Condensation of Benzoylcyanamide with Aromatic Amino Esters, Acids, and Amides

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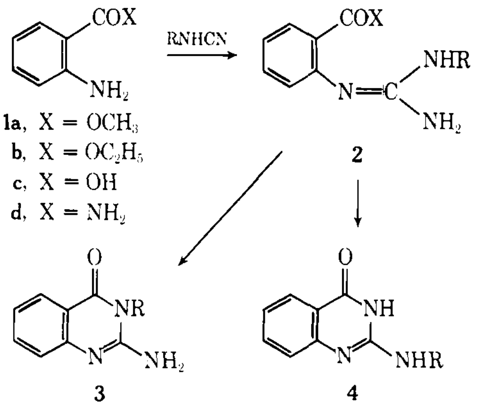
The condensation of alkyl and aryl cyanamides with methyl anthranilate (**1a**) has been shown to give two possible products, **3** and **4** (Scheme I). The distribution of these two products varies dramatically with changes in the substituent, examples being found where **4** was the sole product.[2]

Scheme I



Previous work in this laboratory had shown that benzoylcyanamide and anthranilic acid reacted to give what appeared to be a single product, which was not completely characterized.[3] When this investigation was continued, a white crystalline material was obtained from the condensation of benzoylcyanamide (*N*-cyanobenzamide) with either anthranilic acid (**1c**), ethyl anthranilate (**1b**), or anthranilamide (**1d**). This material analyzed for $C_{15}H_{11}N_3O_2$, and the nmr and ir spectra (Table I) indicated that the compound was 2-amino-3-benzoyl-4(3*H*)-quinazolinone (**7**) (Scheme II). The mass spectrum (70 eV) gave a molecular ion at *m/e* 265, verifying the molecular weight (calcd, 265). In addition to the spectral evidence, the insolubility of the material in alkali indicated that it was not the isomeric 2-benzamido-4(3*H*)quinazolinone (**4**, R = COPh).

Scheme II

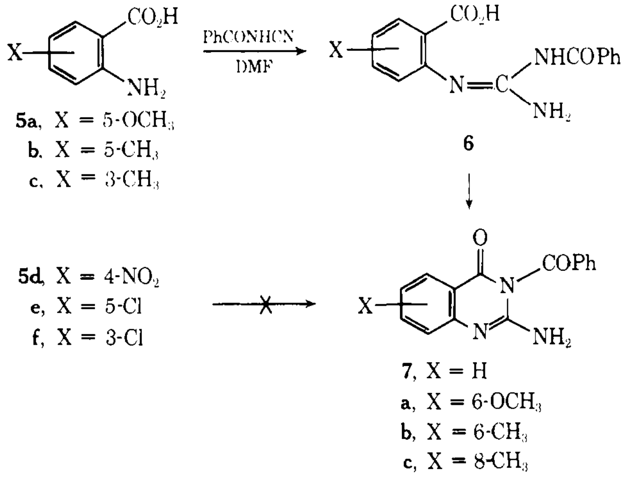


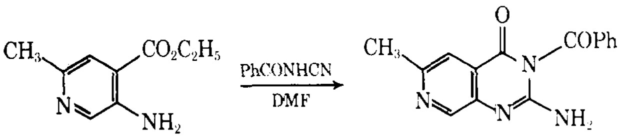
Table I
Ir and Nmr Spectra of Products

Product	Ir max, cm^{-1a}	Nmr, δ, ppm^{b}
7	3175, 3060, 1675, 1645, 1610, 1275	7.28–7.93 (m, 6), 8.05–8.38 (m, 3), 12.40 (br, 2)
7a	3200–2930, 1680, 1655, 1630–1615, 1030	3.99 (s, 3), 7.61–7.99 (m, 6), 8.29–8.55 (m, 2), 12.42 (br, 2)
7b	3190, 3050, 1685, 1665, 1635, 1280	2.48 (s, 3), 7.48–7.95 (m, 5), 8.00–8.50 (m, 3), 12.35 (br, 2)
7c	2990, 1680, 1640, 1625, 1610, 1585, 1560	2.57 (s, 3), 7.38 (t, *J* = 7 Hz, 1), 7.47–7.88 (m, 4), 7.98–8.43 (m, 3), 12.38 (br, 2)
9	3200, 3110, 3050, 1680, 1660–1610, 1270	2.60 (s, 3), 7.60–7.90 (m, 3), 7.85 (s, 1), 8.10–8.40 (m, 2), 8.95 (s, 1), 12, 40 (br, 2)

[a] Obtained as KBr pellets. [b] Spectra obtained in DMSO-d_6/$CDCl_3$ (70/30, v/v) solutions, with TMS as an internal standard.

Further investigation of the synthetic utility of this condensation was suggested by the fact that only one isomer (**7**) was isolated, and the yields (Table II) were equal to or greater than the best yields reported by Grout and Partridge.[2] A variety of anthranilic acids possessing electron-donating groups (**5a,b,c**) reacted as expected, and reasonable yields (Table II) of the 2-amino-3-benzoyl-4(3*H*)-quinazolinones (**7a,b,c**) were obtained. Once again, only one isomer was isolated in these condensations. The presence of electron-withdrawing groups on anthranilic acid apparently decreased the nucleophilicity of the aromatic amine, since no products were observed with **5d–f**.[4]

Condensation of a few heterocyclic amino esters, acids, and amides with benzoylcyanamide was then examined. 2-Methyl-4-carbethoxy-5-aminopyridine (**8**) gave the corresponding 2-amino-3-benzoyl-6-methylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one (**9**) in reasonable yield (Table II). Ethyl 2-aminonicotinate and 2-aminonicotinic acid failed to react, presumably because of the non-nucleophilic character of some 2-aminopyridine derivatives.[5] 2-Amino-3-carbethoxy-4-methylthiophene and 2-amino-3-carbamyl-4,5-dimethylfuran[6] decomposed rapidly, giving intractable materials upon work-up. Further compounds are presently being investigated in an effort to determine what systems will undergo this condensation.



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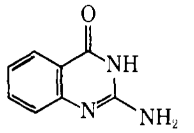

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In addition to observing the products and scope of this condensation, mild conditions for hydrolysis[3] were devel-

Table II

Substrate	Reaction time, hr.	Product[a]	Mp, °C	Yield, %[b]
1b	48	7	188.5–190	58
1c	48	7		45
1d	48	7		57
5a	20	7a	203–204	57, 62[c]
5b	20	7b	209.5–210.5	24, 39[c]
5c	27	7c	226–227	21, 24[c]
8	20	9	269–270.5	35, 43[c]

[a] Satisfactory analyses (±0.4% for C, H, N) were reported for compounds **7**, **7a–c**, and **9**: Ed. [b] Based upon substrate. [c] Based upon unrecovered substrate.

oped that allowed conversion of **7** to the corresponding 2-amino-4(3*H*)-quinazolinone (**10**) in 86% yield.

Experimental Section

Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained on a Jeol C60HL spectrometer. Infrared spectra were obtained on a Perkin-Elmer Model 257 spectrophotometer. The mass spectrum was obtained with a Hitachi Perkin-Elmer RMU-6E spectrometer. The ultraviolet spectrum was obtained on a Unicam SP-800B spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. The dimethylformamide (DMF) used as solvent was reagent grade and was stored over 4A molecular sieves (Linde). The benzoylcyanamide[7] was recrystallized from benzene/petroleum ether (30–60) and had a melting point of 139–40° dec (lit.[7] 143°).

Synthesis of 7, 7a–c, and 9. Two millimoles of the amino ester, acid, or amide were dissolved in 10 ml of DMF and benzoylcyanamide (146 mg, 1 mmol) was added. The solution was stirred and heated at 90–95° for 5 hr, then an additional 1 mmol of benzoylcyanamide was added and stirred until this portion had completely reacted (tlc). The solution was then concentrated (*in vacuo*) to a volume of 3–4 ml and poured into 5–10 ml of 95% ethanol, which was then poured into 35 ml of ice water. The mixture was stirred overnight, cooled, filtered, and washed with water. A further washing of the solid material with diethyl ether removed any of the unreacted substrates studied, which could then be recovered. The powdered material remaining was recrystallized from 70% ethanol (Norit). Analytical samples were recrystallized twice. Yields (based upon powdered material) and melting points are listed in Table II.

Hydrolysis of 7. Fifty milligrams of an analytical sample of **7** was heated on a steam bath with 3 ml of 0.5 *N* sodium hydroxide for 15 min. Complete dissolution required approximately 10 min. The solution was filtered hot (Norit), then allowed to cool, and acidified to pH 5.5–6.0 with acetic acid. The fine white powder (86%) was filtered, washed with water and ether, and dried *in vacuo*. Purification was achieved by dissolution in dilute alkali and reprecipitation with acetic acid. The uv spectrum of **10** (95% ethanol) was identical with that reported.[8]

Registry No.—**1b**, 87-25-2; **1c**, 118-92-3; **1d**, 88-68-6; **5a**, 6705-03-9; **5b**, 2941-78-8; **5c**, 4389-45-1; **7**, 52393-73-4; **7a**, 52393-74-5; **7b**, 52393-75-6; **7c**, 52393-76-7; **8**, 52393-72-3; **9**, 52393-77-8; benzoylcyanamide, 15150-25-1.

References and Notes

(1) NDEA Title IV Fellow, 1973.
(2) R. J. Grout and M. W. Partridge, *J. Chem. Soc.*, 3540 (1960).
(3) C. E. Cook, Ph.D. Thesis, The University of North Carolina, Chapel Hill, N.C., 1960.
(4) Reaction of 3-methoxyanthranilic acid gave an anomalous product whose analysis corresponded to $C_{24}H_{22}N_4O_6$, suggesting the product was derived from 2 equiv of the anthranilic acid and one equivalent of benzoylcyanamide. A complete structure proof has not been accomplished, because of the lack of additional structural evidence.
(5) S. J. Angyal and C. L. Angyal, *J. Chem. Soc.*, 1461 (1952).
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(8) P. Grammaticakis, *C. R. Acad. Sci.*, **247**, 2013 (1958).

Photochemical and Thermal Internal Cycloadditions in *retro*-γ-Ionylidenemalononitrile

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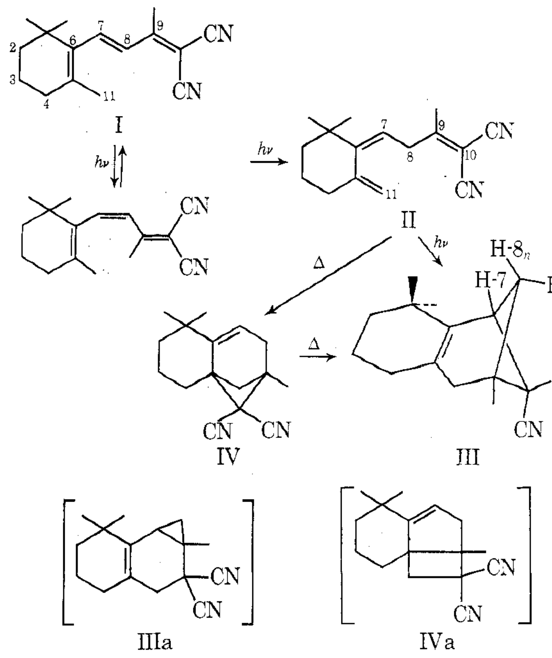
In connection with studies of hindered 7-cis isomers of retinal analogs,[1] we have reinvestigated reactions from direct irradiation of several dienes and trienes in this series. Similar to previous reports,[2] we observed in most cases primarily rapid, reversible geometric isomerization, electrocyclization (trienes), and irreversible 1,5-sigmatropic hydrogen migration products (dienes and trienes). Therefore, with a typical ionylidene derivative during the initial period of irradiation a mixture of 7,8 and 9,10 geometric isomers is produced,[2,3] along with less efficient formation of a cyclohexadiene, all of which eventually disappear to give the final product, a *retro*-γ-ionylidene derivative. However, in one instance we observed an additional secondary photoreaction and unexpected thermal rearrangements. These are described below.

retro-γ-Ionylidenemalononitrile (II) is the principal end product from direct irradiation of a dilute ether solution of β-ionylidenemalononitrile (I) when light of >360 nm (Corning 0-51 filter) is used. Upon further irradiation with light >290 nm (Pyrex filter) a new photoproduct is formed. The spectroscopic properties of the product, after its isolation by column chromatography (silica gel), suggest that it is formally an internal 4 + 2 cycloadduct, III.[4]



The mass spectrum of III shows that it is isomeric to I and II (*m/e* for M^+ 240). The compound is clearly not a cyclohexadiene because of the absence of vinyl hydrogens from its nmr and ir spectra. The pmr spectrum is in fact quite indicative of the structure. The three methyl groups (δ 1.17, 1.19, and 1.35) are now nonequivalent as expected for III. A broad singlet at δ 2.32, attributable to the allylic hydrogens at C-11, overlaps with a quartet (d of d) at 2.38. The latter (H-8_{exo}) is shown by double irradiation to couple with two single H's at 3.19 (d, J = 8.5 Hz, H-7) and 1.51 (d, J = 6.0 Hz, H-8_{endo}). This pattern of coupling is in agreement with compounds of a bicyclo[*n*.1.1] structure in which the bridgehead hydrogens are known to couple only with