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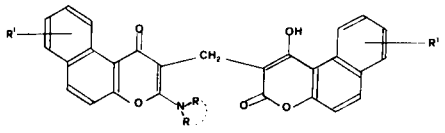
Received December 19, 1977

Reaction of 1-oxo-3-dialkylamino-1*H*-naphtho[2,1-*b*]pyrans, 4-hydroxycoumarin and formaldehyde gave rise to the formation of 1-oxo-2-[(2′-oxo-4′-hydroxy-2′*H*-1′-benzopyran-3′-yl)-methyl]-3-dialkylamino-1*H*-naphtho[2,1-*b*]pyrans. When these compounds were refluxed in glacial acetic acid, cyclization occurred and 6,8-dioxo-6*H*,7*H*,8*H*-5,15,16-trioxadibenzo[*a*,*j*]-naphthacene arose by cleavage of the dialkylamino group. In a similar manner, starting from suitable products, many other trioxanaphthacene or azadioxanaphthacene derivatives were synthesized.

J. Heterocyclic Chem., 15, 605 (1978)

In earlier papers we have reported the synthesis of naphtho[1′,2′:5,6]pyrano[2,3-c]pyrazoles and 12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidines starting from suitable 1*H*-naphtho[2,1-*b*]pyran derivatives. Thus, 1-oxo-3-dialkylamino-1*H*-naphtho[2,1-*b*]pyrans (structure II) were formylated in position 2 and in turn treated with hydrazines or amidines, guanidine, *etc.*, cyclization occurring by cleavage of the dialkylamino group from position 3 (1,2,3).

On the other hand, during our previous researches we pointed out that the attempted Mannich reaction on compounds of structure II sometimes gave rise, under particular experimental conditions, to the formation of derivatives I instead of the expected Mannich bases. Moreover, compounds of type I arose in a quantitative yield from the reaction of formaldehyde and equimolar amounts of II and 1-hydroxy-3-oxo-3*H*-naphtho[2,1-*b*]pyran (4,5).

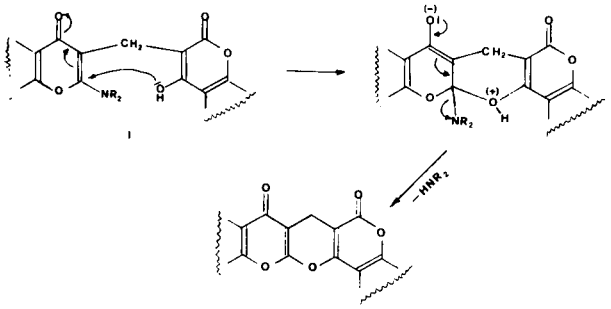


I

Compounds I were insoluble or sparingly soluble in most hot organic solvents and showed some tendency to undergo transformation when crystallized from the few suitable solvents.

As a further part of our interest in the chemistry of pyran derivatives and on account of these results, we regarded compounds of structure I as helpful starting materials to achieve the synthesis of new polycyclic pyran ring systems.

Actually, in these products intramolecular cyclization with the formation of a new pyran ring can occur by nucleophilic attack of the hydroxylic oxygen at the carbon atom bearing the dialkylamino group, proton shift and then elimination of amine, as detailed in the following pattern.

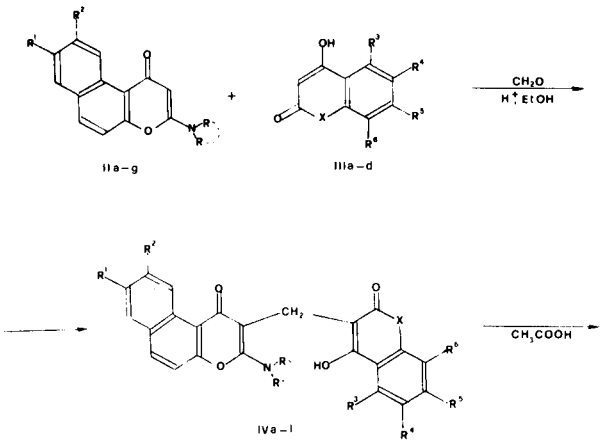


I

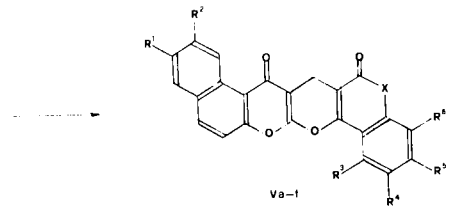
This reaction can represent a very simple route to synthesize new complex polycyclic pyran derivatives whose structure is connected with the starting compounds used to achieve derivatives of type I.

Thus, the reaction of 1*H*-naphtho[2,1-*b*]pyrans II, formaldehyde and 4-hydroxy-substituted coumarin, benzocoumarins or 1-methylcarbostyril (III) gave rise to the formation of compounds IV which in turn were easily transformed into polycyclic compounds V (6) by heating in glacial acetic acid. In this connection, protonation of the dialkylamino substituent due to the solvent made a positive contribution to the elimination of amine.

In the same way, 2-dialkylaminochromones (VI), afforded compounds VII and then polycyclic derivatives VIII, as reported in the following reaction sequences.



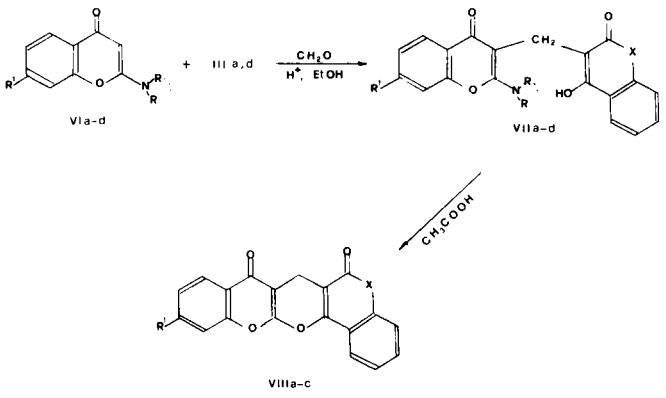
IIa–g IIIa–d IVa–l



Tabulation I

Compounds	$N\langle^{R}_{R}$	R^1	R^2	R^3	R^4	R^5	R^6	X
IIIa	---	---	---	H	H	H	H	O
IIIb	---	---	---	H	H	benzo		O
IIIc	---	---	---	benzo		H	H	O
IIId	---	---	---	H	H	H	H	NMe
IIa, IVa	NMe_2	H	H	H	H	H	H	O
IIb, IVb	NEtMe	H	H	H	H	H	H	O
IIc, IVc	NEt_2	H	H	H	H	H	H	O
IId, IVd	$N(CH_2)_4$	H	H	H	H	H	H	O
IIe, IVe	NEtMe	H	OMe	H	H	H	H	O
IIf, IVf	$N(CH_2)_5$	H	OMe	H	H	H	H	O
IIg, IVg	NMe_2	Me	Me	H	H	H	H	O
IVh	NMe_2	H	H	H	H	H	H	NMe
IVi	$N(CH_2)_4$	H	H	H	H	H	H	NMe
IVj	NMe_2	H	H	H	H	benzo		O
IVk	NMe_2	H	H	benzo		H	H	O (a)
IVl	$N(CH_2)_4$	H	H	benzo		H	H	O (a)
Va	---	H	H	H	H	H	H	O
Vb	---	H	OMe	H	H	H	H	O
Vc	---	Me	Me	H	H	H	H	O
Vd	---	H	H	H	H	H	H	NMe
Ve	---	H	H	H	H	benzo		O
Vf	---	H	H	benzo		H	H	O

(a) These compounds were reported in a previous paper (4).



Tabulation II

Compounds	$N\langle^{R}_{R}$	R^1	X
VIa, VIIa	$N(CH_2)_5$	H	O
VIb, VIIb	NMe_2	OMe	O
VIc, VIIc	$N(CH_2)_5$	OMe	O
VId, VIId	$N(CH_2)_4$	OMe	NMe
VIIIa	---	H	O
VIIIb	---	OMe	O
VIIIc	---	OMe	NMe

It is noteworthy that usually the preparation of compounds IV and VII was easily achieved, except when the starting γ-pyrone derivative was substituted with the diethylamino group. Perhaps due to a steric hindrance, in this occurrence reaction with 4-hydroxycoumarin and formaldehyde, when carried out under the usual conditions, led to the formation of dicoumarol and to the recovery of the starting γ-pyrone derivative. However, also in this particular case, reaction was accomplished by properly modifying the experimental conditions (see experimental); for instance, IIc gave rise to the formation of IVc in a very good yield.

Compounds IV and VII as well as compound V and VIII were white crystalline products whose elemental analyses, ir, nmr and mass spectral data were consistent with the proposed structures.

Concerning in particular the final polycyclic derivatives, the ir spectra of the compounds Va-c and Ve,f showed bands at about 1720 cm^{-1} (α-pyrone CO) and 1635 cm^{-1} (γ-pyrone CO) (7-10), whereas those of Vd and VIIIc showed the 1685 cm^{-1} =N-CO- band in addition to the γ-pyrone CO band at 1636 cm^{-1} (7-9) or 1617 cm^{-1} (11), respectively.

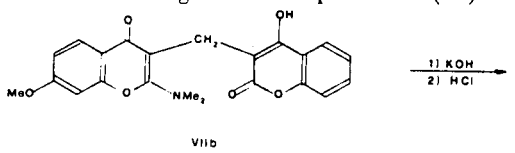
Finally the ir spectra of VIIIa,b showed bands at about 1725 cm^{-1} (α-pyrone CO) and 1610 cm^{-1} (γ-pyrone CO) (11).

The nmr spectrum of Va, in deuteriotrifluoroacetic acid, as an example, showed signals at τ = 7.00 (CH_2), τ = 2.93-1.74 (aromatic H) and τ = 0.51 (H-9), whereas signals for dialkylamino protons of the starting compounds IVa-d were no longer present. Thus, the downfield signal characteristic of the proton which was in the position 10 (deshielding effect of 1-CO) (7-10) of the starting compounds II was a confirmatory evidence that the naphtho[2,1-*b*]-pyran moiety remained in the molecular constitution of Va. The nmr spectrum of VIIIb, in deuteriotrifluoroacetic acid, as a further example, showed signals at τ = 6.10 (CH_2), τ = 5.95 (OCH_3) and τ = 2.80-1.55 (aromatic H), whereas signals for dialkylamino protons of the starting compounds VIIb,c were no longer present.

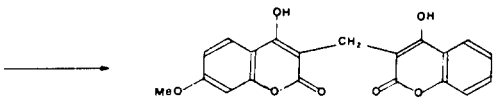
Furthermore, the mass spectra of the compounds Vd, Vf and VIIIb, chosen as significant examples, gave molecular ion values at m/e = 381, 418 and 348, respectively, which were in accordance with the proposed structures.

On the other hand, useful informations were also obtained by some chemical transformations. For instance, as hydrolysis of compounds IV or VII can lead to the formation of analogs of dicoumarol, derivative VIIb, *e.g.*,

was converted into IX by treatment with dilute potassium hydroxide solution. This compound was synthesized in the literature following a different procedure (12).

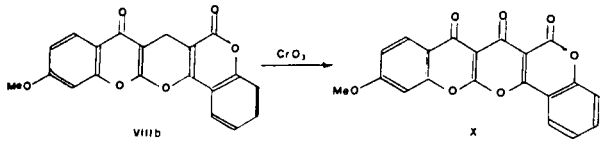


VIIb



IX

Moreover, oxidation of VIIIb, *e.g.*, with chromium trioxide afforded derivative X. The easy conversion of pyran methylene into carbonyl group was consistent with literature references concerning similar polycyclic compounds (13).



VIIIb X

Finally, it is of interest to point out that, as far as we can see, the polyfused pyran ring systems described in the present paper are not reported in the literature.

EXPERIMENTAL

Melting points were taken on a Fisher-Johns (Electrothermal when above 300°) apparatus and are uncorrected. Ir (in potassium bromide pellets), mass and nmr spectra were obtained with a Perkin-Elmer 257, a Varian CH7 (70 eV) and a Perkin-Elmer R12 (tetramethylsilane as internal reference) spectrometer, respectively.

Analyses were performed by Laboratorio di Microanalisi, Istituto Carlo Erba per Ricerche Terapeutiche, Milano.

Compounds IV, VII.

General Method.

A mixture of compound II (or VI) (2.3 mmoles), compound III (2.3 mmoles), 40% aqueous formaldehyde (1.2 ml.), glacial acetic acid (1.2 ml.) and ethanol (15 ml.) was stirred at reflux for 0.5 hour. In a few minutes a white solid started to separate out from the solution and, after cooling, was recovered by filtration and washed with ethanol. Solvents for recrystallization, melting points, yields and analytical data of compounds IV and VII are reported in Table I.

Following the general procedure, when 4-hydroxycoumarin (IIIa) was used in the reaction, IIa (8) gave 1-oxo-2-[(2′-oxo-4′-hydroxy-2′*H*-1′-benzopyran-3′-yl)methyl]-3-dimethylamino-1*H*-naphtho[2,1-*b*]pyran (IVa); IIb (9) gave the 3-(*N*-ethyl, *N*-methyl)amino derivative IVb; (for IVc from IIc see later); IId (8) gave the 3-(*N*-pyrrolidyl) derivative IVd; IIe (10) gave the 3-(*N*-ethyl, *N*-methyl)amino-9-methoxy derivative IVe; IIf (10) gave the 3-(*N*-piperidyl)-9-methoxy derivative IVf; IIg (10) gave the 3-dimethylamino-8,9-dimethyl derivative IVg.

In a similar manner, when 1-methyl-4-hydroxycarbostyril (IIId) was used in the reaction, IIa gave 1-oxo-2-[(1′,2′-dihydro-1′-methyl-2′-oxo-4′-hydroxyquinolin-3′-yl)methyl]-3-dimethylamino-1*H*-naphtho[2,1-*b*]pyran (IVh); IId gave the 3-(*N*-pyrrolidyl) derivative IVi.

By the above procedure, using 2-oxo-4-hydroxy-2*H*-naphtho[1,2-*b*]pyran (IIIb) (14), IIa gave 1-oxo-2-[(2′-oxo-4′-hydroxy-2′*H*-naphtho[1′,2′-*b*]pyran-3′-yl)methyl]-3-dimethylamino-1*H*-naphtho[2,1-*b*]pyran (IVj).

Following the same general procedure, using IIIa in the reaction, VIa (15) gave 2-(*N*-piperidyl)-3-[(2′-oxo-4′-hydroxy-2′*H*-1′-benzopyran-3′-yl)methyl]-4-oxo-4*H*-1-benzopyran (VIIa) (see later); VIb (11) gave the 2-dimethylamino-7-methoxy derivative VIIb; VIc (11) gave the 2-(*N*-piperidyl)-7-methoxy derivative VIIc; using IIId, VId (11) gave 2-(*N*-pyrrolidyl)-3-[(1′,2′-dihydro-1′-methyl-2′-oxo-4′-hydroxyquinolin-3′-yl)methyl]-4-oxo-7-methoxy-4*H*-1-benzopyran (VIId).

During the preparation of VIIa, dicoumarol (0.2 g.) precipitated from the boiling reaction mixture and was separated by filtration, m.p. 288-290° [lit. m.p. 287-293° (16)]; VIIa was then recovered

Table I
Physical and Analytical Data of Compounds IV and VII

Compound	M.p. °C	Yield %	Solvent for recrystallization	Formula	Analysis Calcd. % C	Calcd. % H	Calcd. % N	Found % C	Found % H	Found % N
IVa	229-231	90.0	no recrystallization	$C_{25}H_{19}NO_5$	72.63	4.63	3.39	72.53	4.63	3.34
IVb	200-201	91.7	benzene	$C_{26}H_{21}NO_5$	73.05	4.95	3.28	73.23	4.98	3.32
IVc	146-147	80.0	acetone	$C_{27}H_{23}NO_5$	73.45	5.25	3.17	73.61	5.27	3.14
IVd	233-235	98.1	benzene	$C_{27}H_{21}NO_5$	73.79	4.82	3.19	73.94	4.86	3.14
IVe	180-181	83.6	benzene	$C_{27}H_{23}NO_6$	70.88	5.07	3.06	71.03	5.08	3.02
IVf	286-287	89.1	benzene	$C_{29}H_{25}NO_6$	72.04	5.21	2.90	72.01	5.30	2.94
IVg	230-232	90.2	benzene	$C_{27}H_{23}NO_5$	73.45	5.25	3.17	73.44	5.30	3.15
IVh	229-231	79.1	benzene	$C_{26}H_{22}N_2O_4$	73.22	5.20	6.57	73.28	5.20	6.49
IVi	239-241	88.0	benzene	$C_{28}H_{24}N_2O_4$	74.32	5.35	6.19	74.16	5.40	6.18
IVj	214-215	93.8	benzene	$C_{29}H_{21}NO_5$	75.15	4.57	3.02	75.01	4.57	2.95
VIIa	182-183	46.3	ethanol	$C_{24}H_{21}NO_5$	71.45	5.25	3.47	71.43	5.18	3.39
VIIb	213-215	82.7	benzene	$C_{22}H_{19}NO_6$	67.17	4.87	3.56	67.31	4.88	3.49
VIIc	212-213	88.4	benzene	$C_{25}H_{23}NO_6$	69.27	5.35	3.23	69.41	5.37	3.24
VIId	229-231	91.4	benzene	$C_{25}H_{24}N_2O_5$	69.43	5.59	6.48	69.70	5.69	6.37

Table II

Physical and Analytical Data of Compounds V and VIII

Compound	M.p. °C	Yield %	Solvent for recrystallization	Formula	Analysis Calcd. % C	H	N	Found % C	H	N
Va	328-329	85.4	dioxane	$C_{23}H_{12}O_5$	75.00	3.28	-----	74.82	3.37	-----
Vb	326-328	83.9	dioxane	$C_{24}H_{14}O_6$	72.36	3.54	-----	72.26	3.61	-----
Vc	344-346	80.4	dioxane	$C_{25}H_{16}O_5$	75.75	4.07	-----	75.61	4.10	-----
Vd	318-319	85.2	dioxane	$C_{24}H_{15}NO_4$	75.58	3.96	3.67	75.45	3.95	3.58
Ve	324-325	83.2	*N,N*-dimethyl-formamide	$C_{27}H_{14}O_5$	77.51	3.37	-----	77.30	3.41	-----
Vf	335-336	88.2	dioxane	$C_{27}H_{14}O_5$	77.51	3.37	-----	77.43	3.40	-----
VIIIa	263-264	87.6	toluene	$C_{19}H_{10}O_5$	71.69	3.17	-----	71.70	3.11	-----
VIIIb	265-266	86.1	dioxane	$C_{20}H_{12}O_6$	68.96	3.47	-----	68.82	3.46	-----
VIIIc	304-306	83.8	dioxane	$C_{21}H_{15}NO_5$	69.80	4.18	3.88	69.61	4.14	3.92

from the cooled filtrate.

A variation in the general procedure occurred in the preparation of IVc. Actually, a solution of IIIa (0.37 g., 2.3 mmoles) and glacial acetic acid (1.2 ml.) in ethanol (8 ml.) was added during 1 hour to a stirred boiling solution of IIc (7) (0.80 g., 3.0 mmoles) and 40% aqueous formaldehyde (1.2 ml.) in ethanol (8 ml.) and the mixture refluxed for additional 15 minutes. After cooling, IVc was then collected.

Compounds V, VIII.

General Method.

A mixture of compound IV (or VII) (1.0 g.) and glacial acetic acid (30 ml.) was heated at reflux for 0.5 hour. In a few minutes the precipitation of a white solid occurred; after cooling, it was then collected and washed with ethanol.

Solvents for recrystallization, melting points, yields and elemental analyses of compounds V and VIII are reported in Table II.

By the above conditions, IVa yielded 6,8-dioxo-6*H*,7*H*,8*H*-5,15,16-trioxadibenzo[*a,j*]naphthacene (Va); in a like fashion, IVb, IVc and IVd gave rise to the formation of the same compound Va (ir and melting points) in similar yields; IVe or IVf afforded the 10-methoxy derivative Vb; IVg gave the 10,11-dimethyl derivative Vc.

In a like manner, compound IVh or IVi yielded 5,6-dihydro-5-methyl-6,8-dioxo-7*H*,8*H*-5-aza-15,16-dioxadibenzo[*a,j*]naphthacene (Vd); compound IVj gave 6,8-dioxo-6*H*,7*H*,8*H*-5,15,16-trioxabenzo[*a*]naphtho[2,1-*j*]naphthacene (Ve); both compound IVk (4) or IVl (4) afforded 8,10-dioxo-8*H*,9*H*,10*H*-7,17,18-trioxabenzo[*a*]naphtho[1,2-*j*]naphthacene (Vf).

In a similar fashion, compound VIIa yielded 6,8-dioxo-6*H*,7*H*,8*H*-5,13,14-trioxabenzo[*a*]naphthacene (VIIIa); both compound VIIb or VIIc gave rise to the formation of the same 11-methoxy derivative VIIIb; compound VIId gave 5,6-dihydro-5-methyl-6,8-dioxo-11-methoxy-7*H*,8*H*-5-aza-13,14-dioxabenzo[*a*]naphthacene (VIIIc).

Compound IX.

A mixture of VIIb (1.0 g.), ethanol (15 ml.) and 25% aqueous potassium hydroxide solution (15 ml.) was refluxed for 4 hours. After cooling, the solution was acidified by adding concentrated hydrochloric acid and the white solid compound IX which separated out (0.65 g., 69.8%) was collected and recrystallized from ethanol; m.p. 247-250° [lit. m.p. 245-248° (12)].

Anal. Calcd. for $C_{20}H_{14}O_7$: C, 65.57; H, 3.85. Found: C, 65.65; H, 3.94.

6,7,8-Trioxo-11-methoxy-6*H*,7*H*,8*H*-5,13,14-trioxabenzo[*a*]naphthacene (X).

A suspension of chromium trioxide (2.0 g.) in glacial acetic acid (10 ml.) was slowly added to a boiling solution of VIIIb (1.0 g.) in the same solvent (30 ml.). After the addition was complete, refluxing was continued for an additional few minutes, then the mixture was cooled and filtered to recover the white solid compound X which separated out. There was obtained 0.55 g. (52.9%) of material which melted at 392-395° dec., after recrystallization from *N,N*-dimethylformamide.

Anal. Calcd. for $C_{20}H_{10}O_7$: C, 66.30; H, 2.78. Found: C, 66.12; H, 2.82.

Acknowledgment.

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

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