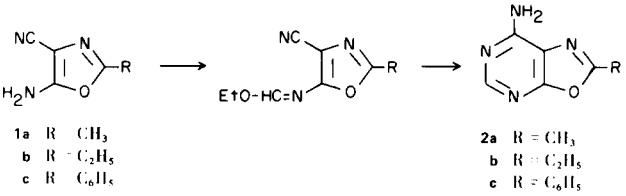
The Synthesis of Certain 2,7-Disubstituted Oxazolo[5,4-*d*]pyrimidines (1)

Vemanna D. Patil and Leroy B. Townsend

Department of Biopharmaceutical Sciences and Department of Chemistry,
University of Utah, Salt Lake City, Utah 84112

Received October 5, 1970

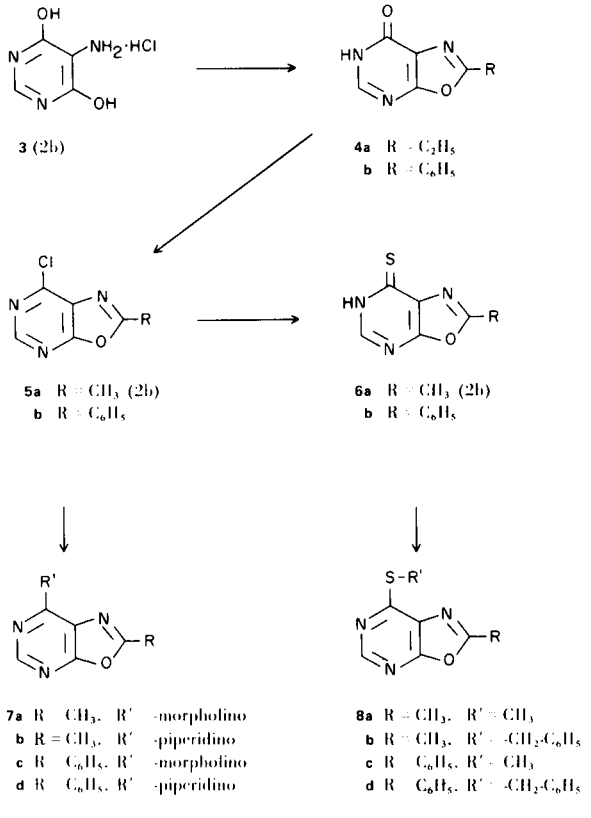
There are two major routes available for the synthesis of oxazolo[5,4-*d*]pyrimidines. A facile ring opening and degradation of **1a-c** was observed on treatment with acid (3b) or hydrogen peroxide in ammonium hydroxide (4) and precluded the use of these oxazoles for the preparation of the desired 2-substituted oxazolo[5,4-*d*]pyrimidin-7-one



1a R = CH_3
b R = C_2H_5
c R = C_6H_5

2a R = CH_3
b R = C_2H_5
c R = C_6H_5

derivatives. Ring opening has been observed previously (2d) with 5-amino-4-cyanooxazole under similar conditions and the present investigation indicates that a 2-substituent



3 (2b)

4a R = C_2H_5
b R = C_6H_5

5a R = CH_3 (2b)
b R = C_6H_5

6a R = CH_3 (2b)
b R = C_6H_5

7a R = CH_3, R' = morpholino
b R = CH_3, R' = piperidino
c R = C_6H_5, R' = morpholino
d R = C_6H_5, R' = piperidino

8a R = CH_3, R' = CH_3
b R = CH_3, R' = $-CH_2-C_6H_5$
c R = C_6H_5, R' = CH_3
d R = C_6H_5, R' = $-CH_2-C_6H_5$

does not impart any significant increase in stability. However, we have prepared some 2-substituted 7-aminooxazolo[5,4-*d*]pyrimidines (5) (**2a-c**) from the above oxazoles *via* the ethoxymethylene intermediates without ring opening of the oxazole ring being observed as determined by pmr and uv spectroscopy.

We then approached the synthesis of the desired heterocycles by ring annulation of the appropriate pyrimidine. Treatment of **3** (2b) with propionic anhydride furnished 2-ethyloxazolo[5,4-*d*]pyrimidin-7-one (**4a**). Benzoic anhydride and **3** (2b) furnished the corresponding 2-phenyl derivative (**4b**) which was converted to 7-chloro-2-phenyloxazolo[5,4-*d*]pyrimidine (**5b**) on treatment with phosphorus oxychloride at reflux temperature. Displacement of the chloro group from **5a** (2b) and **5b** was accomplished with sodium hydrogen sulfide to furnish 2-methyloxazolo[5,4-*d*]pyrimidin-7-thione (2b) (**6a**) and 2-phenyloxazolo[5,4-*d*]pyrimidin-7-thione (**6b**), respectively. Methylation of **6a** (2b) and **6b** was accomplished with methyl iodide in aqueous ammonium hydroxide, without ring opening of the oxazole moiety, to afford 2-methyl-7-methylthiooxazolo[5,4-*d*]pyrimidine (**8a**) and 7-methylthio-2-phenyloxazolo[5,4-*d*]pyrimidine (**8c**), respectively. The site of methylation was established by the use of pmr (6) and uv spectroscopy (6a). Treatment of **6a** (2b) and **6b** with benzyl chloride under similar conditions furnished **8b** and **8d**, respectively. Nucleophilic displacement of the chloro group from **5a** (2b) and **5b** with piperidine and morpholine furnished **7b**, **7d**, **7a** and **7c**. On the basis of the above observations, it would appear that although the oxazole moiety of oxazole [5,4-*d*]pyrimidine derivatives is susceptible toward ring opening under various reaction conditions, nucleophilic displacement of the 7-chloro group from **5a** (2b) and **5b** can be accomplished without ring opening being observed.

EXPERIMENTAL (7)

7-Amino-2-methyloxazolo[5,4-*d*]pyrimidine (**2a**).

5-Amino-4-cyano-2-methyloxazole (3) (**1a**, 1.85 g.) was added to a 50 ml. mixture of triethyl orthoformate and acetic anhydride (molar proportions which were mixed and allowed to stand for

100 hours at room temperature before use). This reaction mixture was heated at reflux temperature for three hours with stirring and the dark brown solution then evaporated *in vacuo* to a syrup. The syrup was dissolved in dry toluene (25 ml.) and evaporated *in vacuo* with this process being repeated three times. The residual solid was cooled to room temperature, treated with methanolic ammonia (125 ml.) and allowed to stand at room temperature for 12 hours. The solid which had separated was filtered and recrystallized from water with the aid of Norit to obtain 1.4 g. (62%) of **2a** as needles, m.p. 250° [Lit. (2d) 251-250°].

Anal. Calcd. for $C_6H_6N_4O$: C, 48.00; H, 4.00; N, 37.33. Found: C, 48.02; H, 4.13; N, 37.52.

7-Amino-2-ethyloxazolo[5,4-*d*]pyrimidine (**2b**).

In a similar manner, 5-amino-4-cyano-2-ethyloxazole (3) (**1b**, 2 g.) was treated with a mixture of triethyl orthoformate and acetic anhydride (50 ml.) to furnish a solid which was crystallized from water to give 1.4 g. (57%) of **2b**, m.p. 188-189° [Lit. (2d) 186-187°]; uv, λ max (*p*H 1) 252 nm (ε, 16,240), (methanol) 252 nm (ε, 16,560), (*p*H 11) 253 nm (ε, 15,740).

Anal. Calcd. for $C_7H_8N_4O$: C, 51.23; H, 4.87; N, 34.15. Found: C, 51.24; H, 5.16; N, 33.95.

7-Amino-2-phenyloxazolo[5,4-*d*]pyrimidine (**2c**).

5-Amino-4-cyano-2-phenyloxazole (3) (**1c**, 1.85 g.) was treated with a mixture of triethyl orthoformate and acetic anhydride (50 ml.) to afford 7-amino-2-phenyloxazolo[5,4-*d*]pyrimidine (**2c**) which was crystallized from aqueous alcohol to afford 1.0 g. (48%) of pale yellow needles, m.p. 304-305° [Lit. (2d) 300-301°].

Anal. Calcd. for $C_{11}H_8N_4O$: C, 62.27; H, 3.77; N, 26.42. Found: C, 62.29; H, 3.88; N, 26.71.

2-Ethyloxazolo[5,4-*d*]pyrimidin-7-one (**4a**).

4,6-Dihydroxy-5-aminopyrimidine hydrochloride (2b) (**3**, 5 g.), was added to 50 ml. of propionic anhydride and the mixture heated at reflux temperature for one hour. The excess propionic anhydride was removed *in vacuo*. The residue was cooled to room temperature, dissolved in 5% aqueous sodium hydroxide (50 ml.), filtered and then acidified to *p*H 4 with acetic acid. The solid was recrystallized from water to give thick needles (2.5 g., 50%) of **4a**, m.p. 247°; uv, λ max (*p*H 1) 239 nm (ε, 15,680) 245 nm Sh (ε, 14,520) 265 nm Sh (ε, 6,601), (methanol) 239 nm (ε, 14,520) 246 nm Sh (ε, 12,870) 269 nm (ε, 6, 436) (*p*H 11) 246 nm (ε, 16,830).

Anal. Calcd. for $C_7H_7N_3O_2$: C, 50.91; H, 4.24; N, 25.45. Found: C, 50.99; H, 4.36; N, 25.71.

2-Phenyloxazolo[5,4-*d*]pyrimidin-7-one (**4b**).

4,6-Dihydroxy-5-aminopyrimidine hydrochloride (2b) (**3**, 2 g.) was mixed with benzoic anhydride (25 g.) and the mixture heated at 190° for one hour. The reaction mixture was cooled to room temperature and triturated with ether (200 ml.) to dissolve any unreacted benzoic anhydride. The residue was dissolved in 5% aqueous sodium hydroxide (25 ml.), solution filtered and then acidified with acetic acid to *p*H 4 to afford a pale brown solid. This solid was recrystallized from ethyl alcohol to give 1.3 g. (50%) of **4b** as needles, m.p. 320-321°.

Anal. Calcd. for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.29; N, 19.72. Found: C, 61.75; H, 2.99; N, 19.93.

7-Chloro-2-phenyloxazolo[5,4-*d*]pyrimidine (**5b**).

2-Phenyloxazolo[5,4-*d*]pyrimidin-7-one (**4b**, 4.25 g.) was mixed with phosphorus oxychloride (30 ml.) and the resulting suspension was heated at reflux temperature for 30 minutes. The excess phosphorus oxychloride was removed under reduced pressure and the residue was added cautiously to an excess of crushed ice with rapid stirring. The precipitate was collected by filtration and washed with cold water (50 ml.). The solid was crystallized from ethyl alcohol to give 3.2 g. (68%) of **5b** as light yellow needles, m.p. 152°.

Anal. Calcd. for $C_{11}H_6ClN_3O$: C, 57.03; H, 2.59; N, 18.14. Found: C, 57.09; H, 2.76; N, 18.22.

2-Phenyloxazolo[5,4-*d*]pyrimidin-7-thione (**6b**).

Sodium hydroxide (2 g.) was dissolved in 50% aqueous ethyl alcohol (100 ml.) and the resulting solution saturated with hydrogen sulfide. 7-Chloro-2-phenyloxazolo[5,4-*d*]pyrimidine (**5b**, 2.3 g.) was added to this solution and the mixture heated on a steam bath to effect a clear solution. The precipitate which began to separate from solution after 15 minutes, was collected by filtration and recrystallized from 50% aqueous alcohol to give 1.8 g. (78%) of **6b** as yellow plates, m.p. 292°.

Anal. Calcd. for $C_{11}H_7N_3OS$: C, 57.65; H, 3.06; N, 18.34. Found: C, 57.78; H, 3.02; N, 18.50.

7-Morpholino-2-methyloxazolo[5,4-*d*]pyrimidine (**7a**).

7-Chloro-2-methyloxazolo[5,4-*d*]pyrimidine (2b) (**5a**, 0.4 g.) was dissolved in anhydrous ethanol (12 ml.) containing 0.35 g. of morpholine. The solution was heated at reflux temperature for 16 hours under anhydrous conditions and then allowed to stand at room temperature for two hours. The solid which had separated was collected by filtration, washed with ethanol and recrystallized from water to give 0.5 g. (96%) of **7a** as needles, m.p. 165°.

Anal. Calcd. for $C_{10}H_{12}N_4O_2$: C, 54.55; H, 5.45; N, 25.46. Found: C, 54.59; H, 5.53; N, 25.52.

7-Morpholino-2-phenyloxazolo[5,4-*d*]pyrimidine (**7c**).

7-Chloro-2-phenyloxazolo[5,4-*d*]pyrimidine (**5b**, 1.0 g.) was dissolved in ethanol (40 ml.) containing 0.7 g. of morpholine and the resulting solution was heated at reflux temperature for 16 hours under anhydrous conditions. The solution was then evaporated to dryness and the residue was crystallized from ethanol to give 1.0 g. (82%) of **7c** as needles, m.p. 196°.

Anal. Calcd. for $C_{15}H_{14}N_4O_2$: C, 63.84; H, 4.97; N, 19.86. Found: C, 63.69; H, 5.01; N, 19.90.

7-Piperidino-2-methyloxazolo[5,4-*d*]pyrimidine (**7b**).

7-Chloro-2-methyloxazolo[5,4-*d*]pyrimidine (2b) (**5a**, 0.4 g.) was dissolved in anhydrous ethanol (12 ml.) containing 0.35 g. of piperidine. The solution was heated at reflux temperature for 15 hours under anhydrous conditions and then allowed to stand at room temperature for 2 hours. The crystals which had separated were collected by filtration and washed with cold ethanol. The filtrate was evaporated to dryness *in vacuo* and the combined product was crystallized from ethanol to furnish 0.4 g. (80%) of **7b** as needles, m.p. 121-122°.

Anal. Calcd. for $C_{11}H_{14}N_4O$: C, 60.54; H, 6.42; N, 25.68. Found: C, 60.65; H, 6.76; N, 25.89.

7-Piperidino-2-phenyloxazolo[5,4-*d*]pyrimidine (**7d**).

Same reactants and conditions as for the preparation of **7c** except that 0.7 g. of piperidine was used instead of morpholine, 0.8 g. (67%) of **7d** as needles, m.p. 131°.

Anal. Calcd. for $C_{16}H_{16}N_4O$: C, 68.57; H, 5.71; N, 20.00. Found: C, 68.54; H, 5.73; N, 20.08.

2-Methyl-7-methylthiooxazolo[5,4-*d*]pyrimidine (**8a**).

2-Methyloxazolo[5,4-*d*]pyrimidin-7-thione (2b) (**6a**, 0.5 g.) was suspended in cold water (10 ml.) and concentrated ammonium hydroxide (2 ml.) was then added with stirring to effect a clear solution.

Methyl iodide (0.5 ml.) was added and the solution stirred at room temperature for two hours. The reaction mixture was allowed to stand at 5° for 16 hours, the crystalline material which had separated was collected by filtration and washed with cold water. The solid was recrystallized from water with the aid of Norit to obtain 0.5 g. (90%) of **8a** as needles, m.p. 126°; u.v., λ max (*p*H 1) 226 nm (ε, 9,956) 285 nm (ε, 12,850) (methanol) 226 nm (ε, 9,956) 284 nm (ε, 14,120), (*p*H 11) 285 nm (ε, 13,940).

Anal. Calcd. for $C_7H_7N_3OS$: C, 46.40; H, 3.87; N, 23.20. Found: C, 46.62; H, 4.02; N, 23.42.

7-Methylthio-2-phenyloxazolo[5,4-*d*]pyrimidine (**8c**).

2-Phenyloxazolo[5,4-*d*]pyrimidin-7-thione (**6b**, 0.5 g.) was dissolved in hot 50% aqueous ethyl alcohol (100 ml.). The solution was then cooled to room temperature and treated with a few drops of ammonium hydroxide to effect a clear solution. Methyl iodide (1 ml.) was added and the procedure described for the preparation of **8a** furnished **8c** which was recrystallized from ethanol to give 0.5 g. (94%) of **8c** as needles, m.p. 158°.

Anal. Calcd. for $C_{12}H_9N_3OS$: C, 59.27; H, 3.70; N, 17.28. Found: C, 59.59; H, 3.79; N, 17.14.

7-Benzylthio-2-methyloxazolo[5,4-*d*]pyrimidine (**8b**).

2-Methyloxazolo[5,4-*d*]pyrimidin-7-thione (2b) (**6a**, 0.5 g.) was dissolved in cold water (10 ml.) containing concentrated ammonium hydroxide (2.5 ml.). To this solution was added benzyl chloride (0.5 ml.) with stirring, the solution warmed to 50° and then stirred at room temperature for an additional five hours. The reaction mixture was allowed to stand at 5° for 12 hours and the solid which had separated was collected by filtration. The solid was recrystallized from ethanol to give 0.4 g. (52%) of **8b** as needles, m.p. 66-67°.

Anal. Calcd. for $C_{13}H_{11}N_3OS$: C, 60.70; H, 4.28; N, 16.34. Found: C, 60.45; H, 4.52; N, 16.15.

7-Benzylthio-2-phenyloxazolo[5,4-*d*]pyrimidine (**8d**).

2-Phenyloxazolo[5,4-*d*]pyrimidin-7-thione (**6b**, 0.5 g.) was dissolved in 50% aqueous ethyl alcohol (100 ml.) by heating on a steam bath. The solution was cooled and a few drops of ammonium hydroxide were added to effect a clear solution. Benzyl chloride (1 ml.) was added to this solution and the reaction mixture was stirred at room temperature for five hours. The solution was then allowed to stand at 5° for 12 hours and the solid which had separated was collected by filtration. This solid was recrystallized from ethanol to give 0.5 g. (71%) of (**8d**) as needles, m.p. 176°.

Anal. Calcd. for $C_{18}H_{13}N_3OS$: C, 67.72; H, 4.08; N, 13.16. Found: C, 68.05; H, 4.19; N, 13.28.

Acknowledgment.

One of the authors (V. D. Patil) wishes to thank Dr. G. R. Revankar for his encouragement.

REFERENCES

(1) This research was supported by research grant CA-11147 from the National Institutes of Health, NCI, PHS.

(2a) E. A. Falco, G. B. Elion, E. Burgi and G. H. Hitchings, *J. Am. Chem. Soc.*, 74, 4897 (1952); (b) M. Ishidate and H. Yuki, *Chem. Pharm. Bull.* (Tokyo), 8, 137 (1960); (c) G. H. Hitchings, G. B. Elion, H. Van der Werff and E. A. Falco, *J. Biol. Chem.*, 174, 765 (1948); (d) Y. Ohtsuka, *Bull. Chem. Soc. Japan*, 43, 187 (1970).

(3a) J. P. Ferris and L. E. Orgel, *J. Am. Chem. Soc.*, 88, 3829 (1966); (b) C. C. Cheng and R. K. Robins, *J. Org. Chem.*, 21, 1240 (1956).

(4) R. L. Tolman, R. K. Robins and L. B. Townsend, *J. Am. Chem. Soc.*, 91, 2102 (1969).

(5) Several 7-aminooxazolo[5,4-*d*]pyrimidines were reported by a similar procedure after we had accomplished the synthesis of **2a-c**; see reference 2d, however, our procedure is a more facile reaction which eliminates isolation of the ethoxymethylene intermediates.

(6) The chemical shift for a methyl group on an exocyclic sulfur group will be observed at ≅δ 2.5-3.0 while a methyl group on a ring nitrogen will be observed at ≅ 3.5-4.0; see G. R. Revankar and L. B. Townsend, *J. Heterocyclic Chem.*, 5, 615 (1968).

(6a) There was observed a significant hypsochromic shift on methylation which established the site of methylation at the sulfur atom.

(7) Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. The pmr spectra were obtained on a Varian A-60 nmr spectrometer using TMS or DSS as an internal standard. Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Missouri.