Reactions of *o*-Aminonitriles with Isocyanates. 1. A Two-Step Synthesis of 2,6-Dihydroimidazo[1,2-*c*]quinazolin-5-(3*H*)one

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The reaction of anthranilonitrile with 2-chloroethyl isocyanate yields 2-[3-(2-chloroethyl)ureido]benzonitrile (**6**) which, upon heating, or treatment with base, undergoes a double cyclization to form 2,6-dihydroimidazo[1,2-*c*]quinazolin-5-(3*H*) one (**8**) in excellent yield. When heated with hydrochloric acid, **6** is converted initially into 2-(2-chloroethylamino)-4*H*-[3,1]benzoxazin-4-one (**18**) and further into 3-(2-chloroethyl)-2,4-(1*H*,3*H*)quinazolinedione (**15**). The acid-catalyzed reaction of 2,3-dihydro-5*H*-oxazolo[2,3-*b*]quinazolin-5-one (**14**) with nucleophilic reagents yields 3-substituted 2,4-(1*H*,3*H*)quinazolinediones.

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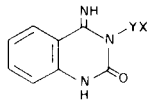
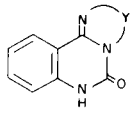
The use of *o*-aminonitriles as synthetic starting materials in heterocyclic chemistry is well established (1). Of special interest to this report is the reaction of these versatile reagents with isocyanates and isothiocyanates, which provides a convenient route to condensed pyrimidines (2). In a typical example, treatment of anthranilonitrile (**1**) with phenyl isocyanate leads to 3,4-dihydro-4-imino-3-phenyl-2-(1*H*)quinazolinone (**2**) (2). The present investigation was prompted by the expectation that an analogous reaction of **1** with an isocyanate containing a suitably located leaving group would allow a second ring closure leading to a 3-ring system **4**, as a result of an intramolecular nucleophilic substitution involving the imino nitrogen atom of the initial cyclization product **3**.



2, YX = Ph

3, X = leaving group



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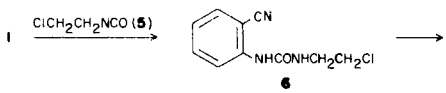
This paper describes the reaction of anthranilonitrile with 2-chloroethyl isocyanate (**5**), which allows preparation of the imidazo[1,2-*c*]quinazoline ring system in a remarkably simple and efficient manner. Treatment of **1** with **5**, in solution, or in the absence of solvent, yields the expected urea, 2-[3-(2-chloroethyl)ureido]benzonitrile (**6**), in essentially quantitative yield. When heated, **6** melts with decomposition at 175-180° to form a hydrochloride salt, the treatment of which with aqueous ammonia gives 2,6-dihydroimidazo[1,2-*c*]quinazolin-5-(3*H*)one (**8**). The same product is obtained when **6** is treated with sodium methoxide in methanol, or, most conveniently, with aqueous ammonia in ethanol (90% yield). Since the presumed intermediate **7** (corresponding to the isolated



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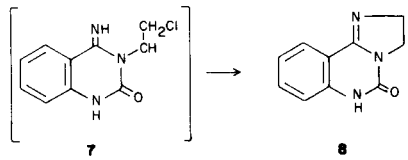
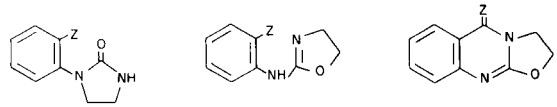


7 **8**

product **2** of the model reaction) (2) has not been isolated or detected, it may be concluded that formation of the dihydroimidazole ring occurs fast.

Structure **8**, for the product of this reaction is supported by the melting point of the isolated compound, as well as its microanalytical and spectral data. Nonetheless, cyclization of **6** with elimination of hydrogen chloride could, in principle, proceed differently to form an isomer of **8**, such as **9**, **10**, or **11**. Structures **9** and **10**, are incompatible



9, Z = CN **10**, Z = CN **11**, Z = NH

12, Z = H **13**, Z = H **14**, Z = O

with the absence of a C≡N stretching band in the ir spectrum of the product. However, since this band exhibits variable intensity and sometimes is so weak as to be undetectable, especially in the case of oxygen containing compounds (3), it was thought desirable to obtain additional evidence against these two structures. Model compounds **12** and **13** were prepared from *N*-2-chloroethyl-*N'*-phenylurea following published procedures (4). In the nmr spectra of these compounds, the CH_2CH_2 protons are represented by roughly symmetrical multiplets (δ 3.2-3.5 and 3.7-4.0 for **12**; 3.6-3.9 and 4.1-4.4 for **13**), in contrast to the singlet (or very narrow multiplet) observed for **8** (δ 3.9). In addition, the NH proton signals of the model compounds appear at a significantly higher field [δ 6.9 (5) for **12**, 8.7 for **13**] than for **8** (δ 10.6). Because the wavenumber of the carbonyl band in the ir spectrum of the isolated pro-

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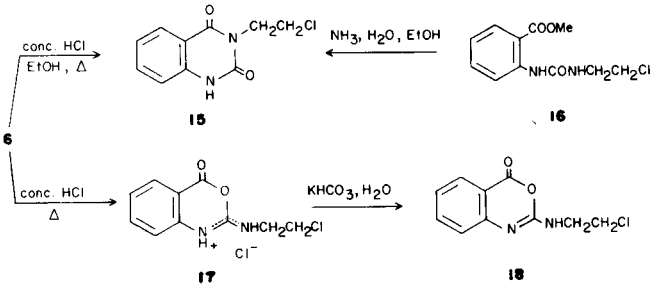
duct is relatively low (1680 cm^{-1}), structure **11** cannot be immediately excluded. However, a compound of such structure would be expected to undergo acid hydrolysis with cleavage of the imino group and formation of the corresponding keto derivative **14**. In fact, the cyclization product of **6** is recovered unchanged after treatment with hydrochloric acid in ethanol, under conditions found to cleave imino groups readily in other systems (2,6). Furthermore, in contrast to the spectrum of the product under discussion, the nmr spectrum of 2,3-dihydro-5*H*-oxazolo-[2,3-*b*]quinazolin-5-one (**14**) contains a pattern of signals for the CH_2CH_2 protons very similar to those observed in the spectra of compounds **12** and **13**.

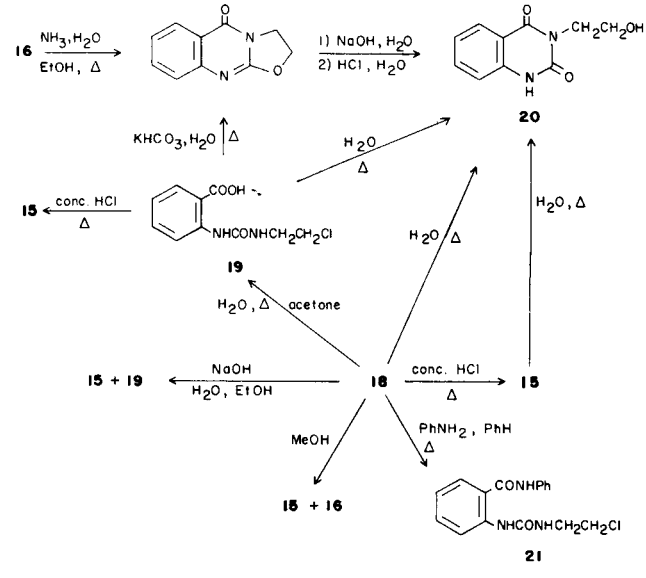
In an attempt to investigate the possibility of an acid-catalyzed cyclization, compound **6** was heated with hydrochloric acid in ethanol. The product of this reaction was identified as 3-(2-chloroethyl)-2,4-(1*H*,3*H*)quinazolinedione (**15**) on the basis of its melting point, ir and nmr spectra, and preparation from methyl 2-[3-(2-chloroethyl)ureido]-benzoate (**16**, obtained from methyl anthranilate and isocyanate **5**) by the action of base. When the same cyclization of **6** was attempted using concentrated hydrochloric



acid alone, a different product was isolated after neutralization, namely 2-(2-chloroethylamino)-4*H*-[3,1]benzoxazin-4-one (**18**). This reaction may be considered to involve intramolecular nucleophilic attack by the urea oxygen on the protonated cyano group of **6**, followed by hydrolytic cleavage of the resulting imino group. The product which precipitates initially has been tentatively identified as hydrochloride salt **17**. Since either **17** or **18** is converted into **15** upon further heating with hydrochloric acid, it is likely that the cation of **17** is involved as an intermediate in the formation of **15** by the reaction in ethanol. This conversion probably proceeds through initial formation and subsequent cyclization of 2-[3-(2-chloroethyl)ureido]benzoic acid (**19**), which has been found to be converted into **15** under the same conditions. The possibility, however, that carboxylic acid **19** is an intermediate in the conversion of nitrile **6** into **17** is unlikely, both because of the rapidity of this transformation and the observation that brief heating of **19** with hydrochloric acid yields a mixture of **15** and unreacted starting material, but no **17**.

Although a correct elemental analysis could not be obtained for **17**, the proposed structure is consistent with the ir spectrum of this compound (broad N-H band at 2700-2300 cm^{-1}, carbonyl band at 1790 cm^{-1}) and its ring opening reactions, which parallel the corresponding reactions of the free base **18**. The latter compound is conveniently obtained from **17** by the action of aqueous ammonia, or bicarbonate, and is converted back to **17** by treatment with concentrated hydrochloric acid. Of the two tautomeric structures possible for **18**, the one with an endocyclic C=N appears more probable, at least in solution in dimethyl sulfoxide. Its nmr spectrum in this solvent exhibits a partially resolved, somewhat broad triplet (J = 5-6 Hz) centered at δ 8.3, which is consistent with an exocyclic NH. Addition of deuterium oxide to the solution removes this signal from the spectrum.

Whereas a brief (5 minutes) treatment of **17** with water yields **18**, a prolonged (24 hours) such treatment leads to 2-[3-(2-chloroethyl)ureido]benzoic acid (**19**), the structure of which has been confirmed by its preparation from potassium anthranilate and **5**. This hydrolytic ring opening of **17** seems to be acid-catalyzed, as observed for other similar reactions (7), since it is incomplete when a large excess of water is used, whereas an analogous treatment of the free base **18** fails to cause any ring opening. However, **18** is readily hydrolyzed into **19** by refluxing with aqueous acetone. When either **17** or **18** is refluxed with water, it is converted into 3-(2-hydroxyethyl)-2,4-(1*H*,3*H*)quinazolinedione (**20**), very likely through the successive, intermediate formation of compounds **19**, **15**, and **14**, each of which is transformed into **20**, under the same conditions.

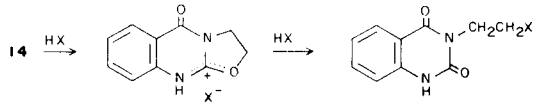


Structure **20**, supported by the melting point of the product and its spectra, has been further confirmed as follows. Treatment with base causes methyl 2-[3-(2-chloroethyl)ureido]benzoate (**16**) to undergo a double cyclization yielding 2,3-dihydro-5*H*-oxazolo[2,3-*b*]quinazolin-5-one (**14**) (8), as evidenced by the melting point and the spectra

of the product. Somewhat surprisingly, compound **14** is obtained in good yield also when a solution of carboxylic acid **19** in aqueous potassium bicarbonate is heated. The oxazolidine ring of **14** opens up by the action of aqueous sodium hydroxide to form 3-(2-hydroxyethyl)-2,4-(1*H*,3*H*)-quinazolinedione (**20**), identical in all respects with the product obtained from **17** or **18**.

When **17** or **18** is allowed to react with methanol, either at room temperature, or at reflux, a mixture of quinazolinedione **15** and ester **16** results. Neither of these two compounds seems to be involved as an intermediate in the formation of the other, since each is recovered unchanged from an acidified mixture with methanol allowed to stand for 24 hours. It may be that formation of **15** and **16** originates in nucleophilic attack by methanol at positions 2 and 4 of the oxazinone ring, respectively (9). Treatment of either **17** or **18** with aqueous-ethanolic sodium hydroxide, followed by acidification, yields a mixture of either **15** and **19**, or **14** and **19**, depending upon the length of interaction with the base. Finally, **18** reacts with aniline to yield anilide **21**.

The convenient availability of compound **14** prompted a brief investigation of its reactivity. As anticipated, it was found to be readily susceptible of acid-catalyzed, ring-opening, nucleophilic attack at C-5 of the oxazolidine ring. Thus, brief warming of **14** with concentrated hydrochloric acid yields quinazolinedione **15**. That this reaction does not proceed through the 2-hydroxyethyl derivative **20** as an intermediate is shown by the fact that the latter compound is recovered unchanged following an analogous treatment. The corresponding 2-bromoethyl derivative **22** is obtained by treatment of **14** with hydrobromic acid. Similarly, when **14** is heated with dilute sulfuric acid,



15, X = Cl **24**, X = OEt
20, X = OH **25**, X = OAc
22, X = Br **26**, X = $OOCCF_3$
23, X = OMe **27**, X = NHPh

a hydrolytic ring opening takes place to form **20**. Analogous reactions with acidified methanol, or ethanol, and acetic, or trifluoroacetic acid yield the methyl (**23**), or ethyl ether (**24**), and acetate (**25**), or trifluoroacetate (**26**) of **20**. Finally, the anilino derivative **27** is obtained by the acid-catalyzed reaction of **14** with aniline.

EXPERIMENTAL

2-[3-(2-Chloroethyl)ureido]benzonitrile (**6**).

A.

A mixture of 5.9 g. (0.050 mole) of anthranilonitrile and 5.3 g. (0.050 mole) of 2-chloroethyl isocyanate was warmed briefly for the crystals of the nitrile to dissolve and then was allowed to stand at room temperature for 48 hours to yield 10.9 g. (97%) of **6**, m.p. 165-167° (partial melting followed by resolidification) (11). Recrystallization from ethanol yielded the pure compound as colorless crystals, m.p. 175-176° (partial melting followed by resolidification) (11); ir: 3320, 3250 (N-H), 2220 (C≡N), 1640 (C=O) cm^{-1}; nmr: δ 3.4-3.7 (m, 4, CH_2CH_2), 7.0-7.8 (m, 4, ArH and $NHCH_2$), 8.1 (d, 1, ArH), 8.7 (s, 1, ArNH).

Anal. Calcd. for $C_{10}H_{10}ClN_3O$: C, 53.70; H, 4.51; N, 18.79. Found: C, 53.61; H, 4.53; N, 18.84.

B.

A mixture of 0.050 mole of **1**, 0.050 mole of **5**, and 15 ml. of benzene was refluxed for 3 hours, then it was cooled and filtered to yield 10.4 g. (93%) of **6**, m.p. 170-172° (partial melting followed by resolidification) (11).

2,6-Dihydroimidazo[1,2-*c*]quinazolin-5-(3*H*)one (**8**).

A.

A mixture of 2.0 g. of **6**, 20 ml. of ethanol, and 10 ml. of concentrated aqueous ammonia was warmed on a steam bath and occasionally swirled for a total of 15 minutes. It was then cooled, diluted with water, and filtered to yield 1.50 g. (89%) of **8**, m.p. 289-292°. An analytical sample was obtained by recrystallization from ethanol as colorless crystals, m.p. 291-293° [lit. (12) m.p. 291-293°]; ir: 1680 (C=O) cm^{-1}; nmr: δ 3.9 [s, (13), 4, CH_2CH_2], 7.0-7.2 (m, 2, ArH), 7.4-7.9 (m, 2, ArH), 10.6 (s, 1, NH).

Anal. Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.13; H, 4.88; N, 22.64.

B.

Thermal decomposition of 1.0 g. of **6** (oil bath at 200°) followed by treatment of the resulting solid with aqueous ammonia (1:1 concentrated ammonia:water) yielded 0.80 g. (95%) of **8**, m.p. 280-284°.

Attempted Hydrolysis of **8**.

A mixture of 0.50 g. of **8**, 5 ml. of concentrated hydrochloric acid and 5 ml. of ethanol was heated on a steam bath for 5 minutes. Addition of water and neutralization with 10% aqueous sodium bicarbonate yielded 0.40 g. of starting material, m.p. 287-292°.

2,3-Dihydro-5*H*-oxazolo[2,3-*b*]quinazolin-5-one (**14**).

A.

A mixture of 3.0 g. of **16**, 10 ml. of ethanol and 20 ml. of concentrated aqueous ammonia was heated on a steam bath until an initially formed precipitate had redissolved (about 15 minutes). The resulting solution was cooled and mixed with water to yield 2.1 g. (95%) of **14**, m.p. 160-162° [lit. m.p. 165° (8a), 156° (8b)]; ir: 1680 (C=O) cm^{-1}; nmr: δ 4.1-4.3 (m, 2, CH_2), 4.6-4.8 (m, 2, CH_2), 7.2-8.1 (m, 4, ArH).

B.

A mixture of 1.0 g. of **16**, 10 ml. of 10% aqueous potassium bicarbonate and 5 ml. of ethanol was heated on a steam bath until a clear solution had been obtained (about 10 minutes) and for an additional 0.5 hour. The resulting solution was cooled and mixed with water to yield 0.65 g. (89%) of **14**, m.p. 155-157°.

C.

A mixture of 1.0 g. of **16** and a solution of 5 pellets of potassium hydroxide in 10 ml. of ethanol was shaken occasionally over a period of 15 minutes. Dilution with water and filtration yielded 0.50 g. (68%) of **14**, m.p. 158-160°.

D.

Upon standing for 0.5 hour, a solution of 1.0 g. of **15** in 10 ml. of 10% aqueous sodium hydroxide precipitated 0.70 g. (83%) of **14**, m.p. 161-163°.

E.

A mixture of 0.50 g. of **19** and 10 ml. of 10% aqueous potassium bicarbonate was heated on a steam bath for 0.5 hour. Cooling and filtration

yielded 0.35 g. (90%) of **14** m.p. 160-162°.

3-(2-Chloroethyl)-2,4-(1*H*,3*H*)quinazolinedione (**15**).

A.

A mixture of 1.0 g. of **16**, 5 ml. of ethanol and 5 ml. of concentrated aqueous ammonia was swirled at intervals over a period of 0.5 hour. Filtration yielded 0.50 g. (57%) of **15**, m.p. 193-195° [lit. (14) m.p. 195.5-196°]; ir: 1710, 1650 (C=O) cm^{-1}; nmr: δ 3.7-3.9 (m, 2, CH_2), 4.2-4.4 (m, 2, CH_2), 7.1-8.0 (m, 4, ArH), 11.4 (s, 1, NH).

B.

After a mixture of 1.0 g. of **6**, 5 ml. of ethanol and 5 ml. of concentrated hydrochloric acid had been heated on a steam bath of 0.5 hour, it was cooled, diluted with water, and filtered to yield 0.65 g. (65%) of **15**, m.p. 185-187°.

C.

When a mixture of 0.30 g. of **14** and 3 ml. of concentrated hydrochloric acid was heated on a steam bath for about 1 minute, initial dissolution was followed rapidly by precipitation. Cooling and filtration yielded 0.30 g. (83%) of **15**, m.p. 192-194°.

Methyl 2-[3-(2-Chloroethyl)ureido]benzoate (**16**).

A mixture of 6.0 g. (0.040 mole) of methyl anthranilate and 4.2 g. (0.040 mole) of 2-chloroethyl isocyanate was cooled occasionally over a period of 15 minutes to prevent overheating, and was then allowed to stand at room temperature for 16 hours to yield 10.2 g. (100%) of **16**, m.p. 137-139°. Recrystallization from ethanol gave the pure compound in the form of colorless crystals, m.p. 140-141°; ir: 3280 (N-H), 1690, 1650 (C=O) cm^{-1}; nmr: δ 3.3-3.8 (m, 4, CH_2CH_2), 3.9 (s, 3, CH_3), 6.9-7.1 (m, 1, ArH), 7.4-8.0 (m, 3, ArH and N*H*CH_2), 8.4 (d, 1, ArH), 9.9 (s, 1, ArNH).

Anal. Calcd. for $C_{11}H_{13}ClN_2O_3$: C, 51.47; H, 5.11; N, 10.91. Found: C, 51.66; H, 5.20; N, 10.93.

2-(2-Chloroethylamino)-4*H*-[3,1]benzoxazin-4-one (**18**).

When a mixture of 5.0 g. of **6** and 25 ml. of concentrated hydrochloric acid was swirled while heated on a steam bath for 2-3 minutes, gradual dissolution was followed by formation of a new precipitate. Cooling and filtration yielded 5.1 g. of a solid compound, tentatively identified as **17**, m.p. 150-152° dec.; ir: (after 1 recrystallization from THF) 2700-2300 (=N⁺-H), 1790 (C=O) cm^{-1}. The nmr spectrum indicated the presence in this product of traces of **15** and some water. An attempt to dry a sample by azeotropic distillation failed, whereas repeated recrystallization resulted in formation of a mixture of **15** and **19**.

A mixture of 3.2 g. of crude, air-dried **17** and 50 ml. of 10% aqueous potassium bicarbonate was allowed to stand at room temperature for 0.5 hour and then it was filtered to yield 2.6 g. (81% overall) of **18**, m.p. 138-140° dec. The pure compound was obtained by recrystallization from benzene-ethyl acetate as colorless crystals, m.p. 143.5-145° dec.; ir: 3320 (N-H), 1730 (C=O) cm^{-1}; nmr: δ 3.6-3.9 (m, 4, CH_2CH_2), 7.1-7.3 (m, 2, ArH), 7.5-8.0 (m, 2, ArH), 8.3 (broad t, 1, NH).

Anal. Calcd. for $C_{10}H_9ClN_2O_2$: C, 53.47; H, 4.04; N, 12.47. Found: C, 53.60; H, 4.03; N, 12.48.

Reaction of **18** (**17**) with Hydrochloric Acid.

A.

After a mixture of 0.30 g. of **18** and 3.0 ml. of concentrated hydrochloric acid had been heated on a steam bath for 5 minutes, it was cooled and filtered to yield 0.25 g. of **17**, m.p. 157-159° dec.

B.

A mixture of 0.50 g. of **18** and 5 ml. of concentrated hydrochloric acid was heated on a steam bath for 1 hour and then it was diluted with water and filtered to yield 0.45 g. of **15**, m.p. 192-193°. Similarly, from 0.90 g. of **17** and 10 ml. of concentrated hydrochloric acid heated for 1 hour, there was obtained 0.73 g. of **15**, m.p. 192-193°.

Reaction of **18** (**17**) with Sodium Hydroxide.

When 0.50 g. of **18** had been swirled with 3 ml. of ethanol and 3 ml. of 10% aqueous sodium hydroxide for about 1 minute, a clear solution was obtained. Acidification with concentrated hydrochloric acid yielded a precipitate, which was collected and then treated with 10% aqueous potassium bicarbonate. A new filtration separated 0.35 g. of **15**, m.p. 192-194°. Acidification of the bicarbonate solution with concentrated hydrochloric acid afforded 0.10 g. of **19**, m.p. 152-154° dec. When the solution obtained by treatment of 0.50 g. of **18** with 3 ml. of ethanol and 3 ml. of 10% aqueous sodium hydroxide had been allowed to stand for 5 minutes, a precipitate was formed. Filtration separated 0.30 g. of **14**, m.p. 160-162° and acidification of the filtrate precipitated 0.10 g. of **19**, m.p. 152.5-154° dec. In the case of **17**, the solution obtained from 0.20 g. of this compound, 3 ml. of ethanol and 3 ml. of 10% aqueous sodium hydroxide was acidified to yield 0.15 g. of a solid, the ir spectrum of which indicated a mixture of **15** and **19**.

Reaction of **18** (**17**) with Water.

A.

Filtration of a mixture of 0.10 g. of **17** and 10 ml. of water which had stood at room temperature for 5 minutes yielded 0.070 g. of **18**, m.p. 136-138° dec.

B.

After a mixture of 0.50 g. of **17** and 30 ml. of water had stood for 24 hours, it was filtered to give 0.42 g. of **19**, m.p. 152-153.5° dec.

Following the refluxing of a mixture of 0.50 g. of **18**, 10 ml. of acetone and 5 ml. of water of 0.5 hour, acetone was removed by distillation, and the residue cooled and filtered to yield 0.45 g. of **19**, m.p. 153-154° dec.

C.

A mixture of 0.50 g. of **18** and 30 ml. of water was refluxed for 2 hours and then it was cooled and filtered to yield 0.35 g. of **20**, m.p. 249-251°. Similarly, from 0.50 g. of **17**, there was obtained 0.30 g. of **20**, m.p. 244-248°.

Reaction of **18** (**17**) with Methanol.

A mixture of **18** (or **17**) and methanol was refluxed for 1 hour, or allowed to stand at room temperature overnight. Removal of the solvent by distillation under reduced pressure, or addition of water to the solution yielded a broad melting solid, the ir spectrum of which indicated a mixture of **15** and **16**.

2-[3-(2-Chloroethyl)ureido]benzoic Acid (**19**).

A cold solution of 4.1 g. (0.030 ml.) of anthranilic acid in 35 ml. of 10% aqueous potassium bicarbonate was shaken vigorously with 3.2 g. (0.030 mole) of 2-chloroethyl isocyanate and the mixture was cooled occasionally over a period of 3-4 minutes. After removal of traces of a solid by filtration, the solution was acidified with concentrated hydrochloric acid to yield 6.2 g. (85%) of **19**, m.p. 147-149° dec. The pure compound was obtained by recrystallization from aqueous ethanol as colorless crystals; m.p. 153-154° dec. [lit. (15) m.p. 171°]; ir: 3330, 3300 (N-H), 1660 (C=O) cm^{-1}; nmr: δ 3.4-3.8 (m, 4, CH_2CH_2), 7.0 (m, 1, ArH), 7.4-8.1 (m, 3, ArH and N*H*CH_2), 8.5 (d, 1, ArH), 10.3 (s, 1, ArNH), 12.0-13.5 (broad signal, 1, COOH).

Anal. Calcd. for $C_{10}H_{11}ClN_2O_3$: C, 49.50; H, 4.57; N, 11.54. Found: C, 49.69; H, 4.58; N, 11.29.

Reaction of **19** with Water.

The solution obtained when a mixture of 0.20 g. of **19** and 20 ml. of water had been refluxed for 0.5 hour was cooled to yield 0.13 g. of **20**, m.p. 246-248°.

Reaction of **19** with Hydrochloric Acid.

A mixture of 1.0 g. of **19** and 10 ml. of concentrated hydrochloric acid

was heated on a steam bath for 5 minutes. After addition of water, filtration yielded a solid the ir spectrum of which indicated a mixture of **15** and **19**. When this reaction was repeated using a 1-hour heating period, the product was 0.73 g. of **15**, m.p. 188-190°.

3-(2-Hydroxyethyl)-2,4-(1*H*,3*H*)quinazolinedione (**20**).

A.

The solution obtained by heating a mixture of 0.50 g. of **14** and 10 ml. of 10% aqueous sodium hydroxide on a steam bath for 5 minutes was cooled and acidified to yield 0.50 g. (91%) of **20**, m.p. 243-247° raised to 250-252° by recrystallization from aqueous ethanol [lit. (14) m.p. 253.5-254°]; ir: 3370 (O-H), 1700, 1650 (C=O) cm^{-1}; nmr: δ 3.5-3.7 (m, 2, CH_2), 3.9-4.1 (m, 2, CH_2), 4.8 (broad signal, 1, OH), 7.0-7.3 (m, 2, ArH), 7.5-8.0 (m, 2, ArH), 11.3 (broad signal, 1, NH).

B.

A mixture of 0.40 g. of **14** and 10 ml. of 10% sulfuric acid was refluxed for 0.5 hour and the resulting solution was cooled, neutralized with aqueous potassium bicarbonate and filtered to yield 0.35 g. (80%) of **20**, m.p. 250-252°.

C.

A mixture of 1.0 g. of **6** and 15 ml. of water was heated on a steam bath for 16 hours and then it was cooled and filtered to yield 0.40 g. of **20**, m.p. 248-250°.

D.

Refluxing of a mixture of 0.20 g. of **15** and 50 ml. of water for 1 hour yielded 0.15 g. of **20**, m.p. 247-249°.

Attempted Reaction of **20** with Hydrochloric Acid.

A mixture of 0.30 g. of **20** and 3.0 ml. of concentrated hydrochloric acid was heated on a steam bath for 2-3 minutes. Cooling, addition of water, and filtration yielded 0.28 g. of starting material, m.p. 247-249°.

N-Phenyl-2-[3-(2-chloroethyl)ureido]benzamide (**21**).

After a mixture of 0.25 g. of **18**, 0.30 g. of aniline, and 5 ml. of benzene had been refluxed for 0.5 hour it was cooled and filtered to yield 0.30 g. (85%) of **21**, m.p. 197-198° dec. (11). The pure compound was obtained by recrystallization from ethanol as colorless crystals, m.p. 200-202° dec. (11) ir: 3370, 3270 (N-H), 1660, 1640 (C=O) cm^{-1}; nmr: 3.3-3.8 (m, 4, CH_2CH_2), 7.0-7.8 (m, 9, ArH and N*H*CH_2), 8.3 (d, 1, ArH), 9.5 (s, 1, NH), 10.5 (s, 1, NH).

Anal. Calcd. for $C_{16}H_{16}ClN_3O_2$: C, 60.47; H, 5.08; N, 13.22. Found: C, 60.47; H, 5.11; N, 13.28.

3-(2-Bromoethyl)-2,4-(1*H*,3*H*)quinazolinedione (**22**).

Upon brief (1-2 minutes) heating on a steam bath of a mixture of 0.35 g. of **14**, 3 ml. of concentrated hydrobromic acid and 2 ml. of water there was formed 0.45 g. (90%) of **22**, m.p. 205-208°. The pure compound was obtained by recrystallization from ethanol as colorless crystals, m.p. 206-208°; ir: 1710, 1650 (C=O) cm^{-1}; nmr: δ 3.5-3.7 (m, 2, CH_2), 4.2-4.4 (m, 2, CH_2), 7.0-7.3 (m, 2, ArH), 7.5-8.0 (m, 2, ArH), 11.4 (s, 1, NH).

Anal. Calcd. for $C_{10}H_9BrN_2O_2$: C, 44.63; H, 3.37; N, 10.41. Found: C, 44.69; H, 3.46; N, 10.44.

3-(2-Methoxyethyl)-2,4-(1*H*,3*H*)quinazolinedione (**23**).

After a solution of 0.40 g. of **14** and 0.050 g. of *p*-toluenesulfonic acid in 5 ml. of methanol had been refluxed for 1 hour, it was cooled, diluted with water, and neutralized with 10% aqueous potassium bicarbonate to yield 0.33 g. (71%) of **23**, m.p. 147-149°. Recrystallization from benzene-petroleum ether (b.p. 60-80°) yielded the pure compound as colorless crystals, m.p. 148-150°; ir: 1700, 1640 (C=O) cm^{-1}; nmr: δ 3.3 (s, 3, CH_3), 3.4-3.6 (m, 2, CH_2), 4.0-4.2 (m, 2, CH_2), 7.0-7.3 (m, 2, ArH), 7.5-8.0 (m, 2, ArH), 11.4 (s, 1, NH).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.13; H, 5.45; N, 12.74.

3-(2-Ethoxyethyl)-2,4-(1*H*,3*H*)quinazolinedione (**24**).

As for the preceding reaction, from 0.60 g. of **14**, 10 ml. of ethanol and 0.050 g. of *p*-toluenesulfonic acid refluxed for 0.5 hour, there was obtained 0.70 g. (93%) of **24**, m.p. 149-154°. The pure compound was obtained by recrystallization from benzene-petroleum ether (b.p. 60-80°) as colorless crystals, m.p. 156-157.5°; ir: 1710, 1660 (C=O) cm^{-1}; nmr: δ 1.1 (t, 3, CH_3), 3.3-3.7 (m, 4, CH_2OCH_2), 4.0-4.2 (m, 2, NCH_2), 7.0-7.4 (m, 2, ArH) 7.5-8.0 (m, 2, ArH), 11.4 (s, 1, NH).

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.62; H, 5.93; N, 12.17.

3-(2-Acetoxyethyl)-2,4-(1*H*,3*H*)quinazolinedione (**25**).

A mixture of 0.30 g. of **14** and 1 ml. of acetic acid was refluxed for 15 minutes and then it was cooled and mixed with water to yield 0.37 g. (93%) of **25**, m.p. 166-167°. Recrystallization from ethanol yielded the pure compound as colorless crystals, m.p. 167-168.5°; ir: 1730, 1700, 1650 (C=O) cm^{-1}; nmr: δ 2.0 (s, 3, CH_3), 4.2 [(s, (13) 4, CH_2CH_2], 7.0-7.3 (m, 2, ArH), 7.5-8.0 (m, 2, ArH), 11.5 (s, 1, NH).

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.07; H, 4.66; N, 11.30.

3-(2-Trifluoroacetoxyethyl)-2,4-(1*H*,3*H*)quinazolinedione (**26**).

After a mixture of 0.60 g. of **14** and 2 ml. of trifluoroacetic acid had been heated on a steam bath for 15 minutes, it was cooled, diluted with water, and filtered to give 0.70 g. (72%) of colorless crystals of **26**, m.p. 176-178°. Recrystallization from benzene did not change the m.p.; ir: 1780, 1700, 1650 (C=O) cm^{-1}; nmr: δ 4.2-4.4 (m, 2, CH_2), 4.6-4.8 (m, 2, CH_2), 7.1-7.3 (m, 2, ArH), 7.5-8.0 (m, 2, ArH), 11.6 (s, 1, NH).

Anal. Calcd. for $C_{12}H_9F_3N_2O_4$: C, 47.69; H, 3.00; N, 9.27. Found: C, 47.91; H, 3.14; N, 9.33.

3-(*N*-Phenyl-2-aminoethyl)-2,4-(1*H*,3*H*)quinazolinedione (**27**).

A mixture of 0.60 g. of **14**, 0.60 g. of aniline, 5 ml. of benzene, and 0.050 g. of *p*-toluenesulfonic acid was refluxed for 1.5 hour and then it was cooled, mixed with petroleum ether (b.p. 60-80°) and filtered to yield a solid material. This was dried, treated with aqueous potassium bicarbonate and recrystallized from ethanol to yield 0.35 g. (39%) of **27**, m.p. 197-199°. The pure compound was obtained by further recrystallization from ethanol as colorless crystals, m.p. 200-202°; ir: 3400 (N-H), 1720, 1650 (C=O) cm^{-1}; nmr: δ 3.1-3.4 (m, 2, CH_2), 3.9-4.2 (m, 2, CH_2), 5.8 (broad t, 1, CH_2NH), 6.4-6.7 (m, 3, ArH), 6.9-7.3 (m, 4, ArH), 7.5-8.0 (m, 2, ArH), 11.3 (broad signal 1, ArNH).

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.50; H, 5.38; N, 14.96.

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