# SYNTHESIS OF PYRROLO[2,3-b]AZEPIN-4-ONE DERIVATIVES

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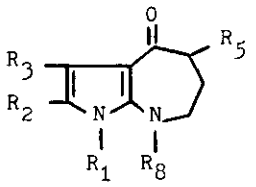
Abstract - The Dieckmann reaction has been successfully applied for the first time in the synthesis of pyrrolo[2,3-b]azepin-4-ones.

As part of a program to prepare potential antineoplastic[2] and antimalarial agents, we became interested in the synthesis of various substituted pyrrolo-[2,3-b]azepines (1), which could possibly act as antimetabolites of riboflavin. In contrast to the numerous reports[3,4] which have appeared for the



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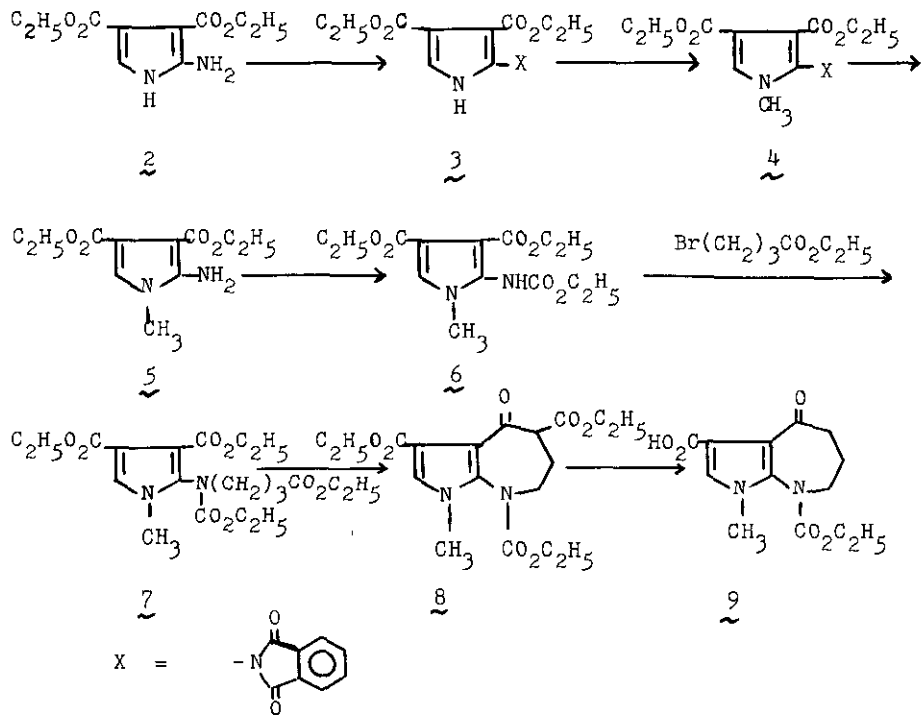
synthesis of benzazepines, few references are prevalent for preparation of pyrroloazepines. Synthesis of several pyrroloazepinones was accomplished by Beckmann[5-8] or Schmidt[9] type ring-enlargement reactions on the corresponding pyrrolocyclohexanones. Intramolecular cyclization of amino esters has also been employed to yield pyrroloazepinones.[10,11]

The Dieckmann reaction[12] does not appear to have been utilized in the synthesis of pyrroloazepinones. Scheme I outlines a route which can be utilized to synthesize various substituted derivatives of 1. 2-Amino-3,4-dicarbethoxypyrrole (2) was prepared by the method of Gewald and co-workers.[13] 1-Methyl-2-amino-3,4-dicarbethoxypyrrole (5) was obtained by preparation of the phthalimido derivative (3), N-1 alkylation with methyl iodide in presence of potassium tert-butoxide (4), and hydrazinolysis (5).[14] To overcome the poor nucleophilicity associate with the 2-amino group[2] in 5, this nitrogen atom

SCHEME I.



may be activated toward alkylation by converting 5 to the acetyl, tosyl, or carbethoxy derivatives (6). The latter compound was alkylated with ethyl 4-bromobutyrate in the presence of sodium hydride, and the intermediate 7 was cyclized under Dieckmann conditions to yield the pyrrolo[2,3-b]azepin-4-one (8). Room temperature hydrolysis by dilute acid or sodium hydroxide led to compound 9. Hydrolysis of the carbamate requires more severe conditions,[15] but this investigation was not explored in the present study. Further studies utilizing the procedure successfully applied in this report for the synthesis of the pyrrolo[2,3-b]azepin-4-one should consider the use of a variety of substituents in order to establish meaningful structure-activity relationships.

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 467 Grating Spectrophotometer. The nmr spectra were determined on a Hitachi

Perkin-Elmer R20 A High Resolution nmr spectrometer using tetramethylsilane (TMS) as internal reference. Mass spectra were determined on a Dupont 21-490 mass spectrometer. Elemental analyses were determined by Atlantic Microlab, Inc., Atlanta, Georgia.

2-Carbethoxyamino-3,4-dicarbethoxy-1-methylpyrrole (6)

To a solution of 2-amino-3,4-dicarbethoxy-1-methylpyrrole 5[14] (6g, 0.025 mol) and N,N-dicyclohexylmethylamine (4.9g, 0.025 mol) in 200 ml of dry benzene was added ethyl chloroformate (3g, 0.027 mol) in one portion. The mixture was heated at 90°C for 16 h. After cooling, the N,N-dicyclohexylmethylamine hydrochloride was filtered, and the benzene solution was washed with water and dried over sodium sulfate. After removal of the benzene in vacuo, the crude product was recrystallized from benzene-petroleum ether (30-60°C) to yield a white fluffy solid (5.2g, 67%); mp 65-67°C; ir (KBr): 3300, 2995, 1735, 1060, 780 $cm^{-1}$, nmr ($CDCl_3$): δ 7.40 (s, 1H, NH at C-2), 7.05 (s, 1H, H at C-5), 4.2 - 4.3 (3q, 6H, $CH_2$'s of esters), 3.56 (s, 3H, $NCH_3$), 1.34 (t, 6H, $CH_3$'s of esters at C-3,4), 1.3 (t, 3H, $CH_3$ of C-2 ester); Anal. for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.97. Found: C, 53.75; H, 6.49; N, 8.96.

2-[N-Carbethoxy-N-(3-carbethoxypropyl)]amino-3,4-dicarbethoxy-1-methylpyrrole (7)

Sodium hydride (0.68g, 14 mmol of 50% oil dispersion) and 6 (4g, 12.8 mmol) in 200 ml of dry xylene was heated for 0.5 h under a nitrogen atmosphere. Ethyl 4-bromobutyrate (2.75g, 14 mmol) was added and the mixture was refluxed for 16 h. After cooling, 2 ml of acetic acid in 200 ml of water was added. The xylene layer was separated, dried over magnesium sulfate, and removed in vacuo. The crude oil was purified on a silica gel column eluted with 40% chloroform/60% hexane (yield: 55-61%); ir (neat): 2980, 1730, 1540, 875 $cm^{-1}$; nmr ($CDCl_3$): δ 7.15 (s, 1H, H at C-5); 4.2 - 4.3 (m, 8H, $CH_2$'s of esters), 3.56 (t, 2H, N-$CH_2$ at C-2), 3.5 (s, 3H, N-$CH_3$), 2.25 and 1.9 (m, 4H, N-C-$CH_2CH_2$ at C-2), 1.22 - 1.32 (m, 9H, $CH_3$'s of esters); Anal. Calcd. for $C_{20}H_{30}N_2O_8$: C, 56.33; H, 7.09; N, 6.50. Found: C, 56.19; H, 7.11; N, 6.50.

3,5,8-Tricarbethoxy-1-methylpyrrolo[2,3-b]azepin-4-one (8)

Sodium hydride (1.6g, 0.033 mol of 50% oil dispersion) was placed in a 200 ml

three necked round-bottomed flask, washed four times with anhydrous ether, and covered with 10 ml of dry benzene. Compound 7 (8.5g, 0.02 mol) in 40 ml of dry benzene was added to the refluxing solution of sodium hydride under a nitrogen atmosphere. The reaction mixture was heated at 85-90°C in an oil-bath for 12 h. After cooling, 5 ml of acetic acid in 50 ml of benzene was added to the mixture, followed by 100 ml of water. The benzene layer was separated and the water layer was extracted with benzene. The combined benzene layers were concentrated in vacuo to yield a slightly brown oil (7g). This layer was purified on a silica gel column eluted with petroleum ether (30-60°C), benzene, and chloroform. The benzene fraction gave the major cyclized product (5g, 66%). The oil was crystallized from benzene-petroleum ether; mp 102-103°C; ir (neat): 2980, 1720, 1540, 1450 $cm^{-1}$; nmr ($CDCl_3$): δ 12.64 (s, 1H, enolic C-4 OH), 7.18 (s, 1H, H at C-2), 4.26 (q, 6H, $CH_2$'s of esters), 3.7 (m, 2H, $CH_2$ at C-7), 3.48 (s, 3H, $NCH_3$), 2.7 - 2.0 (m, 2H, $CH_2$ at C-6), 1.32 and 1.28 (2t, 9H, $CH_3$'s of esters); mol. wt. (ms) Calcd 380. Found: 380; Anal. Calcd for $C_{18}H_{24}N_2O_7$: C, 56.82; H, 6.36; N, 7.39. Found: C, 56.81; H, 6.38; N, 7.37.

8-Carbethoxy-1-methylpyrrolo[2,3-b]azepin-4-one-3-Carboxylic Acid (9)

The pyrroloazepinone 8 (3.3g, 8.6 mmol) was stirred at room temperature for 24 h with 300 ml of 0.2N sodium hydroxide. The basic solution was washed with 50 ml of chloroform and then acidified with dilute hydrochloric acid. The acidic solution was extracted with chloroform. After evaporation of the chloroform in vacuo, the residue was crystallized from benzene-petroleum ether (30-60°C) to yield fine needle crystals (1.6g, 66%); mp 174-175°C; ir (KBr): 2950, 2500, 1695, 1590, 1440, 750 $cm^{-1}$; nmr ($CDCl_3$): δ 14.1 (broad s, 1H, COOH), 7.37 (s, 1H, H at C-2), 4.3 (q, 2H, $CH_2$ of ester), 3.62 (s, 3H, $NCH_3$), 2.7 (m, 6H, $CH_2$'s at C-5, C-6, C-7), 1.3 (t, 3H, $CH_3$ of ester); Anal. Calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.96. Found: C, 55.88; H, 5.79; N, 9.96.

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REFERENCES

1. Taken in part from the thesis submitted by M.M. Vora to the Graduate School of the University of Georgia in partial fulfillment of the requirement for the Ph.D. degree, August, 1978.
2. R.F. Koebel, L.L. Needham, and C.D. Blanton, Jr., J. Med. Chem., 18, 192 (1975).
3. J.A. Moore and E. Mitchell, in "Heterocyclic Compounds," Vol. 9, R.C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N.Y., 1967, p. 224.
4. S. Kasparek, in "Advances in Heterocyclic Chemistry," Vol. 17, A.R. Katritsky and A.J. Boulton, Eds., Academic Press, Inc., New York, N.Y., 1974, p. 45.
5. A.P. Stoll and E. Troxler, Helv. Chim. Acta, 51, 1864 (1968).
6. M.J. Weiss, G.J. Gibs, J.F. Poletto and W.A. Remers, U.S. Patent 3,758,501 (1973); Chem. Abstr., 79, 115550c (1973).
7. M.J. Weiss, G.J. Gibs, J.F. Poletto and W.A. Remers, U.S. Patent 3,846,446 (1974); Chem. Abstr., 82, 57663r (1975).
8. M.J. Weiss, G.J. Gibs, J.F. Poletto and W.A. Remers, U.S. Patent 3,849,441 (1974); Chem. Abstr., 82, 72969p (1975).
9. J.B. Hester, Jr., U.S. Patent 3,824,230 (1974); Chem. Abstr., 82, 43482u (1975).
10. W. Flitsch, B. Müter, and U. Wolf, Chem. Ber., 106, 1993 (1973).
11. A.R. Battersby, J.F. Beck and E. McDonald, J. Chem. Soc., Perkin Trans. I, 160 (1974).
12. J.P. Schaefer and J.J. Bloomfield, in "Organic Reactions," Vol. 15, R. Adams, Ed., John Wiley and Sons, Inc., New York, N.Y., 1967, p. 1.
13. K. Gewald, M. Kleinert, B. Thiele and M. Hentschel, J. Prakt. Chem., 314, 303 (1972).
14. M.M. Vora, C.S. Yi, C. DeWitt Blanton, Jr., J. Heterocycl. Chem., submitted.
15. T.S. Moore, M. Boyle, and V.M. Thorn, J. Chem. Soc., 39 (1929).

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