Naphtho[1',2':5,6]pyrano[2,3-*c*]pyrazole Derivatives

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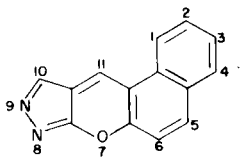
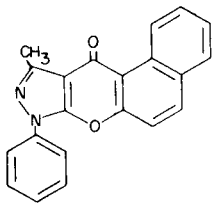
Reaction of 1-oxo-3-dialkylamino-1*H*-naphtho[2,1-*b*]pyrans with *N,N*-dimethylformamide in the presence of phosphorus oxychloride afforded the corresponding 1-oxo-2-formyl-3-dialkylamino-1*H*-naphtho[2,1-*b*]pyrans.

Condensation of 1-oxo-2-formyl-3-dimethylamino-1*H*-naphtho[2,1-*b*]pyran with hydrazine or monosubstituted hydrazines was found to lead to the formation of 8-alkyl(aryl)-11-oxo-8*H*,11*H*-naphtho[1',2':5,6]pyrano[2,3-*c*]pyrazoles through the intermediate hydrazones and subsequent cyclization. The same result was achieved starting from other 3-dialkylamino derivatives but in a lower yield.

Until recently the naphtho[1',2':5,6]pyrano[2,3-*c*]pyrazole heterocyclic system (I) (1) and related compounds had not been reported in the literature. The derivative II was then described in the only paper on this topic (2). Reaction of 1-phenyl-3-methyl-5-chloropyrazole-4-carboxaldehyde with β-naphthol, oxidation to carboxylic acid and cyclization were the main steps for the synthesis of II (2).



I



II

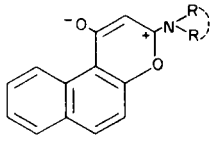
The present paper describes the facile formation of some novel naphtho[1',2':5,6]pyrano[2,3-*c*]pyrazole derivatives starting from suitable 1*H*-naphtho[2,1-*b*]pyrans.

In connection with our chemical and pharmacological studies we were interested in preparing substituted 1*H*-naphtho[2,1-*b*]pyrans, some of which showed remarkable sedative, anticonvulsant and C.N.S. depressant properties (3-8).

Particularly, as a route to the compounds V, whose distinctive feature is the presence of a 3-dialkylamino substituent, we proposed the condensation of β-naphthol with *N,N*-dialkylethoxycarbonylacetamides (IV) in the presence of phosphorus oxychloride (3,4,6).

In these compounds the 2 position is available for electrophilic substitutions; for instance, the introduction of *N,N*-dialkylaminomethyl group *via* Mannich reaction occurred readily (7,8). Furthermore, in this reaction as well as in some other cases, the γ-pyrone ring has been shown to readily eliminate the dialkylamino group and to rearrange into the α-pyrone derivative (7,3,4).

The easy splitting of the dialkylamino group may be explained by the resonance of γ-pyrone ring, the mesomeric form III being especially significant (9). We regarded this property as a helpful tool to achieve, after the introduction of a proper active group in position 2, the condensation of a new heterocyclic ring with the 1*H*-naphtho[2,1-*b*]pyran system, since the γ-carbonyl group is known to react very slowly with most ketone reagents (10).



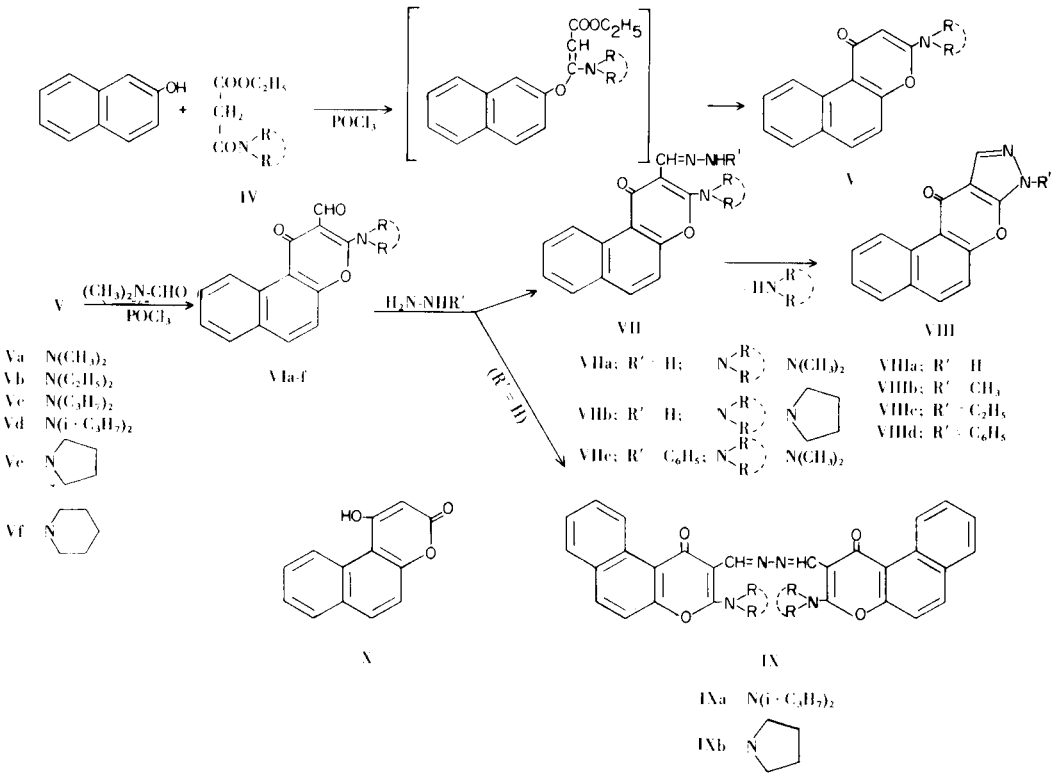
III

Concerning this problem, since the carbonyl group was suitable for our purpose, Vilsmeier–Haack acylation of 1-oxo-3-dialkylamino-1*H*-naphtho[2,1-*b*]pyrans (V) was then attempted.

Actually, reaction with *N,N*-dimethylformamide in the presence of phosphorus oxychloride afforded 1-oxo-2-formyl-3-dialkylamino-1*H*-naphtho[2,1-*b*]pyrans (VI) in excellent yields, whereas reaction with *N,N*-dimethylacetamide led only to the recovery of starting material. Sometimes, in this last reaction, the formation of a small amount of 1-oxy-3-oxo-3*H*-naphtho[2,1-*b*]pyran (X) was pointed out, identified by direct comparison with an authentic sample (11,3).

Therefore, 1-oxo-2-formyl-3-dialkylamino-1*H*-naphtho[2,1-*b*]pyrans (VI) were considered the right starting ma-

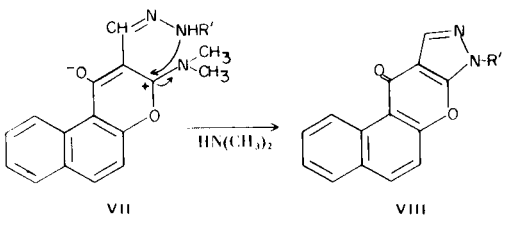
Chart I



terial for the formation of new heterocyclic rings condensed with the γ-pyrone system by reaction with proper reagents.

As a part of our research on this kind of condensation, we studied first the reaction of 1-oxo-2-formyl-3-dimethylamino-1*H*-naphtho[2,1-*b*]pyran (VIa) with hydrazine or monosubstituted hydrazines in ethanol.

Indeed, the expected 8-alkyl(aryl)-11-oxo-8*H*,11*H*-naphtho[1',2':5,6]pyrano[2,3-*c*]pyrazoles (VIII) were formed by the cyclization of the intermediate hydrazones (VII) and elimination of the 3-dimethylamino moiety.



Moreover, in this connection, it was possible to verify the important role played by the steric hindrance of the 3-dialkylamino group on the formation of compounds VIII. The yield of these compounds decreased, while increasing the hindrance of the 3-substituting group, that is, passing from 3-dimethylamino, to 3-diethylamino and to 3-dipropylamino substituted compounds VI. A further evidence of this occurrence was the formation of hydrazones (VII) and (IX) only from compounds VI which presented in position 3 the diisopropylamino or pyrrolidyl groups, namely the highest steric hindrance.

1-Oxo-2-formyl-3-dialkylamino-1*H*-naphtho[2,1-*b*]pyrans (VI), naphtho[1',2':5,6]pyrano[2,3-*c*]pyrazoles (VIII) and hydrazones (VII) and (IX) were crystalline compounds, whose elemental analyses, ir and nmr spectral data were consistent with the proposed structures.

Actually, ir spectra of compounds VI showed an aldehyde carbonyl band (1660-1674 cm^{-1}) in addition to the bands (1630 cm^{-1} and 1550 cm^{-1} about) which distinguished naphtho[2,1-*b*]pyrans (V) (3,4,6). Nmr spectra of VI showed signals for 2-formyl, 3-substituent and heterocyclic system protons, among which the downfield H-10 signal [deshielding effect of 1-CO (12,3,4,6)].

Spectral data of VIII afforded an evidence that cyclization involved both 2-formyl and 3-dialkylamino substituents of the starting compounds VI. Actually, ir showed the lack of the aldehyde carbonyl band and nmr showed only signals for 8-substituent and heterocyclic system protons, among which the downfield H-1 signal (deshielding effect of 11-CO), whereas signals for 3-dialkylamino protons were no longer present.

Research is continuing using other reagents, such as guanidine, *O*-methylisourea, *etc.*, for the formation of further interesting heterocyclic structures.

EXPERIMENTAL

Melting points were determined using a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 instrument in potassium bromide pellets.

Nuclear magnetic resonance spectra were determined using a Perkin-Elmer R12 instrument with TMS as internal standard ($\tau = 10$). Elemental analyses were performed by Laboratorio di Microanalisi, Istituto Carlo Erba per Ricerche Terapeutiche, Milano.

1-Oxo-2-formyl-3-dialkylamino-1*H*-naphtho[2,1-*b*]pyrans (VI).

General procedure.

A 3.68 g. (24 mmoles) quantity of phosphorus oxychloride was added dropwise with stirring to 8 ml. of *N,N*-dimethylformamide, which was contained in a flask cooled in an ice bath and protected from moisture with a calcium chloride drying tube. After the addition of all the phosphorus oxychloride, the mixture was removed from the ice bath and held at room temperature for 30 minutes. To the resulting yellow solution, a suspension of 16 mmoles of 1-oxo-3-dialkylamino-1*H*-naphtho[2,1-*b*]pyran (V) in 30-40 ml. of *N,N*-dimethylformamide was added slowly while stirring. The reaction mixture was then heated for 1.5-6 hours at 95°, cooled and poured onto crushed ice.

Sodium carbonate was then added to the stirred mixture until it was definitely basic and the mixture was stirred for 2 hours. The white crystals that separated were collected, washed with water, and recrystallized from ethanol or benzene.

By the above procedure, the following compounds VI were prepared:

1-Oxo-2-formyl-3-dimethylamino-1*H*-naphtho[2,1-*b*]pyran (VIa).

This compound was prepared from Va (4) after heating for 2 hours; recrystallization from benzene afforded VIa.

1-Oxo-2-formyl-3-diethylamino-1*H*-naphtho[2,1-*b*]pyran (VIb).

This compound was prepared from Vb (3), after heating the reaction mixture for 90 minutes; recrystallization from benzene gave VIb.

1-Oxo-2-formyl-3-dipropylamino-1*H*-naphtho[2,1-*b*]pyran (VIc).

This compound was prepared from Vc (4), heating the reaction mixture for 90 minutes; recrystallization from ethanol gave VIc.

1-Oxo-2-formyl-3-diisopropylamino-1*H*-naphtho[2,1-*b*]pyran (VId).

This compound was prepared from Vd (6), after heating for 2 hours; recrystallization from ethanol afforded VId.

1-Oxo-2-formyl-3-(1-pyrrolidyl)-1*H*-naphtho[2,1-*b*]pyran (VIe).

This compound was prepared from Ve (4) after heating the reaction mixture for 6 hours; recrystallization from ethanol afforded VIe.

1-Oxo-2-formyl-3-(1-piperidyl)-1*H*-naphtho[2,1-*b*]pyran (VIf).

This compound was prepared from Vf (4) after heating for 90 minutes; recrystallization from benzene gave VIf.

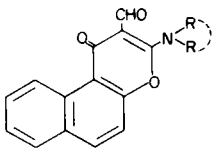
The analyses, melting points and yields of the above compounds are reported in Table I, while their nmr spectral data are included in Table II.

11-Oxo-8*H*,11*H*-naphtho[1',2':5,6]pyrano[2,3-*c*]pyrazole (VIIIa).

A mixture of 0.48 g. (1.8 mmoles) of 1-oxo-2-formyl-3-dimethylamino-1*H*-naphtho[2,1-*b*]pyran (VIa), 0.09 g. (1.8 mmoles) of hydrazine hydrate and 30 ml. of ethanol was heated at reflux for 8 hours. After removal of the solvent under reduced pressure, the yellow solid residue was shaken with a small amount of ethanol at room temperature. The insoluble yellowish VIIIa was filtered (0.16 g.) and recrystallized from ethanol. The filtrate was vacuum

TABLE I

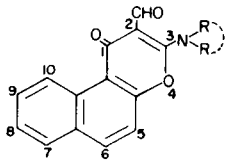
1-Oxo-2-formyl-3-dialkylamino-1*H*-naphtho[2,1-*b*]pyrans (VI)



Compound	N(R)(R)	M.P. °C	Yield %	Formula	Analysis Calcd., % C	H	N	Found, % C	H	N
VIa	$N(CH_3)_2$	218-9	94.4	$C_{16}H_{13}NO_3$	71.90	4.90	5.24	71.73	4.84	5.26
VIb	$N(C_2H_5)_2$	140-1	85.5	$C_{18}H_{17}NO_3$	73.20	5.80	4.74	72.94	5.84	4.88
VIc	$N(C_3H_7)_2$	123-4	77.7	$C_{20}H_{21}NO_3$	74.28	6.55	4.33	74.15	6.39	4.43
VId	$N(i\text{-}C_3H_7)_2$	185-6	81.7	$C_{20}H_{21}NO_3$	74.28	6.55	4.33	73.99	6.54	4.37
VIe		230-1	95.5	$C_{18}H_{15}NO_3$	73.70	5.15	4.78	73.56	5.04	4.94
VIf		183-4	93.6	$C_{19}H_{17}NO_3$	74.25	5.58	4.56	74.16	5.49	4.66

TABLE II

Nmr Spectral Data (τ, deuteriochloroform) of 1-Oxo-2-formyl-3-dialkylamino-1*H*-naphtho[2,1-*b*]pyrans (VI) (a)

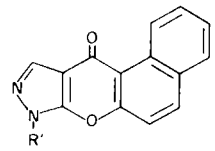


Compound	N(R)(R)	CH_3	β-CH_2 ($+\gamma$-CH_2)	α-CH_2	CH	H-5,6,7,8,9	H-10	C(H)=O
VIa	$N(CH_3)_2$	s, 6.77	–	–	–	m, 2.82-1.88	mc, -0.05	s, -0.32
VIb	$N(CH_2-CH_3)_2$	t, 8.66	–	q, 6.33	–	m, 2.82-1.88	mc, -0.04	s, -0.34
VIc	$N(CH_2-CH_2-CH_3)_2$	t, 9.06	mc, 8.28	t, 6.42	–	m, 2.82-1.87	mc, -0.02	s, -0.30
VId	$N(CH(CH_3)_2)_2$	d, 8.46	–	–	mc, 5.98	m, 2.78-1.85	mc, 0.00	s, -0.22
VIe		–	mc, 7.98	mc, 6.36	–	m, 2.98-2.00	mc, -0.08	s, -0.42
VIf		–	mc, 8.20	mc, 6.40	–	m, 2.88-1.91	mc, -0.08	s, -0.32

(a) s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, mc = multiplet center; the integrations of peak areas were consistent with the assigned structures.

TABLE III

8-Alkyl(aryl)-11-oxo-8*H*,11*H*-naphtho[1′,2′:5,6]pyrano[2,3-*c*]pyrazoles (VIII)



Compound	R′	M.P. °C	Yield %	Formula	Analysis Caled., % C	H	N	Found, % C	H	N
VIIIa	H	298-9	37.6	$C_{14}H_8N_2O_2$	71.18	3.41	11.86	71.00	3.48	11.78
VIIIb	CH_3	186-7	52.9	$C_{15}H_{10}N_2O_2$	71.99	4.03	11.20	71.82	3.99	11.20
VIIIc	C_2H_5	154-5	48.7	$C_{16}H_{12}N_2O_2$	72.71	4.58	10.60	72.55	4.60	10.60
VIIId	C_6H_5	286-7	38.4	$C_{20}H_{12}N_2O_2$	76.91	3.87	8.97	76.73	3.93	8.93

treated to remove the solvent. The yellow solid residue after recrystallization from ethanol yielded 0.15 g. of hydrazone (VIIa); pale yellow crystals, m.p. 236-237°.

Anal. Caled. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.08; H, 5.47; N, 14.75.

In similar fashion to that given above, reaction of VIb or VIc with hydrazine afforded the same compound (VIIIa), but in a lower yield (11% and 5%, respectively).

8-Methyl-11-oxo-8*H*,11*H*-naphtho[1′,2′:5,6]pyrano[2,3-*c*]pyrazole (VIIIb).

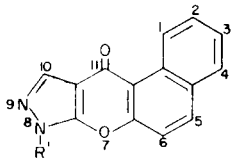
A mixture of 1.07 g. (4 mmoles) of VIa, 0.28 g. (6 mmoles) of methylhydrazine and 15 ml. of ethanol was refluxed for 8 hours.

The white solid which separated out after cooling, was collected (0.53 g.) and recrystallized from ethanol.

8-Ethyl-11-oxo-8*H*,11*H*-naphtho[1′,2′:5,6]pyrano[2,3-*c*]pyrazole (VIIIc).

TABLE IV

Nmr Spectral Data (τ) of 8-Alkyl(aryl)-11-oxo-8*H*,11*H*-naphtho[1′,2′:5,6]pyrano[2,3-c]pyrazoles (VIII) (a)



Compound	Solvent	R′	CH_3	CH_2	C_6H_5	H-2,3,4,5,6	H-10	H-1
VIIIa	$(CD_3)_2SO$	H				m, 2.69-1.57	s, 1.42	mc, 0.19
VIIIb	CF_3-COOD	CH_3	s, 5.88			m, 2.86-1.88	s, 1.84	mc, 0.63
VIIIc	CF_3-COOD	CH_2-CH_3	t, 8.23	q, 5.33		m, 2.48-1.55	s, 1.36	mc, 0.33
VIIId	CF_3-COOD	C_6H_5			mc, 2.44	m, 3.03-1.87	s, 1.64	mc, 0.72

(a) See note to Table II.

After heating at reflux for 8 hours the mixture of 2.14 g. (8 mmoles) of VIa, 1.80 g. (12 mmoles) of ethylhydrazine oxalate and 40 ml. of ethanol, the solvent was removed under reduced pressure and the solid residue was shaken with dilute sodium hydroxide. The insoluble white product was collected (1.03 g.) and recrystallized from ethanol.

8-Phenyl-11-oxo-8*H*,11*H*-naphtho[1′,2′:5,6]pyrano[2,3-c]pyrazole (VIIId).

A mixture of 1.07 g. (4 mmoles) of VIa, 0.65 g. (6 mmoles) of phenylhydrazine and 20 ml. of ethanol was heated at reflux for 7 hours. The yellow solid material which separated out after cooling was collected and then shaken with a relatively large amount of acetone at room temperature. The insoluble white crystalline VIIId was collected (0.48 g.) and recrystallized from pyridine.

Concentration of the acetonic solution afforded 0.50 g. of yellow crystalline phenylhydrazone (VIIe) which was recrystallized from acetone and melted at 189-191°.

Anal. Calcd. for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.90; H, 5.38; N, 11.66.

The elemental analyses, melting points and yields of compounds VIIIa-d are reported in Table III, while their nmr spectral data are included in Table IV.

Compound IXa.

A mixture of 0.58 g. (1.8 mmoles) of VId, 0.09 g. (1.8 mmoles) of hydrazine hydrate and 30 ml. of ethanol was refluxed for 8 hours. After cooling, the yellow precipitate was recovered and recrystallized from pyridine to give 0.27 g. of compound IXa, m.p. 303-304° dec.

Anal. Calcd. for $C_{40}H_{42}N_4O_4$: C, 74.74; H, 6.59; N, 8.72. Found: C, 74.48; H, 6.59; N, 8.83.

Compounds IXb and VIIb.

A mixture of 0.53 g. (1.8 mmoles) of VIe, 0.09 g. (1.8 mmoles) of hydrazine hydrate and 12 ml. of ethanol was refluxed for 7 hours. The material was then cooled and filtered. The yellow solid product (IXb, 0.23 g.) was recrystallized from benzene and melted at 284-285° dec.

Anal. Calcd. for $C_{36}H_{30}N_4O_4$: C, 74.21; H, 5.19; N, 9.62. Found: C, 74.08; H, 5.25; N, 9.81.

The filtrate was vacuum treated to remove the solvent and the yellow residue recrystallized from ethanol to give 0.14 g. of VIIb, m.p. 253-254°.

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.13; H, 5.50; N, 13.53.

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