Tetrahedron Vol. 43, No. 6, pp. 1157 to 1160, 1987
Printed in Great Britain.

0040-4020/87 $3.00 + .00
Pergamon Journals Ltd

SYNTHESIS OF PARTIALLY SATURATED DIPYRIDO[1,2-a:4,3-d] PYRIMIDIN-11-ONES VIA CATALYTIC HYDROGEN-TRANSFER REACTION[1]

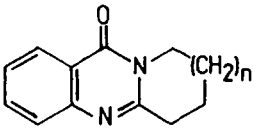
FERENC FÜLÖP, IMRE HUBER, GYÖRGY DOMBI and GÁBOR BERNÁTH*

Institute of Pharmaceutical Chemistry, University Medical School, H-6720 Szeged, Eötvös u. 6, Hungary

(*Received in UK* 11 *February* 1987)

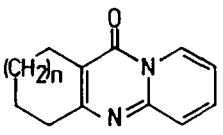
Abstract - 1,2,3,4-Tetrahydrodipyrido[1,2-a:4,3-d]pyrimidin-11-ones (2-azapyracridones), a novel type of heterocycles, were synthesized by cyclization of 2-amino-6-methylpyridine with 3-methoxycarbonyl-4-piperidone or its N-benzyl derivative. In the presence of palladium-on-carbon under mild conditions, the 2-azapyracridones undergo intermolecular hydrogen-transfer reactions. The product distributions can be shifted by applying solvents of proton donor or proton acceptor character; in this way, three differently saturated members of this ring system were prepared.

6,7,8,9-Tetrahydropyrido[2,1-b]quinazolin-11-ones, i.e. the pyracridones,[2] and their ring C homologues (1) are alkaloids occurring in a number of plants.[3-5] Syntheses of type 2 analogues and their ring A homologues have been achieved through the cyclization of alicyclic β-ketocarboxylates with 2-aminopyridines.[6-11] Several of these compounds have proved to display significant analgetic and antiasthmatic effects.[11,12] Recently, partially or fully saturated stereoisomeric derivatives of compounds 2 were synthesized and subjected to spectroscopic and X-ray diffraction structure analyses.[13-16]



n = 0, 1, 2

1

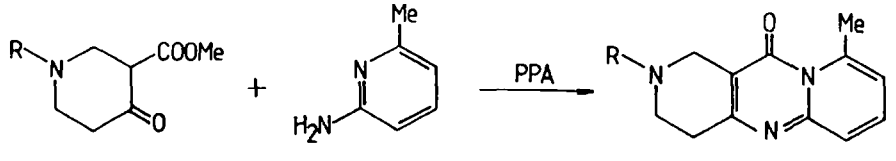


n = 0, 1, 2, 3

2

A number of recent publications have been concerned with analogues of 1 and 2 containing an additional hetero atom in ring A[17-19] or C[20,21]. Continuing our synthetic and stereochemical studies[6,7,12-16] on compounds of type 2, we set out to synthesize dipyrido [1,2-a:4,3-d]pyrimidin-11-ones, i.e. the hitherto unknown 2-azapyracridone ring system (3).

The syntheses were performed in good yields by the cyclization of 3-methoxycarbonyl-4-piperidone[22] or its N-benzyl derivative[23] with 2-amino-6-methylpyridine in the presence of polyphosphoric acid (PPA).

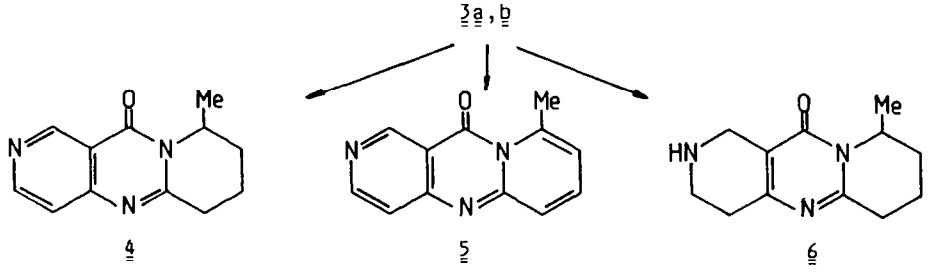


3a: R = H
3b: R = CH_2Ph

In the course of the debenzylation, and also in order to prepare aromatic derivatives, the reactions of 3a,b in the presence of palladium-on-carbon in xylene

were investigated. Surprisingly, the N-unsubstituted 3a gave not the expected aromatic compound 5, but the 6,7,8,9-tetrahydro derivative 4. Under similar conditions, the N-benzyl derivative 3b furnished a mixture of the aromatic (5) and the C-ring saturated (4) compounds.

The above reaction, involving a high yield, is one of the rare hydrogen-transfer reactions in which one part of the molecule (ring A) acts as hydrogen donor, and another part (ring C) as hydrogen acceptor.[24-27]



4 5 6

Under identical conditions, 9-methyl-1,2,3,4-tetrahydropyrido[2,1-b]quinazolin-11-one[6] (2, n = 1, 9-CH_3) did not undergo any change. However, when the reaction was carried out with a 1:1 mixture of 2 (n = 1, 9-CH_3) and the dihydropyrimidinone 3b, ^{1}H NMR study of the crude product revealed the presence of about 15% of 9-methyl-1,2,3,4,6,7,8,9-octahydropyrido[2,1-b]quinazolin-11-one,[6,28] which is evidence of the intermolecular mechanisms of the catalytic hydrogen-transfer observed.

When the reaction of 3 was performed in nitrobenzene, acting as hydrogen acceptor, the product distributions were shifted towards the formation of 5 (Table 1).

Table 1. Product districations in the reactions of 3a,b and 6 with palladium-on-carbon

Starting compound	Solvent	Product distribution 4	5	6
3a	xylene	1	0	0
3b	xylene	0.4	0.6	0
3a	nitrobenzene	0	1	0
3b	nitrobenzene	0.2	0.8	0
3a	cyclohexene	0.8	0	0.2
3b	cyclohexene	1	0	0
6	xylene	1	0	0

In contrast, when a hydrogen donor, e.g. cyclohexene, was used, the main product was 4, the 6,7,8,9-tetrahydro derivative. The results of experiments in nitrobenzene and cyclohexene provide evidence of the intermolecular pathway of the catalytic hydrogen-transfer. The crude product of the reaction of 3a in cyclohexene contained about 20% of the octahydro derivative 6. The latter was readily obtainable by the catalytic hydrogenation of 3a and gave 4 on heating in the presence of palladium-on-carbon in xylene.

Accordingly, through appropriate utilization of this hydrogen-transfer reaction in suitably selected solvent of proton donor or proton acceptor character, three differently saturated variants of the new dipyrido[1,2-a:4,3-d]pyrimidine ring system can be synthesized.

EXPERIMENTAL

Melting points are uncorrected and were determined on a Boetius micro melting point apparatus. IR spectra were determined in KBr pills on a Unicam SP 200 spectrometer. ^{1}H NMR spectra were recorded at room temperature in $CDCl_3$ solution on a Bruker WM-250 FT instrument, with TMS as internal standard.

9-Methyl-1,2,3,4-tetrahydro-11H-dipyrido[1,2-a:4,3-d]pyrimidin-11-one (3a)

2-Amino-6-methylpyridine (1.08 g, 0.01 mol) and 3-methoxycarbonyl-4-piperidone hydrochloride (1.94 g, 0.01 mol) were heated in polyphosphoric acid (10 g) (Fluka)

for 6 h, with stirring, in an oil-bath at 120 °C. The mixture was cooled to about 70 °C and water (10 ml) was added. After neutralization with 10% NaOH solution, the product was extracted with $CHCl_3$ (4x100 ml). The combined extract was dried (Na_2SO_4) and evaporated to afford pale-yellow crystals of 3a (1.85 g, 86%). mp 134-135 °C (ethyl acetate). ^{1}H NMR δ1.88 (1H, s, NH), 2.74 (2H, t, H_2-4, $J_{3,4}$ = 5.85 Hz),[29] 3.05 (3H, s, CH_3-9), 3.18 (2H, t, H_2-3, $J_{3,4}$ = 5.85 Hz),[30] 3.86 (2H, s, H_2-1), 6.58 (1H, d, H-8, $J_{7,8}$ = 7.50 Hz), 7.27 (1H, d, H-6, $J_{6,7}$ = 9.01 Hz), 7.35 (1H, dd, H-7, $J_{6,7}$ = 9.01, $J_{7,8}$ = 7.50 Hz). IR 1690 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.76; H, 6.22; N, 19.73.

In a similar procedure, 3b was prepared from 1-benzyl-3-methoxycarbonyl-4-piperidone hydrochloride. After neutralization, the required compound crystallized (66%). mp 146-147 °C (ethyl acetate). ^{1}H NMR δ2.80 (2H, 6, H_2-4, $J_{3,4}$ = 5.80 Hz),[29] 2.85 (2H, 6, H_2-3, $J_{3,4}$ = 5.80 Hz),[28] 3.02 (3H, s, CH_3-9), 3.55 (2H, s, $CH_2C_6H_5$), 3.76 (2H, s, H_2-1), 6.56 (1H, dd, H-8, $J_{7,8}$ = 7.10 Hz, $J_{6,7}$ = 0.89 Hz), 7.28 (1H, dd, H-6, $J_{6,7}$ = 9.09 Hz, $J_{6,8}$ = 0.89 Hz), 7.3 (5H, m, $CH_2C_6H_5$), 7.38 (1H, dd, H-7, $J_{6,7}$ = 9.09 Hz, $J_{7,8}$ = 7.10 Hz). IR 1680 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 75.01; H, 6.41; N, 13.66.

Reactions of compounds 3a, 3b and 6 in the presence of palladium-on-carbon

The 11H-dipyrido[1,2-a:4,3-d]pyrimidin-11-one derivative 3a, 3b or 6 (0.5 g) was refluxed for 7 h in the presence of 10% palladium-on-activated carbon (0.25 g) in xylene, cyclohexene or nitrobenzene, respectively (15 ml). After removal of the catalyst by filtration, the solvent was evaporated under reduced pressure to afford crystalline products. The total yields were between 65 and 78%; product distributions were determined by ^{1}H NMR spectroscopy (Table 1) 4: mp 117-119 °C (diisopropyl ether). ^{1}H NMR 1.41 (3H, d, CH_3-9, J = 6.61 Hz),[30] 2.0 (4H, m, H_2-7, H_2-8),[31] 3.0 (2H, m, H_2-6),[31] 5.09 (1H, m, H-9), 7.39 (1H, d, H-4, $J_{3,4}$ = 5.73 Hz), 8.77 (1H, dd, H-3, $J_{3,4}$ = 5.73 Hz, $J_{1,3}$ = 0.79 Hz), 9.46 (1H, d, H-1, $J_{1,3}$ = 0.79 Hz). IR 1660 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.76; H, 6.34; N, 19.66.

5: mp 125-126 °C (diisopropyl ether). ^{1}H NMR δ2.54 (3H, s, CH_3-9), 6.74 (1H, d, H-8, $J_{7,8}$ = 7.98 Hz), 6.84 (1H, d, H-6, $J_{6,7}$ = 7.62 Hz), 7.54 (1H, dd, H-7, $J_{6,7}$ = 7.62 Hz, $J_{7,8}$ = 7.98 Hz), 8.43 (1H, d, H-4, $J_{3,4}$ = 6.24 Hz), 8.77 (1H, d, H-3, $J_{3,4}$ = 6.24 Hz), 9.07 (1H, s, H-1).[32] IR 1680 (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.08; H, 4.41; N, 19.74.

9-Methyl-1,2,3,4,6,7,8,9-octahydro-11H-dipyrido[1,2-a:4,3-d]pyrimidin-11-one (6)

9-Methyl-1,2,3,4-tetrahydro-11H-dipyrido[1,2-a:4,3-d]pyrimidin-11-one (3a) (0.5 g) was dissolved in methanol (50 ml) and hydrogenated in the presence of palladium-on-carbon (0.1 g) at ambient temperature and atmospheric pressure. After absorption of the calculated volume of hydrogen (2 h), the catalyst was removed by filtration, and the filtrate was evaporated to give the crystalline octahydro derivative 6 (0.47 g, 92%). mp 105-108 °C (diisopropyl ether). ^{1}H NMR δ1.36 (3H, d, CH_3-9, J = 6.6 Hz),[30] 1.95 (4H, m, H_2-7, H_2-8), 2.63 (2H, t, H_2-4, $J_{3,4}$ = 5.80 Hz), 2.8-3.0 (2H, m, H_2-6), 3.15 (2H, t, H_2-3, $J_{3,4}$ = 5.80 Hz), 3.83 (2H, s, H_2-1), 4.96 (1H, m, H-9). The NMR spectrum of 6 suggests a rapid conformational motion for ring A (equivalent methylene protons) and a stable, fixed conformation for ring C. This means that the conformationally stable position of the hetero atom in the ring (a bridgehead nitrogen attached to a planar ring) and the methyl substituent at position 9 make the ring conformationally stable. Rings with the hetero atom at other positions are conformationally labile, even when a bulky substituent is present (e.g. N-benzyl, 3b). IR (C=O) cm^{-1}. Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.72; H, 7.82; N, 19.16. Found: C, 65.54; H, 8.01; N, 19.34.

Acknowledgements

The authors wish to thank the CHINOIN Chemical and Pharmaceutical Works Ltd., Budapest, Hungary, for financial support. Thank are due to Prof. Z. Mészáros, Dr. I. Hermecz (CHINOIN) and Dr. J. A. Szabó (József Attila University, Szeged, Hungary) for valuable discussions.

REFERENCES AND NOTES

1. This paper is regarded as Part 86 of the series "Saturated Heterocycles", Part 85: K. Pihlaja, P. Vainiotalo, G. Bernáth, Gy. Göndös, L. Gera, Org. Mass. Spectrom., 21, 55 (1986).
2. M. Davis, R. J. Hook, W. Y. Yu, J. Heterocyclic Chem., 21, 369 (1984).
3. T. Kametani, C. V. Loc, T. Higa, M. Koizumi, M. Ihara, K. Fukumoto, J. Am. Chem. Soc., 99, 2306 (1977).
4. T. Kametani, T. Higa, C. V. Loc, H. Ihara, M. Koizumi, K. Fukumoto, Ibid., 98, 6186 (1976).

5. W. L. F. Armarego, Quinazolines Part I. (In series: "Fused Pyrimidines") Interscience Publishers, New York, 1968.
6. G. Bernáth, F. Fülöp, I. Hermecz, Z. Mészáros, G. Tóth, J. Heterocyclic Chem., 16, 137 (1979).
7. F. Fülöp, G. Bernáth, I. Hermecz, Z. Mészáros, Acta Phys. Chem. Szeged, 25, 79 (1979).
8. Y. Halleux, H. G. Viehe, J. Chem. Soc. C, 1970, 881.
9. K. Bowden, T. H. Brown, Ibid., 1971, 2163.
10. H. L. Yale, J. Heterocyclic Chem., 14, 207 (1977).
11. C. F. Schwender, B. R. Sunday, D. J. Herzig, J. Med. Chem., 22, 114 (1979).
12. I. Hermecz, F. Fülöp, Z. Mészáros, G. Bernáth, J. Knoll, Ger. Pat. 2836449; Chem. Abstr., 91, 57048 (1979).
13. G. Bernáth, G. Tóth, F. Fülöp, Gy. Göndös, L. Gera, J. Chem. Soc. Perkin Trans. 1, 1979, 1675.
14. F. Fülöp, R. Simon, G. Tóth, I. Hermecz, Z. Mészáros, G. Bernáth, Ibid., 1982, 2801.
15. K. Simon, I. Hermecz, Z. Mészáros, F. Fülöp, G. Bernáth, G. Tóth, G. Reck, J. Chem. Soc. Perkin Trans. 2, 1986, 551.
16. G. Tóth, F. Fülöp, G. Bernáth, R. Simon, I. Hermecz, Z. Mészáros, Ibid., 1983, 237.
17. P. C. Unangst, J. Heterocyclic Chem., 20, 495 (1983).
18. C. F. Schwender, B. R. Sunday, J. J. Kerbleski, D. J. Herzig, J. Med. Chem., 23, 964 (1980).
19. T. George, D. V. Mehta, D. A. Dabholkar, J. Org. Chem., 36, 2192 (1971).
20. F. J. Tinney, W. A. Cetenko, J. J. Kerbleski, D. T. Connor, R. J. Sorenson, J. Med. Chem., 24, 878 (1981).
21. D. T. Connor, R. J. Sorenson, F. J. Tinney, W. A. Cetenko, J. J. Kerbleski, J. Heterocylic Chem., 19, 1185 (1982).
22. M. J. Bishop, Z. Naturforsch., 25b, 1249 (1970).
23. S. Morosawa, Bull. Chem. Soc. Jap., 31, 418 (1959).
24. G. Brieger, T. J. Nestrick, Chem. Reviews, 74, 567 (1974).
25. R. A. W. Johnstone, A. H. Wilby, I. D. Entwistle, Chem. Reviews, 85, 129 (1985).
26. I. Ya. Postowskii, O. N. Chupakhin, A. I. Matern, Khim. Get. Soed., 1984, 1299.
27. F. Fülöp, G. Bernáth, Heterocycles, 23, 3095 (1985).
28. I. Hermecz, B. Podányi, Z. Mészáros, G. Tóth, J. Heterocyclic Chem., 16, 137 (1979).
29. The chemical equivalence of the protons in the methylene groups suggests that in the saturated ring there is a rapid conformational motion averaging the different shielding effects of the axial and equatorial protons.
30. The δ-value for the signal of the 9-methyl group (~1.4 ppm) (split to a doublet) is characteristic of a saturated ring.
31. The complicated second-order spectrum of the saturated ring means that there is a fixed conformation for this part of the molecule due to the planar ring systems and the attached methyl group.
32. A typical value for an α-proton in a pyridine ring with a large shielding effect of the carbonyl group.