Syntheses of Heterocyclic Fused Thiazolecarboxylic Acids I.

Stanley C. Bell, Carl Gochman and Peter H. L. Wei*

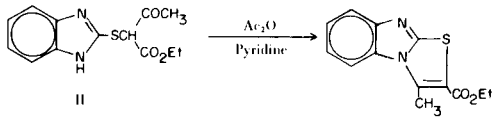
Research Division, Wyeth Laboratories Inc., Radnor, Pennsylvania 19087

Received July 28, 1975

A number of thiazolo 5-carboxylic acid derivatives were prepared which were fused to other heterocycles such as 1,2,4-benzothiadiazine, quinazoline, and pyrimidine rings at the 2,3-position of the thiazole ring. In several instances unexpected products were obtained, depending on the reaction conditions. The chemistry of these reactions and the identification of the products are discussed.

The preparation of heterocyclic fused 2,3-thiazole ring compounds has been reported by a number of workers (1). Since aromatic and heterocyclic carboxylic acids have been known to possess a variety of pharmacological activities (2), our interests were directed to the preparation of a series of fused heterocyclic 2,3-thiazolo compounds with carboxylic acid functions.

D'Amico, *et al.* (3) have described the preparation of 2-carbethoxythiazolo[3,2-*a*]benzimidazole (I) from the reaction of 2-mercaptobenzimidazole with ethyl α-chloroacetoacetate followed by cyclization of the intermediate

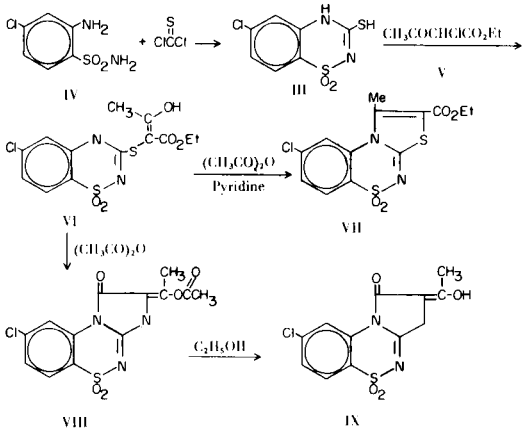


II I

sulfide II. Following the procedure of D'Amico we embarked upon the syntheses of carboxylic acids of several related heterocyclic ring systems (4).

Thus, 6-chloro-3-mercapto-4*H*-1,2,4-benzothiadiazine 1,1-dioxide (III), prepared from the reaction of 2-amino-4-chlorobenzenesulfonamide IV with thiophosgene, was reacted with α-chloroacetoacetate V to form the sulfide VI. Compound VI, however, did not exhibit an ester band in the infrared at the expected wave length, but there was a weak band at 6.02 μ and an intense band at 6.2 μ. This apparently resulted from VI existing as the chelated β-keto ester (5). An NH peak present at 3.14 and a broad band at 3.3 μ were also indicative of the enol proton of the chelate. The nmr spectrum had expected peaks for the methyl group and the ethyl ester group and there was no evidence of a methine peak.

Cyclization of VI with acetic anhydride containing pyridine produced the expected thiazolo[2,3-*c*][1,2,4]-benzothiadiazine-2-carboxylate (VII) as indicated by analytical and spectral data. However, when the cyclization reaction was repeated in acetic anhydride without the presence of pyridine a different product was obtained which was identified by analytical and the following spectral data as VIII. The nmr spectrum showed no ethyl ester group, but there were 2 methyl singlets at δ 2.32 and 2.72, while the ir spectrum exhibited 2 carbonyl peaks at 5.79 μ and 5.65 μ. The band at 5.79 μ was attributed to the cyclization of the ester group (rather than the carbonyl group) onto the aromatic nitrogen thus forming the 5-membered lactam, and the band at 5.65 μ was due to the acetylated exo enol group. Cyclization onto the nitrogen adjacent to the aromatic ring, rather than onto the sulfonamide nitrogen, was confirmed by the large down field meta proton peak at δ 8.95 (6). As expected, refluxing VIII in ethanol caused hydrolysis of the labile acetate group to form the enol IX.

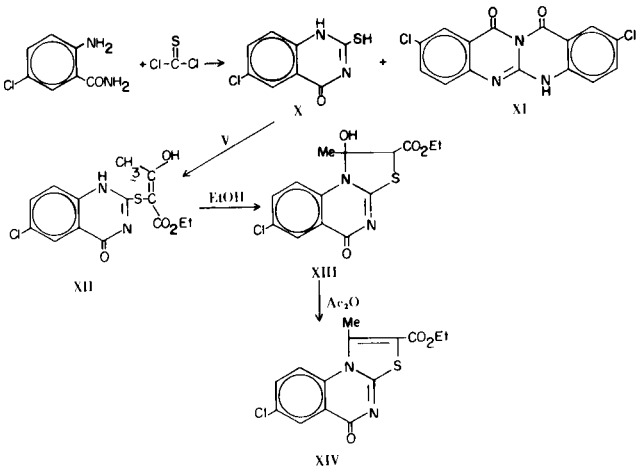


IV III V VI VII VIII IX

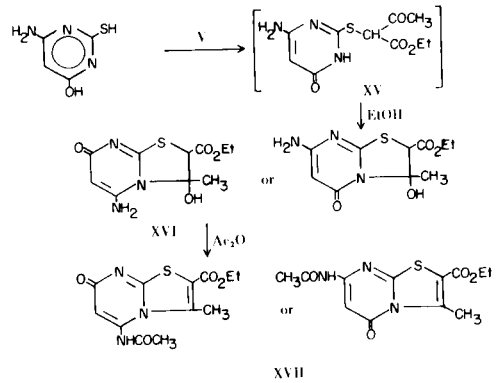
Similar reactions were extended to other heterocycles. 5-Chloroanthranilamide was reacted with thiophosgene in

order to form the intermediate 2-mercaptoquinazoline X (7). Also formed in the reaction mixture was a considerable amount of a by-product which was identified, on the basis of analyses and ir data, as the tetracyclic compound XI (8). When X was reacted with V the resultant sulfide was also obtained in the enol form XII. The ir spectrum showed the quinazoline lactam absorbance at 5.91 μ, the chelated β-keto ester band at 6.2 μ, and a broad band at 3.5 μ for the enol proton.

Interestingly, recrystallization of XII from ethanol provided a different, but isomeric compound XIII whose infrared now had an ester band at 5.72 μ, a lactam band at 5.98 μ, a sharp band at 3.0 μ and no ketone band. The nmr spectrum now exhibited the presence of a methine proton. Apparently XII, when dissolved in ethanol, had undergone cyclization to form the tricyclic compound XIII. When treated with hot acetic anhydride, without pyridine, XIII underwent dehydration to form the aromatized tricyclic derivative XIV.



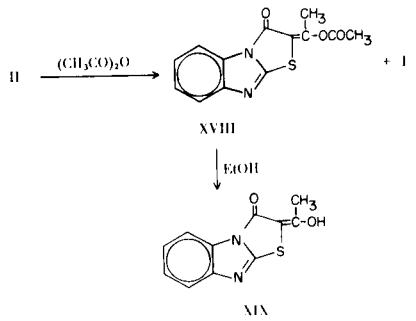
In order to prepare a fused bicyclic thiazole carboxylic acid derivative, 6-amino-4-hydroxy-2-mercaptopyrimidine was reacted with V and the resultant intermediate recrystallized from ethanol. As in the previous example XIII, the presence of an ester band and the lack of the ketone band in the infrared indicated that the sulfide intermediate XV had undergone cyclization to the hydroxy thiazoline



XVII

XVI. Heating XVI in acetic anhydride resulted in both dehydration and acetylation on the amino group to give XVII. We were unable however, to verify which nitrogen on the pyrimidine ring had taken place in the cyclization.

We re-investigated the reaction of D'Amico in order to determine whether reacting the sulfide II in acetic anhydride without pyridine would, as in the benzothiadiazine example VIII, provide an alternative cyclic thiazolone. Heating II in acetic anhydride produced two products. An insoluble compound was identified as the thiazolone enol acetate XVIII, while a second component in the soluble fraction was compound I, obtained by D'Amico. Refluxing of XVIII in ethanol also caused hydrolysis of the enol acetate group to XIX.



EXPERIMENTAL

Melting points were taken in a Thomas-Hoover oil bath and are uncorrected. Infrared spectra were obtained in potassium bromide pellets (except where noted) using a Perkin-Elmer Model 21 spectrophotometer. Nmr spectra were obtained in DMSO-d_6 (except where noted) on either a Varian A-60 or Jeolco HL60 spectrometer. The analyses and spectra were obtained under the supervision of Mr. Bruce Hofmann whose assistance in determining the structures of the compounds was greatly appreciated.

6-Chloro-3-mercapto-4*H*-1,2,4-benzothiadiazine 1,1-Dioxide (III).

To a mixture of 41.2 g. (0.2 mole) of 2-amino-4-chlorobenzenesulfonamide in 300 ml. of dioxane was added a solution of 25.0 g. of thiophosgene in 50 ml. of dioxane resulting in a thick solid. The reaction mixture was heated to reflux for 1.5 hours during which time all the solid dissolved. After cooling, 1500 ml. of water was added and the reaction mixture was made basic with sodium bicarbonate, neutralized with acetic acid and filtered from impurities. The filtrate was acidified with excess hydrochloric acid and chilled. There was obtained 29 g. of product, m.p. 234-236°.

Anal. Calcd. for $C_7H_5ClN_2O_2S_2$: C, 33.80; H, 2.02; N, 11.27; Cl, 14.25; S, 25.7. Found: C, 33.80; H, 2.07; N, 11.19; Cl, 14.5; S, 25.7.

2-(6-Chloro-1,1-dioxo-2*H*-1,2,4-benzothiadiazin-3ylthio)-3-hydroxycrotonic Acid Ethyl Ester (VI).

To a solution of 26 g. of compound III dissolved in 800 ml. of ethanol and 90 ml. of water was added a solution of 4.28 g. of potassium hydroxide, followed by 13.0 g. of 2-chloroacetoacetic ester (97%) V. The mixture was stirred at room temperature overnight and the resultant solid was collected and washed with water to give 16 g. of product. The mother liquor was concentrated and

the residue was also washed with water. The combined solids were recrystallized from alcohol to give 23.8 g. of product, m.p. 200-206°; ir: 3.1 μ, 3.3 μ, 6.02 μ; nmr: δ 1.23 (t), 4.26 (q) [CH_3CH_2O], 2.32 (s, CH_3).

Anal. Calcd. for $C_{13}H_{13}ClN_2O_5S_2$: C, 41.44; H, 3.48; Cl, 9.41; N, 7.44; S, 17.02. Found: C, 41.61; H, 3.80; Cl, 9.6; N, 7.14; S, 16.7.

8-Chloro-1-methylthiazolo[2,3-*c*][1,2,4]benzothiadiazine-2-carboxylic Acid, 5,5-Dioxide Ethyl Ester (VII).

A suspension of 5.0 g. of VI in 50 ml. of acetic anhydride containing 2 ml. of pyridine was heated to reflux for 4 hours. The solvent was removed and the residue was treated with ether and collected. The crude material was recrystallized from alcohol to give 2.0 g. pure product; m.p. 193-195°; ir: 5.79 μ; nmr: δ 1.43 (t), 4.42 (q) [CH_3CH_2O], 2.96 (s, CH_3).

Anal. Calcd. for $C_{13}H_{11}ClN_2O_4S_2$: C, 43.51; H, 3.08; Cl, 9.88; N, 7.81; S, 17.87. Found: C, 43.47; H, 3.24; Cl, 9.9; N, 9.73; S, 18.2.

8-Chloro-2-(α-hydroxyethylidene)thiazolo[2,3-*c*][1,2,4]benzothiadiazin-1(2*H*)one 5,5-Dioxide Acetate (VIII).

A mixture of 5.0 g. of VI and 50 ml. of acetic anhydride was heated to reflux for 3 hours. The dark solution was treated with Darco. The solvent was removed and the residue treated with ether and collected to give 3.7 g. of crude material. Recrystallization from benzene gave a product of m.p. 198-200°; ir: 5.65 μ, 5.79 μ; nmr (deuteriochloroform): δ 2.32 (s, CH_3), 2.72 (s, CH_3), 8.95 (d, 1H, J = 2).

Anal. Calcd. for $C_{13}H_9ClN_2O_5S_2$: C, 41.89; H, 2.43; Cl, 9.51; N, 7.52; S, 17.21. Found: C, 41.92; H, 2.42; Cl, 9.2; N, 7.48; S, 17.2.

8-Chloro-2-(α-hydroxyethylidene)thiazolo[2,3-*c*][1,2,4]benzothiadiazin-1(2*H*)one 5,5-Dioxide (IX).

A mixture of 4.0 g. of VIII and 200 ml. of ethanol was refluxed for 2 hours and concentrated to 150 ml. On cooling there was obtained 3.2 g. of product (as the alcoholate), m.p. 235-245°. After recrystallization from acetonitrile, the compound had a m.p. of 266-268°; ir: 5.96 μ.

Anal. Calcd. for $C_{11}H_7ClN_2O_4S_2$: C, 39.94; H, 2.13; N, 8.47; Cl, 10.72. Found: C, 40.22; H, 2.17; N, 8.74; Cl, 10.77.

6-Chloro-2-mercapto-4(1*H*)quinazolinone (X) and 2,9-Dichloro-11*H*-quinazolino[2,3-*b*]quinazoline-11,13(5*H*)dione (XI).

To a solution of 34.1 g. (0.20 mole) of 5-chloroanthranilamide in 200 ml. of dioxane was added a solution of 25.3 g. (0.22 mole) of thiophosgene in 200 ml. of dioxane and the reaction mixture was refluxed for 2 hours. After cooling 12.3 g. of yellow solid was filtered off (XI) which on recrystallization from DMF had a m.p. of 335-340°; ir: 5.79-5.98 μ doublet (CO-N-CO).

Anal. Calcd. for $C_{15}H_7Cl_2N_3O_2$: C, 54.24; H, 2.13; N, 12.65; Cl, 21.35. Found: C, 54.40; H, 2.12; N, 12.82; Cl, 21.13.

A large volume of water was added to the above dioxane filtrate precipitating 18.3 g. of X, which was purified by reprecipitation from base.

2-(6-Chloro-3,4-dihydro-4-oxo-2-quinazolinylthio)-3-hydroxycrotonic Acid Ethyl Ester (XII).

To a suspension of 8.02 g. (0.04 mole) of X in 300 ml. of ethanol and 20 ml. of water was added 2.24 g. of potassium hydroxide followed by 6.95 g. of V. The mixture was stirred at room temperature overnight. After removal of some solid the filtrate was concentrated and the residue washed with water to give 10.5 g. of crude material which was recrystallized from benzene. The compound had a m.p. of 163-165°; ir: 3.5 (broad) μ, 5.91 μ, 6.20 μ.

Anal. Calcd. for $C_{14}H_{13}ClN_3O_4S$: C, 49.34; H, 3.84; Cl, 10.40; N, 8.22. Found: C, 49.45; H, 3.54; Cl, 10.87; N, 8.33.

7-Chloro-2,3-dihydro-1-hydroxy-1-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]quinazoline-2-carboxylic Acid Ethyl Ester (XIII).

This product was obtained by recrystallizing XII, obtained from the above reaction, from ethanol, had a m.p. 200-205° dec.; ir: 3.0 μ, 5.72 μ, 5.98 μ; nmr: δ 1.27 (t), 4.28 (q) [CH_3CH_2O], 2.25 (s, CH_3), 4.88 (s, methine).

Anal. Calcd. for $C_{14}H_{13}ClN_2O_4S$: C, 49.34; H, 3.84; Cl, 10.40; N, 8.22. Found: C, 49.61; H, 3.95; Cl, 10.82; N, 8.19.

7-Chloro-1-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]quinazoline-2-carboxylic Acid Ethyl Ester (XIV).

A mixture of 4.0 g. of XIII in 50 ml. of acetic anhydride was heated to reflux for 1 hour. The hot solution was treated with Darco, cooled, and the solid which separated was collected to give 2.0 g. of crude material. The product after recrystallization from dimethoxyethane had a m.p. 166-168°; ir: 5.85 μ; nmr (deuteriochloroform): δ 1.40 (t), 4.40 (q) [CH_3CH_2O]; 3.17 (s, CH_3).

Anal. Calcd. for $C_{14}H_{11}ClN_2O_3S$: C, 52.08; H, 3.44; Cl, 10.98; N, 8.68; S, 9.93. Found: C, 52.30; H, 3.27; Cl, 11.03; N, 8.60; S, 10.29.

5(or 7)-Amino-2,3-dihydro-3-hydroxy-3-methyl-7(or 5)oxo-7(or 5)*H*-thiazolo[3,2-*a*]pyrimidine-2-carobxylic Acid Ethyl Ester (XVI).

To a suspension of 14.3 g. of 6-amino-4-hydroxy-2-mercaptopyrimidine in 400 ml. of ethanol and 30 ml. of water was added 5.6 g. of potassium hydroxide followed by 16.5 g. (0.10 mole) of V. The mixture was stirred at room temperature overnight and the solid was collected and washed with water to give 7.3 g. of product. By concentrating the mother liquor additional solid (14.0 g.) was obtained and washed with water. The crude material was recrystallized from ethanol to give 21.3 g., m.p. 141-143°; ir: 3.1 (broad) μ, 5.80 μ, 6.16 μ.

Anal. Calcd. for $C_{10}H_{13}N_3O_4S$: C, 44.26; H, 4.83; N, 15.49; S, 11.81. Found: C, 44.45; H, 4.65; N, 15.72; S, 11.86.

5(or 7)Acetamido-3-methyl-7(or 5)-oxo-7(or 5)*H*-thiazolo[3,2-*a*]-pyrimidine-2-carboxylic Acid Ethyl Ester (XVII).

A mixture of 5.0 g. (0.0185 mole) of XVI in 50 ml. of acetic anhydride was heated to reflux for 2 hours. The solution was cooled and the solid collected, washed with acetic anhydride and ether. The crude material was recrystallized from dimethoxyethane to give 2.5 g., m.p. 278-280°; ir: 3.1 μ, 5.81 μ, 5.90 μ, 6.01 μ.

Anal. Calcd. for $C_{12}H_{13}N_3O_4S$: C, 48.81; H, 4.44; N, 14.23; S, 10.86. Found: C, 48.80; H, 4.42; N, 14.01; S, 10.86.

2-(α-Hydroxyethylidene)thiazolo[3,2-*a*]benzimidazol-1(2*H*)one Acetate (XVIII).

A mixture of 10.0 g. of 2-(2-benzimidazolylthio)acetic acid ethyl ester (II) and 100 ml. of acetic anhydride was heated on the steam bath for 2 hours with stirring. The solution was allowed to cool to room temperature and seeded. After standing for 2 days there was filtered off 1.1 g. of a light brown solid, m.p. 191-193°. Recrystallization from DMF gave back a light brown solid m.p. 192-194°; ir: 5.76 μ, 5.97 μ.

Anal. Calcd. for $C_{13}H_{10}N_2O_3S$: C, 56.92; H, 3.67; N, 10.22; S, 11.67. Found: C, 56.62; H, 2.83; N, 10.86.

The acetic anhydride filtrate from the above reaction mixture was concentrated *in vacuo* to dryness and the residue recrystallized

from acetonitrile producing 3.8 g. of ethyl 3-methylthiazolo[3,2-*a*]benzimidazole-2-carobxylate (I), m.p. 122-123°. Recrystallization from ethanol increased the m.p. to 126-128°[3]; ir: 5.84 μ; nmr: δ 1.38 (t), 4.33 (q) [CH_3CH_2O], 2.85 (s, CH_3).

2-(α-Hydroxyethylidene)thiazolo[3,2-*a*]benzimidazol-1(2*H*)one (XIX).

A mixture of XVIII and alcohol was refluxed for several hours, the solution allowed to cool and the precipitate collected, m.p. 218-222°. Subsequent recrystallizations from ethanol and acetonitrile increased the m.p. to 231-233°; ir: (chloroform): 5.95 μ; nmr: δ 2.69 (s, CH), 11.75 (enol-OH).

Anal. Calcd. for $C_{11}H_8N_2SO_2$: C, 56.88; H, 3.47; N, 12.06; S, 13.81. Found: C, 56.85; H, 3.19; N, 12.29.

REFERENCES

(1) For a general review see, W. L. Mosby, "Heterocyclic Systems with Bridgehead Nitrogen Atoms, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, Vol. 1 and 2.

(2) For example see, K. J. Doebel, "The Chemistry of Non Steroidal Anti-inflammatory Agents", *Pure Appli. Chem.*, **19**, 49 (1969).

(3) J. J. D'Amico, R. H. Cambell and E. C. Guinn, *J. Med. Chem.*, **29**, 865 (1964).

(4) The information described in this manuscript has been described in part in the following U.S. Patents, 3,471,497; 3,475,424; 3,474,426; 3,516,996.

(5) D'Amico (reference 3) had shown that mild treatment of the benzimidazole keto sulfide II with acetic anhydride in pyridine resulted in the acetylated derivative of the enol form of II.

(6) The large downfield shift of *o*-protons of acetanilides has been discussed by S. C. Bell and G. Conklin, *J. Heterocyclic Chem.*, **5**, 179 (1968) and by Zanger, Simons and Gennaro, *J. Org. Chem.*, **33**, 3673 (1968).

(7) Compound X was prepared by an alternative procedure by H. S. Sached and K. Narang, *J. Indian Chem. Soc.*, **32**, 631 (1955); *Chem. Abstr.*, **50**, 12062F (1956).

(8) Unsubstituted compounds of type XI have been prepared by an alternative route, K. Butler and M. Partridge, *J. Chem. Soc.*, 1512 (1959).