Synthesis of 2,3-Dihydro-5*H*-oxazolo[2,3-*b*]quinazolin-5-ones

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Iodide-catalyzed ring expansion of 2-[(1-aziridinylcarbonyl)amino]benzoic acid methyl ester (**2**) gave 2,3-dihydro-5*H*-oxazolo[2,3-*b*]quinazolin-5-one (**3**) in quantitative yield. Treatment of the dimethyl analog of **2** (**9**) with sodium iodide in acetone gave a mixture of the 2,3-dihydro-2,2-dimethyl- (**10**) and 2,3-dihydro-3,3-dimethyl-5*H*-oxazolo[2,3-*b*]quinazolin-5-ones (**11**). However, rearrangement of **9** with sulfuric acid produced only **10**. Synthesis of **11** by another route for comparison is described, and the known syntheses of 2,3-dihydro-5*H*-oxazolo[2,3-*b*]quinazolin-5-ones are reviewed.

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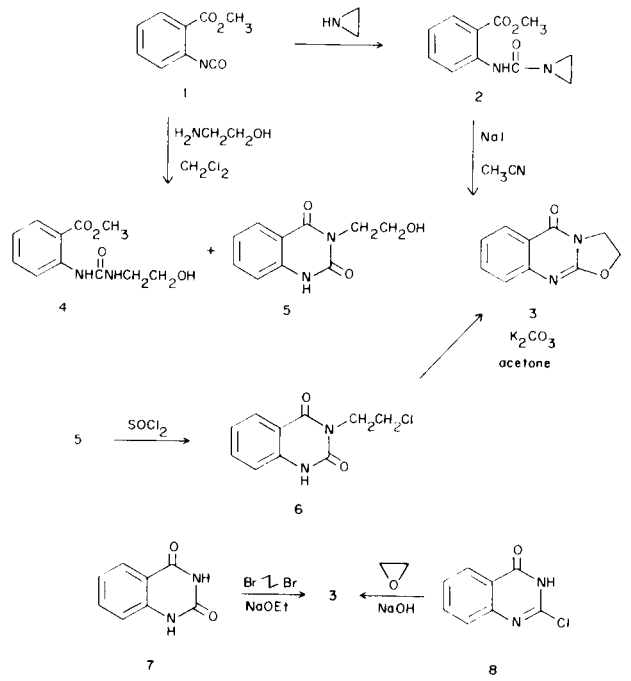
2-Carbomethoxyphenyl isocyanate (**1**) is a convenient (1) and useful (2,3) starting material for the construction of heterocyclic systems. This report describes syntheses of 2,3-dihydro-5*H*-oxazolo[2,3-*b*]quinazolin-5-ones from **1** in exceedingly high yields.

Treatment of **1** with ethyleneimine afforded aziridinylurea (**2**) in 98% yield. When **2** was then treated with sodium iodide in acetone, 2,3-dihydro-5*H*-oxazolo-[2,3-*b*]quinazolin-5-one (**3**) was produced quantitatively. The use of nucleophilic catalysts such as iodide ion for the expansion of aziridinylamides to oxazolines is well-documented, as is the use of strong acid and Lewis acid catalysts (4). We did not anticipate the direct formation of **3** from **2** under the mild catalytic conditions which were employed (5) (Scheme I).

Scheme I



Compound **3** has been previously prepared from 3-(2-chloroethyl)-2,4-(1*H*,3*H*)-quinazolinedione (**6**) by Grout and Partridge (7), and it was this method which we chose for the preparation of an authentic sample of **3** for comparison. Hydroxy compound **5**, the precursor to **6**, has been prepared by a variety of routes; *i.e.*, from isatoic anhydride *via* 2-(carbethoxyamino)-*N*-(2-hydroxyethyl)-benzamide and phosgene (8) or ethyl chloroformate (9), 2-(methoxysulfonyl)phthalimide (10), and others (11,12). We chose to prepare **5** from **1**. Treatment of **1** with ethanolamine in methylene chloride afforded a mixture of **5** and 2-[[(2-hydroxyethyl)amino)carbonyl]amino]benzoic acid methyl ester (**4**), which is a previously unreported compound. Recrystallization of the mixture from ethanol afforded mainly **5**; hydroxyethylurea **4** was isolated from the mother liquor and purified by recrystallization from methylene chloride-hexane.

Grout and Partridge (7) report two additional routes to oxazoloquinazolone **3**, which are indicated in Scheme I. Treatment of 2,4-(1*H*,3*H*)quinazolinedione (**7**) with sodium ethoxide and 1,2-dibromoethane gave **3**, as did treatment of 2-chloro-3*H*-quinazolin-4-one (**8**) with sodium hydroxide and ethylene oxide.

The dimethyl analog of **2**, compound **9**, was also prepared (from **1** and 2,2-dimethylethyleneimine) for rearrangement studies. Treatment of **9**, however, with sodium iodide in acetone produced a mixture of oxazolo-quinazolones **10** and **11** in approximately equivalent amounts (Scheme II). This mixture was inseparable by thin layer chromatography or column chromatography (silica gel). The substantial presence of **10** was surprising, in view of the accepted mechanism for iodide-catalyzed ring expansion of aziridinyl amides. Apparently there is no appreciable steric barrier to iodide attack imposed by the methyl groups.

Brief treatment of aziridinyl urea **9**, however, with sulfuric acid produced a single oxazoloquinazolone in

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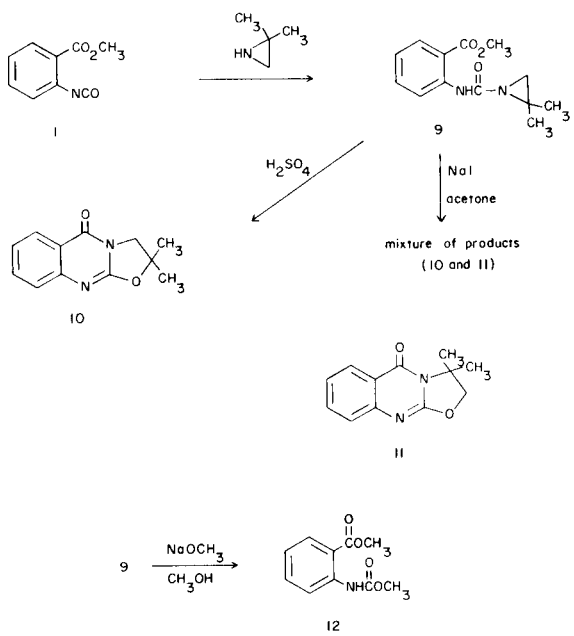
86% yield, which was shown to be **10** (*vide infra*). This single product can be easily rationalized mechanistically. Protonation and ring opening of the aziridinyl urea should give, exclusively, the tertiary carbonium ion, which would be trapped by the urea oxygen and lead to **10** (where the methyl groups are adjacent to oxygen).

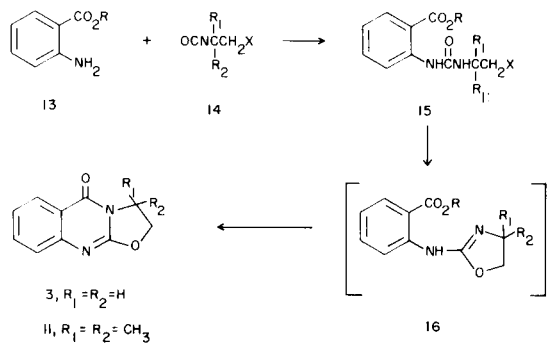
Interestingly, cyclization of **9** was not induced with base. Treatment of **9** with sodium methoxide gave isatoic acid dimethyl ester (**12**).

Scheme II



In order to firmly establish the identity of the single oxazoloquinazolone produced from **9** and sulfuric acid, we felt that we needed to produce an authentic sample of either **10** or **11**. A synthesis of **11** has appeared in the patent literature by Kampe (13). When 2-haloethylisocyanates (**14**) were treated with anthranilates (**13**), using several sets of described reaction conditions, oxazoloquinazolones resulted. Thus, syntheses of **3**, **11**, and others were reported (Scheme III).

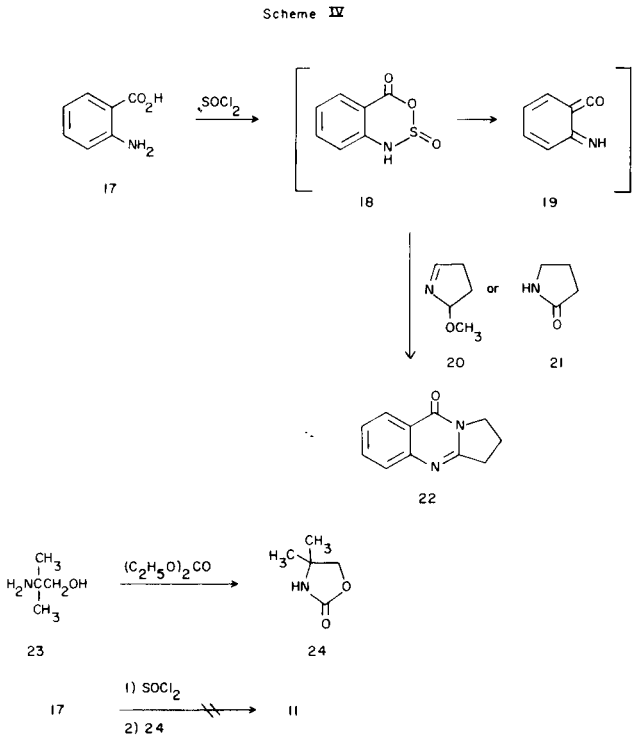
Scheme III



Since the isocyanate which we needed (**14**, $R_1 = R_2 = CH_3$) for the Kampe synthesis was difficult to prepare, we investigated alternate approaches to the synthesis of **11**. Kametani and co-workers (14) have recently prepared pyrroloquinazolone **22** (deoxyvasicinone) from anthranilic acid (**17**) and the *O*-methyl derivative of 2-pyrrolidinone (**20**). Treatment of **17** with thionyl chloride initially produces sulfinamide anhydride **18** which could react in stepwise fashion with imine **20** to give **22**. Alternatively, iminoketene **19** could react in concerted fashion with **20** to give **22** (Scheme IV). Even more recently, Kametani and coworkers (15) have found that **18** (or **19**) will react with amides, and have used 2-pyrrolidinone (**21**) in the preparation of **22**. We felt it worthwhile to investigate the reactivity of **18** (or **19**) toward 4,4-dimethyloxazolidin-2-one (**24**), since oxazoloquinazolone **11** would result if **24** proved to be as reactive as **21**.

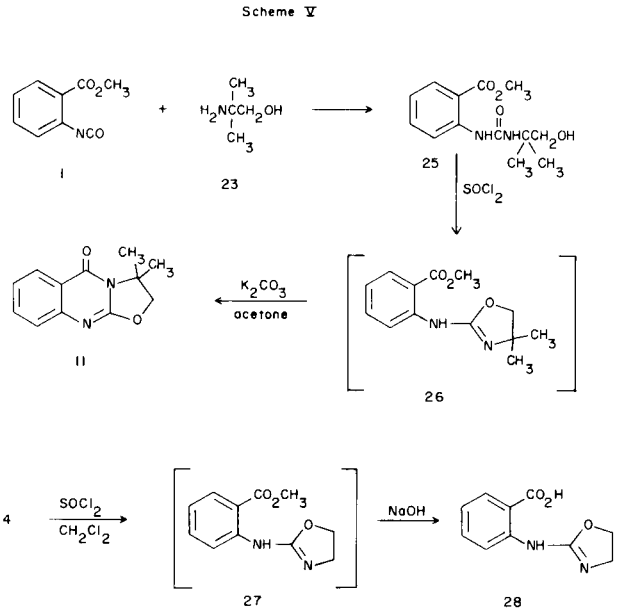
Accordingly, we prepared **24** from 2-amino-2-methyl-1-propanol (**23**) and diethyl carbonate. Unfortunately, treatment of **17** with thionyl chloride followed by **24**, using the procedure of Kametani and co-workers (15), did not yield **11**.

Scheme IV



We next treated 2-carbomethoxyphenyl isocyanate (**1**) with **23** to give the dimethyl analog of **4** (**25**), as shown in Scheme V. Compound **25** showed no propensity to cyclize to the corresponding quinazolinedione, as had compound **4**. Treatment of **25** with thionyl chloride gave a product mixture, from which we were unable to isolate (silica gel chromatography notwithstanding) proposed component

Scheme V



26 (or a tautomer). However, treatment of the resulting mixture with potassium carbonate in acetone led to a mixture of products from which oxazoloquinazolone **11** was isolated by chromatography. The authentic sample of **11** confirmed our assignment of **10** as the product obtained from the rearrangement of **9** in sulfuric acid. In addition, the nmr spectra of pure **10** and **11** clearly indicated that the mixture obtained by the iodide-catalyzed rearrangement of **9** was composed of **10** and **11**.

An additional experiment which offers support to the proposed intermediate **26** involved the treatment of **4** with thionyl chloride. Again, a product or tautomeric mixture resulted, which contained **27** (or a tautomer). Treatment of this mixture with sodium hydroxide produced 2-[(2-oxazolinyl)amino]benzoic acid (**28**), which was readily purified and characterized.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a Perkin-Elmer Model 727B Spectrophotometer, nmr spectra with Varian T-60 and Varian EM360A spectrometers, and mass spectra with a Finnigan gc/ms Model 3000D (electron impact and chemical ionization) mass spectrometer at 70 eV. Combustion analyses for C, H and N were performed by Dow Analytical Laboratories.

Materials.

2-Carbomethoxyphenyl isocyanate (**1**), b.p. 80° (0.05 mm) [lit. (16) b.p. 80° (0.05 mm)] was prepared as previously described (16); 3-(2-chloroethyl)-2,4-(1*H*,3*H*)quinazolinedione (**6**), m.p. 194.5-196° [lit. (17) m.p. 195.5-196°] was prepared as described by Grout and Partridge (17); and 4,4-dimethyloxazolidin-2-one (**24**), m.p. 55-56° [lit. (18) m.p. 55-56°] was prepared using the procedure of Homeyer (18).

2-[(1-Aziridinylcarbonyl)amino]benzoic Acid Methyl Ester (**2**).

To a solution of 7.11 g. (0.165 mole) of ethyleneimine (19) and 1 g. of triethylamine in 50 ml. of methylene chloride was added 26.6 g. (0.150 mole) of 2-carbomethoxyphenyl isocyanate (**1**) at icebath temperature. After 2 hours of stirring the solution was concentrated to leave 32.8 g. (98%) of **2**, m.p. 74.5-76° (hexane); ir (Nujol): 3300 (NH), 1720 (ester C=O), 1690 (urea C=O) cm^{-1}; nmr (deuteriochloroform): δ 11.00 (s, 1H, NH), 8.66-8.40 (m, 1H, aromatic), 8.07-7.80 (m, 1H, aromatic), 7.65-7.27 (m, 1H, aromatic), 7.15-6.78 (m, 1H, aromatic), 3.88 (s, 3H, CH_3), 2.25 (s, 4H, CH_2CH_2).

Anal. Calcd. for $C_{11}H_{12}N_3O_2$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.20; H, 5.53; N, 12.73.

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

A. From **2**.

A solution of 6.17 g. (28.0 mmoles) of **2** and 0.5 g. of sodium iodide in 100 ml. of acetonitrile was heated at reflux for 15 hours. The solution was cooled, concentrated, and partitioned between methylene chloride and water. The organic phase was dried (sodium sulfate) and concentrated to leave 5.27 g. (100%) of **3**, m.p. 159-162°, m.p. 160-162° (hexane) [lit. (7) m.p. 165°]; ir (Nujol): 3600-3100 (NH), 1690 (C=O), 1640 (C=N) cm^{-1}; nmr (deuteriochloroform): δ 8.28-8.10 (m, 1H, aromatic), 7.80-7.20 (m, 3H, aromatic), 4.93-4.65 (m, 2H, OCH_2), and 4.53-4.24 (m, 2H, NCH_2); ms (electron impact, 70 eV): m/e 188 (molecular ion).

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.70; H, 4.27; N, 14.77.

B. From 3-(2-Chloroethyl)-2,4-(1*H*,3*H*)quinazolinedione (**6**).

To a solution of 0.600 g. (2.67 mmoles) of **6** in 25 ml. of acetone was added 1 g. of potassium carbonate. The mixture was heated at reflux for 3 hours, cooled and concentrated. The residue was slurried with water and the suspended solid was collected and dried to give 0.470 g. (94%) of **6**, m.p. 159-161°. This material was spectrally equivalent with the material prepared in Part A, and a mixture melting point of the two materials was undepressed.

Treatment of **1** with 2-Aminoethanol.

To a solution of 12.0 g. (0.196 mole) of 2-aminoethanol in 100 ml. of methylene chloride was added a solution of 34.6 g. (0.196 mole) of **1** in 75 ml. of methylene chloride, with icebath cooling. After a few minutes of stirring, a voluminous precipitate appeared which was collected, washed with methylene chloride and air-dried to yield 39.4 g. of white solid. A 25.0 g. portion of this white solid was recrystallized from a large volume of ethanol to yield 6.28 g. of 3-(2-hydroxyethyl)-2,4-(1*H*,3*H*)quinazolinedione (**5**), m.p. 248-250° [lit. (10) m.p. 246-249°]; ir (Nujol): 3400 (OH), 3300-3000 (NH), 1720 (C=O), 1665 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 8.32-7.18 (m, 4H, aromatic), 4.40-3.48 (m, 4H, CH_2CH_2).

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.58. Found: C, 57.90; H, 4.91; N, 13.79.

The filtrate was concentrated to leave 7.80 g. of white solid. Recrystallization from methylene chloride-hexane gave 6.28 g. of 2-[[(2-hydroxyethyl)amino]carbonyl]amino]benzoic acid methyl ester (**4**), m.p. 104-106°; ir (Nujol): 3420 (OH), 3340 (NH), 1710 (ester C=O), 1650 (urea C=O) cm^{-1}; nmr (deuteriochloroform): δ 14.20 (broad s, 1H, deuterium oxide-exchangeable), 8.64-6.80 (m, 4H, aromatic), 5.92-5.60 (broad t, 1H, NH, deuterium oxide-exchangeable), 4.0-3.0 [m, 8H, CH_3, CH_2CH_2 and OH (deuterium oxide-exchangeable), CH_3 s at 3.90].

Anal. Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.44; H, 5.88; N, 11.59.

2-[[(2,2-Dimethyl-1-aziridinyl)carbonyl]amino]benzoic Acid Methyl Ester (**9**).

To a solution of 7.82 g. (0.110 mole) of 2,2-dimethylethyleneimine and 1 ml. of triethylamine in 50 ml. of methylene chloride was added 17.7 g. (0.100 mole) of **1**, with icebath cooling. Concentration of the reaction solution gave 25.3 g. of visious oil, which crystallized on standing. Recrystallization from hexane afforded 21.3 g. (86%) of **9**, m.p. 54-55.5°; ir (Nujol): 3330 (NH), 1690 (C=O) cm^{-1}; nmr (deuteriochloroform): δ 10.90 (broad s, 1H, NH), 8.76-8.52 (m, 1H, aromatic), 8.10-7.89 (m, 1H, aromatic), 7.67-7.33 (m, 1H, aromatic), 7.15-6.82 (m, 1H, aromatic), 3.90 (s, 3H, OCH_3), 2.22 (s, 2H, CH_2), 1.37 [s, 6H, $C(CH_3)_2$].

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found:

C, 63.25; H, 6.56; N, 10.97.

2,3-Dihydro-2,2-dimethyl-5*H*-oxazolo[2,3-*b*]quinazolin-5-one (**10**).

A 2.00-g. (8.06 mmoles) quantity of **9** was added to 10 ml. of concentrated sulfuric acid. Dissolution and an exotherm immediately followed. The tan solution was cooled and very carefully added to 100 ml. of cold water. The resulting solution was basified by the addition of solid sodium carbonate. The resulting white precipitate was collected (two crops) and air-dried to give 1.49 g. (86%) of **10**, m.p. 147-149°, m.p. 150-151.5° (hexane); ir (Nujol): 1695 (C=O), 1625 (C=N) cm^{-1}; nmr (deuteriochloroform): δ 8.37-8.00 (m, 1H, proton ortho to C=O), 8.00-7.00 (m, 3H, remaining aromatic), 4.10 (s, 2H, CH_2), 1.68 (s, 6H, both CH_3 groups); ms (70 eV, chemical ionization, methane): m/e 217 (M^++1), 245 (M^++29), 257 (M^++41).

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.69; H, 5.44; N, 13.09.

Treatment of **9** with Sodium Methoxide.

A solution of 1.24 g. (5.00 mmoles) of **9** and 0.270 g. (5.00 mmoles) of dry sodium methoxide in 30 ml. of methanol was heated at reflux for 5 hours. The reaction was followed by ir. The cooled reaction solution was diluted with water (75 ml.) and extracted with chloroform (3 x 30 ml.). The organic extracts were dried (magnesium sulfate) and concentrated to leave 0.800 g. (76.4%) of isatoic acid dimethyl ester (**12**) as an oil which solidified on standing, m.p. 59° [lit. (20) m.p. 59-60°]; ir (Nujol): 3300 (NH), 1735 (ester C=O), 1680 (carbamate C=O) cm^{-1}; nmr (deuteriochloroform): δ 10.52 (broad s, 1H, NH), 8.58-8.34 (m, 1H, aromatic), 8.10-7.88 (m, 1H, aromatic), 7.68-7.27 (m, 1H, aromatic), 7.16-6.83 (m, 1H, aromatic), 3.90 (s, 3H, CH_3), 3.78 (s, 3H, CH_3).

2-[[((2-Hydroxy-1,1-dimethylethyl)amino)carbonyl]amino]benzoic Acid Methyl Ester (**25**).

To a solution of 26.6 g. (0.150 mole) of **1** in 450 ml. of dry benzene was added 13.4 g. (0.150 mole) of 2-amino-2-methyl-1-propanol (**23**). The resulting mixture was heated at reflux for 5 hours, cooled, and the resulting solid was collected and air-dried to yield 33.3 g. (83.3%) of **25**, m.p. 177-178°; ir (Nujol): 3310, 3280 and 3200 (NH and OH), 1700 (ester C=O), 1665 (urea C=O) cm^{-1}; nmr (DMSO-d_6): δ 8.44-8.20 (m, 1H, aromatic), 8.04-7.80 (m, 1H, aromatic), 7.70-7.36 (m, 1H, aromatic), 7.17-6.83 (m, 2H, aromatic and NH), 4.82 (t, J = 5 Hz, 1H, OH), 3.89 (s, 3H, OCH_3), 3.48 (d, J = 5 Hz, 2H, CH_2), 1.24 [s, 6H, $C(CH_3)_2$].

Anal. Calcd. for $C_{13}H_{18}O_4N_2$: C, 58.63; H, 6.81; N, 10.52. Found: C, 59.00; H, 6.48; N, 10.62.

Treatment of **25** with Thionyl Chloride.

A solution of 8.00 g. (30.0 mmoles) of **25** in 80 ml. of thionyl chloride was heated at reflux for 36 hours. Concentration left 7.2 g. of oil, which was a mixture of products by tlc. A solution of 6.0 g. of this product mixture in 250 ml. of acetone, in the presence of 20 g. of potassium carbonate, was heated at reflux for 36 hours. The mixture was filtered and the filtrate was concentrated. The residue was suspended in ether and the mixture was filtered and concentrated to yield 4.7 g. of oil. This oil was applied to a 200-g. column of Silica Gel 60 (EM Reagents, 70-230 mesh) and eluted with ether to remove a fraction (1 g.) containing **11**. This fraction was applied to two 20 cm. x 20 cm. x 2 mm. Silica Gel 60 F-254 preparatory chromatography plates (EM Reagents) and eluted with 96:4 methylene chloride:ethyl acetate. Two materials were cleanly separated on the plates (21). The lower material was collected, by methylene chloride extraction, to yield 75 mg. of **11**, m.p. 141-142° (carbon tetrachloride) [lit. (13) m.p. 141-142°]; nmr (deuteriochloroform): δ 8.28-8.08 (m, 1H, proton ortho to C=O), 7.73-7.20 (m, 3H, remaining aromatic), 4.35 (s, 2H, CH_2), 1.80 (s, 6H, both CH_3 groups); ms (70 eV, chemical ionization, methane): 217 (M^++1), 245 (M^++29), 257 (M^++41).

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.40; H, 5.32; N, 12.97.

2[(2-Oxazolinyl)amino]benzoic Acid (**28**).

To a slurry of 11.9 g. (50.0 mmoles) of **4** in 125 ml. of methylene chloride was added 5.95 g. (50.0 mmoles) of thionyl chloride. Reflux was maintained for 1 hour, during which time solution resulted and a precipitate began forming. The mixture was concentrated to leave 13.4 g. of material, which vpc indicated to be a mixture of products. An 11.1-g. quantity of this material was dissolved in a mixture of 15 ml. of 20% sodium hydroxide, 35 ml. of water and 100 ml. of dimethoxyethane and heated at reflux for 30 minutes. The solution was cooled, washed with methylene chloride and acidified. The resulting voluminous white precipitate was collected and air dried to afford 9.00 g. of **28**, m.p. 249-250° (ethanol); ir (Nujol): 3700-2800 (OH), 3400 (NH), 1710 (C=O), 1670 (C=N) cm^{-1}; nmr (DMSO-d_6): δ 8.06-6.95 (m, 4H, aromatic), 4.21-3.80 (m, 2H, OCH_2), 3.80-3.38 (m, 2H, NCH_2).

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.58. Found: C, 58.30; H, 4.85; N, 13.69.

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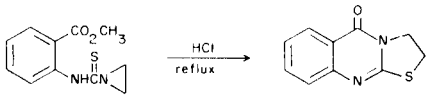
(5) A rearrangement analogous to that of **2** to **3**, employing vigorous conditions of acid-catalysis, has been reported by Howard and Klein (6). Thus, treatment of 2-[(1-aziridinylthiocarbonyl)amino]benzoic acid methyl ester (**i**) with concentrated hydrochloric acid at reflux produced 2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (**ii**).



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(19) This material should be handled with extreme caution.

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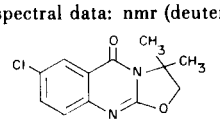
(21) The upper (major) material obtained from this separation was assigned as **iii** from spectral data: nmr (deuteriochloroform):



iii

δ 8.09 (d, J = 2 Hz, 1H, proton ortho to C=O), 7.70-7.28 (m, 3H, remaining aromatic), 4.36 (s, 2H, CH_2), 1.80 (s, 6H, both CH_3 groups); ms (70 eV, chemical ionization, methane): 251 (M^++1), 279 (M^++29), and 253 (M^++1 for ^{37}Cl isotope).