12*H*-Naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine Derivatives

Giorgio Roma, Aldo Ermili and Mauro Mazzei

Istituto di Chimica Farmaceutica Applicata dell'Università di Genova, 16132 Genoa, Italy

Received March 3, 1976

Reaction of 1-oxo-2-formyl-3-dimethylamino-1*H*-naphtho[2,1-*b*]pyran with amidines, guanidine, *O*-methylisourea, *S*-methylisothiourea afforded 9-substituted 12-oxo-12*H*-naphtho[1′,2′:-5,6]pyrano[2,3-*d*]pyrimidines.

When the reaction with *O*-methylisourea was carried out in anhydrous pyridine, 10,20-dioxo-10*H*,20*H*-dinaphtho[1,2-*e*:1′,2′-*e*′][1,5]diazocino[2,3-*b*:6,7-*b*′]dipyran was formed.

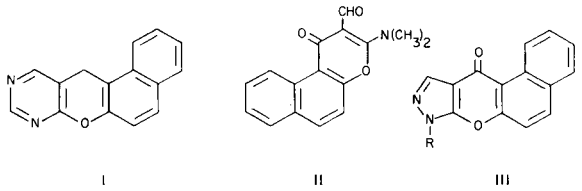
J. Heterocyclic Chem., 13, 761 (1976).

Naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine heterocyclic system derivatives have been sporadically reported in the literature in only a few instances. For instance, during researches concerning the behavior of barbituric acids in the condensation with aldehydes, some 9*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine derivatives were obtained when 2-hydroxynaphthaldehyde was employed in the reaction (1,2).

Subsequently two compounds I, with substituents in the 9 and 11 positions, were described in the only paper which appeared on this specific topic. Cyclization of properly substituted 5-(2′-oxynaphthyl-1′-methyl)-6-oxypyrimidines was the conclusive step of a rather laborious method to achieve the synthesis of such compounds starting from 3-acyl-5,6-benzocoumarins (3). Moreover, attempts to obtain in the 9 position other substituents than a methyl group were unsuccessful (3).

In connection with our chemical and pharmacological researches on a new class of 1*H*-naphtho[2,1-*b*]pyran derivatives, some of which showed interesting antidepressant, anticonvulsant or sedative activities (4-10), in a previous paper we described the reaction of 1-oxo-2-formyl-3-dimethylamino-1*H*-naphtho[2,1-*b*]pyran (II) with hydrazine or monosubstituted hydrazines as a route to achieve the condensation of a new heterocyclic ring with the 1*H*-naphtho[2,1-*b*]pyran system. Indeed, the easy cleavage of the dimethylamino group from the 3 position led, through the intermediate hydrazones, to the formation of 8*H*,11*H*-naphtho[1′,2′:5,6]pyrano[2,3-*c*]pyrazole derivatives (III) (11).

As a further part of our continuing interests in the chemistry of 1*H*-naphtho[2,1-*b*]pyrans, we have extended our investigations to the condensation of compound II



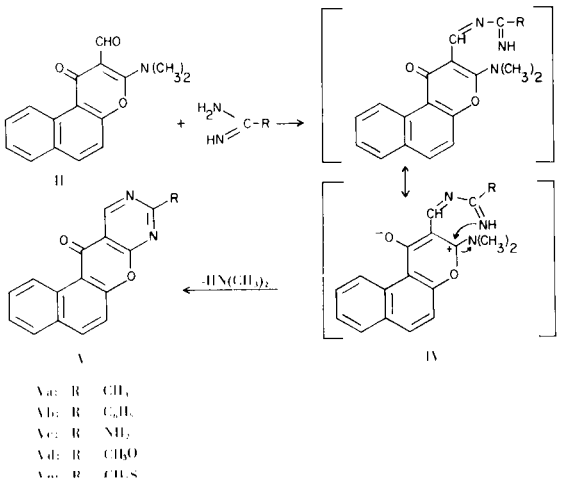
I II III

with reagents other than hydrazine or monosubstituted hydrazines.

Therefore, the present paper describes the facile synthesis of novel 12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine derivatives (12).

Actually, 1-oxo-2-formyl-3-dimethylamino-1*H*-naphtho-[2,1-*b*]pyran (II) underwent reaction with amidines, guanidine, *O*-methylisourea, *S*-methylisothiourea affording the

Chart I



II V IV

Va: R = CH_3
Vb: R = C_6H_5
Vc: R = NH_2
Vd: R = CH_3O
Ve: R = CH_3S

corresponding 9-substituted 12-oxo-12*H*-naphtho[1′,2′:-5,6]pyrano[2,3-*d*]pyrimidines (V), as shown in the following reaction pattern (Chart I).

The peculiar mesomeric form of γ-pyrone ring, illustrated in the presumable intermediate IV, may explain the easy splitting of the 3-dimethylamino group, as previously reported (11).

Naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidines (V) were crystalline compounds whose structure was supported by elemental analyses, ir and nmr spectral data.

As previously reported for compounds III (11), spectral data of V afforded an evidence that both 2-formyl and 3-dimethylamino groups of the starting compound II were involved in the reaction. Actually, the ir spectra showed the lack of the aldehyde carbonyl band and the nmr spectra showed only signals for the 9-substituent and heterocyclic system protons, among which the downfield H-1 [deshielding effect of 12-CO (13,4,5,6)] and H-11 signals, whereas signals for the 3-dimethylamino protons were no longer present.

It is of interest to note that, although compound II was converted to the 9-substituted 12-oxo-12*H*-naphtho[1′,2′:-5,6]pyrano[2,3-*d*]pyrimidines (V) by condensation with amidines, guanidine or *S*-methylisothiourea without any difficulty, the reaction with *O*-methylisourea was found to be very difficult. In this case, the cyclization might be hindered by the electron withdrawing effect of the methoxyl group.

Actually, the preparation of 9-methoxy-12-oxo-12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine (Vd) was attempted a number of times using different conditions and the procedure described in the Experimental section which involved the use of ethanol as solvent in the presence of triethylamine represents the optimum found.

In this connection, although pyridine was generally a suitable solvent to obtain compounds V, in the case of Vd the reaction occurred in this solvent with the formation of 10,20-dioxo-10*H*,20*H*-dinaphtho[1,2-*e*:1′,2′-*e*′][1,5]-diazocino[2,3-*b*:6,7-*b*′]dipyran (VI) most likely in accordance with the following intermolecular condensation pattern.

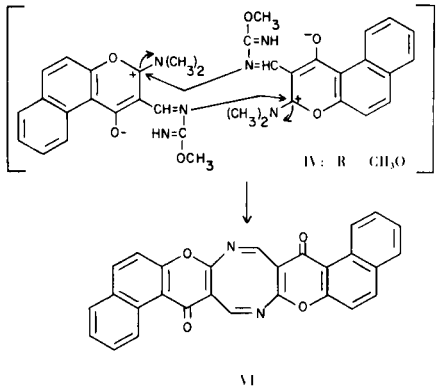
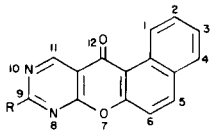


Table 1

Ir and Nmr Spectral Data (τ) of 9-Substituted 12-Oxo-12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidines (V) (a).



Compound	Solvent	R	CH_3	H-2,3,4,5,6 (plus C_6H_5)	H-1	H-11	ν-CO
Va	Deuteriotrifluoro-acetic Acid	CH_3	s, 6.74	m, 2.37-1.33	mc, 0.32	s, 0.01	1640 cm^{-1}
Vb	Deuteriotrifluoro-acetic Acid	C_6H_5	---	m, 2.53-1.40	mc, 0.47	s, 0.07	1650 cm^{-1}
Vc	Deuteriotrifluoro-acetic Acid	NH_2	---	m, 2.60-1.56	mc, 0.56	s, 0.63	1646 cm^{-1}
Vd	Deuteriochloroform	CH_3O	s, 5.79	m, 2.61-1.71	mc, 0.09	s, 0.56	1652 cm^{-1}
Ve	Deuteriotrifluoro-acetic acid	CH_3S	s, 7.00	m, 2.46-1.47	mc, 0.45	s, 0.37	1643 cm^{-1}

(a) s = singlet, m = multiplet, mc = multiplet center: the integrations of peak areas were consistent with the assigned structures.

The structure of the crystalline compound VI was deduced from elemental analysis, nmr and mass spectral data. Particularly the nmr spectrum of VI no longer showed signals for the 3-dimethylamino protons of the starting compound II; only signals for the heterocyclic system protons were present, among which those downfield for H-1, H-11 (deshielding effect of 20-CO and 10-CO, respectively), H-9 and H-19. The downfield H-1 and H-11 signals were a confirmatory evidence that the naphtho-[2,1-*b*]pyran moiety remained in the molecular constitution of the compound. Moreover, the mass spectrum of VI showed the expected and molecular (m/e = 442) and fragment ions.

EXPERIMENTAL

Melting points were determined using a Fisher-Johns (Electrothermal when above 300°) apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 instrument in potassium bromide pellets. Nuclear magnetic resonance spectra were determined with a Perkin-Elmer R12 spectrometer using TMS as internal standard (τ = 10). Mass spectra were recorded on a Varian CH 7 instrument (70 eV). Elemental analyses were performed by Laboratorio di Microanalisi, Istituto Carlo Erba per Ricerche Terapeutiche, Milano.

9-Methyl-12-oxo-12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine (Va).

A mixture of 0.96 g. (3.6 mmoles) of 1-oxo-2-formyl-3-dimethylamino-1*H*-naphtho[2,1-*b*]pyran (II) (11), 0.34 g. (3.6 mmoles) of acetamidine hydrochloride and 20 ml. of anhydrous pyridine was refluxed for 8 hours. Removal of solvent under reduced pressure and treatment of the residue with dilute aqueous sodium carbonate gave a yellow solid which was collected by filtration, washed with water and crystallized from acetone with the addition of charcoal. There was obtained 0.41 g. (43.6%) of nearly pure crystalline Va. On recrystallization from ethanol, the product melted at 191-191.5°.

Anal. Calcd. for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.19; H, 3.87; N, 10.71.

9-Phenyl-12-oxo-12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine (Vb).

A mixture of 0.96 g. of II, 0.56 g. (3.6 mmoles) of benzamidine hydrochloride and 20 ml. of anhydrous pyridine was refluxed for 8 hours. The solvent was removed *in vacuo* and the residue was treated with dilute aqueous sodium carbonate. The solid ultimately obtained was boiled with acetone. The insoluble white material (0.86 g. of pure Vb) was collected and recrystallized from benzene or pyridine; m.p. 264°. Concentration of the acetone solution afforded an additional crop of product (0.13 g.; total yield 84.6%).

Anal. Calcd. for $C_{21}H_{12}N_2O_2$: C, 77.77; H, 3.73; N, 8.64. Found: C, 77.55; H, 3.71; N, 8.70.

9-Amino-12-oxo-12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine (Vc).

A suspension of 0.96 g. of II, 0.32 g. (1.8 mmoles) of guanidine carbonate and 40 ml. of ethanol was refluxed for 8 hours. After cooling, the precipitate was collected and crystallized from pyridine. There was obtained 0.68 g. (71.6%) of white crystalline Vc, m.p. 381-383° dec

Anal. Calcd. for $C_{15}H_9N_3O_2$: C, 68.43; H, 3.45; N, 15.96. Found: C, 68.41; H, 3.47; N, 16.00.

Acetyl Derivative of Vc.

A suspension of 0.25 g. of Vc in 15 ml. of acetic anhydride was refluxed for 3 hours. There was obtained the white crystalline acetyl derivative (89.9%) which melted at 334-335° dec., after crystallization from pyridine; ir: 1686 cm^{-1} (amide CO), 1656 cm^{-1} (12-CO); nmr (deuteriotrifluoroacetic acid) τ: 7.37 (s, 3, CH_3), 2.47-1.50 (m, 5, H-2,3,4,5,6), 0.41 (mc, 1, H-1), 0.26 (s, 1, H-11).

Anal. Calcd. for $C_{17}H_{11}N_3O_3$: C, 66.88; H, 3.63; N, 13.77. Found: C, 66.70; H, 3.63; N, 13.79.

9-Methoxy-12-oxo-12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine (Vd).

A mixture of 0.96 g. of II, 1.24 g. (7.2 mmoles) of *O*-methylisourea sulfate, 9 ml. of triethylamine and 60 ml. of anhydrous ethanol was refluxed for 8 hours. After cooling, the precipitate was collected and treated with dilute aqueous sodium carbonate. There was obtained 0.40 g. of crude material from which an analytically pure sample of white crystalline Vd was obtained after several recrystallizations from benzene, m.p. 207-208°.

Anal. Calcd. for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.07. Found: C, 69.25; H, 3.62; N, 10.08.

9-Methylthio-12-oxo-12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine (Ve).

A suspension of 0.96 g. of II, 1.0 g. (3.6 mmoles) of *S*-methylisothiourea sulfate and 20 ml. of anhydrous pyridine was refluxed for 8 hours. After cooling, the white crystalline precipitate was recovered and treated with dilute aqueous sodium carbonate. There was obtained 0.79 g. (74.5%) of pure Ve which was crystallized from acetone and melted at 220-220.5°.

Anal. Calcd. for $C_{16}H_{10}N_2O_2S$: C, 65.30; H, 3.43; N, 9.52; S, 10.88. Found: C, 65.21; H, 3.43; N, 9.56; S, 10.93.

The ir and nmr spectral data of the compounds Va-e are included in Table I.

10,20-Dioxo-10*H*,20*H*-dinaphtho[1,2-*e*:1′,2′-*e*′][1,5]diazocino-[2,3-*b*:6,7-*b*′]dipyran (VI).

A mixture of 0.96 g. of II, 0.62 g. (3.6 mmoles) of *O*-methylisourea sulfate and 20 ml. of anhydrous pyridine was refluxed for 8 hours. After cooling, the precipitate was separated by filtration and treated with dilute aqueous sodium carbonate, then with hot acetone. The insoluble nearly pure VI (0.35 g., 43.8%) was collected and recrystallized from pyridine; pale yellow crystals, m.p. 351-352°; ir: 1636 cm^{-1} (CO); nmr (deuteriotrifluoroacetic acid) τ: 2.43-1.31 (m, 10, H-2,3,4,5,6,12,13,14,15,16), 0.30 (mc, 2, H-1 and H-11), 0.12, 0.00 (singlets, 1 plus 1, H-9 plus H-19); mass spectrum, m/e (relative intensity %): 442 (100), 414 (25), 386 (5), 222 (5), 221 (20), 193 (6), 170 (9), 165 (11), 155 (5), 154 (2), 142 (12), 126 (10), 114 (33).

Anal. Calcd. for $C_{28}H_{14}N_2O_4$: C, 76.01; H, 3.19; N, 6.33. Found: C, 75.80; H, 3.19; N, 6.32.

Acknowledgment.

The authors are grateful to the Italian Research Council (C.N.R.) for the financial support which made this work possible.

REFERENCES AND NOTES

(1) M. Ridi, *Gazz. Chim. Ital.*, 82, 14 (1952).

(2) V. M. Vvedenskii, *Khim. Geterotsikl. Soedin.*, 1092 (1969);

Chem. Abstr., **72**, 111406t (1970).

(3) H. Wamhoff and F. Korte, *Chem. Ber.*, **100**, 1324 (1967).

(4) A. Ermili and G. Roma, *Gazz. Chim. Ital.*, **101**, 269 (1971).

(5) A. Ermili, G. Roma and A. Balbi, *ibid.*, **101**, 651 (1971).

(6) A. Ermili, G. Roma, M. Mazzei, A. Balbi, A. Cuttica and N. Passerini, *Il Farmaco, Ed. Sci.*, **29**, 225 (1974).

(7) A. Ermili, G. Roma, M. Mazzei, A. Ambrosini and N. Passerini, *ibid.*, **29**, 237 (1974).

(8) A. Ermili, M. Mazzei, G. Roma, A. Cuttica and N. Passerini, *ibid.*, **30**, 870 (1975).

(9) A. Ermili, M. Mazzei, G. Roma, A. Ambrosini and N. Passerini, *ibid.*, **30**, 1001 (1975).

(10) A. Ermili, A. Balbi, G. Roma, A. Ambrosini and N. Passerini, *ibid.*, in press.

(11) G. Roma, A. Ermili and M. Mazzei, *J. Heterocyclic Chem.*, **12**, 31 (1975).

(12) Orientations of formulas, numbering and naming are consistent with recommendations of A. M. Patterson, L. T. Capell and D. F. Walker, "The Ring Index," 2nd Ed., American Chemical Society, Washington, D.C., 1960.

(13) R. H. Martin, N. Defay and F. Geerts-Evrard, *Tetrahedron*, **20**, 1505 (1964).