Ring Closure Reactions with Nitriles. II. Formation of Pyrrolo[1,2-*a*]quinazolines and Thiazolo[3,2-*a*]quinazolines

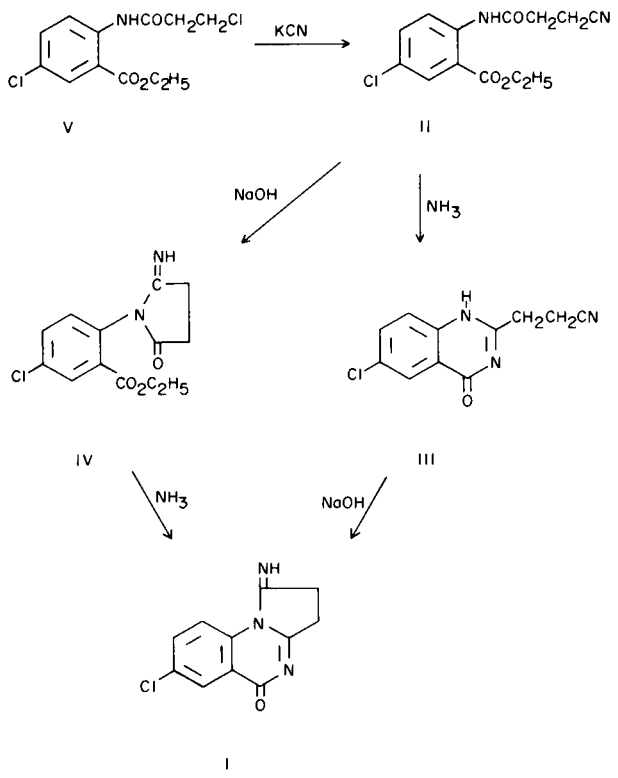
Stanley C. Bell and Peter H. L. Wei

Research Division, Wyeth Laboratories, Inc.

2-Quinazolinepropionic acids have been obtained from the reactions of potassium cyanide with *o*-carboxy- or *o*-acyl-3-chloropropionanilides. Some of these compounds have been cyclized to pyrrolo[1,2-*a*]quinazolines. The reaction of an *o*-carbethoxy-2-chloroacetanilide with potassium thiocyanate formed a 2-quinazolinylthioacetic acid, which was cyclized to a thiazolo-[3,2-*a*]quinazoline. A mechanism is presented for the formation of these compounds.

We have recently reported (1) on the preparation of pyrrolo[1,2-*a*]quinazolines from the cyclization reactions of 2-(2-cyanoethyl)-1,2-dihydro-4(3H)quinazolines and 1,4-dihydro-4-oxo-2-quinazolinepropionic acids. As an extension of this work, we sought to prepare pyrrolo[1,2-*a*]-quinazolines by other methods. One of the possible routes leading to 7-chloro-2,3-dihydro-1-iminopyrrolo-[1,2-*a*]quinazoline-5(4*H*)-one (I) was by the reaction of ethyl 5-chloro-*N*-(3-cyanopropionyl)anthranilate (II) with ammonia to form 6-chloro-2-(2-cyanoethyl)-4(3*H*)-quinazolinone (III), followed by the cyclization of the cyano group with alkali. Another route considered for the synthesis of I was the reaction of II with alkali to form 1-(2-carbethoxy-5-chlorophenyl)-5-imino-2-pyrrolidinone (IV), followed by the condensation of IV with ammonia.

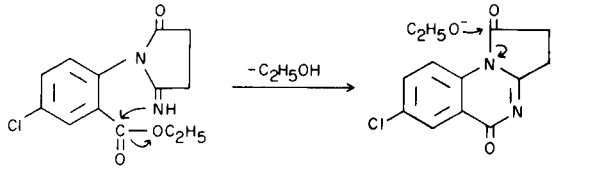
Proposed Syntheses



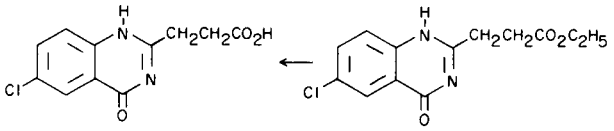
The attempt was made to prepare the nitrile (II) through the reaction of ethyl 5-chloro-*N*-(3-chloropropionyl)anthranilate (V) with potassium cyanide in ethanol. Compound II was obtained, but only as the minor product. The major product was the unexpected ethyl ester (VI) of the previously reported (1) 6-chloro-1,4-dihydro-4-oxo-2-quinazolinepropionic acid (VII). We therefore investigated the formation of 2-quinazolinepropionic acids from the reaction of 3-chloropropionanilides with potassium cyanide. This paper reports our results.

The formation of VI can be explained by the following series of reactions. The cyanopropionyl anthranilate (II) that was first formed underwent cyclization in the alkaline reaction medium to the 5-imino-2-pyrrolidone (IV). Elimination of ethanol from IV by condensation of the imino group with the ortho carbethoxy group produced 7-chloro-2,3-dihydropyrrolo[1,2-*a*]quinazoline-1,5-dione (VIII) (1) which in the alkaline reaction medium underwent alcoholysis to form VI. Compound VI was also prepared by reaction of an authentic sample of VIII with ethanolic sodium hydroxide. On hydrolysis in aqueous alkali, VI produced the acid VII (1).

The formation of VI from the reaction of V with cyanide suggested that the reaction of ethyl 5-chloro-*N*-(2-chloroacetyl)anthranilate (IX) with potassium thiocyanate in ethanol should produce ethyl (6-chloro-1,4-dihydro-4-oxo-2-quinazolinylthio)acetate (X). Since a good yield of compound X was obtained it was apparent that an analogous reaction had taken place. Thus, the unisolated intermediate 2-thiocyanatoanthranilate (XI)

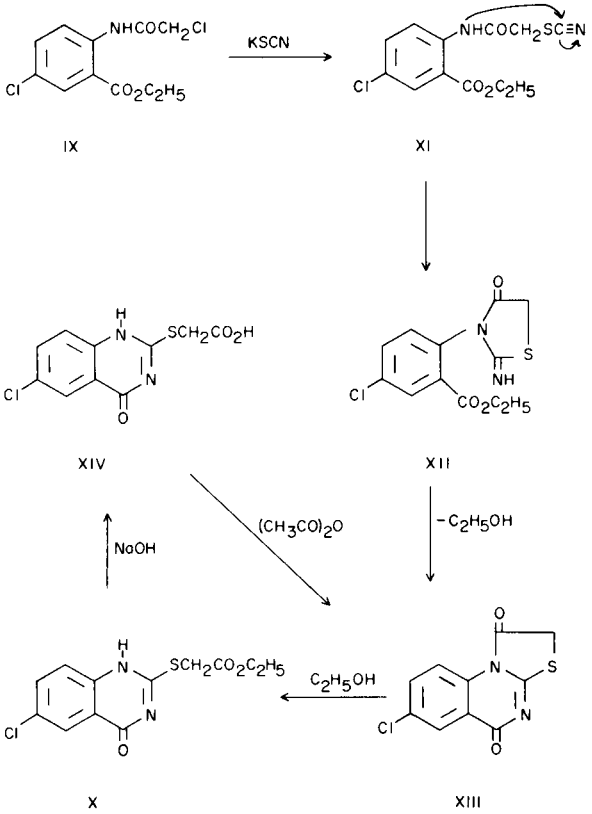


IV VIII



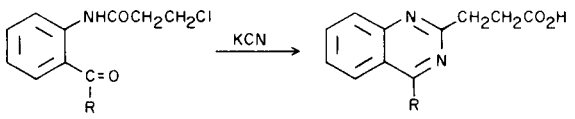
VII VI

had undergone one cyclization to a 5-imino-2-thiazolone (XII) followed by a second cyclization to 7-chloro-5*H*-thiazolo[3,2-*a*]quinazoline-1,5(2*H*)-dione (XIII). The thiazolone ring of compound XIII, however, was unstable in the alkaline reaction mixture and reacted with ethanol to give X. 6-Chloro-1,4-dihydro-4-oxo-2-quinazolinylthioacetic acid (XIV), subsequently obtained by alkaline hydrolysis of X, underwent cyclization by heating in acetic anhydride to form XIII.



IX XI XIV XII X XIII

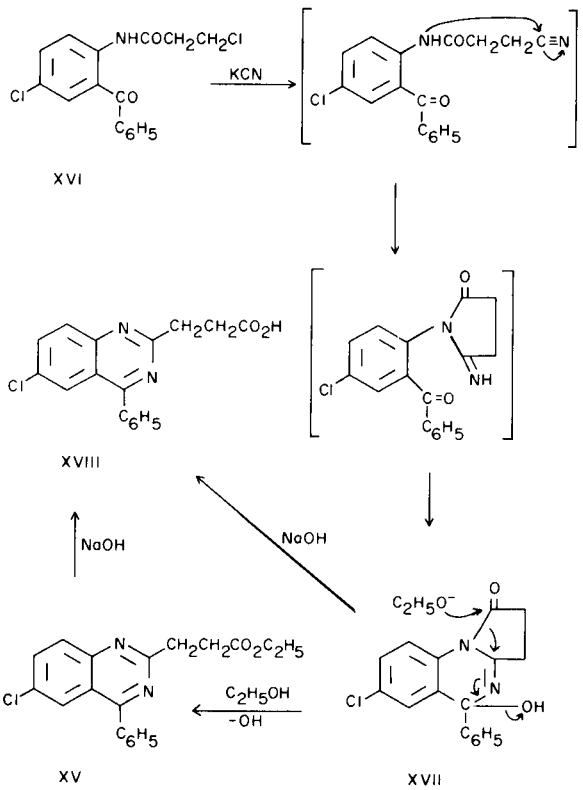
Since the reaction of potassium cyanide with *o*-carbethoxy-3-chloropropionanilides yielded 4-oxo-2-quinazolinepropionic acids, it seemed reasonable to expect that the reaction of 3-chloropropionanilides substituted in the ortho position with acyl groups would provide the corresponding 4-substituted quinazoline-2-propionic acid. Ethyl 6-chloro-4-phenyl-2-quinazolinepropionate (XV),



XIV XV

the anticipated product from the reaction of potassium cyanide in ethanol with 2′-benzoyl-3,4′-dichloropropionanilide (XVI), was obtained in good yield. Several other esters of the quinazoline-2-propionic acids (XVa-d) were prepared using various alcohols as the solvents in the reactions of the 3-chloropropionanilides with potassium cyanide. By using a mixture of water and a nonreactive solvent such as dimethoxyethane, the free quinazoline-2-propionic acid (XVIII, Method A) was obtained.

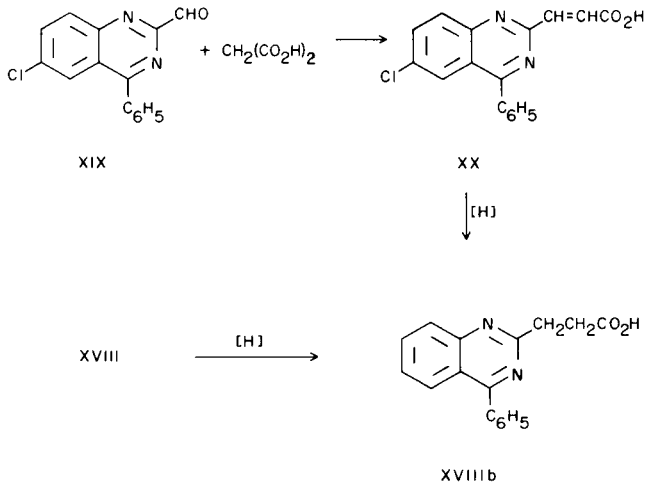
From the reaction mixture of XV, a small quantity of a nonacidic isomer (XVII) of XVIII was isolated. Compound XVII, identified from analytical and spectral determina-



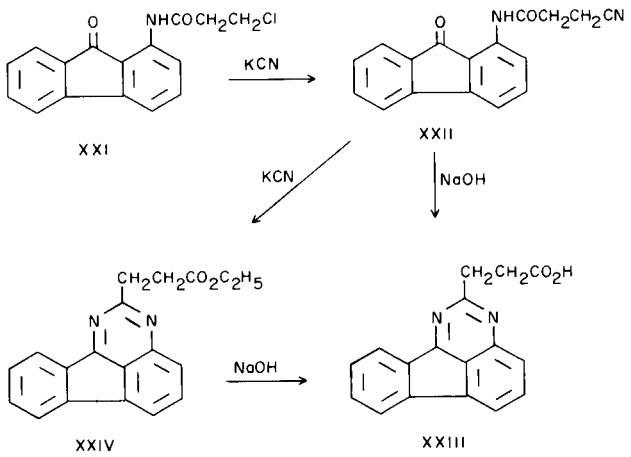
XVI XVIII XV XVII

tions as 7-chloro-5-hydroxy-5-phenyl-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinazolin-1-one, is one of the proposed intermediates leading to XV. Treating compound XVII with acid or base produced 6-chloro-4-phenyl-2-quinazolinepropionic acid (XVIII), which was also obtained by alkaline hydrolysis of XV. The following shows the probable steps leading to the above compounds.

The structure of XVIII was verified by alternative synthesis of the deschloro compound (XVIIIb) of XVIII from 6-chloro-4-phenyl-2-quinazoline carboxaldehyde (XIX) (2) and malonic acid according to a procedure of Taylor (3).

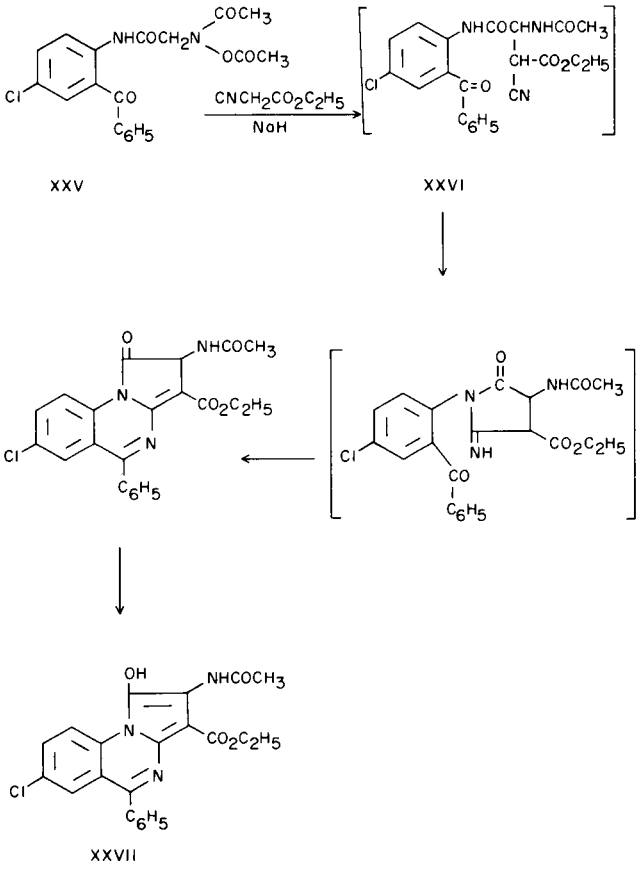


Usually, in the preparation of a 2-quinazolinepropionic acid from the reaction of the corresponding 2′-acetyl-3-chloropropionanilide, the intermediate 2′-acyl-3-cyanopropionanilide was not obtained. In the reaction of 1-(3-chloropropionamido)-9-fluorenone (XXI) with potassium cyanide, however, the intermediate 3-cyanopropionamide (XXII) was isolated. Further treatment with dilute sodium hydroxide converted XXII to indeno[1,2,3-*de*]quinazoline-2-propionic acid (XXIII). The reaction of XXII with potassium cyanide in ethanol produced the ethyl ester (XXIV) of XXIII.



3-Cyanopropionanilides containing functional groups in the side chain were obtained from the elimination-addition reaction (4) of 2-(*N*-acetoxyacetamido)-2′-benzoyl-4′-chloroacetanilide (XXV) with the appropriate nitrile. Thus, when XXV was treated with the sodium salt of ethyl cyanoacetate, the unisolated intermediate 2-acetamido-3-cyanopropionanilide (XXVI) underwent the cyclization reactions and gave a low yield of ethyl 2-acetamido-7-chloro-1-hydroxy-5-phenylpyrrolo[1,2-*a*]quinazoline-3-carboxylate (XXVII).

The aromatized 1-hydroxypyrrolo structure assigned to XXVII rather than the tautomeric cyclic amide structure (ethyl 2-acetamido-7-chloro-1-oxo-5-phenyl-2*H*-pyrrolo-[1,2-*a*]quinazoline-3-carboxylate) was based on the infrared and nmr spectra. In the infrared there are carbonyl peaks for the conjugated ester at 6.00 μ and for the acetamido group at 6.15 μ, whereas the lower wavelength carbonyl peak expected for a fused pyrrolone ring (1) was not present. The nmr spectrum for XXVII had peaks at δ 1.47 and δ 4.38 (ethoxy), δ 2.29 (acetamido methyl singlet), δ 10.05 (NH), δ 8.95 (5) (ortho aromatic proton doublet), and δ 12.60 (exchangeable enolic 1-hydroxy proton). There was no peak in the aliphatic region which could be ascribed to a proton in the 2-position.



Compound XXV reacted under similar conditions with diethylcyanophosphonate, producing the corresponding pyrrolo[1,2-*a*]quinazoline-3-phosphonate (XXVIIa). Compound XXVIIa had one peak in the carbonyl region at 6.11 μ for the acetamido group. The nmr spectrum had absorptions at δ 1.31 and 4.22 for the two ethoxy groups, δ 2.30 for the acetamido methyl, δ 7.4-7.9 for the aromatic multiplet, δ 8.60 for the ortho aromatic proton, δ 10.10 for the amide NH, and δ 12.60 for the 1-hydroxy proton.

The reactions of cyanide with 3-chloropropionanilides have provided a one-step synthesis of cyclic compounds which would otherwise be difficult to prepare. We have synthesized a number of 2-quinazolinepropionic acids by this method and are continuing the investigation of this reaction and the intermediates leading to the final products.

EXPERIMENTAL (6)

2′-Carbethoxy-3,4′-dichloropropionanilide (V).

A mixture of 61.4 g. of ethyl 5-chloroanthranilate hydrochloride, 45.7 g. of 3-chloropropionyl chloride, and 500 ml. of chloroform was heated to reflux for 1 hour, during which time all the solid dissolved. The solvent was removed in vacuo and cyclohexane was added to the residue, precipitating 67 g. of product, m.p. 80-85°. Pure V, m.p. 87-89°, was obtained by recrystallization from ethanol.

Anal. Calcd. for $C_{12}H_{13}Cl_2NO_3$: C, 49.67; H, 4.52; N, 4.83. Found: C, 49.35; H, 4.29; N, 4.95.

Ethyl 6-Chloro-1,4-dihydro-4-oxo-2-quinazolinepropionate (VI).

A solution of 23.6 g. of V, 5.9 g. of potassium cyanide, and 200 ml. of 95% ethanol was refluxed for 18 hours, cooled, and the precipitate collected and washed with water. Recrystallization from dimethoxyethane gave 7.6 g. of product, m.p. 227-229°.

Anal. Calcd. for $C_{13}H_{13}ClN_2O_3$: C, 55.62; H, 4.67; Cl, 12.63; N, 9.98. Found: C, 55.49; H, 4.66; Cl, 12.70; N, 9.83.

Ethyl 5-Chloro-*N*-(3-cyanopropionyl)anthranilate (II).

Ethanol was removed from the mother liquor from the preparation of VI. The residue was first washed with water and then with a small amount of ethanol. The crude material was recrystallized twice from cyclohexane, giving 3.0 g. of II, m.p. 118-120°, λ max (potassium bromide), 4.45 μ.

Anal. Calcd. for $C_{13}H_{13}ClN_2O_3$: C, 55.62; H, 4.67; Cl, 12.63; N, 9.98. Found: C, 55.77; H, 4.32; C, 12.4; N, 9.83.

Ethyl 5-Chloro-*N*-(2-chloroacetyl)anthranilate (IX).

To a mixture of 60 g. of ethyl 5-chloroanthranilate in 600 ml. of 1,2-dimethoxyethane was added 17.5 g. of chloroacetyl chloride. The starting amine hydrochloride was filtered off and the solution concentrated to dryness. The residue was washed with water and recrystallized from 2-propanol to give 25 g. of IX, m.p. 130-132°.

Anal. Calcd. for $C_{11}H_{11}Cl_2NO_3$: C, 47.84; H, 4.02; N, 5.07. Found: C, 47.82; H, 4.07; N, 5.42.

Ethyl (6-Chloro-1,4-dihydro-4-oxo-2-quinazolinylthio)acetate (X).

A solution of 21.2 g. of IX, 9.35 g. of potassium thiocyanate, and 250 ml. of 95% ethanol was refluxed overnight. The precipitate was collected and washed with water to give 11.0 g. of product, m.p. 192-194° after recrystallization from ethanol.

Anal. Calcd. for $C_{12}H_{11}ClN_2O_3S$: C, 48.25; H, 3.70; Cl, 11.87; N, 9.38; S, 10.74. Found: C, 48.08; H, 3.63; Cl, 11.70. N, 9.20; S, 10.6.

Methyl (6-Chloro-1,4-dihydro-4-oxo-2-quinazolinylthio)acetate (Xa).

This compound m.p. 208-210°, was prepared from IX and potassium thiocyanate in methanol according to the procedure for X.

Anal. Calcd. for $C_{11}H_9ClN_2O_3S$: C, 46.39; H, 3.19; Cl, 12.46; N, 9.84; S, 11.27. Found: C, 46.53; H, 3.22; Cl, 12.40. N, 9.63; S, 11.2.

7-Chloro-5*H*-thiazolo[3,2-*a*]quinazoline-1,5(2*H*)-dione (XIII).

A suspension of 5.3 g. of XIV in 100 ml. of acetic anhydride was heated at 100-120° for 40 minutes. The solution was treated with Darco, filtered, and the acetic anhydride removed *in vacuo*. The addition of dimethoxyethane to the residue precipitated the product, which was collected and recrystallized from dimethoxyethane to give 2.9 g. of pure XIII, m.p. 207-210°.

Anal. Calcd. for $C_{10}H_5ClN_2O_2S$: C, 47.52; H, 2.00; Cl, 14.03; N, 11.09; S, 12.69. Found: C, 47.61; H, 1.96; Cl, 13.90; N, 10.78; S, 12.40.

(6-Chloro-1,4-dihydro-4-oxo-2-quinazolinylthio)acetic acid (XIV).

A suspension of 4.5 g. of X in 50 ml. of 1 *N* sodium hydroxide solution was warmed on the steam bath for 10 minutes during which time the solid dissolved. The solution was filtered from impurities and acidified with acetic acid. The precipitate was collected and recrystallized from dimethoxyethane, giving 3.6 g. of XIV, m.p. 225-227°.

Anal. Calcd. for $C_{10}H_7ClN_2O_3S$: C, 44.36; H, 2.61; Cl, 13.10; N, 10.35; S, 11.84. Found: C, 44.62; H, 2.76; Cl, 12.7; N, 10.32; S, 11.6.

Ethyl 6-Chloro-4-phenyl-2-quinazolinepropionate (XV).

A mixture of 129 g. of XVI, 1000 ml. of 90% ethanol, and 31.2 g. of potassium cyanide was refluxed for 18 hours, filtered from potassium chloride, and concentrated *in vacuo*. The addition of ethanol precipitated 62 g. of product, which after recrystallization had a m.p. of 72-73°.

Anal. Calcd. for $C_{19}H_{17}ClN_2O_2$: C, 66.90; H, 5.02; Cl, 10.40; N, 8.22. Found: C, 66.48; H, 4.98; Cl, 10.40; N, 8.11.

Methyl 6-Chloro-4-phenyl-2-quinazolinepropionate (XVa).

This compound, m.p. 118-120°, was prepared from XVI, potassium cyanide, and methanol according to the procedure for XV.

Anal. Calcd. for $C_{18}H_{15}ClN_2O_2$: C, 66.15; H, 4.63; Cl, 10.85; N, 8.57. Found: C, 66.27; H, 4.65; Cl, 10.8; N, 8.67.

Ethyl 6-Chloro-4-(*o*-chlorophenyl)-2-quinazolinepropionate (XVb).

This compound, m.p. 65-66°, was prepared from XVIa, potassium cyanide, and ethanol according to the procedure for XV.

Anal. Calcd. for $C_{19}H_{16}Cl_2N_2O_2$: C, 60.75; H, 4.29; Cl, 18.95; N, 7.47. Found: C, 60.77; H, 4.24; Cl, 18.80; N, 7.55.

Ethyl 4-Methyl-2-quinazolinepropionate (XVc).

This compound, m.p. 36-37°, was prepared from XVIb, potassium cyanide, and ethanol according to the procedure for XV.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.75; H, 6.60; N, 11.48. Found: C, 68.75; H, 6.83; N, 11.69.

2-Hydroxyethyl 6-Chloro-4-phenyl-2-quinazolinepropionate (XVd).

A solution of 32 g. of XVI, 7.8 g. of potassium cyanide, 40 ml. of ethylene glycol, and 200 ml. of dimethoxyethane was heated to

reflux for 18 hours, filtered from potassium chloride, and concentrated in vacuo. The residue was dissolved in benzene and washed with water. The benzene solution was concentrated to precipitate 9.0 g. of product. On recrystallization from cyclohexane, the compound had a m.p. of 80-82°.

Anal. Calcd. for $C_{19}H_{17}ClN_2O_3$: C, 63.96; H, 4.80; N, 7.85; Cl, 9.94. Found: C, 63.96; H, 4.67; N, 7.72; Cl, 9.84.

2′-Benzoyl-3,4′-dichloropropionanilide (XVI).

To a solution of 231 g. of 2-amino-5-chlorobenzophenone in 1100 ml. of chloroform was added, slowly and with stirring, 144 g. of β-chloropropionyl chloride. The solution was stirred for 2 hours, the solvent removed *in vacuo*, and the residue recrystallized from ethanol to give 268 g. of product. A second recrystallization from cyclohexane gave pure XVI, m.p. 75-76°.

Anal. Calcd. for $C_{16}H_{13}Cl_2NO_2$: C, 59.60; H, 4.07; Cl, 22.02; N, 4.35. Found: C, 59.41; H, 3.89; Cl, 21.90; N, 4.08.

2′-*o*-Chlorobenzoyl-3,4′-dichloropropionanilide (XVIa).

This compound, m.p. 81-83°, was prepared from 2-amino-2′,5-dichlorobenzophenone and β-chloropropionyl chloride according to the procedure for XVI.

Anal. Calcd. for $C_{16}H_{12}Cl_3NO_2$: C, 53.88; H, 3.39; Cl, 29.83; N, 3.94. Found: C, 53.76; H, 3.48; Cl, 29.70; N, 3.77.

2′-Acetyl-3-chloropropionanilide (XVIb).

To a solution of 26 g. of *o*-aminoacetophenone, 500 ml. of chloroform, and 41 g. of triethylamine was added, slowly and with stirring, 36.5 g. of β-chloropropionyl chloride. After 1 hour the solution was washed with water, dried, and concentrated *in vacuo*. The residue was recrystallized from ethanol to give 36.5 g. of product, m.p. 92-94°.

Anal. Calcd. for $C_{11}H_{12}ClNO_2$: C, 58.54; H, 5.37; Cl, 15.77; N, 6.22. Found: C, 58.74; H, 5.72; Cl, 15.30; N, 5.92.

7-Chloro-5-hydroxy-5-phenyl-1,2,3,5-tetrahydropyrrolo[1,2-*a*]-quinazolin-1-one (XVII).

A solution of 48.3 g. of XVI, 11.7 g. of potassium cyanide, 25 ml. of water, and 300 ml. of dimethoxyethane was heated to reflux for 9 hours and cooled. The precipitate of 23.2 g. was collected and placed in a large volume of water and 8.0 g. of insoluble product was filtered. Recrystallization of the solid from dimethoxyethane gave 5.8 g. of XVII, m.p. 236-238°, λ max (potassium bromide), 3.30, 5.66, 6.15 μ.

Anal. Calcd. for $C_{17}H_{13}ClN_2O_2$: C, 65.20; H, 4.18; Cl, 11.35; N, 8.96. Found: C, 64.91; H, 4.49; Cl, 11.30; N, 8.90.

6-Chloro-4-phenyl-2-quinazolinepropionic acid (XVIII).

Method A.

The filtrate from the collection of XVII was acidified to precipitate 8.2 g. of XVIII, m.p. 163-165° after recrystallization from benzene.

Method B.

A suspension of 0.12 g. of XVII in 5 ml. of 0.1 *N* sodium hydroxide solution was warmed on the steam bath. The resultant solution, after cooling and acidification with acetic acid, gave 50 mg. of XVIII, m.p. 163-165°,

Method C.

A mixture of 13 g. of XV and 200 ml. of a 10% sodium hydroxide solution was heated on the steam bath until solution was complete. The solution was filtered from impurities, cooled, and acidified with dilute hydrochloric acid. Recrystallization of the resultant precipitate gave 8.0 g. of XVIII, m.p. 163-165°.

Anal. Calcd. for $C_{17}H_{13}ClN_2O_2$: C, 65.20; H, 4.18; Cl, 11.35; N, 8.95. Found: C, 64.89; H, 3.95; Cl, 11.30; N, 9.22.

6-Chloro-4-(*o*-chlorophenyl)-2-quinazolinepropionic acid (XVIIIa).

This compound, m.p. 156-158°, was prepared from the hydrolysis of XVb according to the procedure for XVIII, Method C.

Anal. Calcd. for $C_{17}H_{12}Cl_2N_2O_2$: C, 58.80; H, 3.49; Cl, 20.42; N, 8.07. Found: C, 58.70; H, 3.37; Cl, 20.00; N, 7.86.

6-Chloro-4-phenyl-2-quinazolineacrylic acid (XX).

A mixture of 16.0 g. of 6-chloro-4-phenyl-2-quinazolinecarboxaldehyde (2), 14.4 g. of malonic acid, 1.5 ml. of piperidine, and 150 ml. of pyridine was heated on a steam bath for 3.5 hours. The solution was concentrated to half of the original volume and then poured into water. The solid was collected, redissolved in an aqueous alcohol solution of sodium hydroxide, and reprecipitated by acidification. Recrystallization from a mixture of ethanol-dimethoxyethane yielded 10 g. of XX, m.p. 270-272°.

Anal. Calcd. for $C_{17}H_{11}ClN_2O_2$: C, 65.70; H, 3.56; Cl, 11.41; N, 9.02. Found: C, 65.45; H, 3.33; Cl, 11.3; N, 8.89.

4-Phenyl-2-quinazolinepropionic acid (XVIIIb).

Method A.

A solution of 1.5 g. of XX in 25 ml. of 10% sodium hydroxide solution was hydrogenated in the presence of 0.15 g. of 5% palladium on carbon, filtered from the catalyst, and acidified with dilute hydrochloric acid. The precipitate was collected, washed with water, and recrystallized from benzene, giving 0.8 g. of product, m.p. 164-166°.

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 72.90; H, 4.99; N, 10.13.

Method B.

An alkaline solution of XVIII was hydrogenated according to the above procedure. The compound obtained was identical with XVIIIb from Method A.

1-(3-Chloropropionamido)-9-fluorenone (XXI).

This compound, m.p. 146-148°, was prepared from 1-amino-9-fluorenone and 3-chloropropionyl chloride according to the procedure for XVI.

Anal. Calcd. for $C_{16}H_{12}ClNO_2$: C, 67.25; H, 4.23; Cl, 12.41; N, 4.90. Found: C, 67.25; H, 4.61; Cl, 12.10; N, 4.94.

1-(3-Cyanopropionamido)-9-fluorenone (XXII).

A mixture of 6.8 g. of XXI, 3.1 g. of potassium cyanide, and 250 ml. of ethanol was heated to reflux for 2.5 hours and cooled. The product was filtered and washed with water. Recrystallization from ethanol gave 3.9 g. of XXII, m.p. 159-161°.

Anal. Calcd. for $C_{17}H_{12}N_2O_2$: C, 73.89; H, 4.38; N, 10.14. Found: C, 73.82; H, 3.97; N, 9.95.

Indeno[1,2,3-*de*]quinazoline-2-propionic Acid (XXIII).

Method A.

A mixture of 2.5 g. of XXII and 100 ml. of 0.1 *N* sodium hydroxide solution was heated on the steam bath for 2 hours until the solid had dissolved. The solution was filtered from impurities and extracted with chloroform. Acidification with acetic acid produced a solid. Recrystallization from a mixture of dimethoxyethane and benzene gave 1.5 g. of product, m.p. 207-209°.

Anal. Calcd. for $C_{17}H_{12}N_2O_2$: C, 73.89; H, 4.38; N, 10.14. Found: C, 73.62; H, 4.33; N, 9.89.

Method B.

Compound XXIII was also obtained by alkaline hydrolysis of XXIV followed by acidification of the salt according to the procedure for XVIII, Method B.

Ethyl Indeno[1,2,3-*de*]quinazoline-2-propionate (XXIV).

A mixture of 5.0 g. of XXII, 200 ml. of ethanol, and 2.0 g. of potassium cyanide was heated to reflux for 1 hour, cooled, and filtered from solid impurities. The solvent was removed *in vacuo* and the residue was extracted with hot cyclohexane, which on cooling gave 1.2 g. of XXIV, m.p. 98-100° (from cyclohexane).

Anal. Calcd. for $C_{19}H_{16}N_2O_2$: C, 74.99; H, 5.30; N, 9.21. Found: C, 75.00; H, 5.46; N, 9.14.

Ethyl 2-Acetamido-7-chloro-1-hydroxy-5-phenylpyrrolo[1,2-*a*]-quinazoline-3-carboxylate (XXVII).

To a mixture of 4.8 g. of 55% sodium hydride in 30 ml. of dimethylformamide was added, with stirring, a solution of 14 g. of ethyl cyanoacetate and 10 ml. of dimethylformamide. After the vigorous reaction subsided, a solution of 20 g. of 2-(*N*-acetoxy-acetamido)-2′-benzoyl-4′-chloroacetanilide (XXV) and 50 ml. of dimethylformamide was slowly added, causing a rise in temperature to 50°. The red reaction mixture was stirred for 0.5 hour and diluted with water. The aqueous solution was decanted from insoluble material. Recrystallization of the residue from ethanol gave 1.5 g. of product, m.p. 208-211°.

A second recrystallization from benzene raised the m.p. of the yellow solid to 218-220°, λ max (potassium bromide), 6.00 and 6.15 (w) μ. The nmr had peaks for CH_3CH_2O- at δ 1.47 (triplet, J = 7 cps) and δ 4.38 (quartet); for the methyl singlet at δ 2.29; for NH- at δ 10.05; for the *ortho* aromatic proton at δ 8.95 (doublet, J = 9 cps); and for the hydroxy proton at 12.60.

Anal. Calcd. for $C_{22}H_{18}ClN_3O_4$: C, 62.34; H, 4.28; Cl, 8.30; N, 9.91. Found: C, 62.53; H, 4.51; Cl, 8.60; N, 9.77.

Diethyl α-Acetamido-7-chloro-1-hydroxy-5-phenylpyrrolo[1,2-*a*]-quinazolinephosphonate (XXVIIa).

This compound, m.p. 195-196°, was prepared from XXV and diethyl cyanomethylphosphonate according to the procedure for XXVII. The nmr had peaks for the two CH_3CH_2O- groups at δ 1.31 (triplet, J = 7 cps) and δ 4.22 (quintet, (overlapping quarter)); for the acetyl methyl group at δ 2.30 (singlet); for the *ortho* aromatic proton at δ 8.60 (doublet, J = 9 cps); for the amide NH at δ 10.10; and for the hydroxy proton at δ 12.60. The infrared had one peak in the carbonyl region at 6.11 μ.

Anal. Calcd. for $C_{23}H_{23}ClN_3O_5P$: C, 56.63; H, 4.75; Cl, 7.27; N, 8.61. Found: C, 56.26; H, 4.41; Cl, 7.10; N, 8.98.

REFERENCES

(1) S. C. Bell and G. Conklin, *J. Heterocyclic Chem.*, in press.

(2) S. C. Bell and S. J. Childress, *J. Org. Chem.*, 29, 506 (1964).

(3) E. C. Taylor and A. McKillop, *J. Am. Chem. Soc.*, 87, 1984 (1965).

(4) S. C. Bell, R. J. McCaully, and S. J. Childress, *Tetrahedron Letters*, 2889 (1965).

(5) See reference 1, in which the large downfield shift of similar *ortho* aromatic protons has been described.

(6) Melting points are uncorrected. Nmr spectra were obtained in DMSO-d_6 on a Varian A-60 spectrometer using tetramethylsilane as the internal reference. The authors are indebted to Mr. Bruce Hofmann for the infrared spectra.

Received November 11, 1967 Radnor, Pa. 19087