Benzopyranopyridine Derivatives 3. Reaction of 1-Azaxanthone with Grignard Reagents

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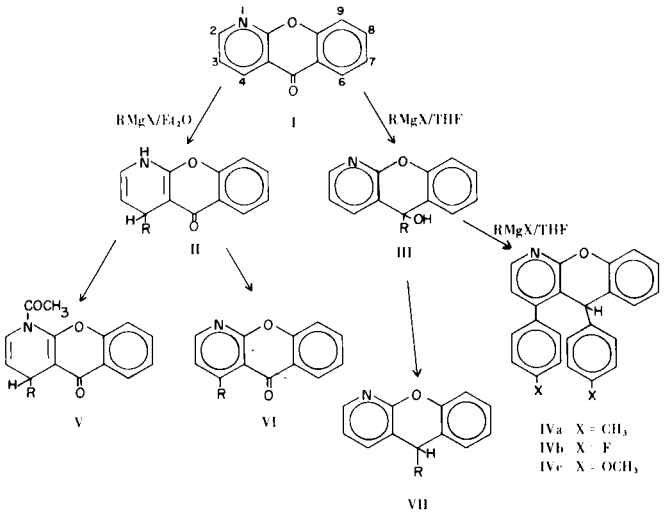
Three different classes of compounds were isolated in the reaction of Grignard reagents with 5-*H*[1]benzopyrano[2,3-*b*]pyridin-5-one, commonly called 1-azaxanthone. The formation of (a) 4-substituted 1,4-dihydro-1-azaxanthones (II), (b) 5-substituted-5-hydroxy-1-azaxanthenes (III) or (c) 4,5-disubstituted-1-azaxanthenes (IV) is dependent on the solvent used in the preparation of the Griganrd reagent (*i.e.* ether or tetrahydrofuran), the steric properties of the reagent and on the temperature. The isolated compounds were characterized by chemical derivatives and/or spectroscopic analyses.

We wish to report an unusual solvent, steric and temperature dependent effect in the reaction of Grignard reagents with 1-azaxanthone (I) (2). When I was treated with phenylmagnesium bromide prepared in ether, only 4-phenyl-1,4-dihydro-1-azaxanthone (II) was obtained. The formation of II was not entirely unexpected especially since this type of addition has been previously reported in the case of 3-benzoylpyridine (3a,3b). However, the addition of I to phenylmagnesium bromide prepared in tetrahydrofuran resulted in the formation of the tertiary carbinol III in good yield. This observation was extended to include a study of the reaction of I with a variety of Grignard reagents and forms the basis of the present communication.

Throughout this work, no attempt was made to maximize yields as all reactions were carried out under an arbitrarily standardized procedure. It was soon apparent that the steric properties of the Grignard reagent and the solvent in which it was prepared played a major role in the course of the reaction. Aromatic type Grignard reagents including substituted phenyl, benzyl, thienyl in addition to the highly strained cyclopropyl and the bulky cyclohexyl, when prepared in ether gave the 5-substituted-1,4-dihydro-1-azaxanthones (II) in all cases. These compounds, (listed in Table I) were converted into the 1-acetyl derivatives (V) in the usual way (included in Table I). In addition, the dihydropyridines II were aromatized to the pyridyl derivatives VI by dehydrogenation with chloranil. These compounds are listed in Table II. The structures of all compounds were confirmed by the usual spectral analyses. The important spectral properties supporting the assigned structures II and V are listed in Table IV.

SCHEME I



SCHEME II

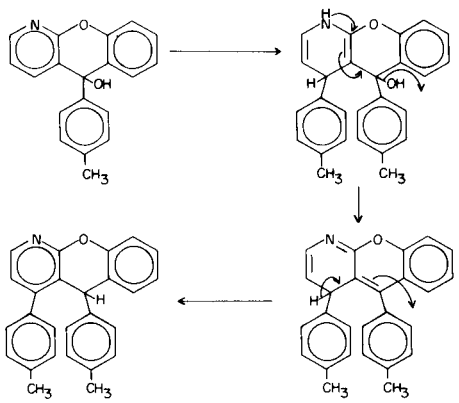
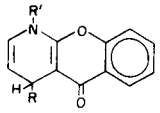
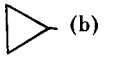
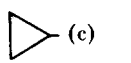


Table I

Compounds of Formula

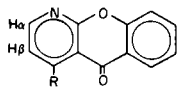


Compound	R	R^1	Yield	M.p. °C (a)	Formula	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	C_6H_5 (b)	H	43	230-232	$C_{18}H_{13}NO_2$	78.53	4.76	5.09	78.34	4.87	5.28
2	C_6H_5 (c)	$COCH_3$	80	134-135	$C_{20}H_{15}NO_3$	75.69	4.76	4.41	75.33	4.71	4.27
3	*p*-CH_3-C_6H_4 (b)	H	36	221-223	$C_{19}H_{15}NO_2$	78.87	5.23	4.84	78.90	4.88	4.89
4	*p*-CH_3-C_6H_4 (c)	$COCH_3$	51	187-188 (d)	$C_{21}H_{17}NO_3$	76.11	5.17	4.23	76.37	4.96	4.13
5	*p*-F-C_6H_4 (b)	H	28	225-226	$C_{18}H_{12}FNO_2 \cdot \frac{1}{2}H_2O$	71.52	4.30	4.63	71.57	4.08	4.95
6	*p*-F-C_6H_4 (c)	$COCH_3$	78	157-160	$C_{20}H_{14}FNO_3$	71.63	4.20	4.17	71.53	4.28	4.10
7	*p*-OCH_3-C_6H_4 (b)	H	41	230-232	$C_{19}H_{15}NO_3$	74.74	4.95	4.59	74.70	4.98	4.49
8	*p*-OCH_3-C_6H_4 (c)	$COCH_3$	64	148-150	$C_{21}H_{17}NO_4$	72.61	4.93	4.03	72.41	4.96	3.80
9	$C_6H_5CH_2$ (b)	H	50	208-210	$C_{19}H_{15}NO_2$	78.89	5.19	4.84	78.67	5.41	4.75
10	$C_6H_5CH_2$ (c)	$COCH_3$	51	110-112	$C_{21}H_{17}NO_3$	76.13	5.13	4.12	75.80	5.19	3.99
11	2-C_4H_3S (b)	H	47	254-256	$C_{16}H_{11}NO_2S$	68.32	3.94	4.98	68.20	3.79	4.88
12	2-C_4H_3S (c)	$COCH_3$	40	189-190	$C_{18}H_{13}NO_3S$	66.87	4.05	4.33	66.68	4.13	4.27
13	C_6H_{11} (b)	H	36	230-232 (e)	$C_{18}H_{19}NO_2$	76.84	6.80	4.97	76.78	6.43	4.73
14	 (b)	H	47	180-182	$C_{15}H_{13}NO_2$	75.31	5.44	5.86	75.06	5.56	5.73
15	 (c)	$COCH_3$	81	162-163	$C_{17}H_{15}NO_3$	72.59	5.38	4.98	72.42	5.32	4.94

(a) All compounds recrystallized from methanol except as noted. (b) Method 1. (c) Method 3. (d) Recrystallized from acetonitrile. (e) Recrystallized from ethyl acetate.

Table II

Compounds of Formula

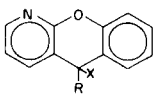


Compound	R	Yield	M.p. °C (a)	Formula (b)	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
16	C_6H_5	74	210-212	$C_{18}H_{11}NO_2$	79.11	4.06	5.13	78.92	4.00	5.11
17	p-$CH_3C_6H_4$	78	191-192 (c)	$C_{19}H_{13}NO_2$	79.43	4.56	4.88	79.60	4.34	4.72
18	p-F-C_6H_4	42	205-207	$C_{18}H_{11}FNO_2$	73.72	3.43	4.81	73.50	3.51	4.70
19	p-$OCH_3C_6H_4$	85	190-192	$C_{19}H_{13}NO_3$	75.23	4.32	4.61	74.99	4.47	4.52
20	$C_6H_5CH_2$	87	113-115 (d)	$C_{19}H_{13}NO_2$	79.43	4.56	4.88	79.82	4.22	4.54
21	2-C_4H_3S	64	168-170 (c)	$C_{16}H_9NO_2S$	68.82	3.25	5.02	68.52	3.40	5.05
22	C_6H_{11}	87	142-143	$C_{18}H_{17}NO_2$	77.39	6.14	5.02	77.35	6.11	4.88
23		90	130-131	$C_{15}H_{11}NO_2$	75.93	4.61	5.90	75.69	4.49	5.66

(a) All compounds recrystallized from methanol except as noted. (b) For all compounds the Hα proton appears as a doublet between δ 8.50 and δ 8.90 with a coupling constant of 5 Hz. The Hβ proton is found in the aromatic multiplet between δ 7.15-8.0. In all cases the integration supports the structures shown. The carbonyl frequency in the ir spectrum appears at 5.95-6.0 μ for all compounds. (c) Recrystallized from acetonitrile. (c) The $C_6H_5CH_2$ protons appear as a singlet at δ 4.98.

Table III

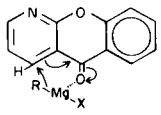
Compounds of Formula



Compound	R	X	Yield	M.p. °C (a)	Formula	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
24	C_6H_5 (b)	OH	51	227-228	$C_{18}H_{13}NO_2$	78.53	4.76	5.09	78.84	4.83	5.00
25	C_6H_5 (c)	H	81	153-154	$C_{18}H_{13}NO$ (d)	83.37	5.05	5.40	83.53	5.19	5.65
26	p-CH_3-C_6H_4 (b)	OH	54	200-201	$C_{19}H_{15}NO_2$	78.87	5.23	4.84	79.08	5.35	4.52
27	p-CH_3-C_6H_4 (c)	H	85	150-152	$C_{19}H_{15}NO$	83.49	5.53	5.12	83.19	5.61	4.90
28	p-F-C_6H_4 (b)	OH	28	198-200	$C_{18}H_{12}FNO_2$ (d)	73.71	4.09	4.77	73.68	4.29	5.12
29	p-F-C_6H_4 (c)	H	46	105-107	$C_{18}H_{12}FNO$	77.92	4.33	5.05	77.62	4.55	4.72
30	p-OCH_3-C_6H_4 (b)	OH	56	170-172	$C_{19}H_{15}NO_3$	74.74	4.95	4.59	74.60	5.08	4.43
31	p-OCH_3-C_6H_4 (c)	H	35	95-97	$C_{19}H_{15}NO_2$ (e)	78.87	5.23	4.84	78.38	5.30	4.65
32	2-C_4H_3S (b)	OH	46	185-187	$C_{16}H_{11}NO_2S$	68.32	3.94	4.98	68.41	3.91	5.11
33	2-C_4H_3S (c)	H	70	174-176	$C_{16}H_{11}NOS$	72.44	4.18	5.28	72.31	4.22	5.40
34	 (b)	OH	27	135-136	$C_{15}H_{13}NO_2$	75.30	5.48	5.85	74.93	5.43	5.76

(a) All compounds recrystallized from acetonitrile except as noted. (b) Method 2. (c) Method 4. (d) Recrystallized from hexane. (e) Recrystallized from isopropyl ether.

In tetrahydrofuran, however, in the majority of cases the reaction followed a different course with attack on the carbonyl function and isolation of compounds of type III. Two exceptions in tetrahydrofuran were noted, namely the cyclohexyl and the benzyl Grignard reagents which gave exclusively the dihydroazaxanthone derivatives of formula II. We suggest that this variance in results is due to the steric nature of these reagents favoring a 6-membered transition state as shown in VIII.



VIII

The tertiary carbinols prepared in this work are listed in Table III and their spectral characteristics are listed in Table V. Reduction of III to the 5-substituted azaxanthenes (VII) was effected in formic acid and sodium carbonate (4). Compounds of formula VII exhibited sharp singlets between δ 5.27-5.62 in their nmr spectra such resonances assigned to the azaxanthydryl proton at position 5.

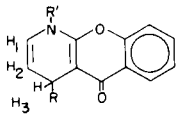
p-Methylphenylmagnesium bromide prepared in tetrahydrofuran on reaction with I, under the standard conditions used in this work, resulted in the isolation of a third type of reaction product shown in IVa. This same type of compound (IVb and IVc) was obtained, albeit in small yield as a side product, in the reaction of the *p*-fluorophenyl and *p*-methoxyphenyl Grignard reagents with I. In the last two mentioned examples the tertiary carbinols (III) were obtained as the major products in yields of 28 and 56% respectively. 5-*p*-Methylphenyl-5-hydroxy-1-azaxanthene (III R = *p*-MeC_6H_4) was obtained in 54% yield by modifying the reaction conditions and carrying out the reaction at 0-5° for a short reaction time.

The structure of IVa was confirmed by its nmr spectrum which showed in addition to the doublet at δ 8.2, J = 5 Hz, (α pyridyl proton), a singlet at δ 5.28 (1 Azaxanthydryl proton at position 5) and 2 sharp singlets at δ 2.15 and δ 2.45 (3 protons each due to the two *p*-methyl groups).

To explain the formation of IVa, the tertiary carbinol III (R = *p*-MeC_6H_4) was treated with *p*-methylphenylmagnesium bromide prepared in tetrahydrofuran and compound IVa was obtained (34%). A proposed mechanism for the formation of IVa is shown in Scheme II.

Table IV

Spectral Data for Compounds of Table I of Formula

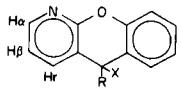


Compound	NH	Ir μ C=O	δ R_1 = H	δ R_1 = $COCH_3$	δ H_1 (J Hz)	H_2 (J Hz)	H_3 (J Hz)	δ Other		
1	3.2	6.00	9.46		6.24 (7.5)	4.76 (a)				
2		6.08; 6.15		2.78	(b)	5.62 (4.5)	4.86 (4.5)			
3	3.2	6.00	9.60		6.24 (7.5)	5.07 (a)		pCH_3	2.20	
4		5.85; 6.00		2.22	(b)	5.58 (5)	4.96 (5)	p-CH_3	2.70	
5	3.2	6.00	8.81		6.30 (7.5)	4.94 (a)	4.84 (4.5)			
6		5.90; 6.00		2.72	(b)	5.60 (5)	5.03 (5)			
7	3.2	6.0	9.62		6.28 (7.5)	4.88 (a)		OCH_3	3.80	
8		5.85; 6.00		2.22	(b)	5.70 (5)	5.08 (5)	OCH_3	3.89	
9	3.2	6.00	9.13		6.03 (8.5)	4.67 (4.5)	4.01 (4.5)	CH_2	2.90	(4 Hz)
10		5.85; 6.00		2.26	(b)	5.44 (5)	3.98 (5)	CH_2	2.85	(5 Hz)
11	3.2	6.00	9.78		6.38 (7.5)	5.15 (a)				
12		5.90; 6.05		2.70	(b)	5.85 (5)	5.18 (5)			
13	3.2	6.0	9.36		6.28 (7.5)	4.87 (4.5)	3.65	C_6H_{11}	1.2	
14	3.2	6.0	9.36		6.22 (7.5)	4.76 (4.5)	3.57 (4.5)		1.05	
15		5.90; 6.00		2.70	(b)	5.50 (5.0)	3.62 (5)		1.00	

(a) In the nmr spectra of compounds **1**, **3**, **7** and **11** the H_2 and H_3 protons appear as a complex multiplet whereas in compound **5**, these two protons appear at δ 4.94 [($J_{H_2H_1}$ 7.5 Hz and $J_{H_2H_3}$ 4.5 Hz)] and δ 4.84 ($J_{H_3\text{-}H_2}$ 4.5 Hz). (b) In compounds **2**, **4**, **6**, **8**, **10**, **12** and **15**, the H_1 protons resonate with the aromatic protons as a multiplet in the region between δ 7.58 and δ 8.87.

Table V

Nmr Data for Compounds of Table III having Formula



Compound	δ Hα(a)(b)	δ Hγ	δ X	Other δ
24	8.18	7.8 (c)	3.68	
25	8.20	7.36 (d)	5.30 (e)	
26	8.18	7.8 (c)	3.42	*p*-CH_3 2.30 (e)
27	8.23	7.45 (d)	5.27 (e)	*p*-CH_3 1.69 (e)
28	8.35	5.8 (c)	3.21	
29	9.61	8.28 (d)	5.35 (e)	
30	8.17	7.8 (c)	3.3	p-OCH_3 5.75 (e)
31	8.18	7.47 (d)	5.24 (e)	p-OCH_3 3.72 (e)
32	8.30	8.13 (c)	3.3	
33	8.31	7.71 (d)	5.62 (e)	
34	8.25	7.78 (c)	2.85	 1.18 (f)(g)

(a) $J_{\alpha,\beta}$ 5 Hz; $J_{\alpha,\gamma}$ 2 Hz. (b) Hβ appears under the aromatic multiplet. In all cases the integration supports the structures. (c) $J_{\gamma,\beta}$ 8 Hz: $J_{\gamma,\alpha}$ 2 Hz. (d) $J_{\gamma,\beta}$ 3 Hz; $J_{\gamma,\alpha}$ 2 Hz. (e) Singlet. (f) Multiplet. (g)  appears as a doublet at δ 0.43 (J 7 Hz) 4 protons.

These results indicate a marked qualitative difference in chemical properties of the Grignard reagents prepared in ether or in tetrahydrofuran. To further test this hypothesis, phenylmagnesium bromide was prepared in both solvents and the solvents were displaced by benzene (Method 5A, 5B). Addition of I to the benzene solutions of the preformed Grignard reagents resulted in the isolation of II and III respectively indicating that the solvent plays an important role in the formation and structure of the Grignard reagent (5).

EXPERIMENTAL

All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by the Physical Analytical Services Department of the Schering Corporation. Ir spectra were taken on a Perkin-Elmer model 137 spectrometer in Nujol mulls. Nmr spectra of compounds of Table I were obtained on a Varian A-60-A spectrometer in DMSO-d6 using tetramethylsilane as internal reference. The nmr spectra of all other compounds were run in deuteriochloroform.

1,4-Dihydro-4-phenyl-1-azaxanthone (II). General Method 1.

The Grignard reagent was prepared in the usual manner from magnesium (3.6 g., 0.15 g.-atoms) and bromobenzene (23.6 g.; 0.15 mole) in ether (100 ml.) using a crystal of iodine. To this solution was added with cooling in an ice bath a suspension of I (19.7 g., 0.1 mole) in 200 ml. of ether. There was an immediate precipitation of an orange-brown solid mass causing difficulty in stirring. Stirring was continued for 30 minutes and the mixture was heated on the steam bath under reflux for 3 hours. Aqueous ammonium chloride (20% solution) was added dropwise and the mixture was filtered, the precipitate washed with water and after air drying was recrystallized from the solvent indicated in Table I.

5-Hydroxy-5-phenyl-1-azaxanthene (III). General Method 2.

The Grignard reagent was prepared as above using THF as solvent. Ketone I (19.7 g., 0.1 mole in 200 ml. of THF) was added as a suspension and the dark red brown solution was heated under reflux with stirring for 3 hours. Most of the THF was removed by distillation *in vacuo* on the steam bath and the residue was decomposed by cautious addition of aqueous ammonium chloride solution (20%). The product was extracted with chloroform, the extracts were washed with water and the solvent removed. The residue was triturated with hexane and recrystallized.

4,5-Di-*p*-methoxyphenyl-1-azaxanthene (IVc).

By concentration of the hexane triturates from the reaction of *p*-methoxyphenylmagnesium bromide in tetrahydrofuran using general method 2, the title compound was obtained; yield 2. g. (5.1%), m.p. 149-150°; nmr: δ 8.35 ($J_{\alpha\beta}$ 5 Hz, α pyridyl proton); δ 5.35 (5-azaxanthydryl proton) and δ 3.93 and δ 3.75 (*p*-OCH_3 protons); m/e 395.

Anal. Calcd. for $C_{26}H_{21}NO_3$: C, 78.76; H, 5.59; N, 3.53. Found: C, 78.46; H, 5.45; N, 3.44.

Similarly compound IVb was obtained in yield of 10.8%, m.p. 180-185°; m/e 371; nmr: δ 8.3 (5 Hz) and δ 4.7.

1-Acetyl-1,4-dihydro-4-phenyl-1-azaxanthone (V). General Method 3.

A mixture of the dihydropyridine compound II (1 g.), sodium acetate (4 g.) and acetic anhydride (5 ml.) was warmed on the steam bath for 4 hours with occasional manual swirling, poured into ice water and allowed to crystallize (2-3 hours). The precipitate was filtered, washed well with water and recrystallized.

4-Phenyl-1-azaxanthone-5 (VI). Method 4.

A mixture of II (2.7 g., 0.01 mole) 2.5 g. of freshly recrystallized chloranil and 150 ml. of benzene was heated for 6 hours on the steam bath and allowed to cool overnight. The mixture was transferred to a separatory funnel and washed successively 5 times with

15% aqueous sodium hydroxide, with water and the solvent removed. The residue was recrystallized from acetonitrile.

5-Phenyl-1-azaxanthene (VII).

Sodium carbonate (3 g.) was dissolved in a solution of 100 ml. of 99% formic acid and 10 ml. of water. To this mixture was added in one portion, 5.8 g. (0.021 mole) of carbinol III and the mixture was heated on the steam bath for 1.5-2 hours or until the original red color was changed to a pale lemon yellow solution and the evolution of carbon dioxide stopped. The solution was concentrated to a small volume *in vacuo* on the steam bath and the residue was dissolved in water, layered with ether and made basic by the addition of solid sodium carbonate. The product was extracted with chloroform, washed with water, the solvent removed and the residue was recrystallized.

5-Hydroxy-5(*p*-methylphenyl)-1-azaxanthene.

To a solution of 0.2 mole of *p*-methylphenyl Grignard reagent in 200 ml. of THF at 0-5° was added a suspension of the azaketone I (19.7 g.) in 200 ml. of THF and the reaction stirred at 0-5° for 2 hours. The excess solvent was removed and the reaction mixture was decomposed (ammonium chloride solution) and processed as in Method 2 to give 15.5 g. (54%) of carbinol m.p. 200-201°.

4,5-Di(*p*-methylphenyl)-1-azaxanthene (IVa).

The Grignard reagent was prepared in THF (200 ml.) using 34.2 g. (0.2 mole) of *p*-bromotoluene and 4.8 g. (0.2 g.-atoms) of magnesium metal. To this solution was added with cooling a suspension of 19.7 g. of I in 300 ml. of THF. The mixture was then heated under reflux with stirring for 2 hours and approximately 80% of the THF removed *in vacuo* on steam bath. Ammonium chloride solution was added and the product was extracted with chloroform, washed with water and the solvent removed. The crude product (18.3 g., m.p. 149-152°) was recrystallized several times from acetonitrile to give 12.3 g. (43%) of IVa, m.p. 155-156°; m/e 364.

Anal. Calcd. for $C_{26}H_{21}NO$: C, 85.92; H, 5.82; N, 3.85. Found: C, 85.53; H, 5.10; N, 3.93.

Conversion of III to IVa.

To a freshly prepared solution of *p*-methylphenylmagnesium bromide (0.1 mole) in 50 ml. of THF was added dropwise at room temperature a solution of 15.3 g. (0.05 mole) of II (R = *p*-Methylphenyl) in 100 ml. of THF. The mixture was stirred under reflux on the steam bath for 6 hours, decomposed with ammonium chloride solution, extracted with chloroform, washed and the solvent removed. The residue was triturated with hexane and recrystallized from acetonitrile; yield 6.3 g. (35%) m.p. 150-153° which did not depress the melting point on admixture with the compound prepared above. The ir and nmr spectra of both samples were superimposable.

Grignard Reaction in Benzene. Method 5A.

Phenylmagnesium bromide was prepared in ether using Method 1. When all the magnesium had reacted, the ether was distilled off by heating on the steam bath maintaining constant volume of the solution by the continuous addition of dry benzene. The benzene solution was cooled to room temperature and a suspension of 0.1 mole of I in 100 ml. of dry benzene was added. The mixture was refluxed with stirring for 4 hours and processed as described in Method 1. After several recrystallizations from methanol, the product (7.3 g., 26.5%) was identical (m.p. and ir) with the dihydropyridine derivative obtained in Method 1.

Method 5B.

Similar to 5A except that the reagent was prepared in tetrahydrofuran (as in method 2). The solvent was then displaced by dry benzene. The addition of ketone I as a suspension in dry benzene resulted in the isolation of 8 g. (29.0%) of compound III.

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(1) For paper 2 in this series, see F. J. Villani, J. Hannon, E. A. Wefer, T. A. Mann and J. Morton, *J. Org. Chem.*, **40**, 1734 (1975).

(2) For consistency and convenience throughout this series, the numbering system shown in I has been adopted. The correct *Chem. Abstr.* name for this compound is 5-*H*[1]benzopyrano[2,3-*b*]pyridin-5-one.

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