SYNTHESIS OF 3-ETHYLPYRAZOLO[3,4-e][1,3]OXAZIN-5,7-DIONE, A DERIVATIVE OF A NEW HETEROCYCLIC RING SYSTEM

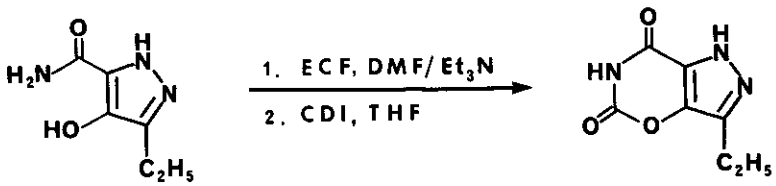
Vladimir G. Beylin and Leroy B. Townsend*

Department of Medicinal Chemistry, College of Pharmacy, and Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109-1065, USA

Abstract-The synthesis of 3-ethylpyrazolo[3,4-e][1,3]oxazin-5,7-dione, a derivative of a new ring system, by annulation of 3(5)-ethyl-4-hydroxy-5(3)-carboxamidopyrazole with ethyl chloroformate or N,N'-carbonyldiimidazole is described.

Modifications of the purine ring has furnished a number of new biologically active compounds which are structurally related to the naturally occurring purines.[1-3] The replacement of a nitrogen atom in the pyrimidine ring with an oxygen atom is of considerable interest since the 1,3-oxazine ring has been reported to exist in several naturally occurring compounds including some azolo[1,3]oxazine nucleosides.[4-6] The synthesis of certain derivatives in the azolo[1,3]-oxazine ring systems, *e.g.* several imidazo[4,5-d][1,3]oxazines[7,8] and pyrazolo[3,4-d][1,3]-oxazines[9-11] have already been reported.

We now wish to describe the first synthesis of a derivative of the new azolo[1,3]oxazine ring system, pyrazolo[3,4-e][1,3]oxazine. For our initial synthetic approach, we elected to use 3(5)-ethyl-4-hydroxy-5(3)-carboxamidopyrazole[12](1) as our starting material. However, all attempts to effect a ring annulation of 1 using standard reagents such as bromocyanogen, chloroformamidine, S-methylthiourea, etc., were unsuccessful. We subsequently found that ethyl chloro-



1 2

formate (ECF) would effect a ring closure of 1 to furnish 3-ethylpyrazolo[3,4-e][1,3]oxazin-5,7-

dione (2). For this reaction to occur, a twofold excess of ECF was added to a DMF solution of 1 (10 mmol) containing triethylamine (22 mmol) at -10°C. The reaction mixture was then heated at reflux for 2-3 h. The solvent was removed in vacuo to give a solid which was washed with 10 ml of ice cold water. The precipitate was recrystallized from 9 ml of ethanol to yield 0.85 g (75%) of 2, mp 217-220°C. A second recrystallization from ethanol, with charcoal, furnished the analytically[13] pure product 2, mp 220.5-222°C.

We subsequently found that a significant increase in the yield of 2 could be obtained by using the versatile ring closing reagent N,N'-carbonyldiimidazole (CDI). When 1 (1 mmol) and CDI (1.05 mmol) were heated at reflux in dry tetrahydrofuran under nitrogen for 4.5 h, a white precipitate was formed in approximately 15 min and then gradually redissolved. The solution was then allowed to stand at 5°C for 18 h, the precipitate was collected by filtration, washed with 4 ml of ice cold water and dried in vacuo (63°C, 0.5 mm Hg) to yield 2 (0.136 g, 75%). Recrystallization of this solid from ethanol furnished a product with mp, uv, ^{1}H-nmr, ir and Rf values essentially identical to the product obtained with ECF.

This facile ring closure using CDI to obtain new heterocyclic ring systems is under active investigation in our laboratory.

ACKNOWLEDGEMENT This work was supported by PHS Grant CA28381 awarded by the National Cancer Institute, DHHS. The authors would like to thank Ms. Deanna VanSickle for assistance in the preparation of this manuscript.

REFERENCES

1. L. B. Townsend, in "Nucleoside Analogs, Chemistry, Biology, and Medical Applications", Plenum Press, N.Y., 1979, p. 193.

2. R. K. Robins, in "Heterocyclic Compounds", 8, p. 162, 393, John Wiley, Inc., N.Y., (1967).

3. T. D. Miniker and M. N. Preobrazhenskaya, "Chemistry of Heterocyclic Compounds" (Engl. Transl.), 17, 97 (1981).

4. M. Ohno, in "Medicinal Chemistry, A Series of Monographs", 16, p. 73, Academic Press (1980).

5. Z. Eckstein and T. Urbanski, in "Advances in Heterocyclic Chemistry", 23, p. 50, Academic Press, Inc. (1978).

6. H. Nakamura, N. Yagisawa, N. Shimada, T. Takita, H. Umezawa and Y. Iitaka, J. Antibiot., 34, 1219 (1981).

7. P. C. Srivastava, G. A. Ivanovics, R. J. Rousseau and R. K. Robins, J. Org. Chem., 40, 2920 (1975).

8. N. Yagisawa, T. Takita, H. Umezawa, K. Kato and N. Shimada, Tetrahedron Lett., 931

(1983).

9. P. Klaus, K. Kollhoff, Ger.(East)DD148, 778 (1981), C.A. 96, 6742x (1982).

10. F. L. Merchan, Synthesis, 965 (1981).

11. B. Chantegreland S. Gelin, Synthesis, 584 (1979).

12. P. F. Crain, J. A. McCloskey, A. F. Lewis, K. H. Schram and L. B. Townsend, J. Heterocycl. Chem., 10, 843 (1973).

13. UV, λ max,nm(ξ): (pH 1) 232 (8900), 269(4170); (pH 7) 232 (8900), 269(4100); (pH 11) 242 (13200), 265 (sh, 5800). IR (KBr, cm^{-1}):3250, 3000-2900, 1760, 1625. ^{1}H-NMR (DMSO-d_6): δ 13.95 (s, 1H, N_1-H); 11.88 (s, 1H, N_6-H); 2.76 (q, 2H, CH_2); 1.30 (t, 3H, CH_3). Ms(m/z): 181 (M), 138, 109, 83, 70, 55. R_f by tlc 0.76 (CH_2Cl_2: CH_3OH/5:1/v:v). Anal. Calcd. for $C_7H_7N_3O_3$: C,46.40; H,3.87; N,23.20. Found: C,46.37; H,4.06; N,22.98.

Received, 2nd April, 1984