Pergamon

Tetrahedron Vol. 50, No. 16, pp. 4905-4912, 1994

0040-4020/94 $6.00+0.00

0040-4020(94)E0145-J

Benzopyrans - XXXIII[1]. [4+2]Cycloaddition of *N,N*-Dimethylhydrazones and Anils of 2-Unsubstituted and 2-Methyl-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde with *N*-Phenylmaleimide

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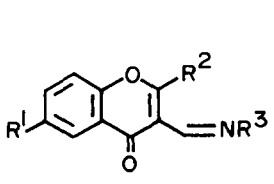
Abstract : The chromone derivatives **1**, **2**, and **4** give with *N*-phenylmaleimide the cycloadducts **5**, **12**, and **13** which are converted by palladised charcoal into 2-azaxanthone **6**, xanthones **14** and **15**, respectively. Treatment of the azaxanthone **5** with acidic ethanol produces a mixture of salicyloylpyridines **7-9**.

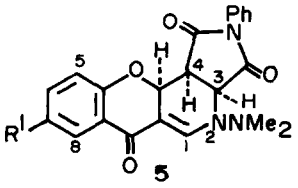
N,N-Dimethylhydrazones of α,β-unsaturated aldehydes undergo [4+2]cycloaddition with a number of representative dienophiles and the resultant cycloadducts on aromatisation with elimination of dimethylamine provide substituted pyridines[2]. Several attempts to synthesise pyridine fused with a heteroaromatic ring by similar cyclisation involving hetaryl aldehyde-*N,N*-dimethylhydrazones as the azadienes have, however, been abortive[3]. Recently, the indolo[2,1-c]pyridine system has been constructed from the *N,N*-dimethylhydrazone of indole-3-carboxaldehyde and *N*-methylmaleimide[4]. So far as the [1]benzopyran system is concerned, 4-oxo-4*H*-1-benzopyran-3-carboxaldehyde (3-formylchromone) has its pyran 2,3- and aldehydic double bonds in the cisoid configuration[5] and its heterodiene activity in the Diels-Alder reaction is well demonstrated[6]. [4+2]Cycloaddition of the Schiff base of 3-formylchromone with highly reactive dienophiles like ketenes is also successful[7]. Low azadiene activity of the Schiff base corresponding to 3-formylchromone is due to electron withdrawing effect of the pyrone carbonyl group. We contended that in the hydrazones **1** and **2**, the strongly electron donating dimethylamino group was likely to compensate for, if not overcome, the electron withdrawing effect of the carbonyl group so that these two hydrazones **1** and **2** might

function as reasonably reactive 1-azadienes and consequently good synthons for the pyranopyridine system; again, the anils **3** and **4** due to the electron donating methyl group attached to their aniline moiety were anticipated to be at least more active azadienes than the analogous anils (**3** and **4**, Ph in place of C_6H_4Me-*p*). In order to prove the validity or otherwise of these contentions, the chromones **1–4** were subjected to reaction with *N*-phenylmaleimide (NPMI), a moderately active dienophile and the results are presented in this paper.

The hydrazone **1**, derived from the appropriate 3-formylchromone and 1,1-dimethylhydrazine, on being refluxed with NPMI in toluene gave the endo-adduct *cis* -2-dimethylamino-*N*-phenyl-2,3,4,4a-tetrahydro-9-oxo-9*H*-2-azaxanthene-3,4-dicarboximide **5** (Table 1); dienophile mediated elimination of dimethylamine[3,4] from the dimethylhydrazone **1** leading to the corresponding 3-cyanochromone did not take place at all. In the PMR spectrum of the adduct, 4-H appears at *ca* δ 4.05 as a pseudo



	R^2	R^3
1	H	NMe_2
2	Me	NMe_2
3	H	C_6H_4Me-*p*
4	Me	C_6H_4Me-*p*



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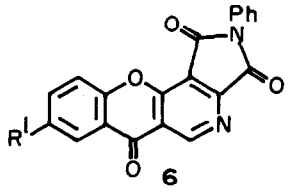
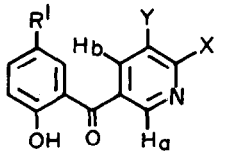
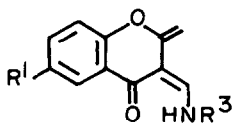


6



	X	Y
7	CONPhCO	
8	CO_2Et	CONHPh
9	H_c	CONHPh



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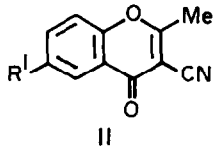

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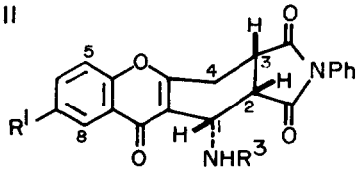
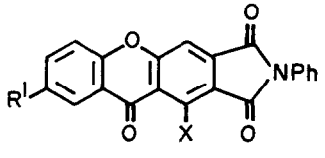


12 $R^3 = NMe_2$

13 $R^3 = C_6H_4Me$-*p*



14 X = H

15 X = NHC_6H_4Me-*p*

1-15	**a**	**b**	**c**	**d**
R^1	H	Me	Cl	Br

triplet (double doublets with middle two peaks merging together) with J 8 and 8 Hz. Examination of the molecular models generated by energy minimization in Desk Top Molecular Modeller (DTMM) (Version 1.2, Oxford University Press) shows that the isomeric structure **5** having its nitrogen containing six membered ring in semi-boat conformation and all its ring juncture hydrogen cis to each other is to be preferred for the adduct, since it can explain the observed J values better. This stereochemical feature is similar to that present in an all-carbon Diels-Alder adduct obtained from a 3-vinylindole derivative and NPMI[8]. Pd-C converted the cycloadduct **5** to *N*-phenyl-9-oxo-9*H*-2-azaxanthene-3,4-dicarboximide **6** (Table 1). When heated under reflux in ethanol containing a few drops of sulphuric acid, **5** gave a mixture of varying amounts of 5-salicyloylpyridines **7-9**. Here protonation of the pyran ring oxygen and dimethylamino nitrogen of **5** triggers pyran ring opening and elimination of dimethylamine leading to pyridine **7** (Table 2), aromatic stabilisation facilitating the reaction. Acid catalysed nucleophilic attack of ethanol to the relatively more positive carbon of pyridine-2-carbonyl group of **7** resulted in **8** (Table 2), the latter undergoing hydrolysis and subsequent decarboxylation to **9** under reaction conditions.

The hydrazone **2** behaved differently from its homologue **1** towards NPMI in giving the tetrahydroxanthone **12** together with a little amount (~10%) of 3-cyano-2-methylchromone **11**. The appearance of 2-H at δ 3.30 having coupling constants of 3.5 and 9.0 Hz respectively with 1-H and 3-H as observed after simplification of the complicated nature of the spectrum at δ 3.80-2.90 region by appropriate

Table 1. 2-Azaxanthones **5** and **6**

Comp[a].	Yield (%)	M.p. (°C)	δ (100 MHz, $CDCl_3$, TMS)							
			8-H (m)	1-H (s)	ArH (m)	4a-H[b]	3-H[b]	4-H[c]	NMe_2 (s)	ArMe (s)
5a	64	180	8.00	7.92	7.60-6.88	5.26	4.76	4.04	2.80	-
5b	58	186	7.80	7.92	7.60-6.80	5.22	4.74	4.04	2.82	2.32
5c	61	186	7.96	7.96	7.64-6.84	5.24	4.76	4.06	2.80	-
5d	48	200	8.10	7.94	7.58-6.78	5.24	4.76	4.06	2.80	-
6a	25	d	8.20	9.88	7.80-7.40	-	-	-	-	-
6b	32	d	8.20	9.88	7.76-7.44	-	-	-	-	2.52
6c	30	d	8.40	9.90	8.00-7.36	-	-	-	-	-
6d	24	d	8.38	9.90	7.80-7.42	-	-	-	-	-

[a]All the compounds gave satisfactory microanalyses; [b]Doublet, J 8Hz; [c]Double doublet J 8,8 Hz; [d]The compounds decomposed at about 270°.

Table 2. 5-Salicyloylpyridines **7** and **8**

Comp.[a]	Yield (%)	M.p. (°C)	δ (100 MHz, $CDCl_3$, TMS) OH (s)	NH (brs)	Ha(d) J 1.5	H_b(d) J 1.5	ArH (m)	OCH_2 (q)	CH_2Me (t)
7a	32	220	11.64	-	9.32	8.56	7.76-6.88	-	-
7c	20	258	11.52	-	9.36	8.56	7.68-7.04	-	-
7d	15	270	11.56	-	9.36	8.58	7.70-7.02	-	-
8a	16	170	11.76	9.80	9.00	8.20	7.88-6.88	4.56	1.36
8b[b]	28	178	11.56	9.76	8.92	8.16	7.84-6.96	4.48	1.40
8c	22	195	11.60	9.76	8.96	8.20	7.88-6.96	4.56	1.36
8d	36	198	11.70	9.78	8.96	8.20	7.86-6.92	4.56	1.36

[a]All the compounds gave satisfactory elemental analysis; [b]Aromatic methyl protons appear as a singlet at δ 2.24.

decoupling experiments is compatible with the energy minimised structure **12** obtained with the help of DTMM, the ring C of **12** assuming a semi-boat conformation. Here the unsaturated hydrazone **2**, like several β-alkyl-α,β-unsaturated imines[9], participates through its enehydrazine tautomer **10** (R^3 = NMe_2) in the normal Diels-Alder reaction with NPMI giving the endo-adduct **12**. It is relevant to mention here that 1,2,3-trisubstituted tetrahydroxanthones obtained by cycloaddition of 2-styrylchromone with maleic anhydride and *N*-phenylmaleimide[10] have the same relative stereochemical feature as present in the cycloadduct **12**. Formation of **11** from **2** and NPMI indicates that an elimination reaction[3,4] competes to some extent with the cycloaddition process. The adduct **12** was dehydrogenated and dehydrazinated by Pd-C to the 2,3-disubstituted xanthone **14**.

The anil **3** failed to react with NPMI whereas its homologue **4**, like the analogous hydrazone **2**, gave through its imine tautomer **10** (R^3 = C_6H_4Me-*p*) a cycloadduct, the PMR spectrum of which is compatible with the isomer **13**, an energy minimised structure procured through DTMM modelling studies. The cycloadduct **13** was dehydrogenated by Pd-C to the substituted xanthone **15**.

The results presented in this paper reveal that [4+2]cycloaddition of various dienophiles with the dimethylhydrazone **1** followed by treatment with palladised carbon is a new addition to the known methods[11,12] for constructing 2-azaxanthone system from easily accessible chromone derivatives. Again, the presently reported formation of xanthones involving [4+2]cycloaddition of 2-alkyl-3-iminomethylchromones like **2** and **4** even with moderately active dienophiles compares well with the various methods for utilising chromone derivatives as synthons for xanthones[10,13].

EXPERIMENTAL

The reported melting points are uncorrected. PMR spectra were recorded at 300 MHz for **12** and **13**, and at 100 MHz for others in $CDCl_3$ solution. The chemical shifts are recorded as δ values and J values in Hz. Light petroleum refers to the fraction with b.p. 60–80°.

2-Unsubstituted and 2-methyl-3-(N,N-dimethylhydrazonomethyl)chromone **1** *and* **2**

The compound **1d** (82%), m.p. 132° was prepared from 6-bromo-3-formylchromone and 1,1-dimethylhydrazine following the method reported earlier for the preparation of its analogues **1a,b,c**[14]. Preparation of the hydrazone **2a** was described earlier[11]. The other member **2c** similarly prepared in 72% yield from 6-chloro-3-acetylchromone had m.p. 122°.

2-Methyl-3-(p-tolyliminomethyl)chromone **4**

Refluxing a mixture of *p*-toluidine (535 mg, 5 mmol) and the appropriate 3-acetylchromone (5 mmol) in benzene (100 ml) in a Dean-Stark apparatus for 4 h followed by usual work-up afforded the yellow coloured anil **4**. The compound **4a** (57%) and **4c** (65%) melted at 164° and 172°, respectively.

2-Dimethylamino-N-phenyl-2,3,4,4a-tetrahydro-9-oxo-9H-2-azaxanthene-3,4-dicarboximide **5**

A mixture of the hydrazone **1** (1 mmol) and *N*-phenylmaleimide (173 mg, 1 mmol) was heated under reflux in toluene for 6 h. A portion of the solvent was distilled off, the reaction mixture cooled, the deposited solid filtered off and crystallised from benzene to afford azaxanthene **5** (Table 1) as grey crystals.

2-Dimethylamino-N-phenyl-9-oxo-9H-2-azaxanthene-3,4-dicarboximide **6**

The preceding tetrahydroxanthene **5** (0.5 mmol) and catalytic amount of Pd-C were heated together under reflux in *p*-cymene (15 ml) for 15 h. The reaction mixture was filtered hot, the filtrate cooled and diluted with light petroleum when a yellow coloured solid compound precipitated out. It was collected by filtration and crystallised from chloroform-light petroleum to give the azaxanthone **6** (Table 1).

Treatment of the azaxanthone **5** *with acidic ethanol*

The compound **5** (0.75 mmol) was heated under reflux in ethanol (25 ml) containing water (3–5 ml) and conc. sulphuric acid (6–8 drops) for 15 h. The reaction mixture was then concentrated, cooled, and poured into ice-water (25 ml). The deposited solid was collected by filtration, washed with water, dried, and subjected to column chromatography over silica gel using a 1:6 mixture of ethyl acetate and light petroleum as the eluant. Ethyl 3-phenylcarbamoyl-5-salicyloylpyridine-2-

carboxylate **8**, *N*-phenyl-5-salicyloylpyridine-2,3-dicarboximide **7**, and *N*-phenyl-5-salicyloylpyridine-3-carboxamide **9** came out in order of elution. Each of these products was further crystallised from chloroform–light petroleum. The characterisation data of **7** and **8** are presented in Table 2 and those of **9** given below.

9a : Yield 10%; m.p. 165° (Found : C, 71.9; H, 4.0; N, 8.6. $C_{19}H_{12}N_2O_3$ requires C, 71.7; H, 4.4; N, 8.8%); PMR : 11.76 (1H, s, exchangeable, OH), 9.30 (1H, m, Ha), 9.08 (1H, m, Hc), 8.52 (1H, m, Hb), 8.00 (1H, m, PhH *ortho* to CO), and 7.80–6.88 (9H, m, NH + other PhH).

9b : Yield 8%; m.p. 120° (Found : C, 71.9; H, 4.5; N, 8.6. $C_{20}H_{14}N_2O_3$ requires C, 72.3; H, 4.9; N, 8.4%); PMR : 11.76 (1H, s, exchangeable, OH), 9.28 (1H, m, Ha), 9.04 (1H, m, Hc), 8.48 (1H, m, Hb), 8.10 (1H, m, PhH *ortho* to CO), 7.92–7.00 (8H, m, NH + other PhH), and 2.24 (3H, s, PhMe).

The pyridines **9c** and **9d** could not be isolated.

Treatment of the hydrazone **2** *with N-phenylmaleimide*

The hydrazone **2a** (2.0 g, 8 mmol) and NPMI (1.50 g, 8 mmol) were heated together in toluene (50 ml) for 8 h. The reaction mixture was then concentrated and diluted with light petroleum. The resultant oily mass was triturated with acetone, the precipitated solid was filtered off, and crystallised from chloroform to afford *cis*-1-(2,2-dimethylhydrazino)-*N*-phenyl-1,2,3,4-tetrahydro-9-oxo-9*H*-xanthone-2,3-dicarboximide **12a** (1.33 g, 40%), m.p. 200° (Found : C, 68.8; H, 5.2; N, 10.7. $C_{23}H_{21}N_3O_4$ requires C, 68.5; H, 5.2; N, 10.4%); PMR : 8.24 (1H, dd, J 8, 1.7, 8-H), 7.80–7.32 (8H, m, other ArH), 5.33 (1H, d, J 3.5, 1-H), 3.65 (1H, dd, J 16.5, 6.5, 4β-H), 3.53 (1H, ddd, J 10, 9, 6.5, 3-H), 3.30 (1H, dd, J 9, 3.5, 2-H), 3.10 (1H, dd, J 16.5, 10, 4α-H), and 2.28 (6H, s, NMe_2). The mother liquor from the above filtration was chromatographed over silica gel using ethyl acetate–light petroleum (1:2) as eluant. The eluate on concentration afforded the nitrile **11a** (100 mg, 10%), m.p. 192° (lit.[15], m.p. 194°).

The hydrazone **2c** on similar treatment with NPMI gave **11c** (14%), m.p. 198°, identical with an authentic sample derived from 6-chloro-3-acetylchromone and hydroxylamine[15], and the dicarboximide **12c** (54%), m.p. 280° (decomp.) (Found : C, 62.8; H, 4.2; N, 10.0. $C_{23}H_{20}N_3ClO_4$ requires C, 63.1; H, 4.6; N, 9.6%); PMR : 8.34 (1H, d, J 1.5, 8-H), 7.70–7.32 (7H, m, other ArH), 5.30 (1H, d, J 3.5, 1-H), 3.64 (1H, dd, J 16.5, 6.5, 4β-H), 3.52 (1H, ddd, J 10,9,6.5, 3-H), 3.30 (1H, dd, J 9,3.5, 2-H), 3.10 (1H, dd, J 16.5, 10, 4α-H), and 2.30 (6H, s, NMe_2).

Treatment of the anils **3** *and* **4** *with N-phenylmaleimide*

A solution of **3a**[16] (263 mg, 1 mmol) and NPMI (173 mg, 1 mmol) in toluene (50 ml) was refluxed for 10 h. TLC of the reaction mixture showed the presence of only two starting materials, each of which was recovered by fractional crystallisation. The anil **4** was similarly treated with NPMI. A small amount of white

amorphous solid (m.p. >280°) that separated out from the reaction mixture even under boiling condition was filtered off and rejected. The mother liquor from the above filtration was concentrated and chromatographed over silica gel. The solid material eluted by a 1:2 mixture of ethyl acetate-light petroleum was crystallised from chloroform to give *cis*-*N*-phenyl-1-(*p*-tolylamino)-1,2,3,4-tetrahydro-9-oxo-9*H*-xanthene-2,3-dicarboximide **13** as colourless crystals.

13a : Yield 52%; m.p. 160° (Found : C, 74.9; H, 4.5; N, 6.5. $C_{28}H_{22}N_2O_4$ requires C, 74.6; H, 4.9; N, 6.2%); PMR : 8.17 (1H, dd, J 7.9, 1.2, 8-H), 7.68-6.73 (12H, m, other ArH), 5.83 (1H, d, J 4.3, 1-H), 3.68 (1H, m, 3-H), 3.55 (1H, dd, J 18.3, 5.9, 4β-H), 3.30 (1H, dd, J 9, 4.3, 2-H), 3.21 (1H, dd, J 18.3, 10.6, 4α-H), and 2.22 (3H, s, Me).

13c : Yield 47%; m.p. 240° (decomp.) (Found : C, 69.0; H, 3.9; N, 5.6. $C_{28}H_{21}N_2ClO_4$ requires C, 69.3; H, 4.4; N, 5.8%); PMR : 8.12 (1H, d, J 1.5, 8-H), 7.72-6.68 (11H, m, other ArH), 5.86 (1H, d, J 4.3, 1-H), 3.70 (1H, m, 3-H), 3.56 (1H, dd, J 18.3, 5.9, 4β-H), 3.30 (1H, dd, J 9, 4.3, 2-H), 3.22 (1H, dd, J 18.3, 10.6, 4 -H), and 2.20 (3H, s, Me).

1-Unsubstituted and 1-(p-tolylamino)-N-phenyl-9-oxo-9H-xanthene-2,3-dicarboximide **14** and **15**

Each of the tetrahydroxanthones **12** and **13** (0.1 mmol) was heated under reflux in *p*-cymene (15-20 ml) containing catalytic amount of Pd-C for 10-12 h. The reaction mixture was filtered hot, the solid residue washed with hot benzene, the combined filtrate was concentrated and cooled. The deposited solid was filtered off and crystallised from chloroform. This process converted **12** into **14** as yellow crystals and **13** into red crystalline **15**, the characterisation data of these xanthone derivatives being given below.

14a : Yield 46%; m.p. >300° (Found : C, 74.2; H, 3.0; N, 4.2. $C_{21}H_{11}NO_4$ requires C, 73.9; H, 3.2; N, 4.1%); PMR : 8.98 (1H, s, 1-H), 8.40 (1H, dd, J 8, 2, 8-H), 8.08 (1H, s, 4-H), and 7.88-7.32 (8H, m, ArH).

14c : Yield 38%; m.p. >300° (Found : C, 67.5; H, 2.4; N, 3.3. $C_{21}H_{10}NClO_4$ requires C, 67.1; H, 2.7; N, 3.7%); PMR : 8.98 (1H, s, 1-H), 8.44 (1H, d, J 2, 8-H), 8.04 (1H, s, 4-H), and 7.88-7.32 (7H, m, ArH).

15a : Yield 58%; m.p. 228° (Found : C, 75.4; H, 3.8; N, 6.0. $C_{28}H_{18}N_2O_4$ requires C, 75.3; H, 4.1; N, 6.3%); PMR : 12.08 (1H, brs, NH), 8.32 (1H, dd, J 8,2, 8-H), 7.84-6.96 (16H, m, ArH).

15c : Yield 42%; m.p. 242° (Found : C, 70.2; H, 3.3; N, 5.6. $C_{28}H_{17}N_2ClO_4$ requires C, 69.9; H, 3.6; N, 5.8); PMR : 12.06 (1H, brs, NH), 8.42 (1H, d, J 2, 8-H), 7.86-6.94 (15H, m, ArH).

Acknowledgement : Research associateship awarded to K. B. by C S I R, New Delhi is gratefully acknowledged. Thanks are due to Dr. A. Patra, Department of Chemistry,

Calcutta University for helpful discussion and to Dr.(Mrs.) N. Ghosal, IICB, Calcutta for help with modelling studies.

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(*Received in UK* 31 *December* 1993; *revised* 2 *February* 1994; *accepted* 4 *February* 1994)