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Coumarins. VI. The Acid-catalyzed Reaction of Phenols with β-Aminocrotononitrile[1]

Kikumasa SATO and Masao ŌHASHI

Department of Applied Chemistry, Faculty of Engineering, Yokohama National University, Minami-ku, Yokohama

and Takeshi AMAKASU and Katsuhiko TAKEDA

Chemical Laboratory, Seimi Chemical Co., Ltd., Chigasaki, Chigasaki-shi, Kanagawa

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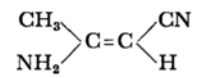
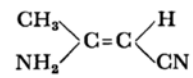
A new synthesis of 4-methylcoumarins has been developed by means of the acid-catalyzed condensation of phenols with β-aminocrotononitrile. Such monohydric phenols as phenol or cresols reacted with β-aminocrotononitrile in polyphosphoric acid (PPA) to give 4-methylcoumarins in poor yields, along with a good yield of 6-amino-3-cyano-2,4-lutidine (III). In contrast, 7-substituted-4-methylcoumarins were obtained in 23—44% yields from resorcinol and its monomethyl ether. On the other hand, when β-aminocrotononitrile was heated in PPA, the lutidine (III) was obtained in a high yield. Its precursor, 4-amino-1,3-dicyano-2-methylpenta-1,3-diene (XI), was isolated under mild conditions. These results suggest that β-aminocrotononitrile may undergo the preferential self-dimerization to the lutidine (III) rather than the intermolecular condensation with phenols.

The preceding paper in this series[2] described the direct synthesis of several coumarins by the acid-catalyzed reaction of phenols with β-oxonitriles. These studies have now been extended to β-aminocrotononitrile, *i. e.*, diacetonitrile. Although the hydrogen chloride-catalyzed reaction of polyhydric phenols such as resorcinol with β-aminocinnamonitriles has previously been shown[3] to give the corresponding 4-phenylcoumarins, we could find no report concerning the acid-catalyzed reaction of phenols with such aliphatic β-amino-α,β-unsaturated nitriles as β-aminocrotononitrile.

The sodium-induced dimerization of acetonitrile has been shown[4-6] to give β-amino-*cis*-crotononitrile (Ia) and mixture (Ic) of Ia and Ib. The *cis*-isomer (Ia) may be readily isomerized, in part, to the *trans*-configuration (Ib) by placing it in contact with a protic solvent such as ethanol.[5,6] The conversion is subject to an acid-base catalyst.[6]

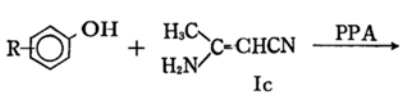


Ia

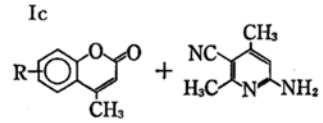


Ib

In the present study we have examined the acid-catalyzed reaction of phenols with β-aminocrotononitrile (Ic), using polyphosphoric acid (PPA).



Ic



IIa, R=H
b, R=6-CH_3
c, R=7-CH_3
d, R=7-OCH_3
e, R=7-OH

III

When equimolar amounts of resorcinol and Ic were treated in a PPA solution, 4-methylumbelliferone (IIe) (44%) was obtained along with 6-amino-3-cyano-2,4-lutidine (III). Resorcinol monomethyl ether behaved analogously when treated with Ic under the same conditions and gave the corresponding coumarin, IId, as well as III.

In contrast, a poor yield of 4-methylcoumarins (IIa—c) was isolated from the reaction of such less reactive phenols as cresols with Ic under similar conditions. The structure of the coumarins II follows from the infrared spectra, which showed

1) This investigation was presented at the 21st Annual Meeting of the Chemical Society of Japan, Osaka, April, 1968.

2) K. Sato and T. Amakasu, *J. Org. Chem.*, **33**, 2446 (1968).

3) E. Von Meyer, *J. Prakt. Chem.*, [2] **67**, 342 (1903); A. Sonn, *Ber.*, **51**, 821 (1918).

4) a) R. Holtwart, *J. Prakt. Chem.*, [2] **39**, 230 (1889). b) J. Moir, *J. Chem. Soc.*, **81**, 111 (1902).

5) J. J. Conn and A. Taurins, *Can. J. Chem.*, **31**, 1211 (1953).

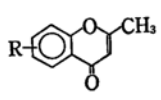
6) E. Bullock and B. Greogry, *Can. J. Chem.*, **43**, 332 (1965).

Table 1. The acid-catalyzed reaction of phenols with diacetonitrile (Ic)[a]

No.	Phenol	Reaction[b] Temp., °C	Time, hr	Product	Yield, %
1	Phenol	125—130	3	IIa	4
2	*p*-Cresol	125—130	4	IIb	7
3	*m*-Cresol	125—130	4	IIc	7
4	Resorcinol monomethyl ether	115—120	4	IId	23
5	Resorcinol	100—105	3	IIe	44

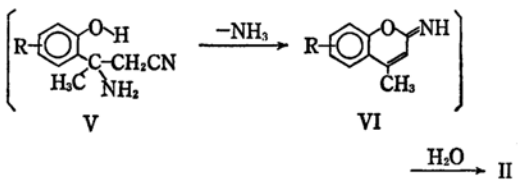
No.	Mp, °C Obsd[c]	Lit	IR (KBr) cm^{-1} C=O	UV (EtOH) λ_{max} mμ (ε)
1	82—82.5	83—84[d]	1705	213 (19000) 274 (9000) 315 (5000)
2	148.5—149	151[e]	1710	218 (24000) 276 (12000) 324 (6000)
3	132—132.5	132[e]	1700	222 (19000) 282 (11000) 319 (10000)
4	158.5—159	158.5—159[e]	1730	222 (16000) 252 ± 2(2000)[f] 324 (14000)
5	184—184.5	185	1680	222 (14000) 254 ± 2(2300)[f] 326 (13000)

a) 6-Amino-3-cyano-2,4-lutidine (III) was isolated along with II.
b) See Experimental Section for molar ratio of reagents.
c) Recrystallized from aqueous ethanol.
d) E. W. Woodruff, "Organic Syntheses," Coll. Vol. III, p. 581 (1955).
e) See Ref. 2.
f) Flat.



IV

lactone C=O bands at 1680—1730 cm^{-1}, and the ultraviolet data, which make it possible to distinguish[7] clearly between coumarins II and isomeric chromones IV. These results, summarized in Table 1, indicate that the reactions proceed through the addition of phenols to Ic, as is shown below:



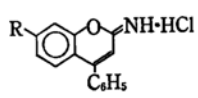
V VI II

The resulting addition product (*i.e.*, V) is then converted, by the intramolecular cyclization, to an iminocoumarin, VI. The intermediate VI then readily undergoes acid hydrolysis to II. Neither V nor VI could be isolated in any case, whereas the acid-promoted condensation of phenols with benzoylacetonitrile has been demonstrated[2] to furnish 4-phenyl-2-iminocoumarins, VII, corresponding to VI, while 3-cyano-4-methyliminocoumarin (VIII)[8] and 3-substituted-2-iminocoumarins, IXa—d,[9] may be obtained by the base-catalyzed condensation of 2-hydroxyacetophenone as malononitrile. This is probably to be attributed and salicylaldehyde respectively, with such cyano compounds to the difference in resonance stability between the intermediate VI and VII, VIII, or IX. It is interesting to note that no para condensation product, X, could be isolated from the reaction of phenol, while the acid-catalyzed reaction of phenol

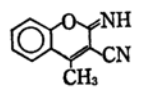
7) a) B. K. Ganguly and P. Bagchi, *J. Org. Chem.*, **21**, 1415 (1956). b) K. Sen and P. Bagchi, *ibid.*, **24**, 316 (1956); c) L. L. Wood and J. Sapp, *ibid.*, **27**, 3703 (1962).

8) H. Junek, *Monatsh.*, **95**, 234 (1964).

9) R. Kuhn and D. Weiser, *Ann.*, **600**, 144 (1956); G. P. Schiemenz, *Ber.*, **95**, 483 (1962); H. Junek, *Monatsh.*, **94**, 192 (1963).

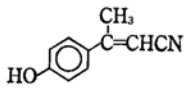


VII
R=-OH, -OCH$_3$, -CH$_3$



VIII IXa, R=-C$_6$H$_5$
b, R=-CONH$_2$
c, R=-CN
d, R=-CCH(CN)$_2$ (=NH)

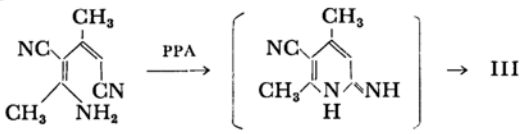
with benzoylacetonitrile may furnish β-(*p*-hydroxyphenyl)cinnamonitrile as the sole product.[2]



X

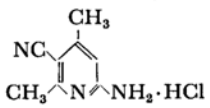
Although the dimerization of β-aminocrotononitrile (Ic) under various conditions has previously been reported to give the lutidine III[4,10] *via* 4-amino-1,3-dicyano-2-methylpenta-1,3-diene (XI),[6,11] no report could be found concerning the use of PPA for the condensation.

The nitrogenous product, III, described above, was obtained together with 4-methylcoumarins, II, when phenols were treated with Ic in the presence of PPA. The analytical data agreed with the formula $C_8H_9N_3$, which is itself in accord with the structure of the lutidine derivative, III, and the precursor, XI. The physical properties, along

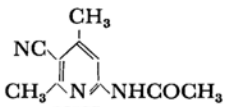


XI

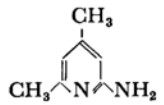
with the infrared and ultraviolet spectra, suggest that the product is assignable to the cyclic compound III. When treated with 12 N hydrochloric acid, the product, III, was converted to the salt, XII, while treatment with acetic anhydride gave the N-acetyl-derivative, XIII. Moreover, this lutidine, III, when refluxed with 75% sulfuric acid, yielded 6-amino-2,4-lutidine (XIV), while when it was refluxed with 48% hydrobromic acid, it afforded



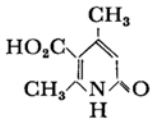
XII



XIII



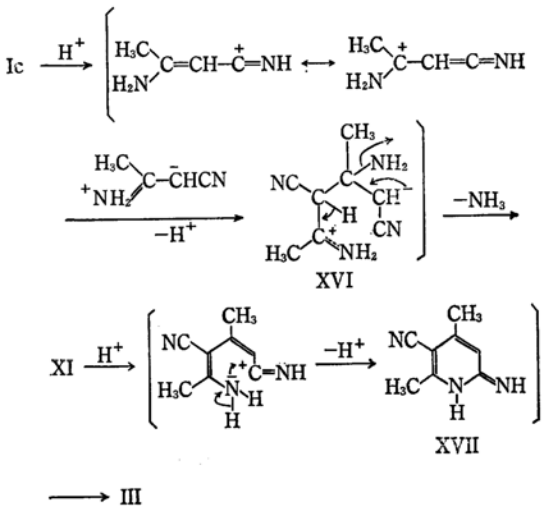
XIV



XV

2,4-lutid-6-on-3-carboxylic acid (XV). These results confirm the structure III for 6-amino-3-cyano-2,4-lutidine. On the other hand, we have found a convenient method for preparing III by means of the PPA-catalyzed self-condensation of Ic. When the nitrile Ic was heated in PPA at 160—165°C for 1 hr, the lutidine, III, was obtained in an 81% yield. In contrast, under mild conditions Ic gave a dienaminonitrile, XI (13%), as well as III. The dienaminonitrile, XI, readily underwent intramolecular cyclization, through isomerization, to III when heated in PPA or an alkaline solution. The results, along with the infrared spectra and the ultraviolet spectra, confirm the structures of III and XI for the lutidine and pentadiene derivatives respectively.

The following discussion is presented to account



XVI

XVII

for the formation of XI and III from β-aminocrotononitrile (Ic). The protonation of Ic, followed by interaction between the electrophilic β- and nucleophilic α-centers of Ic, provides, *via* deprotonation, the unstable betaine XVI, which then undergoes deamination to XI. Furthermore, compound XI is converted to III through intramolecular cyclic addition to XVII and subsequent isomerization. The data are consistent with this view.

Accordingly, the usual poor yield of 4-methylcoumarins II, is due to such a predominant dimerization of Ic as is shown above.

Experimental[12]

Materials. β-Aminocrotononitrile (Ic), mp 52—53°C, was prepared by the dimerization of acetonitrile

10) E. Von Meyer, *J. prakt. Chem.*, [2] **52**, 89 (1895).
11) a) E. von Meyer, *ibid.*, [2] **78**, 517 (1908). b) E. von Meyer, *ibid.*, [2] **90**, 41 (1914). c) P. J. Brignell, E. Bullock, U. Einsner, B. Gregory, A. W. Johnson and H. Williams, *J. Chem. Soc.*, **1963**, 4819.

12) All melting points, determined on a Shimadzu Type MM-2 micro hot stage, are uncorrected. Infrared and ultraviolet spectra were recorded, respectively, on a Hitachi Model EPI-S2 and Hitachi Model EPS-3T spectrophotometers. NMR spectra were taken in d_6-dimethylsulfoxide on a JEOL Model C-60H instrument with tetramethylsilane as an internal standard.

with sodium metal.[4b] The monoetherification of resorcinol with dimethylsulfate was carried out by means of the procedure of Kinugawa and his co-workers.[13] 3-Cyano-2,4-lutid-6-one was obtained by the treatment of Ic with boiling water.[4a]

PPA-Catalyzed Reaction of Phenols with Ic; 4-Methylcoumarins. *General Procedure.* Finely-powdered Ic (4.1 g, 0.05 mol) was added slowly to a mixture of the phenol (0.05 mol) and 41 g of PPA at 90°C, after which stirring was vigorously continued at 90—100°C. Then the mixture was gradually heated on an oil bath and kept under the conditions shown in Table 1. Thereafter the resulting mixture was chilled, poured into water containing crushed ice (200—300 m*l*), and extracted with ether. After the extract had been washed with water and dried over anhydrous magnesium sulfate, the removal of the solvent, followed by recrystallization from aqueous ethanol, gave the pure 4-methylcoumarin (II). The results with individual compounds are presented in Table 1.

The aqueous layer was basified with 10% sodium hydroxide and then filtered to afford orange crystals. Recrystallization from 95% ethanol furnished 6-amino-3-cyano-2,4-lutidine (III) as colorless needles; mp 226—227°C (lit[6] 227—228°C); sublimed at *ca.* 160°C; ν_{max}^{KBr} 3400, 3330 (N–H), 3130, 2200 (C≡N), 1665 (C=N), 1605, 1492 (C=C), 1413, 1380 (CH_3), 1175, and 840 cm^{-1}; NMR: τ 7.76 (2-CH_3), 7.60 (4-CH_3), 6.50 (NH_2), and 3.75 (nuclear proton).

Found: C, 65.39; H, 6.43%. Calcd for $C_8H_9N_3$: C, 65.31; H, 6.12%.

4-Amino-1,3-dicyano-2-methylpenta-1,3-diene (XI). *a)* Compound Ic (1.0 g) was added to 10 g of PPA at room temperature. A vigorously exothermic reaction occurred. The mixture was allowed to stand at 30—50°C for 1.5 hr, during which time the solution was sometimes stirred by means of a glass rod. The neutralization of the resulting mixture with an alkaline solution, followed by filtration, gave quantitatively a mixture of crude-orange products, III and XI. Fractional crystallization from water afforded III, mp 226—227°C. XI (0.12 g, 13%) was obtained from the mother liquor; mp 167—168°C (lit[6] mp 166—166.5°C) (from water). ν_{max}^{KBr}: 3380, 3320, 3200 (NH_2), 2200 (C≡N), 1655 (C=N), 1600, 1545 (C=C), 1250 cm^{-1}; λ_{max}^{EtOH} mμ (ε): 220 (6920), 256 (4530), 327 (9920); NMR: τ 7.83 (CH_3, 6H), 6.57 (NH_2, 2H), and 4.57 (olefinic proton, 1H).

Found: C, 65.51; H, 6.44%. Calcd for $C_8H_9N_3$: C, 65.31; H, 6.12%.

b) Acetyl chloride (5.0 g) was stirred, drop by drop, into a solution of Ic (2.5 g) in absolute ether (30 m*l*) over a period of 10 min and then kept for 30 min at room temperature. Thereafter the yellow mass which was deposited was filtered to afford the adduct, which was then washed with ether. The treatment of the adduct with water (7 m*l*), followed by filtration, gave the crude XI; this product was recrystallized from water to provide the pure XI (0.7 g, 31%) as colorless needles, mp 167—168°C. The infrared spectrum was identified with that of XI presented above.

6-Amino-3-cyano-2,4-lutidine (III). *a) From Ic.* The nitrile Ic (2.1 g) was added slowly to 21 g of PPA at 90—100°C over a period of 10 min; the mixture was then gradually heated and stirred on an oil bath at 160—165°C for 1 hr. After the resulting mixture had cooled to about 90°C, it was poured into an ice-water slurry (80 g), and neutralized with 10% sodium hydroxide; then the mixture was allowed to stand for a long time. Filtration gave a yellow crystal mass, which was recrystallized from aqueous ethanol to provide the pure III (1.5 g, 81%) as colorless needles, mp 226—227°C; λ_{max}^{EtOH} 272 mμ (ε=7200). A mixed-melting-point determination with an authentic sample such as that already prepared (mp 226—227°C) showed no depression.

b) From XI. A mixture of XI (140 mg) and PPA (1.4 g) was heated on an oil bath at 160°C for half an hour. A treatment of the resulting mixture similar to that shown above gave III (80 mg, mp 226—227°C).

c) The Base-catalyzed Cyclization of XI.[6] A mixture of XI (100 mg) and 5% potassium hydroxide (10 m*l*) was stirred at 100°C for 3 hr chilled to room temperature, and allowed to stand for some time. Filtration, followed by recrystallization from ethanol, afforded the pure III (28 mg); mp 226—227°C.

6-Amino-3-cyano-2,4-lutidine Hydrochloride (XII). A mixture of III (130 mg) and 12 N hydrochloric acid (5 m*l*) was heated at 100—105°C for 2.5 hr. The removal of the hydrochloric acid furnished the crude salt XII (160 mg), which was then recrystallized from ethanol to give the pure product as colorless needles; mp 248—249°C; ν_{max}^{KBr}: 3300 (N–H), 2650—2750 (–$\overset{+}{N}H_3\bar{C}l$) cm^{-1}.

Found: C, 52.04; H, 5.74%. Calcd for $C_8H_{10}ClN$: C, 52.32; H, 5.45%.

6-Acetylamino-3-cyano-2,4-lutidine (XIII). A solution of III (140 mg) in acetic anhydride was warmed at 80°C for 1 hr and then chilled. After the solution had stood in an ice-box for 1 day, filtration and subsequent recrystallization from ethanol provided the product, XIII, as colorless needles; mp 255—256°C (lit[10] mp 250°C); ν_{max}^{KBr}: 3230 (N–H), 2230 (C≡N), 1680 (C=O), 1580, 1530 (C=C) cm^{-1}.

Found: C, 63.22; H, 6.11; N, 21.97%. Calcd for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21%.

6-Amino-2,4-lutidine (XIV). A mixture of III (1.0 g) and 75% sulfuric acid (10 g) was heated at 150—160°C for 3 hr. The cooled mixture was neutralized with dilute sodium hydroxide and extracted with ether (30 m*l*). After the extract had been washed with water and dried over anhydrous magnesium sulfate, the solvent was removed; recrystallization from ethanol then gave colorless plates (0.6 g, 72%); mp 66—67°C (lit[14] 65—67°C); ν_{max}^{KBr}: 3450, 3350 (NH_2), 3130, 1615 (C=C), 1570, 1450, 1390, 1380 (CH_3), 1235, 820, and 810 cm^{-1}.

2,4-Lutid-6-on-3-carboxylic Acid (XV). A solution of III (1.0 g) in 48% hydrobromic acid (10 m*l*) was heated at 120—130°C for 3 hr. The removal of the hydrobromic acid gave the crude product; this was recrystallized from ethanol to give pure XV (0.62 g, 55%) as colorless needles; mp 271—272°C (dec); ν_{max}^{KBr}: 3400 (w. OH), 3000, 2800, 1670, 1640—1620, 1460, 1420, 1385 (CH_3), 1350, 1240, 955, 905, 825, and 710 cm^{-1}.

Found: C, 57.25; H, 5.71; N, 8.12%. Calcd for

13) J. Kinugawa, M. Ochiai and H. Yamamoto, *Yakugaku Zasshi (J. Pharm. Soc. Japan)*, **79**, 931 (1959).

14) B. Rudner, U. S. Pat. 2892841 (1959).

$C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38%.

3-Cyano-2,4-lutid-6-one. This compound was prepared from III according to the procedure of Bullock and Gregory.[6] The treatment of III with sodium nitrite in dilute hydrochloric acid gave the product; mp>300°C (lit mp 293°C[4]; mp 305—307°C[6]). A mixed-melting-point determination with an authentic sample from III[4] (mp>300°C) indicated no depression. ν_{max}^{KBr}: 3400 (w. OH), 1660 (C=O), 1615 (C=C), 1410, 1370 (CH_3), 870, and 720 cm^{-1}.