Reactions of *o*-Aminonitriles with Isocyanates. 2. A Facile Synthesis of Imidazo[1,2-*c*]quinazoline-2,5-(3*H*,6*H*)dione

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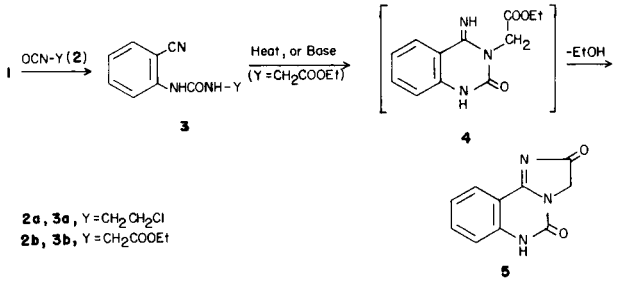
Received November 3, 1980

Anthranilonitrile reacts with ethyl isocyanatoacetate to form 2-(3-ethoxycarbonylmethylureido)benzonitrile (**3b**) which, upon heating, or treatment with a base, undergoes a double cyclization to yield imidazo[1,2-*c*]-quinazoline-2,5-(3*H*,6*H*)dione (**5**) in excellent yield. In the presence of acid, **3b** is converted into 1,4-dihydro-2,4-dioxo-3-(2*H*)quinazolineacetic acid (**11**), or its ethyl ester (**10**). The action of concentrated sulfuric acid converts the adduct **13** of anthranilic acid and ethyl isocyanatoacetate into 2-ethoxycarbonyl-methylamino-4*H*-3,1-benzoxazin-4-one (**14**).

J. Heterocyclic Chem., **18**, 515 (1981).

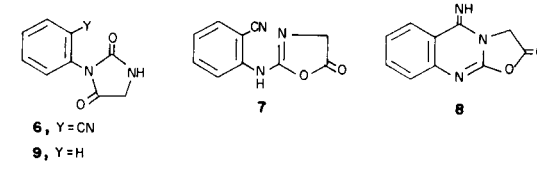
Among a wealth of synthetically useful transformations (1), *o*-aminonitriles undergo cyclization reactions with isocyanates to form condensed derivatives of 2,4-(1*H*,3*H*)-pyrimidinedione (2). Use of an isocyanate containing a suitably located leaving group in such a reaction may be expected to allow formation of a second ring fused to positions 3 and 4 of the pyrimidinedione system. Thus, the substituted urea **3a**, obtained from anthranilonitrile (**1**) and 2-chloroethyl isocyanate (**2a**), was found to undergo a remarkably easy and efficient double cyclization to 2,6-dihydro[1,2-*c*]quinazolin-5-(3*H*)one, as well as a variety of other ring forming reactions (3).

The present paper describes the results of an analogous investigation involving anthranilonitrile and ethyl isocyanatoacetate (**2b**). These two compounds react neat, or in solution to yield 2-(3-ethoxycarbonylmethylureido)-benzonitrile (**3b**) in essentially quantitative yield. When heated to a temperature 30-40° above its melting point, **3b** decomposes with loss of ethanol to form imidazo[1,2-*c*]-quinazoline-2,5-(3*H*,6*H*)dione (**5**). The same product is formed when **3b** is treated with a basic reagent, such as



aqueous, or ethanolic sodium hydroxide, or ammonia, sodium methoxide in methanol, triethylamine in ethanol (100% yield), or even when it is simply heated with water. As in the case of cyclization of 2-[3-(2-chloroethyl)ureido]-benzonitrile (**3a**) (3), the presumed intermediate product **4** of the initial ring formation has not been isolated or detected.

Structure **5**, is consistent with the spectra (ir, nmr) of the isolated compound and its microanalytical data. However, cyclization of **3b** with loss of ethanol could in principle follow a different reaction pathway to yield compound **6**, **7**, or **8**, instead of **5**. Structures **6** and **7** may be rejected



because of the absence of a C≡N stretching band in the ir spectrum of the product, as well as the following reasons. In the nmr spectrum of 1-phenyl-2,5-imidazolidinedione (**9**, prepared as a model compound from the phenyl isocyanate adduct of glycine) (4), the NH proton signal appears at a much higher field (δ 8.3) than observed for compound **5** (δ 11.8). On the other hand, the ir spectrum of a compound with a 2-oxazolin-5-one moiety like **7** would be expected to exhibit a carbonyl stretching band at a wavenumber significantly larger than the 1710 cm^{-1} observed for **5**. Structure **8** is inconsistent both with the absence of a high wavenumber carbonyl band in the ir spectrum of the isolated product and the fact that this compound is recovered unchanged after a treatment with aqueous or ethanolic hydrochloric acid expected to cleave an imino group (2,5). Furthermore, ethyl 1,4-dihydro-2,4-dioxo-3-(2*H*)quinazolineacetate (**10**), a close analog of an intermediate that would lead to **8**, shows no tendency whatever to form a third, lactone-like ring (as in **8**), under reaction conditions which readily convert **3b** into **5**.

When heated with concentrated hydrochloric acid in ethanol, urea **3b** reacts like its 2-chloroethyl analog **3a** (3) and forms ester **10**. Unlike **3a**, however, **3b** yields 1,4-dihydro-2,4-dioxo-3-(2*H*)quinazolineacetic acid (**11**), instead of a substituted 2-amino-4*H*-3,1-benzoxazin-4-one, when heated with concentrated hydrochloric acid alone. The structures of compounds **10** and **11** are readily interrelated by hydrolysis of **10** into **11** and esterification of **11** into **10**.

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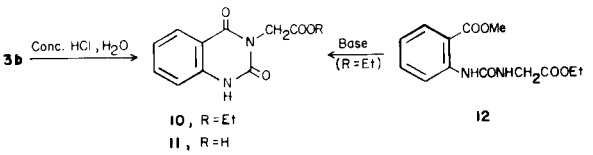
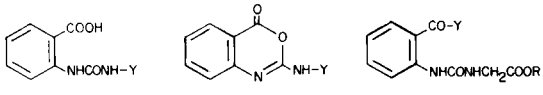


10, R=Et
11, R=H
12

They are further confirmed through preparation of **10** by base catalyzed cyclization of methyl 2-(3-ethoxycarbonylmethylureido)benzoate (**12**), conveniently obtained from methyl anthranilate and isocyanate **2b**.

The fact that traces of 2-ethoxycarbonylmethylamino-4*H*-3,1-benzoxazin-4-one (**14**) could be isolated from a solution of **3b** in concentrated hydrochloric acid allowed to stand at room temperature for 1 hour, whereas only carboxylic acid **11** could be obtained after 24 hours, suggested the possibility that initially formed **14** is subsequently converted into **11**. Because of a possible role of chloride ions in the opening of the oxazinone ring of **14**, conversion of **3b** into **14** was then attempted using concentrated sulfuric acid as the condensing agent. A 3-hour, room temperature treatment with this reagent, however, led to recovery of **3b** as the only nonacidic component of the reaction mixture. Preparation of benzoxazinone **14** was next attempted using 2-(3-ethoxycarbonylmethylureido)benzoic acid (**13**, prepared from anthranilic acid and isocyanate **2b**) as starting material. It was found that treatment with concentrated hydrochloric acid at room temperature (1-15 hours) does not cause **13** to change, whereas such treatment on a steam bath (20 minutes) yields a mixture of mostly carboxylic acid **11** and some ester **10**. However, the action of concentrated sulfuric acid at room temperature (2-3 hours) converts **13** smoothly into the desired benzoxazinone **14**. This last treatment has



13, Y = CH_2COOEt
15, Y = CH_2CH_2Cl
14, Y = CH_2COOEt
16, Y = CH_2CH_2Cl
17, Y = NHPh, R = Et
18, Y = OH, R = H

been found to convert **15** into **16** equally well and appears to be generally as effective as the literature method using acetic anhydride as the dehydrating agent (6).

Structure **14** is supported by the ir and nmr spectra of the product as well as the results of its microanalysis. The presence in the nmr spectrum of a relatively broad, partly resolved triplet (J = 6 Hz) at δ 8.4, which disappears upon addition of deuterium oxide to the sample, indicates attachment of the exchangeable hydrogen atom to the exocyclic nitrogen atom, at least in dimethyl sulfoxide solution. As expected, the oxazinone ring of **14** opens up easily. Thus brief heating with acifidied water hydrolyzes **14** back to **13**, and acid-catalyzed, room temperature treatment with methanol converts it into diester **12**. Similarly, anilide **17** is formed when **14** is heated briefly with aniline.

To test the possibility of its conversion into a tricyclic derivative analogous to the 2,3-dihydro-5*H*-oxazolo[2,3-*b*]-quinazolin-5-one obtained from **15** (3), acid-ester **13** was heated with aqueous potassium bicarbonate for periods ranging from 0.5 hour to 3 hours. In all cases, 2-(3-carboxymethylureido)benzoic acid (**18**) was isolated as the major product together with traces of ester **10**. Since the amount of the latter compound does not decrease substantially with longer periods of treatment it appears that the two products are formed by different reaction pathways.

EXPERIMENTAL (7)

2-(3-Ethoxycarbonylmethylureido)benzonitrile (**3b**).

A.

A mixture of 3.55 g. (0.030 mole) of anthranilonitrile and 3.9 g. (0.030 mole) of ethyl isocyanatoacetate was warmed briefly for the crystals of the nitrile to dissolve and then it was allowed to stand at room temperature for 48 hours. There was obtained 7.4 g. (100%) of **3b**, m.p. 145-147°. Recrystallization from ethanol yielded the pure compound as colorless crystals, m.p. 150-152° (decomposition and resolidification at 175-185°); ir: 3370, 3250 (N-H), 2210 (C≡N), 1740, 1630 (C=O) cm^{-1}; nmr: δ 1.2 (t, 3, CH_3), 3.9 (d, 2, CH_2CO), 4.1 (q, 2, CH_2CH_3), 6.9-7.7 (m, 4, ArH and $NHCH_2$), 8.0 (d, 1, ArH), 8.8 (s, 1, ArNH).

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.26; H, 5.37; N, 17.12.

B.

A stirred solution of 0.030 mole quantities of anthranilonitrile and **2b** in 10 ml. of benzene was refluxed for 17 hours. It was then cooled, mixed with petroleum ether (b.p. 60-80°) and filtered to yield 6.9 g. (93%) of **3b**, m.p. 142-147°.

Imidazo[1,2-*c*]quinazoline-2,5-(3*H*,6*H*)dione (**5**).

A.

After a mixture of 3.0 g. of **3b**, 20 ml. of ethanol, and 3 ml. of triethylamine had been stirred on a steam bath for 15 minutes, it was cooled and filtered to yield 2.4 g. (100%) of **5** as a light yellow solid, m.p. > 300°. An analytical sample was obtained by recrystallization from dimethyl sulfoxide-ethanol as pink crystals, m.p. 350° dec. (sealed capillary) (8); ir: 1710 (C=O) cm^{-1}; nmr: δ 4.3 (s, 2, CH_2), 7.2-7.4 (m, 2, ArH), 7.7-8.1 (m, 2, ArH), 11.8 (s, 1, NH).

Anal. Calcd. for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.82; H, 3.65; N, 21.13.

B.

A mixture of 1.0 g. of **3b** and 15 ml. of water was heated on a steam bath for 18 hours. Filtration yielded 0.73 g. (90%) of **5**.

Ethyl 1,4-Dihydro-2,4-dioxo-3-(2*H*)quinazolineacetate (**10**).

A.

A mixture of 1.0 g. of **3b**, 5 ml. of ethanol and 5 ml. of concentrated hydrochloric acid was heated on a steam bath for 0.5 hour. It was then cooled, mixed with water, and filtered to yield 0.60 g. (60%) of **10**, m.p. 217-222°. An analytical sample was obtained by recrystallization from ethanol as colorless crystals, m.p. 227-228.5° [lit. (9) m.p. 242°]; ir: 1730, 1710, 1660 (C=O) cm^{-1}; nmr: δ 1.2 (t, 3, CH_3), 4.2 (q, 2, CH_2CH_3), 4.7 (s, 2, NCH_2), 7.1-7.4 (m, 2, ArH), 7.6-8.0 (m, 2, ArH), 11.6 (s, 1, NH).

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.13; H, 5.07; N, 11.25.

B.

A mixture of 1.0 g. of **12**, 15 ml. of ethanol, and 5 ml. of concentrated aqueous ammonia was shaken intermittently at room temperature for 2 hours and filtered to yield 0.80 g. of **10** m.p. 227-228°. Dilution with water followed by acidification with acetic acid afforded an additional 0.10 g. of **10** (total yield 100%), m.p. 227-228°. Similarly, 0.80 g. (90%) of **10**, m.p. 224-227°, was obtained when a mixture of 1.0 g. of **12** and 10 ml. of 10% aqueous potassium bicarbonate had been heated on a steam bath for 0.5 hour.

C.

A mixture of 0.50 g. of **11**, 20 ml. of absolute ethanol, and 0.10 g. of *p*-toluenesulfonic acid was refluxed for 6 hours. The resulting solution was cooled and filtered to yield 0.50 g. of **12**, m.p. 223-226°.

1,4-Dihydro-2,4-dioxo-3-(2*H*)quinazolineacetic Acid (**11**).

A.

A mixture of 2.0 g. of **3b** and 20 ml. of concentrated hydrochloric acid was heated on a steam bath for 1 hour. The resulting mixture was cooled, mixed with water, and filtered to yield 1.3 g. (72%) of **11**, m.p. 285-290° dec., raised to 290-292° dec., by recrystallization from water [lit. (10) m.p. 296-298°]; ir: 3280 (N-H), 1710, 1650 (C=O) cm^{-1}; nmr: δ 4.6 (s, 2, CH_2), 7.1-7.3 (m, 2, ArH), 7.6-8.0 (m, 2, ArH), 11.6 (s, 2, NH, COOH).

In a similar way, 0.55 g. (61%) of **11**, m.p. 288-290° dec., was obtained from 1.0 g. of **3b** and 10 ml. of concentrated hydrochloric acid allowed to stand at room temperature for 29 hours.

B.

A mixture of 0.50 g. of ester **10**, 10 ml. of water, and 10 ml. of concentrated sulfuric acid was refluxed for 50 minutes and cooled to yield 0.45 g. of **11**, m.p. 289-291° dec.

Methyl 2-(3-Ethoxycarbonylmethylureido)benzoate (**12**).

A mixture of 4.5 g. (0.030 mole) of methyl anthranilate and 3.9 g. (0.030 mole) of **2b** was cooled intermittently, until no further rise in temperature was observed, and was then allowed to stand at room temperature for 16 hours. There was obtained 8.3 g. (99%) of **12**, m.p. 116-118°. Recrystallization from ethanol yielded the pure compound as colorless crystals, m.p. 119-120°; ir: 3300 (N-H), 1730, 1700, 1650 (C=O) cm^{-1}; nmr: δ 1.2 (t, 3, CH_2CH_3), 3.9 (m, 5, $NHCH_2$ and OCH_3), 4.1 (q, 2, CH_2CH_3), 6.9-7.2 (m, 1, ArH), 7.4-7.7 (m, 1, ArH), 7.8-8.1 (m, 2, ArH, and $NHCH_2$), 8.4 (d, 1, ArH), 9.9 (s, 1, ArNH).

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 10.00. Found: C, 55.72; H, 5.95; N, 10.09.

2-(3-Ethoxycarbonylmethylureido)benzoic Acid (**13**).

A cold solution of 2.75 g. (0.020 mole) of anthranilic acid in 20 ml. of 10% aqueous potassium bicarbonate was shaken vigorously with 2.6 g. (0.020 mole) of **2b** for 2-3 minutes, the mixture being occasionally cooled. Filtration followed by acidification of the filtrate with concentrated hydrochloric acid yielded 4.9 g. (92%) of **13**, m.p. 168-170° dec., and recrystallization from aqueous ethanol gave the pure compound as colorless crystals, m.p. 171-172.5 dec; ir: 3390 (N-H), 1720, 1680, 1650 (C=O) cm^{-1}; nmr: δ 1.2 (t, 3, CH_3), 3.9 (d, 2, CH_2CO), 4.1 (q, 2, CH_2CH_3), 6.9-7.1 (m, 1, ArH), 7.3-7.6 (m, 1, ArH), 7.8-8.0 (m, 2, ArH and $NHCH_2$), 8.4 (d, 1, ArH), 10.3 (s, 1, ArNH), 11.5-13.3 (broad signal 1, COOH).

Anal. Calcd. for $C_{12}H_{14}N_2O_5$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.31; H, 5.32; N, 10.71.

Reaction of **13** with Concentrated Hydrochloric Acid.

A mixture of 0.50 g. of **13** and 5.0 ml. of concentrated hydrochloric acid was heated on a steam bath for 20 minutes, then cooled and filtered to yield 0.35 g. of a solid, m.p. 238-268°. The ir spectrum of this product showed it to be a mixture of mostly carboxylic acid **11** with some ester **10**.

An attempted reaction of **13** with concentrated hydrochloric acid at room temperature (15 hours) led to recovery of starting material.

2-Ethoxycarbonylmethylamino-4*H*-3,1-benzoxazin-4-one (**14**).

A solution of 2.0 g. of **13** in 10 ml. of concentrated sulfuric acid was allowed to stand at room temperature for 3 hours. Then it was mixed with ice, neutralized with 10% aqueous potassium bicarbonate (while being cooled), and filtered to yield 1.3 g. (70%) of **14**, m.p. 144-146°. The pure compound was obtained by recrystallization from ethyl acetate-petroleum ether (b.p. 60-80°) as colorless crystals, m.p. 147-148.5°; ir: 3340 (N-H), 1760, 1730 (C=O) cm^{-1}; nmr: δ 1.2 (t, 3, CH_3), 4.0 (d, 2, CH_2CO), 4.2 (q, 2, CH_2CH_3), 7.0-7.3 (m, 2, ArH), 7.5-8.0 (m, 2, ArH), 8.4 (broad t, 1, NH).

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.14; H, 4.85; N, 11.39.

Hydrolysis of **14**.

A mixture of 0.10 g. of **14**, 3 ml. of water, and 5 drops of concentrated hydrochloric acid was boiled for 2-3 minutes, cooled, and filtered to yield 0.10 g. of carboxylic acid **13**, m.p. 170-171° dec.

Reaction of **14** with Methanol.

A solution of 0.20 g. of **14** and 0.020 g. of *p*-toluenesulfonic acid in 5 ml. of methanol was allowed to stand at room temperature for 1 hour. Removal of the solvent by distillation under reduced pressure at room temperature yielded 0.20 g. of diester **12**, m.p. 116-118°.

Reaction of **14** with Concentrated Hydrochloric Acid.

A mixture of 0.50 g. of **14** and 5 ml. of concentrated hydrochloric acid was heated on a steam bath for 15 minutes, then cooled and filtered to yield 0.35 g. of **11**, m.p. 285-287° dec. Similarly, 0.30 g. of **11**, m.p. 285-290° dec., was obtained from an analogous mixture allowed to stand at room temperature for 15 hours.

N-Phenyl-2-(3-ethoxycarbonylmethylureido)benzamide (**17**).

A mixture of 0.30 g. of **14** and 0.50 g. of aniline was heated on a steam bath for 3 minutes, diluted with 1 ml. of benzene and 4 ml. of petroleum ether (b.p. 60-80°), and filtered to yield 0.40 g. (97%), of **17**, m.p. 189-191°. The pure compound was obtained by recrystallization from ethanol as colorless crystals, m.p. 193-194.5°; ir: 3330, 3270 (N-H), 1720, 1660, 1640 (C=O) cm^{-1}; nmr: δ 1.2 (t, 3, CH_3), 3.8 (d, 2, CH_2CO), 4.1 (q, 2, CH_2CH_3), 6.9-7.8 (m, 9, ArH, $NHCH_2$), 8.2 (d, 1, ArH), 9.5 (s, 1, NH), 10.4 (s, 1, NH).

Anal. Calcd. for $C_{18}H_{19}N_3O_4$: C, 63.33; H, 5.61; N, 12.31. Found: C, 63.38; H, 5.70; N, 12.31.

2-(3-Carbomethylureido)benzoic Acid (**18**).

A solution of 2.0 g. of **13** in 20 ml. of 10% aqueous potassium bicarbonate was heated on a steam bath for 3 hours and filtered to yield 0.040 g. of ester **10**, m.p. 224-226°. Acidification of the filtrate with concentrated hydrochloric acid precipitated 0.95 g. (53%) of **18**, m.p. 187-188° dec. Recrystallization from aqueous methanol yielded the pure compound as colorless crystals, m.p. 189-190° dec.; ir: 3360 (N-H), 1725, 1670, 1650 (C=O) cm^{-1}; nmr: δ 3.8 (d, 2, CH_2), 6.8-7.1 (t, 1, ArH), 7.3-7.6 (m, 1, ArH), 7.7-8.0 (m, 2, ArH, $NHCH_2$), 8.4 (d, 1, ArH), 10.3 (s, 1, ArNH), 10.6-13.5 (broad signal 2, COOH, COOH).

Anal. Calcd. for $C_{10}H_{10}N_2O_5$: C, 50.42; H, 4.23; N, 11.76. Found: C, 50.59; H, 4,15; N, 11.72.

Acknowlegement.

Financial support by National Institutes of Health (Minority Biomedical Support) Grant No 2 SO6-RR-08139-07 and the Department of Chemistry of the University of New Mexico is gratefully acknowledged.

REFERENCES AND NOTES

(1) E. C. Taylor and A. McKillop, "The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles," Interscience, New York, N.Y., 1970.

(2) E. C. Taylor and R. V. Ravindranathan, *J. Org. Chem.*, **27**, 2622 (1962).

(3) E. P. Papadopoulos, *J. Heterocyclic Chem.*, **17**, 1553 (1980).

(4) A. Mouneyrat, *Ber.*, **33**, 2393 (1900).

(5) E. P. Papadopoulos, *J. Org. Chem.*, **44**, 3858 (1979).

(6) K. H. David and W. Giessler, German Patent 2,315,303 (1974); *Chem. Abstr.*, **82**, 16851g (1975).

(7) Melting points were determined in capillaries with a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 337 spectrophotometer using mineral oil mulls. ^{1}H nmr spectra were obtained on a Varian EM 360 spectrometer using solutions in hexadeuteriodimethyl sulfoxide and tetramethylsilane as the internal standard. Cross-identification of compounds was accomplished by comparison of ir and nmr spectra, as well as by determination of mixture melting points. Crude reaction products were used in all preparations.

(8) Partial decomposition without appearance of liquid was observed at 320-330°.

(9) E. Wolf and H. Kohl, *Ann. Chem.*, 1245 (1975). The reason for the large difference in the melting point is not known.

(10) E. Kühle and R. Wegler, *ibid.*, **616**, 183 (1958).