Synthesis of an Imidazo[1,2-*c*]pyrimidine Analog of a Thiamine Antagonist Coccidiostat and a Comparison of Several Methods for the Preparation of Imidazo[1,2-*c*]pyrimidines (1)

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Several methods for the preparation of imidazo[1,2-*c*]pyrimidines are presented. Compound **12** was prepared from **11** and chloroacetaldehyde in water using a buffer to control *p*H. Compound **12** was converted in two steps to **14**, the etheno bridged analog of the coccidiostat **1**. Several methods were used to prepare 8-phenylimidazo[1,2-*c*]pyrimidine (**16**). In terms of yield the best method was the reaction of the aminopyrimidine **15** with chloroacetaldehyde in acetone and in the presence of calcium carbonate as an acid scavenger. Reaction of the 4-chloropyrimidine **19** with aminoacetaldehyde diethyl acetal gave **16** directly in modest yield.

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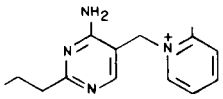
Modification of nucleotide bases through the incorporation of an "etheno" bridge has provided a number of interesting compounds for biochemical and biological studies. Leonard has described a fluorescent 1,N^6-ethenoadenosine 3′,5′-monophosphate modification of cyclic AMP (2). Further work by Leonard and co-workers described fluorescent etheno bridge modifications of adenosine and cytidine (3). Jones and co-workers have reported the preparation of a series of substituted 1,N^6-ethenoadenosine 3′,5′-monophosphate derivatives (4). These compounds showed a wide range of potencies in the activation of protein kinases.

We felt that these results merited the preparation of an etheno-bridged derivative of the coccidiostat Amprolium (**1**) with the objective of evaluating the effect of such a structural change on the biological activity of the molecule. The imidazo[1,2-*c*]pyrimidine **2** represents a modification whereby two carbons have been removed from the *n*-propyl chain of **1** and have been shifted to form a 3,N^4-etheno bridge.



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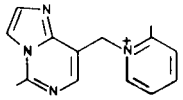

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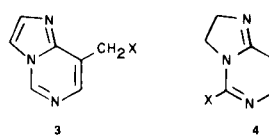
The focal point for our preparation of **2** became the elaboration of an appropriately functionalized imidazo[1,2-*c*]pyrimidine **3**. A survey of the literature uncovered a number of tactics which had been applied to the synthesis of imidazo[1,2-*c*]pyrimidines. Dihydroimidazo[1,2-*c*]pyrimidines such as **4** have been prepared through the cyclization of the 4-β-chloroethylaminopyrimidines **5** (5-7). Imidazo[1,2-*c*]pyrimidine **6** was made by cyclization of 4-β,β-diethoxyethylaminopyrimidine (**7**) with phosphorus oxychloride (8). Condensation of 4-aminopyrimidine with 2-bromopropanal gave **8** (9). Cyclization of a 4-chloroacetylaminopyrimidine **9** with aluminum chloride gave the imidazo[1,2-*c*]pyrimidine **10** (10).

The reaction of a 4-aminopyrimidine with an α-haloacetaldehyde seemed most suited to the preparation of



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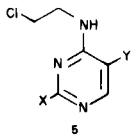

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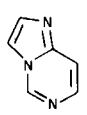

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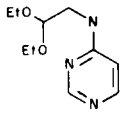

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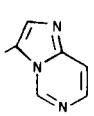

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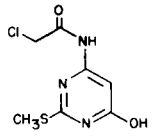

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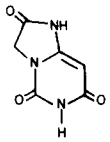
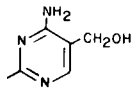


10

imidazo[1,2-*c*]pyrimidine **2**. This method had been used in the preparation of **8** and the etheno-bridged nucleotides. As a matter of record one finds that the reaction of a 4-aminopyrimidine with chloroacetaldehyde is not a perfectly general synthesis of imidazo[1,2-*c*]pyrimidines, since there are reports of this reaction giving exclusively the pyrrolo[2,3-*d*]pyrimidine (10,11), the product derived from bridging N^4 and the 5-position of the pyrimidine. However, since we required a pyrimidine substrate that was substituted in the 5-position, this reaction turned out not to be a problem. Reaction of 2-methyl-4-amino-5-hydroxymethylpyrimidine (**11**) (12) with chloroacetaldehyde in ethanol afforded the fluorescent imidazo[1,2-*c*]pyrimidine **12** in a modest 17% yield. Investigation of the reaction mixture by tlc supported the interpretation that the low yield could be explained in part by a low conversion of the starting pyrimidine caused by protonation by the hydrochloric acid that was formed in the reaction. To circumvent this problem we turned to the observations of Kochetkov, *et al.*, (13) that the rates of formation of etheno-bridged modifications of 9-methyladenine and 1-methylcytidine with aqueous chloroacet-

aldehyde exhibited a bell-shaped dependence on *p*H. By examination of reaction mixtures of **11** and chloroacetaldehyde between *p*H 2 and *p*H 10 we found that the formation of **12** proceeded most smoothly between *p*H 6 and *p*H 6.5. On a preparative scale in aqueous medium using sodium acetate to maintain a *p*H of 6.2 we obtained **12** in 70% yield. The hydroxymethyl compound **12** was cleanly converted to the bromomethyl compound **13** by treatment with hydrobromic acid in acetic acid. Reaction of **13** with 2-picoline in nitromethane gave the desired picolinium salt **14** in 44% yield.



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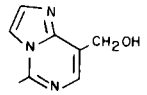

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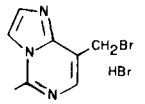

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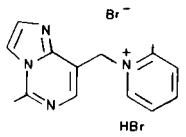

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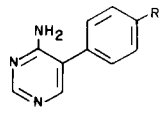
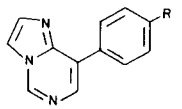
Compound **14** was devoid of anticoccidial activity when tested against *Eimeria tenella* and *E. necatrix* at a concentration of 250 ppm in feed. Amprolium was active at 121 ppm in feed. The lack of activity in **14** supports the conclusion of Rogers (14) that the 4-amino group of the pyrimidine moiety cannot be alkylated without serious loss of activity.

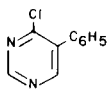
The success of the aqueous reaction conditions used in the preparation of imidazo[1,2-*c*]pyrimidine **12** led us to an investigation of the reaction of chloroacetaldehyde with a model 4-aminopyrimidine. The use of the 5-phenylpyrimidine **15** (15) as a substrate for the reaction with chloroacetaldehyde in aqueous medium at *p*H 6.5 gave the imidazo[1,2-*c*]pyrimidine **16** in only 6% yield. The major reason for the low yield in this case was the low solubility of the substrate in water at that *p*H. By changing the solvent to acetone we increased the yield to 33%. In another example, the reaction of the 5-*p*-chlorophenyl compound **17** (16) with chloroacetaldehyde in acetone gave the imidazo[1,2-*c*]pyrimidine **18** in 47% yield. A major factor behind these relatively low yields in the acetone solution reactions was the lack of complete conversion of the starting 4-aminopyrimidine. Attempts at improving the conversion by prolonging the reaction time or by increasing the amount of chloroacetaldehyde gave rise to a number of by-products and greatly complicated the workup. Since we had observed that there was no reaction between the hydrochloride salt of **15** and chloroacetaldehyde in refluxing acetone, it seemed likely that the low yield of **16** could be traced to protonation of the starting material **15** by hydrochloric acid that was formed during the course of the reaction. Accordingly, we added calcium carbonate to the reaction mixture to serve as an



15 R H
17 R Cl



16 R H
18 R Cl



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acid scavenger. This modification raised the yield of **16** to 61%.

To complete the comparison of methods for preparing imidazo[1,2-*c*]pyrimidines we duplicated the strategy of Armarego (8) by reaction of the 4-chloropyrimidine **19** (17) with aminoacetaldehyde diethyl acetal. Using conditions of ethanol solvent in a sealed vessel at 150° we obtained **16** directly in 20% yield rather than the expected 4-β,β-diethoxyethylaminopyrimidine.

The foregoing results provide a basis for choosing among several methods for preparing imidazo[1,2-*c*]-pyrimidines. In the event that one has a water soluble aminopyrimidine, the aqueous-controlled *p*H conditions provide ahigh yielding route. Given a lipophilic pyrimidine substrate the use of acetone as solvent in combination with calcium carbonate is preferable to the use of an aqueous medium. Finally, we see that the strategy involving reaction of a 4-chloropyrimidine with aminoacetaldehyde diethyl acetal can provide an acceptable, albeit low yielding, method for preparing imidazo[1,2-*c*]-pyrimidines.

EXPERIMENTAL

All melting points were determined on a Fisher-Johns apparatus and are uncorrected. The nmr spectra were determined with a Varian A 60-A and HA 100. Combustion analyses were performed by the Syntex analytical staff and by A. Bernhardt, Muhlheim (Ruhr).

5-Methyl-8-hydroxymethylimidazo[1,2-*c*]pyrimidine (**12**).

4-Amino-5-hydroxymethyl-2-methylpyrimidine (1.02 g., 7.35 mmoles) was dissolved in 50 ml. of water at 40°. Chloroacetaldehyde (5.24 g. of a 45% aqueous solution, 30 mmoles) was added along with sodium acetate trihydrate to obtain a *p*H of 6.2. The solution was stirred for 3 hours with periodic addition of sodium acetate to maintain a *p*H of 6.2. The mixture was extracted with ten 20-ml. portions of chloroform and five 20-ml. portions of 1-butanol. The combined organic extracts were evaporated to a residue which was recrystallized from ethyl acetate to give 842 mg. (70%) of the pure product as light tan crystals, m.p. 188-189°; nmr (deuteriodimethylsulfoxide): δ 2.78 (s, 3 H), 4.81 (d, 2 H, J = 4.5 Hz), 5.36 (t, 1 H, J = 4.5 Hz), 7.63 (b, 1 H), 7.81 (s, 1 H), 7.96 (d, 1 H, J = 1 Hz).

Anal. Calcd. for $C_8H_9N_3O$: C, 58.89; H, 5.56; N, 25.75. Found: C, 58.89; H, 5.47; N, 25.51.

In another experiment 50 mg. (0.36 mmole) of **11**, 76 mg. of 45% aqueous chloroacetaldehyde, and 25 ml. of ethanol were heated at reflux. After 30 minutes an additional 100 mg. of the chloroacetaldehyde solution was added. After 5 hours the solvent was evaporated and the product was isolated by preparative tlc using 10% methanol-chloroform to give 10 mg. (17%), m.p. 182-185°.

5-Methyl-8-bromomethylimidazo[1,2-*c*]pyrimidine Hydrobromide (13).

To 1 g. (6.14 mmoles) of 5-methyl-8-hydroxymethylimidazo-[1,2-*c*]pyrimidine was added 20 ml. of acetic acid. To this solution was added over 5 minutes 10 ml. of a 30% hydrobromic acid solution in acetic acid. The mixture was heated on a steam bath for 3 hours. The mixture was cooled to room temperature and the solid was collected by filtration. The solid was washed with 10 ml. of acetic acid and 100 ml. of diethyl ether. This procedure gave a dark tan powder (1.88 g., 100%) of undefined m.p.; nmr (deuterium oxide): δ 3.02 (s, 3 H), 5.03 (s, 2 H), 8.05 (d, 1 H, J = 2 Hz), 8.15 (d, 1 H, J = 2 Hz), 8.42 (s, 1 H).

Anal. Calcd. for $C_8H_9Br_2N_3$: C, 31.3; H, 2.96; Br, 52.06; N, 13.69. Found: C, 31.41; H, 3.15; Br, 51.78; N, 13.58.

1-[(5-Methylimidazo[1,2-*c*]pyrimidine-8-yl)methyl]-2-methylpyridinium Bromide Hydrobromide (14).

A mixture of 1.6 g. (5.2 mmoles) of 5-methyl-8-bromomethylimidazo[1,2-*c*]pyrimidine hydrobromide, 1.46 g. of 2-picoline (15.6 mmoles), and 25 ml. of nitromethane was stirred at 55° for 2 hours. The mixture was filtered and diethyl ether was added to the filtrate to give 1.45 g. of crude product as an off-white powder. This material was taken up into hot ethanol and diethyl ether was added slowly to give the pure product, 905 mg. (44%), m.p. undefined; nmr (deuterium oxide): δ 2.99 (br s, 6 H), 6.12 (s, 2 H), 7.82 (d, 1 H, J = 1.5 Hz), 7.94 (s, 1 H), 8.09 (d, 1 H, J = 1.5 Hz), 8-8.9 (m, 4 H).

Anal. Calcd. for $C_{14}H_{16}Br_2N_4$: C, 42.02; H, 4.03; N, 14.0; Br, 39.94. Found: C, 42.31; H, 4.2; N, 13.88; Br, 39.71.

8-(4-Chlorophenyl)imidazo[1,2-*c*]pyrimidine (18).

A mixture of 2.05 g. (10 mmoles) of 4-amino-5-(4-chlorophenyl)pyrimidine, 2 g. of 45% aqueous chloroacetaldehyde, and 60 ml. of acetone was heated at reflux. After 1 hour, during which time a precipitate formed, an additional 1.45 g. of chloroacetaldehyde solution was added. The mixture was heated at reflux for an additional 16 hours. After removal of acetone under reduced pressure the mixture was taken up in 40 ml. of water and the solution was basified with 10% sodium hydroxide solution. The mixture was extracted with three 100-ml. portions of ethyl acetate. Concentration of the organic extracts left a residue which was chromatographed on 120 g. of silica gel with 50% ethyl acetate-hexane. This procedure gave 1.1 g. (47%) of a product of 95% purity. Further purification by preparative tlc and vacuum sublimation gave white crystals, m.p. 159-160°; nmr (deuteriochloroform): δ 7.47 (d, 2 H, J = 8 Hz), 7.72 (br s, 2 H), 7.93 and 8.05 (two br s, total 3 H), 9 (s, 1 H).

Anal. Calcd. for $C_{12}H_8ClN_3$: C, 62.75; H, 3.51; N, 18.3. Found: C, 62.53; H, 3.58; N, 18.18.

8-Phenylimidazo[1,2-*c*]pyrimidine (16).

Method A.

A mixture of 1.906 g. (10 mmoles) of 4-chloro-5-phenylpyrimidine, 2 g. (15 mmoles) of aminoacetaldehyde diethyl acetal, and 10 ml. of ethanol was heated in a stainless steel pressure vessel at 150° for 16 hours. After cooling, the vessel was opened and the solvent was removed *in vacuo*. Water (20 ml.) was added and the mixture was made basic with 10% sodium hydroxide solution. The mixture was extracted with methylene chloride. Removal of the methylene chloride left a residue which was chromatographed on 100 g. of silica gel with a solvent gradient of 40% ethyl acetate-hexane to 80% ethyl acetate-hexane. This procedure afforded the product as an off-white solid, m.p. 90-91°, 382 mg. (20%); nmr (deuteriochloroform): δ 7.15-7.65 (m, 5 H), 7.6 (d, J = 2 Hz), 7.95-8.1 (m, 3 H), 7.97 (d, J = 2 Hz), 8.01 (s), 9.03 (s, 1 H).

Anal. Calcd. for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.56; H, 4.49; N, 21.65.

Method B.

A mixture of 340 mg. (2 mmoles) of 4-amino-5-phenylpyrimidine, 1.22 g. (7 mmoles) of 45% aqueous chloroacetaldehyde, 25 ml. of water, and 5 ml. of tetrahydrofuran was adjusted to *p*H 6.5 with sodium acetate trihydrate. The mixture was heated at 50° with stirring. Additional 200 mg. portions of chloroacetaldehyde solution were added at 1, 4, and 6 hours after initiation. Sodium acetate was added periodically to maintain the *p*H at *ca.* 6.5. After 7.5 hours the solution was made basic with ammonium hydroxide solution and the mixture was extracted thoroughly with chloroform. Removal of the chloroform left a residue which was chromatographed on 50 g. of silica gel with a gradient of 40% ethyl acetate-hexane to 80% ethyl acetate-hexane. This procedure afforded 23 mg. (6%) of 8-phenylimidazo[1,2-*c*]pyrimidine, m.p. 89-90°.

Method C.

A mixture of 1.71 g. (10 mmoles) of 4-amino-5-phenylpyrimidine, 2 g. (11.4 mmoles) of 45% aqueous chloroacetaldehyde, 1.5 g. of powdered calcium carbonate, and 60 ml. of acetone was heated at reflux. After 1 hour an additional 1.45 g. of chloroacetaldehyde solution and 0.5 g. of calcium carbonate were added. The mixture was heated at reflux for an additional 16 hours. Evaporation of solvent left a residue which was taken up in 60 ml. of water. This solution was basified with 10% sodium hydroxide solution. The resulting mixture was extracted thoroughly with ethyl acetate. Removal of the ethyl acetate left a residue which was chromatographed on 150 g. of silica gel with a solvent gradient of 40% ethyl acetate-hexane to 80% ethyl acetate-hexane. This procedure gave 1.18 g. (61%) of 8-phenylimidazo-[1,2-*c*]pyrimidine, m.p. 90-91°.

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REFERENCES AND NOTES

(1) Contribution No. 492 from the Institute of Organic Chemistry.

(2) J. A. Secrist III, J. R. Barrio, N. J. Leonard, G. Villar-Palasi, and A. G. Gilman, *Science*, 177, 279 (1972).

(3) J. A. Secrist III, J. R. Barrio, N. J. Leonard, and G. Weber, *Biochemistry*, 11, 3499 (1972).

(4) G. H. Jones, D. V. K. Murthy, D. Tegg, R. Golling, and J. G. Moffatt, *Biochem. Biophys. Res. Commun.*, 53, 1338 (1973).

(5) G. R. Ramage and G. Trappe, *J. Chem. Soc.*, 4410 (1952).

(6) J. Clark and G. R. Ramage, *ibid.*, 2821 (1958).

(7) J. Clark and T. Ramsden, *J. Chem. Soc. (C)*, 679 (1971).

(8) W. L. F. Armarego, *J. Chem. Soc.*, 2778 (1965).

(9) P. Guerret, R. Jacquier, and G. Maury, *J. Heterocyclic Chem.*, 8, 643 (1971).

(10) C. W. Noell and R. K. Robins, *ibid.*, 1, 34 (1964).

(11) R. A. West, K. Ledig, and G. H. Hitchings, British Patent 812,366 (1959); *Chem. Abstr.*, 54, 5921 (1960).

(12) H. Andersag and K. Westphal, *Chem. Ber.*, 70, 2035 (1937).

(13) N. K. Kochetkov, V. N. Shibaev, and A. A. Kost, *Tetrahedron Letters*, 1993 (1971).

(14) E. F. Rogers, *Ann. N. Y. Acad. Sci.*, 98, 412 (1962).

(15) G. Tsatsaronis and F. Effenberger, *Chem. Ber.*, 94, 2876 (1961).

(16) J. A. Hyatt and J. S. Swenton, *J. Org. Chem.*, 37, 3216 (1972).

(17) W. Davies and H. Piggot, *J. Chem. Soc.*, 347 (1945).