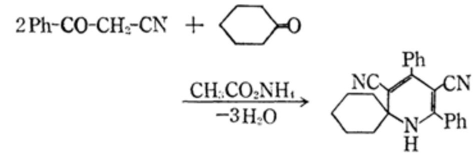
[2] A. Sakurai and H. Midorikawa, *ibid.*, **41**, 165 (1968).

[3] A. Sakurai and H. Midorikawa, *ibid.*, **41**, 430 (1968)

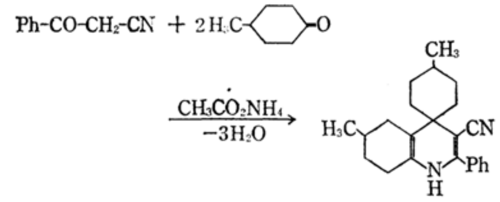
The condensations of benzoylacetonitrile with cyclic ketones are considered to proceed similarly to that of acetone. In these reactions, spiro compounds of such pyridine derivatives as 3,5-dicyano-4,6-diphenyl-1,2-dihydropyridine-2-spiro-1′-cyclopentane (II) and 3,5-dicyano-4,6-diphenyl-1,2-dihydropyridine-2-spiro-1′-cyclohexane (III) were prepared from cyclopentanone and cyclohexanone respectively. On the other hand, the reaction with such an alkylcyclohexanone as 4-methylcyclohexanone was abnormal, and afforded a spiro compound of hexahydroquinoline such as 3-cyano-6,4′-dimethyl-2-phenyl-1,4,5,6,7,8-hexahydroquinoline-4-spiro-1′-cyclohexane (IV), with the elimination of three moles of water from two moles of ketone, one mole each of benzoylacetonitrile and ammonia, as is illustrated below. In this reaction, it was considered that two moles of 4-methylcyclohexanone first condensed, and then cyclized through a Michael reaction such as those of such alkylidenecyclohexanones as 2-benzylidenecyclohexanone and 5-methyl-2-isopropylidenecyclohexanone described below, while the reaction with 2-methylcyclohexanone did not give the dihydropyridine or hexahydroquinoline derivative under similar conditions.



II



III



IV

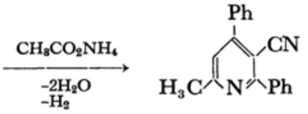
Infrared spectra of compounds I, II and III revealed the absorption bands of imino groups (*ca.* 3200—3290 cm^{-1}) and conjugated cyano groups (*ca.* 2180—2200 cm^{-1}).

The structure of IV was supported by the IR and NMR spectra. Furthermore, the hydrolysis of the cyano group of IV by heating with 60% sulfuric acid gave 6,4′-dimethyl-2-phenyl-1,4,5,6,7,8-hexahydroquinoline-4-spiro-1′-cyclohexane sulfate, melting at 213—215°C with decomposition.

Attempts to prepare the corresponding dihydropyridine derivatives by condensations with such aliphatic higher ketones as methyl ethyl ketone, methyl *n*-propyl ketone, and diethyl ketone or such aromatic ketones as acetophenone and *o*-hydroxyacetophenone were unsuccessful under similar conditions. In these cases, the same compound as that prepared by the self-condensation of benzoylacetonitrile was obtained.

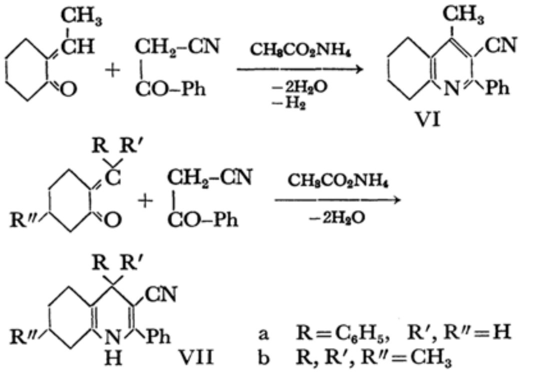
The reaction of benzoylacetonitrile with an *α,β*-unsaturated ketone such as benzalacetone in the presence of ammonium acetate in a 1 : 1 molar ratio took place, and the pyridine derivative was obtained through a Michael addition, with the elimination of two moles of water and one mole of hydrogen, as is illustrated below:

$$\text{Ph–CO–CH}_2\text{–CN} + \text{Ph–CH=CH–CO–CH}_3$$



V

The condensations of benzoylacetonitrile with alkylidenecyclohexanones were considered to proceed similarly to that of the *α,β*-unsaturated ketone (molar ratio 1 : 1). From the reaction with 2-ethylidenecyclohexanone, 3-cyano-4-methyl-2-phenyl-5,6,7,8-tetrahydroquinoline (VI) was prepared through a Michael addition, with the elimination of two moles of water and one mole of hydrogen. On the other hand, the reactions with 2-benzylidenecyclohexanone or 5-methyl-2-isopropylidenecyclohexanone afforded hexahydroquinoline derivatives, such as 3-cyano-2,4-diphenyl-1,4,5,6,7,8-hexahydroquinoline (VIIa) and 3-cyano-4,4,7-trimethyl-2-phenyl-1,4,5,6,7,8-hexahydroquinoline (VIIb). The scheme of these reactions is indicated as follows:

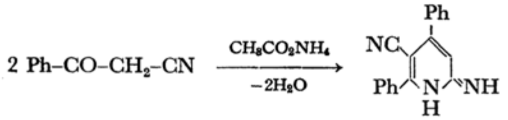


a $R=C_6H_5$, $R', R''=H$
b $R, R', R''=CH_3$

The infrared spectra of VIIa and VIIb exhibited the absorption bands of an imino group (3380—3260 cm^{-1}), but the compound VI gave no absorption band in this region. Also, the compounds VI, VIIa, and VIIb revealed the absorptions at 2200—2180 cm^{-1} due to the presence of a conjugated cyano group. The NMR spectra supported these structures.

The hydrolysis of the cyano group of VI by heating with 60% sulfuric acid gave the corresponding amide melting at 217—219°C.

Benzoylacetonitrile afforded a pyridine derivative by self-condensation in the presence of ammonium acetate. When benzoylacetonitrile was heated with ammonium acetate in glacial acetic acid or alcohol, 6-amino-3-cyano-2,4-diphenylpyridine (VIII) was formed, with the elimination of two moles of water from two moles of benzoylacetonitrile and one mole of ammonia, as is indicated below:



VIII

This compound was also obtained when the reaction was carried out in another solvent, such as benzene or toluene, or without any solvent. The NMR spectrum of the compound VIII showed signals at 7.22 ppm (1H) and 7.85 ppm (1H) due to the presence of imino groups. This fact seems to indicate that the imino form is predominant over the amino form.

The reaction of mesityl oxide with benzoylacetonitrile did not give the expected pyridine derivative, but the same compound as that obtained by the reaction with acetone.

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 trifluoroacetic acid or deuteriodimethylsulfoxide at a frequency of 60 Mc, using tetramethylsilane as an internal standard. The chemical shifts are given as ppm downfield from tetramethylsilane.

The Reaction of Benzoylacetonitrile with Ammonium Acetate. A mixture of benzoylacetonitrile (3 g, 0.02 mol) and ammonium acetate (1.6 g, 0.02 mol) was heated in 7 m*l* of alcohol for 4 hr. After it had then been cooled, a crystalline precipitate was obtained; the precipitate was collected and washed with water, dried, and treated with hot alcohol. It was divided into two parts: a hot alcohol-soluble part (A) and a hot alcohol-insoluble part (B). A small amount of water was added to the hot alcohol solution A. After standing overnight at room temperature, pale yellow crystals precipitated out. Recrystallization from dilute alcohol gave 6-amino-2,4-diphenylnicotinonitrile (VIII) melting at 217—218°C[4]; yield, 2 g (35%).

Found: C, 79.91; H, 4.82; N, 15.36%. Calcd for $C_{18}H_{13}N_3$: C, 79.68; H, 4.83; N, 15.49%.

IR: 3460, 3330 (ν NH), 2210 (ν C≡N), 1620, 1590, 1575, 1535, and 1500 cm^{-1} (hetero ring and C_6H_5).

NMR [$(CD_3)_2SO$]: 6.55 (-CH=, singlet, 1H), 7.22 (NH, singelt, 1H), 7.85 (NH, singelt, 1H), and 7.57 ppm (C_6H_5, singlet, 10H).

The hot alcohol-insoluble precipitate, B, was recrystallized from pyridine and a small amount of dilute methanol to give 0.7 g of yellow crystals, melting at 313—315°C. Its structure could not be confirmed.

3,5-Dicyano-2,2-dimethyl-4,6-diphenyl-1,2-dihydropyridine (I). To a mixture of benzoylacetonitrile (2.5 g, 0.017 mol) and acetone (1 g, 0.017 mol), ammonium acetate (1.2 g, 0.016 mol) was added. When the reaction mixture was then heated for 4 hr, a yellow crystalline matter precipitated. After it had been cooled at room temperature, the crystals were collected and washed with an ether-methanol solution and then with water. Recrystallization from glacial acetic acid afforded pale yellow needles, mp 282—284°C; yield, 1.5 g (56%).

Found: C, 81.17; H, 5.18; N, 13.46%. Calcd for $C_{21}H_{17}N_3$: C, 81.00; H, 5.50; N, 13.50%.

IR: 3250, 3200 (ν NH), 2195, 2205 (ν C≡N), 1640, 1580, and 1500 cm^{-1} (hetero ring and C_6H_5).

NMR (CF_3CO_2H): 1.7 (CH_3, singlet, 6H), 7.24 (NH, broad, 1H), and 7.6 ppm (C_6H_5, singlet, 10H).

3,5-Dicyano-4,6-diphenyl-1,2-dihydropyridine-2-spiro-1′-cyclopentane (II). To a mixture of benzoylacetonitrile (2.5 g, 0.017 mol) and cyclopentanone (1.5 g, 0.017 mol), ammonium acetate (1.2 g, 0.016 mol) was added, and the solution was refluxed for 3 hr. After the reaction mixture had been cooled, a crystalline precipitate was formed. It was collected and washed with acetone and then with water. Recrystallization from glacial acetic acid afforded 1 g (34%) of pale yellow needles, mp 281—283°C.

Found: C, 81.39; H, 5.23; N, 12.58%. Calcd for $C_{23}H_{19}N_3$: C, 81.87; H, 5.68; N, 12.45%.

IR: 3250, 3210 (ν NH), 2200 (ν C≡N), 1640, 1580, 1500, and 1480 cm^{-1} (hetero ring and C_6H_5).

NMR (CF_3CO_2H): 1.7—2.6 (ring CH_2, complex multiplet, 8H), 7.25 (NH, singlet, 1H), and 7.52 ppm (C_6H_5, singlet, 10H).

3,5-Dicyano-4,6-diphenyl-1,2-dihydropyridine-2-spiro-1′-cyclohexane (III). A mixture of benzoylacetonitrile (1.5 g, 0.01 mol), cyclohexanone (1 g, 0.01 mol), and ammonium acetate (0.6 g, 0.008 mol) was heated for 3 hr. The reaction mixture was then left to stand in a refrigerator overnight. The crystalline matter thus formed was separated on a filter, washed with an ether-methanol solution, and dried. It was recrystallized from alcohol-glacial acetic acid to give 1.5 g (27%) of pale yellow crystals metling at 224—227°C.

Found: C, 81.99; H, 5.96; N, 11.85%. Calcd for $C_{24}H_{21}N_3$: C, 82.02; H, 6.02; N, 11.96%.

IR: 3290, 3240 (ν NH), 2195, 2180 (ν C≡N), 1630, 1605, 1575, and 1490 cm^{-1} (hetero ring and C_6H_5).

3-Cyano-6,4′-dimethyl-2-phenyl-1,4,5,6,7,8-hexahydroquinoline-4-spiro-1′-cyclohexane (IV). A mixture of benzoylacetonitrile (2.9 g, 0.02 mol), 4-methylcyclohexanone (2.24 g, 0.02 mol), and ammonium acetate (2.3 g, 0.03 mol) was heated for 3 hr. After being left standing for several hours, a pale yellow precipitate began to separate from the solution. The precipitated crystals were collected and washed with ether-methanol and then with water. Recrystallization from alcohol gave 1.5 g (22.5%) of white needles, mp

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[4] S. Checchi and P. Papini, *Gazz. Chim. Ital.*, **90**, 46 (1960).

196—199°C.

Found: C, 82.76; H, 8.20; N, 8.15%. Calcd for $C_{23}H_{28}N_2$: C, 83.08; H, 8.49; N, 8.43%.

IR: 3280 (νNH), 2180 (ν C≡N), 1670, 1590, 1570, and 1500 cm^{-1} (hetero ring and C_6H_5).

NMR [$(CD_3)_2SO$]: 1.00 (CH_3, doublet, 6H), 1.3—2.4 (ring CH_2 and $-\overset{|}{C}H-$, complex multiplet, 16H), 7.55 (C_6H_5, singlet, 5H), and 8.95 ppm (NH, broad, 1H).

Hydrolysis of 3-Cyano-6,4′-dimethyl-2-phenyl-1,4,5,6,7,8-hexahydroquinoline-4-spiro-1′-cyclohexane (IV). To a solution of 95% sulfuric acid (19.2 g) and water (10.8 g), IV (1.5 g) was added, and the mixture was heated for 1 hr. After it had then cooled, a pale yellow crystalline matter separated. It was collected and recrystallized from dilute alcohol to give 0.8 g of 6,4′-dimethyl-2-phenyl-1,4,5,6,7,8-hexahydroquinoline-4-spiro-1′-cyclohexane sulfate melting at 213—215°C with decomposition.

Found: C, 64.87; H, 7.61; N, 3.49; S, 7.71%. Calcd for $C_{22}H_{31}O_4NS$: C, 65.16; H, 7.71; N, 3.45; S, 7.89%.

6-Methyl-2,4-diphenylnicotinonitrile (V). A mixture of benzoylacetonitrile (2 g, 0.014 mol), benzalacetone (2 g, 0.014 mol), and ammonium acetate (1 g, 0.013 mol) was refluxed in 5 m*l* of glacial acetic acid for 5 hr. After cooling, a small amount of water was added to the reaction mixture and it was allowed to stand in a refrigerator overnight. The crystalline matter which was precipitated was collected on a filter and recrystallized from alcohol to afford 1.2 g (32%) of pale yellow needles, mp 150—151°C.

Found: C, 84.40; H, 5.17; N, 10.61%. Calcd for $C_{19}H_{14}N_2$: C, 84.42; H, 5.22; N, 10.36%.

IR: 2220 (ν C≡N), 1590, 1575, 1535, and 1500 cm^{-1} (hetero ring and C_6H_5).

NMR (CF_3CO_2H): 3.07 (CH_3, singlet, 3H), 8.05 (–CH=, singlet, 1H), and 7.8 ppm (C_6H_5, singlet, 10H).

3-Cyano-4-methyl-2-phenyl-5,6,7,8-tetrahydroquinoline (VI). A mixture of benzoylacetonitrile (2 g, 0.014 mol), ethylidenecyclohexanone (1.73 g, 0.014 mol), and ammonium acetate (1 g, 0.013 mol) was refluxed in 5 m*l* of glacial acetic acid for 6 hr. After cooling, the reaction mixture was neutralized with sodium carbonate and allowed to stand overnight at room temperature. A crystalline matter separated from the solution. It was collected and washed with water and then with dilute methanol. Recrystallization from alcohol gave 1.7 g (50%) of colorless needles, mp 127—129°C.

Found: C, 82.53; H, 6.50; N, 11.24%. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.50; N, 11.28%.

IR: 2220 (ν C≡N), 1585, 1550, and 1500 cm^{-1} (hetero ring and C_6H_5).

NMR (CF_3CO_2H): 2.05 (ring CH_2, broad, 4H), 2.85 (CH_3, singlet, 3H), 2.97, 3.28 (ring CH_2, broad, 4H), and 7.75 ppm (C_6H_5, singlet, 5H).

Hydrolysis of 3-Cyano-4-methyl-2-phenyl-5,6,7,8-tetrahydroquinoline (VI). To a solution of 95% sulfuric acid (9.6 g) and water (5.4 g), VI (0.5 g) was added, and then the mixture was heated for 1 hr.

After being cooled, the solution was poured into ice water. The white precipitate which deposited was collected and dissolved in water, and a few drops of a 10% sodium hydroxide solution were added to it. The precipitated product was washed with water and recrystallized from dilute alcohol to give 0.2 g of 3-carbamoyl-4-methyl-2-phenyl-5,6,7,8-tetrahydroquinoline melting at 217—219°C.

Found: C, 76.48; H, 6.53; N, 10.41%. Calcd for $C_{17}H_{18}ON_2$: C, 76.66; H, 6.81; N, 10.52%.

3-Cyano-2,4-diphenyl-1,4,5,6,7,8-hexahydroquinoline (VIIa). A mixture of benzoylacetonitrile (2 g, 0.014 mol), 2-benzylidenecyclohexanone (2.6 g, 0.014 mol), and ammonium acetate (1.23 g, 0.016 mol) was heated for 5 hr. After the mixture had been left standing for several days, a crystalline mass separated. It was washed with ether, a small amount of a methanol mixture, and then with water. Recrystallization from dilute alcohol afforded 1.5 g (34%) of colorless crystals, mp 132—134°C.

Found: C, 84.42; H, 6.37; N, 8.98%. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97%.

IR: 3380 (ν NH), 2180 (ν C≡N), 1695, 1610, 1600, 1575, 1550, 1505, and 1495 cm^{-1} (hetero ring and C_6H_5).

3-Cyano-4,4,7-trimethyl-2-phenyl-1,4,5,6,7,8-hexahydroquinoline (VIIb). A mixture of benzoylacetonitrile (2 g, 0.014 mol), 2-isopropylidene-5-methylcyclohexanone (2.1 g, 0.014 mol), and ammonium acetate (1.5 g, 0.02 mol) was refluxed in 5 m*l* of glacial acetic acid for 6 hr. After it had stood overnight, a crystalline matter separated; it was collected on a filter, washed with water, and recrystallized from glacial acetic acid to afford 0.9 g (24%) of colorless needles melting at 195—198°C.

Found: C, 81.81; H, 7.84; N, 10.04%. Calcd for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06%.

IR: 3260 (ν NH), 2180 (νC≡N), 1685, 1615, 1600, 1575, 1515, and 1495 cm^{-1} (hetero ring and C_6H_5).

NMR (CF_3CO_2H): 1.2 (7-CH_3, doublet, 3H), 1.45 (4-CH_3, doublet, 6H), 1.8—3.5 (ring CH_2 and $-\overset{|}{C}H-$, complex multiplet), and 7.55 ppm (C_6H_5, singlet, 5H).

The Reaction of Benzoylacetonitrile with Mesityl Oxide. To a mixture of benzoylacetonitrile (1.45 g, 0.01 mol) and mesityl oxide (0.98 g, 0.01 mol), ammonium acetate (0.77 g, 0.01 mol) was added, and the mixture was heated for 5 hr. After the reaction mixture had been left to stand at room temperature, a crystalline matter precipitated. It was collected on a filter, washed with water, and recrystallized from glacial acetic acid and water to afford 0.8 g (26%) of 3,5-dicyano-2, 2-dimethyl-4, 6-diphenyl-1, 2-dihydropyridine (I) as yellow needles, mp 278—281°C.

Found: C, 80.62; H, 4.98; N, 13.68%. Calcd for $C_{21}H_{17}N_3$: C, 81.00; H, 5.50; N, 13.50%.

This substance was identified with the compound obtained by the reaction between acetone and benzoylacetonitrile by a comparison of their infrared spectra.

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