SOME NUCLEOPHILIC SUBSTITUTIONS IN THE 2,4-DIMETHOXYPYRIDO-[3,2-d]PYRIMIDINES

Hassan M. Eisa, Said M. Bayomi*, Abdel-Kader M. Ismaiel, and Mohamed M. El-Kerdawy

Department of Medicinal Chemistry, Faculty of Pharmacy, University of Mansoura, Mansoura, Egypt

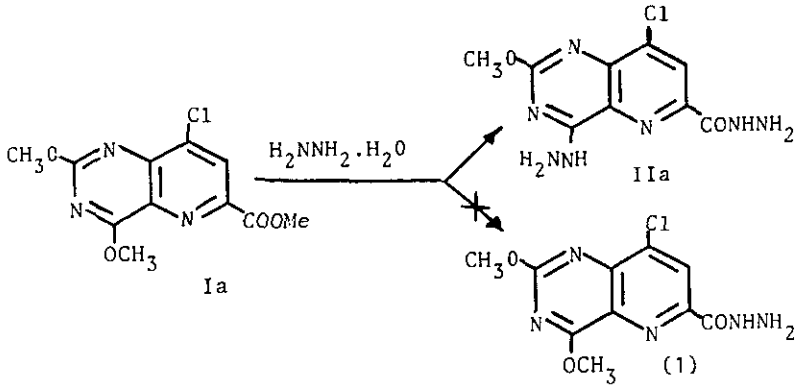
Abstract— Study of the reactivity of substituted pyrido[3,2-d]-pyrimidines (Ia,b), towards nucleophilic substitution reactions revealed that the methoxy substituents at 4- as well as of the ester moiety at 6-positions are readily susceptable to nucleophilic displacement. The observed selectivity enabled the preparation of 4-hydrazino-6-acid hydrazides (IIa,b). Confirmation for formation of (IIa,b) has been done by their reaction with different carbonyl compounds to give the respective hydrazones (IIIa-i) or by reaction with nitrous acid to afford the corresponding 4-azido-6-acid azides, which underwent ring closure with the formation of tetrazole ring derivatives (IVa,b). The synthesized compounds were confirmed by elemental analyses, ^{1}H NMR and mass spectral data.

Since 1945, there has been great efforts involving the synthesis and investigation of biological activity of condensed pyrimidine ring systems[1-5]. Derivatives of these compounds have been extensively studied for their importance as antagonist of the heterocyclic constituents of nucleic acid[2,3] and folic-folinic acid family of vitamines[4-5]. Recently, various pyridopyrimidines have been claimed to be the main precursor in the synthesis of anticancer chemotherapeutic agents[6-8]. It has been reported that, reaction of 5-methoxycarbonyl-2,4,7-trichloropyrido[2,3-d]pyrimidine with ethanolic ammonia gave the corresponding 4-amino-5-carboxamido-2,7-dichloro derivative[9]. Further studies on the same trichloro intermediate revealed that, the reactivity of this compound towards nucleophilic substitution reaction were in the order 4>7>2[9]. Moreover, reaction of 6-methoxycarbonyl-2,4,8-trichloropyrido[3,2-d]-pyrimidine with sodium methoxide or with sodium azide afforded the corresponding

2,4-dimethoxy-8-chloro[7] or 2,4-diazido-8-chloro[8] derivative respectively, indicating that, 2- and 4-positions are more reactive towards nucleophilic substitution reactions than 8-position in the 2,4,8-trichloropyrido[3,2-d]pyrimidie . It has also been demonstrated that, in case of dichloro and dimercaptoquinazoline[10], pyrido[2,3-d]pyrimidines[1] or pyrido[3,2-d]pyrimidines[11], the 4-substituent underwent nucleophilic displacement much more readily than 2-position.

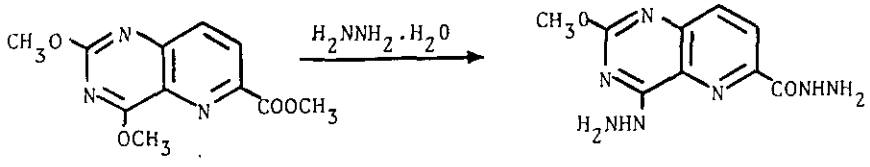
The above findings promote the author's interest in studying and investigating the reactivity of substituted pyrido[3,2-d]pyrimidines towards nucleophilic substitution reactions when there are present methoxy substituents at 2- and 4-positions.

6-Methoxycarbonyl-2,4-dimethoxypyrido[3,2-d]pyrimidine derivatives (Ia,b) were prepared according to the reported procedures[7]. Reaction of 6-methoxycarbonyl-2,4-dimethoxy-8-chloropyrido[3,2-d]pyrimidine (Ia) with hydrazine hydrate in absolute ethanol gave a single new compound in 99% yield, which may assign structure (1) or IIa, both being consistent with molecular weight 284.



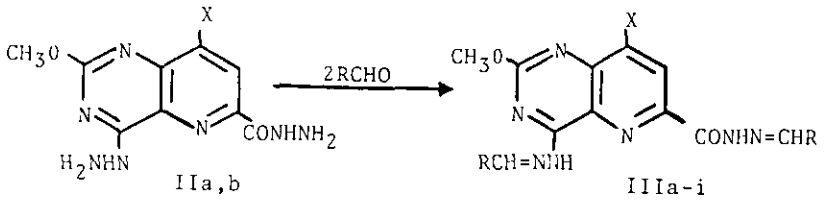
Ia IIa (1)

The obtained compound was determined to be structure IIa on the basis of elemental analysis of its nitrogen contents. For comparative study, the treatment of 6-methoxycarbonyl-2,4-dimethoxypyrido[3,2-d]pyrimidine (Ib) with hydrazine hydrate as above, afforded a single compound assigned with structure IIb as was confirmed from the correct microanalytical data.



Ib IIb

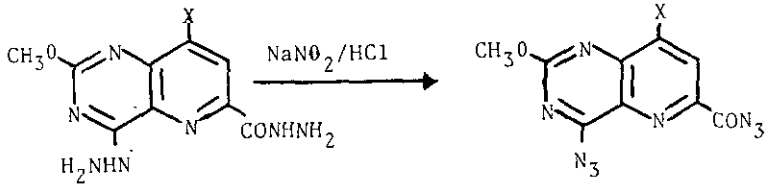
This means that such reaction allowed selective displacement of 4-methoxy group together with that of the ester moiety at position-6, leaving 2- and 8-positions intact. Unequivocal evidence for the existance of IIa,b was provided by their reaction with different aldehydes to give the respective hydrazones (IIIa-i). the structures of compounds III were confirmed by ^{1}H NMR and mass spectroscopy as well as elemental analyses. The presence of chlorine atom in IIIc was varified by the appearance of peaks at m/z 491 and 493 in the ratio of 3:1 for M^+, due to the isotope abundance of chlorine. Peaks were also present for loss of two-C_7H_5NO radicals at (M-119) and (372-119), which confirmed that two equivalents of carbonyl compound have reacted with II to give the corresponding hydrazones III. ^{1}H NMR spectroscopy of IIIb and IIIe confirmed the presence of an O-methyl group in both compounds respectively at δ 3.98 and δ 4.00.



IIa,b IIIa-i

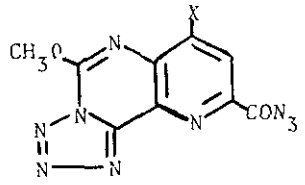
Comp. No.	X	R
a	Cl	p-ClC_6H_4-
b	Cl	o-$NO_2C_6H_4$-
c	Cl	o-OHC_6H_4-
d	Cl	p-$OCH_3C_6H_4$-
e	Cl	C_6H_5CH=CH-
f	H	o-ClC_6H_4-
g	H	m-$NO_2C_6H_4$-
h	H	o-OHC_6H_4-
i	H	p-$OCH_3C_6H_4$-

The selective replacement of the 4-methoxy in Ia,b with hydrazino moiety was further evidenced by reaction of IIa,b with nitrous acid. Thus treatment of IIa or IIb with sodium nitrite in the presence of hydrochloric acid resulted in the formation of 4-azido-6-acid azides, which undergo ring closure with the formation of tetrazole ring derivatives (IVa,b), in the same manner as that reported by Monge Vega et al.[12], and when 3-hydrazinopyridazines are subjected to nitrosation with aqueous hydrochloric acid and sodium nitrite to afford tetrazolo[1,5-b]pyridazines[13].



IIa,b

IVa; X=Cl
b; X=H



IVa,b

The mass spectrum of IVb supported the structural assignment with the molecular ion peak at m/z 271 (M^+). A peak at (M-42) corresponding to the loss of N_3 further supports the stability of the acid azide moiety. The appearance of a peak at (M-123) gave an evidence for the ring closure and existance of the condensed tetrazole ring system.

EXPERIMENTAL

Melting points were recorded on an electrothermal melting point apparatus (Fisher-Johns) and are uncorrected. ^1H NMR spectra were recorded on an IBM FT-200 NMR spectrometer in DMSO-d_6. Mass spectra were taken on a Varian 1125 spectrometer. Statisfactory elemental analysis for C,H and N was obtained for all compounds.

2-Methoxy-4-hydrazinopyrido[3,2-d]Pyrimidine-6-Carbohydrazides (IIa,b):

Hydrazine hydrate (5 g, 0.1 mol) was added to a suspension of Ia or Ib (0.01 mol. in ethanol (100 ml). The reaction mixture was raised to boil and then allowed to set aside for 3 h with occasional shaking. The separated solid product was filtered off, dried and crystallized from water[14].

2'-(Arylmethylene)-4-(arylmethylenehydrazino)-2-methoxypyrido-[3,2-d]pyrimidine-6-carbohydrazides (IIIa-i)

A mixture of IIa or IIb (10 mmol) and the appropriate aldehyde (22 mmol) in glacial acetic acid (10 ml) was heated under reflux for 2-5 h. After cooling, the separated solid was filtered off, dried and crystallized from glacial acetic acid[15].

5-Methoxytetrazolo[1,5-c]pyrido[2,3-e]pyrimidine-9-carbonyl Azides (IVa,b)

Compound IIa or IIb (10 mmol) was dissolved in concentrated hydrochloric acid (5 ml) and then a solution of sodium nitrite (69 mg, 10 mmol) in water (3 ml) was added dropwise over a period of 1 h stirring. The precipitated solid product was filtered off, washed with ice-cold water, dried and crystallized from dry ether[16].

REFERENCES AND NOTES

1. R.K. Robins and G.H. Hitchings, J. Am. Chem. Soc., 1955, 77, 2256.

2. G.H. Hitchings, G.B. Flion, F.A. Falco, P.B. Russell and H. Vanderwerff, Ann. N.Y. Acad. Sci., 1950, 52, 1218.

3. G.H. Hitchings, G.B. Flion, F.A. Falco, P.B. Russell, M.B. Sherwood and H. Vanderwerff, J. Biol. Chem., 1950, 1, 1983.

4. G.H. Hitchings, F.A. Falco and M.B. Sherwood, Science, 1945, 102, 251.

5. G.H. Hitchings, F.A. Falco, H. Vanderwerff, P.B. Russell and G.H. Flion, J. Biol. Chem., 1952, 199, 43.

6. A. Srinivasan and A.D. Broom, Tetrahedron Let., 1982, 23, 1431.

7. A. Srinivasan and A.D. Broom, J. Med. Chem., 1984, 27, 1710.

8. D.I. Brixner, S. Bayomi, H. Eisa and A.D. Broom, 191st ACS National Meeting, New York City, New York, April 13-18, 1986.

9. G.L. Anderson, J.L. Shim and A.D. Broom, J. Org. Chem., 1977, 42, 993.

10. N.J. Leonard and D.Y. Curtin, J. Org. Chem., 1946, 11, 349.

11. R.K. Robins and G.H. Hitchings, J. Am. Chem. Soc., 1956, 78, 973.

12. A. Monge Vega, J. Aldana, M.M. Rabbani and E. Frenandez, Alvarez, J. Heterocyclic Chem., 1980, 17, 77.

13. T. Kuraishi and R.V. Castle, J. Heterocyclic Chem., 1964, 1, 42.

14. IIa: Yellowish brown powder, mp > 290 °C, 99% yield, Calcd: N, 34.57. Found: N, 34.50.
b: Yellowish brown powder, mp >290 °C, 97% yield.

15. IIIa: Yellow crystals, mp>274-276 °C, 85% yield.

b: Yellow crystals. mp>278-280 °C, 85% yield,NMR (DMSO-d_6) : 3.98(3H,S,OCH_3) 12.02 (1H,S,C=NH), 12.32 (1H,S,CONH), 7.54-8. 76 (11H,m,Ar-H & N-CH).

c: Yellow crystals, mp > 290 °C, 83% yield, MS m/z (rel. int.): 491 and 493 [M^+] (50 and 16.67) (calc. for $C_{23}H_{18}ClN_7O_2$: 49.5), 372 (M-C_7H_5NO)(20), 253(372-C_7H_5NO), (75), 210(253-CONH) (100).

d: Yellow crystals, mp > 290 °C, 80% yield,

e: Yellow crystals, mp > 205 °C, 81% yield, NMR (DMSO-d_6) : 4(3H,S,OCH_3), 11.88 (1H, S,C=NH), 12.1 (1H, S, CONH), 7.2-8.4(17H,m,Ar-H &CH=).

f: Yellow crystals, mp > 290 °C, 68% yield,

g: Yellow crystals, mp > 290 °C, 65% yield,

h: Yellow crystals, mp > 290 °C, 61% yield,

i: Yellow crystals, mp > 290 °C, 60% yield.

16. IVa: Yellow powder, mp > 290 °C, 90% yield,

b: Yellow powder, mp > 290 °C, 85% yield, MS m/z (rel. int.): 271 [M^+] (20.69) (Calc. for $C_9H_5N_9O_2$: 271), 243 (M-N_2)(24.57), 229 (243-N)(4.30), 201 (243-CO)(41.76), 148(201-C_3H_3N)(100).

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