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The Reaction of Dicarboximides with Benzonitrile in Liquid Ammonia

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Synopsis. Acyclic dicarboximides were treated with benzonitrile in the presence of sodium amide to give 4-hydroxypyrimidines. However, the reaction of succinimide with benzonitrile gave 5-hydroxy-2-phenyl-2-pyrroline-3-carboxamide. Also, glutarimide gave a similar product.

In a previous paper[1] we reported that β-diketone condensed with benzonitrile (**1**) to give 4(1*H*)-pyridone directly. In this reaction it was assumed that an intermediately-formed imino-β-diketone was dehydrocyclized to 4(1*H*)-pyridone. A similar reaction has been shown in the reaction of **1** with ethyl acetoacetate.[2]

Diacetimide (**2**), *N*-acetylbenzamide (**3**), ethyl *N*-acetylcarbamate (**4**), succinimide (**5**) and glutarimide (**6**) all have the same $-CH_2CONHCO-$group. Since this group is expected to behave in liquid ammonia much like the $-CH_2COCH_2CO-$group, these compounds were subjected to a reaction with **1** in the presence of alkali amide in liquid ammonia.

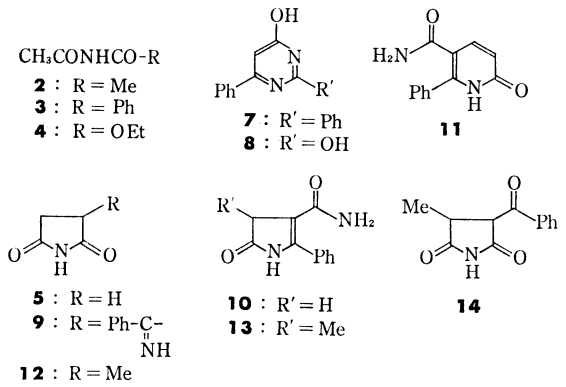

Fig. 1.

Compound **2** did not react with **1** in the presence of sodium amide in liquid ammonia. However, **3** reacted with an equimolar **1** in the presence of three molar equivalents of sodium amide to give 4-hydroxy-2,6-diphenylpyrimidine (**7**). The structure of **7** was verified by comparing the spectral data of **7** with those described in the literature.[3] Compound **7** was also identified with the product which was obtained by the reaction of ethyl benzoylacetate with benzamidine hydrochloride. Ethyl *N*-acetylcarbamate (**4**) also reacted with **1** in the presence of three molar equivalents of potassium amide in liquid ammonia to give 10.8% of 2,4-dihydroxy-6-phenylpyrimidine (**8**). The structure of **8** was identified by mean of a comparison with an authentic sample[4] and was also supported by the infrared spectrum.

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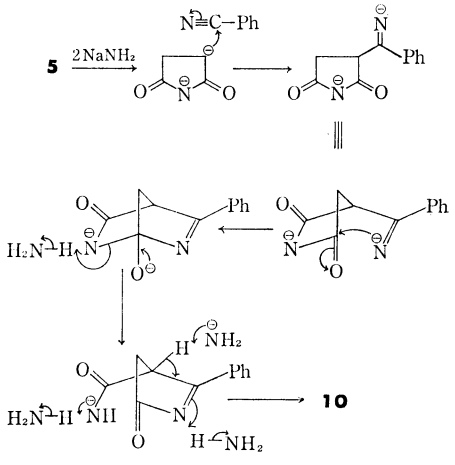
Compound **5** was allowed to react with equimolar **1** in the presence of three molar equivalents of sodium amide in liquid ammonia. However, instead of the expected product, *i.e.*, 3-benzimidoylsuccinimide (**9**),[5] colorless needles were obtained in a 58.2% yield. The infrared spectrum of this compound showed three amide bands, at 3450, 3320, and 3300 cm^{-1}, and two carbonyl bands, at 1730 and 1675 cm^{-1}. The NMR spectrum was assignable for the signals at δ 3.33 and 7.40 ppm for the methylene and aromatic protons; moreover, the amino protons were observed at δ 8.13 and 11.98 ppm, but they disappeared with the use of deuterium oxide. From these spectral data and the elemental analysis, the structure of this compound was proved to be 5-oxo-2-phenyl-2-pyrroline-3-carboxamide (**10**). When glutarimide (**6**) and **1** were treated under conditions similar to those described above, 3,4-dihydroxy-6-phenyl-2(1*H*)-pyridone-5-carboxamide (**11**) was obtained in a 35% yield. The structure of **11** was proved by the spectral data and the elemental analysis. Although this type of synthesis is known in the literature,[6] our synthetic method is still simpler and more useful.

In order to investigate the change in the reactivity of succinimide with a substituent at the 2-position, the reaction of 2-methylsuccinimide (**12**) with **1** was carried out. However, instead of the expected pyrrolinecarboxamide (**13**), 3-benzoyl-2-methylsuccinimide (**14**) was obtained in a 22% yield.



Scheme 1.

The formation mechanism of **10** from **5** and **1** was speculated as follows: Imide **5** reacted with **1** to give **9**, followed by recyclization to **10**, as is illustrated in Scheme 1. On the reaction of **12** and **1**, we supposed that the benzimidoyl intermediate was also formed first and was then hydrolyzed to **14**, because of some steric

hindrance and inductive effect of the methyl group at the cyclization stage.

Experimental

4-Hydroxy-2,6-diphenylpyrimidine (7). *Method A*: To a solution of 0.15 mol of sodium amide in about 300 ml of liquid ammonia in a three-necked flask, we added 0.05 mol (8.15 g) of **3**. After 1 hr's stirring, 0.05 mol (5.2 g) of **1** in 30 ml of anhydrous ether was added. The mixture was then stirred for an additional 3 hr at −33 °C and then neutralized with 8.1 g of solid ammonium chloride. The liquid ammonia was driven off rapidly, and 100 ml of dilute hydrochloric acid was added. The white precipitates thus obtained were collected, washed with ether, and recrystallized from hot pyridine to give 2.80 g (22.6%) of **7** as colorless needles; mp 284—286 °C (lit, 289—290 °C[5]).

Method B: Compound **7** was also prepared by the following method. To a solution of 0.2 mol of sodium amide in 300 ml of liquid ammonia, we added 0.05 mol (8.0 g) of benzamidine hydrochloride dihydrate.[7] After 1 hr's stirring, 0.05 mol (9.6 g) of ethyl benzoylacetate in 30 ml of anhydrous ether was added, drop by drop. The mixture was then stirred for an additional 3.5 hr at −33 °C and subsequently treated as above.

2,4-Dihydroxy-6-phenylpyrimidine (8). According to Method A, **8** was synthesized from 0.15 mol of potassium amide, 0.05 mol (6.6 g) of **4** and 0.05 mol (5.2 g) of **1**. Yield, 1.02 g (10.8%); yellowish white prisms (from hot water); mp 269—271 °C (lit, 270 °C[6]).

Reaction of **2** *with* **1**. According to Method A, 0.05 mol of **2**, 0.05 mol of **1**, and 0.15 mol of sodium amide were treated in liquid ammonia. No pyrimidine compound could be detected.

5-Oxo-2-phenyl-2-pyrroline-3-carboxamide (10). According to Method A, 0.15 mol of sodium amide, 0.05 mol (4.95 g) of **5**,[8] and 0.05 mol of **1** were treated in liquid ammonia. After neutralization with 8.1 g of solid ammonium chloride, the liquid ammonia was completely evaporated. Then 400 ml of ethanol was added to the residue, and the insoluble substance was dissolved in 100 ml of pyridine. The ethanol solution was then concentrated to about 50 ml under reduced pressure to yield 2.98 g of a white precipitate after standing overnight. The pyridine solution was evaporated to dryness under reduced pressure to give 2.90 g of a white substance. The combined precipitate (5.88 g, 58%) was again recrystallized from ethanol to give pure **10** as colorless needles; mp 197—197.5 °C. Found: C, 65.36; H, 5.16; N, 13.76%. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86%. UV: λ_{max}^{EtOH} 230 (ε 5100) and 314 nm (14700).

3,4-Dihydro-6-phenyl-2(1H)-pyridone-5-carboxamide (11). According to Method A, **11** was prepared from 0.15 mol of sodium amide, 0.05 mol of **1**, and 0.05 mol (5.65 g) of **6**.[9] After the evaporation of the liquid ammonia, we added 300 ml of hot pyridine to the residue; after filtration, the filtrate was concentrated to dryness, and to this residue we added a benzene–ethanol mixture. The resulting insoluble substance (2.75 g) was filtered, and the filtrate was concentrated. The residue was chromatographed on a silica gel (Merck 7734, 0.05—0.2 mm) column using a benzene–ethyl acetate (1:1 v/v) mixture. The fraction which showed an R_f value of 0.56 on silica gel (Wakogel B-5) thin layer chromatography (tlc) with the benzene–ethyl acetate (1:1 v/v) mixture was collected and concentrated to give a white solid (1.03 g), which was proved to be the same compound as the above insoluble substance by the results of tlc and by the spectral data. The combined product (3.78 g, 35.0%) was recrystallized from hot pyridine to give pure **11** as colorless crystals; mp 231—232 °C. Found: C, 66.42; H, 5.66; N, 13.19%. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96%. IR (KBr): 3410, 3220, 3130, 1700, 1650, 1635, 1615, and 695 cm^{-1}. UV: λ_{max}^{EtOH} 225 (ε 10600) and 281 nm (8030). NMR: $\delta^{pyridine-d_5}$ 2.80 (m, 4H), 7.05 (broad s, 2H), 7.40 (m, 5H), and 10.90 ppm (broad s, 1H).

3-Benzoyl-2-methylsuccinimide (14). According to Method A, **14** was obtained from 0.15 mol of sodium amide, 0.05 mol of **1**, and 0.05 mol of **12**. After the evaporation of the liquid ammonia, to the residue we added 200 ml of dilute hydrochloric acid and the resulting white precipitate (**14**) was collected. The filtrate was extracted with two 200 ml portions of ether. The ether extracts were combined and washed with water and dried over anhydrous sodium sulfate. After evaporating the solvent, we added an *n*-hexane–benzene (1:1 v/v) mixture to the viscous product. The resulting precipitate was recrystallized from benzene to give 2.40 g (22.1%) of **14** as colorless leaflets; mp 147—149 °C. Found: C, 66.26; H, 5.08; N, 6.56%. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45%. IR (KBr): 3075, 3200, 1780, 1710, 1670, and 700 cm^{-1}. UV: λ_{max}^{EtOH} 250 (ε 13100) and 287 nm (2420). NMR: $\delta^{acetone-d_6}$ 1.77 (d, 3H), 3.22—3.68 (oct, 1H), 4.87 (d, 1H), 7.31—7.81 (m, 3H), 8.04—8.22 (m, 2H) and 10.15 ppm (broad s, 1H, disappeared by D_2O).

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