Reaction of 2-Benzoylamino-2-methylpropionamidine and 2-Benzoylaminoacetamidine with Bifunctional Compounds

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The reaction of 2-benzoylamino-2-methylpropionamidine (III) with 1,3-bifunctional compounds was investigated in connection with studies on 2-benzoylaminoacetamidine (I). In case of the reaction of III an appreciable amount of 5,5-dimethyl-2-phenylimidazolin-4-imide (VIII) was formed, the yield of 2-(1-benzoylamino-1-methylethyl)-4,6-dimethylpyrimidine (VI) being low. On the other hand, III reacted with ethyl acetoacetate to give 2-(1-benzoylamino-1-methylethyl)-4-hydroxy-6-methylpyrimidine (IX) in about 50% yield besides VIII. Both III and I were made to react with ethoxymethyleneacetylacetone to yield 5-acetyl-2-(1-benzoylamino-1-methylethyl)-4-methylpyrimidine (X) and 5-acetyl-2-(*N*-benzoylaminomethyl)-4-methylpyrimidine (XI), respectively. Reaction of I with ethoxymethylenemalononitrile gave 4-amino-2-(*N*-benzoylaminomethyl)-5-cyanopyrimidine (XII), but did not proceed with benzoin, malondialdehyde, tetraethoxypropane or phenacyl bromide.

In a previous paper[1] the reactions of 2-benzoylaminoacetamidine (I)[2] and 2-benzyloxycarbonylaminoacetamidine (II)[2] with various 1,3-bifunctional compounds were described. It was pointed out that both I and II react with acetylacetone to produce 2-amino-3-benzoylamino- and 2-amino-3-benzyloxycarbonylamino-4,6-dimethylpyridine, respectively, erroneously reported by Goldberg and Kelly[3] to be pyrimidine derivatives. Reaction of I with ethyl acetoacetate gave 2-(*N*-benzoylaminomethyl)-4-hydroxy-6-methylpyrimidine. However, in every case, concurrent formation of a considerable amount of acylaminoacetamide was observed. The formation of pyridine derivatives is ascribed to the reactive α-methylene group of amidines and depends on the function of 1,3-bifunctional compounds. An amidine which has no α-hydrogen might therefore produce a pyrimidine derivative exclusively. We have investigated the reaction of 2-benzoylamino-2-methylpropionamidine (III) with acetylacetone and ethyl acetoacetate in the presence of alkali.

Amidine (I and III) hydrochlorides were prepared from the nitriles *via* the imidate hydrochlorides following the usual procedure. Shirai and Kurashige[4] reported that the reaction of 2-(*N*-acetyl-*N*-methylamino)-2-methylpropionitrile (IV) with hydrogen chloride and ethanol afforded the corresponding imidate hydrochloride and imidazolone hydrochloride, and ammonolysis of the imidate hydrochloride afforded imidazolinimide hydrochloride instead of the corresponding amidine hydrochloride.

As regards the imidate hydrochloride or amidine hydrochloride we prepared, contaminants in III hydrochloride were trace amounts of ammonium chloride and 2-benzoylamino-2-methylpropionamide (V), formation of imidazolone or imidazolinimide[4] not being observed. Purification of crude III hydrochloride was effected by fractional precipitation by adding ether to the alcoholic solution of the crude product.

Reaction of III with acetylacetone was carried out under various conditions, as shown in Table 1. It can be seen that attempts to improve the yield of 2-(1-benzoylamino-1-methylethyl)-4,6-dimethylpyrimidine (VI) were unsuccessful under all the conditions. The empirical formula of the main product was $C_{11}H_{13}N_3$ which did not change on heating in water. The compound did not seem to change under alkaline conditions where III and acetylacetone undergo reaction, but turned to 5,5-dimethyl-2-phenyl-4-imidazolone (VII) quantitatively on being left to stand with 10% hydrochloric acid at room temperature. Compound $C_{11}H_{13}N_3$ was warmed with acetic anhydride to give a monoacetylated compound. These results and the spectral data identified the product as 5,5-dimethyl-2-phenylimidazolin-4-imide (VIII).

Reaction of III and acetylacetone in ethanol formed VI in relatively high yield in the presence of weak alkali, and in water moderate temperature seemed to be required. Compound V was obtained in trace amount in Expt. 1—3, in several percent yield in Expt. 4—6, and in 17% yield in Expt. 7. Compound VII was obtained in 7% yield in Expt. 7. This might be caused by hydrolysis of VIII, or by cyclization of V

Table 1. Reaction of III[a] with acetylacetone

Expt. No.	Solvent	Reaction		Alkali	Molar ratio of III·HCl: alkali	Yield of	
		temp. (°C)	time			VI(%)	VIII(%)
1	C_2H_5OH	reflux	7.5 hr	K_2CO_3	1:1	17	72
2	C_2H_5OH	reflux	7.5 hr	C_2H_5ONa	1:0.2[b]	2	75
3	C_2H_5OH	r.t.	3 day	C_2H_5ONa	1:0.3[b]	5	90
4	H_2O	r.t.	5 day	K_2CO_3	1:1.1	5	26
5	H_2O	r.t.	5 day	NaOH	1:2.2	—	55
6	H_2O	55—60	2 hr	K_2CO_3	1:1.1	17	43
7	H_2O	reflux	1 hr	K_2CO_3	1:1.1	—	56

a) Used in the form of hydrochloride with exception of Reactions 2 and 3. b) Ratio of free III: alkali.

in the presence of alkali as reported by Mohr.[5]

Conversion of III hydrochloride itself was examined under nearly the same conditions as in the reaction with acetylacetone. Under reflux for 5.5 hr in ethanol with an equimolecular amount of potassium carbonate, 82% of III hydrochloride was recovered unchanged and a small quantity of amide V was obtained. Refluxing for 4.5 hr with two molar quantities of sodium ethoxide in ethanol gave VIII quantitatively.

Reaction of III and ethyl acetoacetate gave 2-(1-benzoylamino-1-methylethyl)-4-hydroxy-6-methylpyrimidine (IX), which showed a ring carbonyl band at 1682 cm^{-1} and no hydroxyl group absorption, suggesting it to have the keto form in solid state.

The above results show that competitive reactions occurred between intramolecular cyclization of III to VIII and pyrimidine ring formation from III with acetylacetone or ethyl acetoacetate. An attempt to react III with ethoxymethyleneacetylacetone, which is considered to be highly reactive and favorable for pyrimidine ring formation, gave 5-acetyl-2-(1-benzoylamino-1-methylethyl)-4-methylpyrimidine (X) in a satisfactory yield. The reaction with ethoxymethyleneacetylacetone I was also tried, and 5-acetyl-2-(*N*-benzoylaminomethyl)-4-methylpyrimidine (XI) was obtained. In this case α-methylene group of I did not participate in the reaction and no pyridine compound was formed. The reaction of I with ethoxymethylenemalononitrile resulted in the formation of 4-amino-2-(*N*-benzoylaminomethyl)-5-cyanopyrimidine (XII) which was identified by an alternative synthesis from ethyl 2-benzoylaminoacetimidate and aminomethylenemalononitrile. However, reactions of I with benzoin, malondialdehyde, tetraethoxypropane, and phenacyl bromide resulted in the formation of 2-benzoylaminoacetamide.

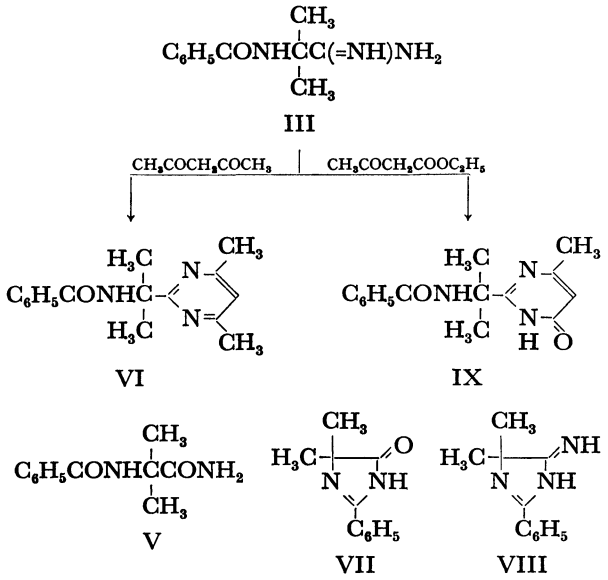

Chart 1

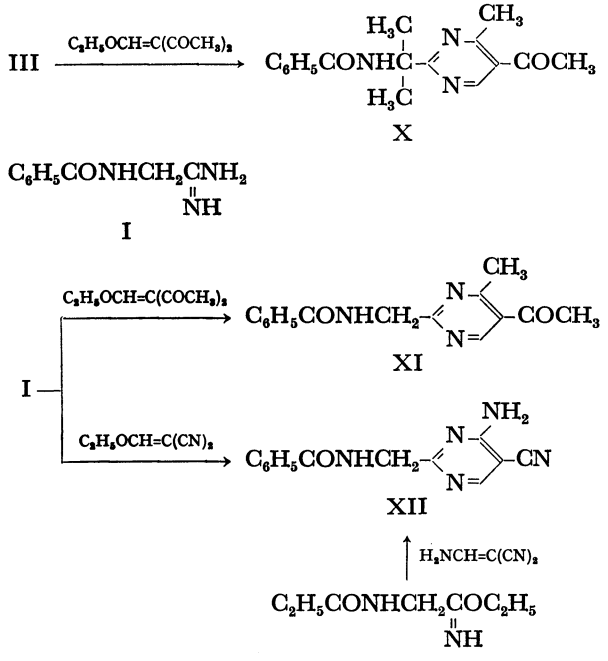

Chart 2

Experimental

All melting points were uncorrected. The NMR spectra were recorded at 60 MHz using tetramethylsilane as an internal standard.

2-Benzoylamino-2-methylpropionamidine(III) Hydrochloride. Hydrogen chloride was introduced to a suspension of 9.4 g (50 mmol) of 2-(*N*-benzoylamino)-2-methylpropionitrile[6] in a mixed solvent of chloroform (55 ml) and benzene (90 ml) containing 2.5 g of ethanol under cooling with ice-salt with occasional shaking, until the nitrile dissolved completely. On being left to stand in a refrigerator a viscous oily product separated which, after removal of the solvent by decantation, was crystallized by the addition of dry ether (150 ml). The resulting crystals were 12.4 g of crude ethyl 2-benzoylamino-2-methylpropionimidate hydrochloride, very hygroscopic, mp 200—202 °C. Found: N, 11.80%. Calcd for $C_{13}H_{19}O_2N_2Cl$: N, 10.35%.

To a solution of ammonia in ethanol (60 ml, 15% by wt) was added the imidate hydrochloride obtained above and the mixture was stirred for 1 hr under cooling with ice. The resulting solution, after being allowed to stand at room temperature for 1 day, was concentrated until crystals began to separate out. Dry petroleum ether (150 ml) was added to the residue, and 10.6 g of crude III hydrochloride was obtained, mp 212—214 °C. Recrystallization from acetonitrile gave colorless needles of III hydrochloride, mp 222—223.5 °C. Found: C, 54.50; H, 6.62; N, 17.68%. Calcd for $C_{11}H_{16}ON_3Cl$: C, 54.66; H, 6.67; N, 17.38%. IR (KBr) cm^{-1}: 3600—2800, 1645, 1536. NMR (DMSO-d_6) τ: 1.09 (s, 4H), 1.31 (s, 1H), 1.83—2.83 (m, 5H), 8.36 (s, 6H).

Crude III hydrochloride (5 g) was dissolved in 70 ml of ethanol, and a small amount of ammonium chloride was precipitated by the addition of 20 ml of dry ether. Additional 125 ml of dry ether gave 4.3 g of colorless needles of III hydrochloride, mp 221—223 °C. The filtrate was concentrated after III hydrochloride had been collected by filtration, and the residue was recrystallized from ethyl acetate to give 0.4 g of colorless needles of V, mp 205—206 °C. Found: C, 63.82; H, 6.89; N, 13.29%. Calcd for $C_{11}H_{14}O_2N_2$: C, 64.06; H, 6.84; N, 13.58%. IR (KBr) cm^{-1}: 3410, 3310, 3225, 3180, 1660, 1640, 1610, 1535. NMR (DMSO-d_6) τ: 1.83 (s, 1H), 1.97—2.69 (m, 5H), 2.97 (bs, 2H), 8.49 (s, 6H).

2-(1-Benzoylamino-1-methylethyl)-4,6-dimethylpyrimidine (VI).

a) Reaction of III with Acetylacetone in Ethanol (Expt. 1, Table 1): To a solution of 1.3 g (13 mmol) of acetylacetone in 30 ml of ethanol was added 2.4 g (10 mmol) of III hydrochloride and 1.5 g (11 mmol) of potassium carbonate, and the mixture was refluxed for 7.5 hr with stirring. The reaction mixture was filtered and the filtrate was concentrated to give crystalline residue. Recrystallization from methanol gave colorless prisms of VIII, mp 246 °C, 0.89 g. Found: C, 70.33; H, 6.88; N, 22.39%. Calcd for $C_{11}H_{13}N_3$: C, 70.56; H, 7.00; N, 22.44%. IR (KBr) cm^{-1}: 3325, 1675, 1603, 1550, 1320, 1290, 703. NMR (DMSO-d_6) τ: 1.65—2.83 (m, 5H), 2.28 (bs, 2H), 8.70 (s, 6H).

The filtrate, after VIII had been collected, was concentrated and the residue was subjected to column chromatography on silica gel. Crystals eluted with methylene chloride were recrystallized from acetonitrile to give colorless prisms of VI, mp 170—171 °C, 0.46 g (17%). Found: C, 71.63; H, 7.10; N, 15.78%. Calcd for $C_{16}H_{19}ON_3$: C, 71.34; H, 7.11; N, 15.60%. IR (KBr) cm^{-1}: 3350, 1664, 1600, 1530, 710. NMR (DMSO-d_6) τ: 1.32 (s, 1H), 2.02—2.63 (m, 5H), 2.86 (s, 1H), 7.58 (s, 6H), 8.27 (s, 6H).

With methylene chloride and ethyl acetate, 0.46 g of VIII was eluted, the total yield being 1.35 g (72%).

b) Reaction of III with Acetylacetone in Water (Expt. 6, Table 1): A solution of 1.5 g (15 mmol) of acetylacetone, 2.4 g (10 mmol) of III hydrochloride, and 1.5 g (11 mmol) of potassium carbonate in 20 ml of water was warmed to 55—60 °C for 2 hr. Crystals, a part of which began to separate out on being warmed for 30 min, were collected by filtration and recrystallized from acetonitrile to give colorless prisms of VI, mp 170—171 °C, 0.45 g (17%). Spectral data were identical with those obtained in the preceding experiment.

The filtrate of the reaction mixture was concentrated, and the residue was subjected to column chromatography on silica gel. Crystals eluted with methylene chloride were recrystallized from ethyl acetate to give colorless prisms of VII, mp 202—204 °C (lit,[7] mp 202 °C), 0.04 g (2%). Found: C, 70.04; H, 6.52; N, 14.94%. Calcd for $C_{11}H_{12}ON_2$: C, 70.18; H, 6.43; N, 14.88%. IR (KBr) cm^{-1}: 3425, 1740, 1713, 1620, 1606, 1550, 702. NMR (DMSO-d_6) τ: 1.46 (s, 1H), 1.69—2.72 (m, 5H), 8.70 (s, 6H).

Continued elution with methylene chloride gave 0.08 g (4%) of V, mp 205—206 °C (ethyl acetate).

With methylene chloride and ethyl acetate, 0.80 g (43%) of VIII was eluted, mp 248—249 °C (ethyl acetate).

2-(1-Benzoylamino-1-methylethyl)-4-hydroxy-6-methylpyrimidine (IX). *a) Reaction of III with Ethyl Acetoacetate in the Presence of Sodium Ethoxide*: An ethanol solution of sodium ethoxide prepared from 0.46 g (20 mmol) of sodium and 20 ml of ethanol was added to a solution of 2.4 g (10 mmol) of III hydrochloride in 30 ml of ethanol under ice cooling, and the precipitated sodium chloride was removed by filtration. To the filtrate was added 1.3 g (10 mmol) of ethyl acetoacetate. The mixture was warmed at 60 °C for 5 hr, and then concentrated. The residue was dissolved in 30 ml of water and neutralized with acetic acid to give a white precipitate. Recrystallization from *n*-butanol gave white powder of IX, mp 276—278 °C, 1.25 g (46%). Found: C, 66.29; H, 6.33; N, 15.22%. Calcd for $C_{15}H_{17}O_2N_5$: C, 66.49; H, 6.32; N, 15.49%. IR (KBr) cm^{-1}: 3230, 1682, 1633, 1600, 1550. NMR (DMSO-d_6) τ: 1.57 (s, 1H), 1.92—2.58 (m, 5H), 3.95 (s, 1H), 7.23 (s, 1H), 7.77 (s, 3H), 8.37 (s, 6H).

The aqueous filtrate, after IX had been separated, was concentrated and the residue was subjected to column chromatography on silica gel. Elution with ethyl acetate gave 0.04 g (2%) of V, mp 207—208 °C (ethyl acetate), and 0.62 g (33%) of VIII, mp 246—248 °C (ethyl acetate).

b) Reaction of III with Ethyl Acetoacetate in the Presence of Sodium Hydroxide: To a solution of III in 40 ml of ethanol, prepared from 2.4 g (10 mmol) of III hydrochloride and 0.23 g (10 mmol) of sodium by the same procedure as in the preceding experiment, was added 1.3 g (10 mmol) of ethyl acetoacetate. The reaction mixture was transferred to an evaporating dish and evaporated to dryness in a desiccator over sulfuric acid. The residue was added to a mixture of 5 ml of 20% aqueous sodium hydroxide and 25 ml of ethanol, and then stirred at room temperature for 1 day. The mixture was concentrated, and the work up as described in the preceding experiment gave white powder of IX, mp 277—278 °C (*n*-butanol), 1.4 g (52%). Spectral data were identical with those of IX obtained in *a*).

The aqueous filtrate after separating IX was concentrated and then subjected to column chromatography on silica gel. The elution with ethyl acetate gave 0.15 g (8%) of VII, mp 201—202 °C (ligroin), and 0.49 g (26%) of VIII, mp 247—248 °C (ethyl acetate).

5,5-Dimethyl-2-phenylimidazoline-4-acetimide. In 10 ml of acetic anhydride, 0.94 g (5 mmol) of VIII was heated at 80 °C for 30 min. The reaction mixture was concentrated and the residue was recrystallized from ethyl acetate to give colorless prisms of 5,5-dimethyl-2-phenylimidazoline-4-acetimide, mp 159 °C, 0.92 g (80%). Found: C, 68.40; H, 6.71; N, 18.45%. Calcd for $C_{13}H_{15}ON_3$: C, 68.10; H, 6.59; N, 18.33%. IR (KBr) cm^{-1}: 3235, 3160, 1690, 1530, 1280. NMR (DMSO-d_6) τ: −0.93 (s, 1H), 1.67—2.73 (s, 5H), 7.50 (s, 3H), 8.54 (s, 6H).

5-Acetyl-2-(1-benzoylamino-1-methylethyl)-4-methylpyrimidine (X). To an ethanol solution of III, prepared from 0.10 g (4.4 mmol) of sodium in 10 ml of ethanol and 1.10 g (4.6 mmol) of III hydrochloride in 15 ml of ethanol, was added 0.78 g (5 mmol) of ethoxymethyleneacetylacetone.[7] The mixture was allowed to stand at room temperature for 13 hr, heated to 80 °C for 1 hr and then concentrated. The residual crystals were recrystallized from ethyl acetate to give colorless needles of X, mp 155—156 °C, 0.83 g (64%). Found: C, 68.92; H, 6.48; N, 14.26%. Calcd for $C_{17}H_{19}O_2N_3$: C, 68.66; H, 6.44; N, 14.13%. IR (KBr) cm^{-1}: 3300, 1688, 1633, 1602, 1532. NMR (DMSO-d_6) τ: 0.63 (s, 1H), 1.10 (s, 1H), 1.73—2.50 (m, 5H), 7.16 (s, 6H), 8.06 (s, 6H).

Crystals insoluble in hot ethyl acetate were recrystallized from ethanol to give colorless needles of unchanged III hydrochloride, mp 225—227 °C, 0.3 g (12%). Spectral data were identical with those of authentic III hydrochloride.

5-Acetyl-2-(N-benzoylaminomethyl)-4-methylpyrimidine (XI). To an ethanol solution of I, prepared from 0.35 g (15 mmol) of sodium in 20 ml of ethanol and 3.2 g (15 mmol) of I hydrochloride in 20 ml of ethanol, was added 2.4 g (15.4 mmol) of ethoxymethyleneacetylacetone. Crystals, once precipitated in large quantities after 5 min stirring, were dissolved completely after 1 hr at room temperature. The mixture, after being allowed to stand at room temperature for 18 hr, was heated at 80 °C for 1 hr and then concentrated. Recrystallization of the residue from benzene gave colorless prisms of XI, mp 110—111 °C, 3.1 g (77%). Found: C, 66.99; H, 5.68; N, 15.72%. Calcd for $C_{15}H_{15}O_2N_3$: C, 66.90; H, 5.61; N, 15.61%. IR (KBr) cm^{-1}: 3410, 1688, 1650, 1600, 1536. NMR (DMSO-d_6) τ: 0.80 (s, 1H), 0.90 (s, 1H), 1.87—2.63 (m, 5H), 5.28 (d, 2H), 7.36 (s, 6H).

4-Amino-2-(N-benzoylaminomethyl)-5-cyanopyrimidine (XII). *a) Reaction of I with Ethoxymethylenemalononitrile*: To an ethanol solution of I, prepared from 0.15 g (6.5 mmol) of sodium in 20 ml of ethanol and 1.1 g (5 mmol) of I hydro-

chloride, was added 0.6 g (5 mmol) of ethoxymethylenemalononitrile[8] at 0 °C. The mixture was stirred at 0 °C for 1 hr and at 30 °C for an additional 1 hr. Crystals separated out were collected and recrystallized from ethanol to give colorless needles of XII, mp 208—209 °C, 0.7 g (56%). Found: C, 61.56; H, 4.43; N, 27.58%. Calcd for $C_{13}H_{11}ON_5$: C, 61.65; H, 4.38; N, 27.66%. IR (KBr) cm^{-1}: 3375, 3325, 3200, 2220, 1670, 1650. NMR (DMSO-d_6) τ: 1.13 (s, 1H), 1.14 (s, 2H), 1.88—2.62 (m, 6H), 5.53 (d, 2H).

b) Reaction of Ethyl Benzoylaminoacetimidate with Aminomethylenemalononitrile: An ethanol solution of sodium ethoxide, prepared from 0.23 g (10 mmol) of sodium and 20 ml of ethanol, was added to a solution of 2.4 g (10 mmol) of ethyl benzoylaminoacetimidate hydrochloride[3] in 30 ml of ethanol under ice cooling and the precipitated sodium chloride was removed by filtration. To the filtrate was added 0.9 g (10 mmol) of aminomethylenemalononitrile.[9] The mixture was warmed at 50 °C for 3 hr, and then concentrated. The oily residue was subjected to column chromatography on alumina. Crystals eluted with ethanol were recrystallized from ethanol to give XII, mp 208—209 °C, 0.25 g (10%). Spectral data were identical with those of XII obtained in the preceding experiment.

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