

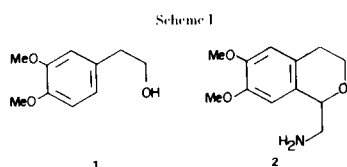
Pyrano Heterocycles I. The Syntheses of Isochromans
and the Novel Thieno[3,2-*c*]pyran, Benzothieno[3,2-*c*]pyran,
Benzothieno[2,3-*c*]pyran and Pyrano[4,3-*b*]benzofuran Systems

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Received November 15, 1974

In a continuing investigation of the synthesis of heterocyclic systems we had occasion to prepare a number of 1-substituted isochromans. Isochroman itself has been synthesized in high yield (1,2) by the reaction of phenethyl



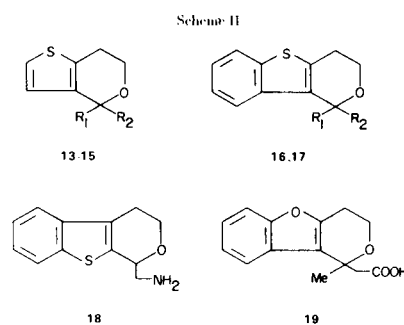
alcohol with paraformaldehyde and anhydrous hydrogen chloride, and it has been converted to 1-aminomethylisochroman *via* the 1-bromo and 1-cyano derivatives (3,4). The direct condensation of benzaldehyde and acetaldehyde with phenethyl alcohol has also been reported (1), to afford 1-phenyl and 1-methylisochromans, in 50% and 7% yields, respectively. It appeared that suitable activation of the aromatic ring would facilitate the synthesis of 1-substituted isochromans.

In practice, we found that 3,4-dimethoxyphenethyl alcohol, **1** (5) reacts readily with aminoacetaldehyde diethylacetal in dioxane with anhydrous hydrogen chloride to give an 82% yield of the hydrochloride of 1-aminomethyl-6,7-dimethoxyisochroman, **2**. (See Scheme I). It was further found that a wide variety of carbonyl derivatives react with 3,4-dimethoxyphenethyl alcohol either in dioxane with hydrogen chloride as catalyst, or, in benzene with *p*-toluenesulfonic acid as catalyst. Thus, aldehydes, acetals and ketones afforded the 1-substituted and 1,1-disubstituted isochromans **2-11** shown in Table I.

In addition, investigation of the condensation of heterocyclic ethanols with various carbonyl components has afforded a number of novel pyrano-heterocycles (See Scheme II). Thus, reaction of 2-thiopheneethanol (6), benzo[*b*]thiophene-2-ethanol (7), benzo[*b*]thiophene-3-ethanol (8) and benzofuran-2-ethanol **12** (see Experimental) with miscellaneous carbonyl components has afforded, respectively, 6,7-dihydro-4*H*-thieno[3,2-*c*]pyrans (**13-15**), 3,4-dihydro-1*H*-[1]benzothieno[3,2-*c*]pyrans (**16,17**), the 1,2-dihydro-1*H*-[1]benzothieno[2,3-*c*]pyran, **18**, and the 3,4-dihydro-

1*H*-pyrano[4,3-*b*]benzofuran, **19**. Data on compounds **13-19** are collected in Table II.

The reactions described, leading to pyranoheterocycles, may be regarded as a variant of the Friedel-Crafts reaction where intramolecular alkylation of an aromatic system by a hemiacetal, hemiketal, or, mixed acetal intermediate affords a pyrano ring.



EXPERIMENTAL

Melting points were taken on a Thomas-Hoover apparatus and are corrected. Analyses were done by Mr. W. Turnbull and staff of Ayerst Research Laboratories. The nmr spectra were recorded on a Varian A-60A instrument. All new compounds gave ir and nmr spectra consistent with their respective structures.

Synthesis of 1-Substituted and 1,1-Disubstituted 6,7-Dimethoxyisochromans (See Table I).

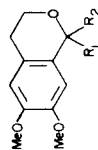
Method I. 1-Aminomethyl-6,7-dimethoxyisochroman (**2**).

A solution of 3,4-dimethoxyphenethyl alcohol **3** (6) (108 g., 0.59 mole) and aminoacetaldehyde diethylacetal (78 g., 0.59 mole) in dry dioxane (150 ml.) was stirred and cooled to 0° for 1 hour while being saturated with hydrogen chloride. The mixture was kept at 22° for 48 hours and the crystalline precipitate was collected, washed with dioxane, then with ether, and dried to afford the product (126 g., 82%).

Method II. 6,7-Dimethoxy-1-(2'-thienyl)isochroman (**9**).

A mixture of 3,4-dimethoxyphenethyl alcohol **3** (20 g., 0.11 mole), thiophene-2-carboxaldehyde (15.1 g., 0.13 mole), anhydrous benzene (350 ml.) and *p*-toluenesulphonic acid (0.55 g.) was heated at reflux in an apparatus fitted with a Dean-Stark trap. The cooled mixture was washed with brine, dried and evaporated. The

(Table I)
1-Substituted and 1,1-Disubstituted-6,7-dimethoxyisochromans



No.	Carbonyl Component	Method (a)	% Yield	Recrystn (b)		M.p. °C	R ¹	R ²	Formula	C%		H%	
				Solvent	Solvent					Calcd.	Found	Calcd.	Found
2	CH(OEt) ₂ CH ₂ NH ₂	I	82	A	A	250-255	H	CH ₂ NH ₂ ·HCl	C ₁₂ H ₁₈ ClNO (c)	55.60	55.85	6.84	7.23
3	CH(OEt) ₂ CH ₂ Br	I	70	B,C	H	78-80	H	CH ₂ Br	C ₁₂ H ₁₅ BrO ₃ (d)	50.18	50.10	5.26	4.98
4	MeCO(CH ₂) ₂ COOH	I	55	C,D	Me	105-108	Me	(CH ₂) ₂ COOH	C ₁₅ H ₂₀ O ₅	64.27	64.40	7.19	7.02
5	MeCOC ₆ H ₅	I	60	C	Me	93-95	Me	C ₆ H ₅	C ₁₈ H ₂₀ O ₃	76.03	76.19	7.09	7.03
6	C ₆ H ₅ CO(CH ₂) ₃ Cl	I	67	A	C ₆ H ₅	125-126	C ₆ H ₅	(CH ₂) ₃ Cl	C ₂₀ H ₂₃ ClO ₃ (e)	69.20	68.98	6.68	6.46
7	C ₅ H ₄ N(3-CHO) (f)	I	75	E	H	143-145	H	3-(C ₅ H ₄ N)·maleate	C ₁₈ H ₁₉ N ₂ O ₇ (g)	59.83	60.02	5.30	5.28
8	C ₄ H ₃ O(2-CHO) (f)	II	90	B,F	H	94-96	H	2-(C ₄ H ₃ O)	C ₁₅ H ₁₆ O ₄	69.21	69.34	6.20	6.17
9	C ₄ H ₃ S(2-CHO) (f)	II	80	C,D	H	78-81	H	2-(C ₄ H ₃ S)	C ₁₅ H ₁₆ O ₃ S (h)	65.21	65.15	5.84	5.64
10	3(OH)C ₆ H ₄ CHO	I	45	D	H	135-137	H	3(OH)C ₆ H ₄	C ₁₇ H ₁₈ O ₄	71.31	71.27	6.34	6.23
11	4(HOOC)C ₆ H ₄ CHO	I	35	D	H	140-143	H	4(HOOC)C ₆ H ₄	C ₁₈ H ₁₈ O ₅	68.78	69.02	5.77	5.79

(a) See Experimental. (b) A, methanol; B, ether; C, hexane; D, benzene; E, 2-propanol; F, petroleum ether (b. p. 30-60°). (c) *Anal.* Calcd. Cl, 13.68; N, 5.40. Found: Cl, 13.68; N, 5.21. (d) *Anal.* Calcd. Br, 27.85. Found: Br, 27.77. (e) *Anal.* Calcd. Cl, 10.24. Found: Cl, 10.18. (f) C₅H₄N = pyridyl; C₄H₃O = furyl; C₄H₃S = thienyl. (g) *Anal.* Calcd. N, 3.88. Found: N, 3.86. (h) *Anal.* Calcd. S, 11.58. Found: S, 11.58.

(Table II)

Pyrano-Fused Heterocyclic Systems (a)

No.	Carbonyl Component	% Yield	Recrystn. Solvent	M.p. °C	R ₁ (b)	R ₂ (b)	Formula	C%		H%		S%	
								Calcd.	Found	Calcd.	Found	Calcd.	Found
6,7-DIHYDRO-4H-THIENO[3,2-c]PYRANS													
13	CH(OEt) ₂ CH ₂ NH ₂	60	2-PrOH	204-206	H	CH ₂ NH ₂ ·HCl	C ₈ H ₁₂ CINOS (c)	46.70	46.46	5.88	6.15	15.60	15.59
14	MeCOCH ₂ COOEt	63	C ₆ H ₆	89-92	Me	CH ₂ COOH (d)	C ₁₀ H ₁₂ O ₃ S	56.60	56.76	5.70	5.74	15.03	15.10
15	N-Methylpiperidone	37	2-PrOH	220-222	MeN	(CH ₂) ₂ - (CH ₂) ₂ -	C ₁₂ H ₁₈ CINOSH ₂ O (f)	51.80	51.57	7.20	6.96	11.50	11.57
3,4-DIHYDRO-1H-[1]BENZOTHIENO[3,2-c]PYRANS													
16	CH(OEt) ₂ (CH ₂) ₂ Cl	70	MeOH	92-94	H	(CH ₂) ₂ Cl	C ₁₃ H ₁₃ CLOS (g)	61.80	61.80	5.18	5.10	12.65	12.64
17	MeCOCH ₂ COOEt	50	EtOH	149-152	Me	CH ₂ COOH (d)	C ₁₄ H ₁₄ O ₃ S	64.11	63.97	5.38	5.42	12.20	12.25
1,2-DIHYDRO-1H-[1]BENZOTHIENO[2,3-c]PYRAN													
18	CH(OEt) ₂ CH ₂ NH ₂	74	2-PrOH	169-171	H	CH ₂ NH ₂ -maleate	C ₁₆ H ₁₇ NO ₅ S (h)	57.31	57.37	5.11	5.19	9.56	9.52
3,4-DIHYDRO-1H-PYRANO[4,3-b]BENZOFURAN													
19	MeCOCH ₂ COOEt	50	2-PrOH	157-158	Me	CH ₂ COOH (d)	C ₁₄ H ₁₄ O ₄	68.28	68.17	5.73	5.80		

(a) All condensations in this Table were done by Method I, see Experimental. (b) See Scheme II for structural formulae. (c) *Anal.* Calcd. Cl, 17.30; N, 6.82. Found: Cl, 17.14; N, 6.64. (d) The primary condensation product, the corresponding ethyl ester, was not isolated but was hydrolysed directly to the acid. (e) Obtained as a monohydrate. (f) *Anal.* Calcd. Cl, 12.80; N, 5.00. Found: Cl, 12.97; N, 5.38. (g) *Anal.* Calcd. Cl, 14.05. Found: Cl, 13.93. (h) *Anal.* Calcd. N, 4.18. Found: N, 4.15.

residue was dissolved in benzene and filtered through a column of neutral alumina (Woelm, activity III), and the eluates were concentrated. Addition of hexane afforded the crystalline product, (24 g., 80%).

Benzofuran-2-ethanol (12).

Butyl lithium in hexane (50 ml. of a 2.2 *M* solution) was added to a solution of benzofuran (11.8 g., 0.1 mole) in ether (200 ml.) during 15 minutes. The mixture was stirred at 22° for 0.5 hour then cooled to 0° while ethylene oxide (4.6 g., 0.105 mole) in ether (50 ml.) was added. After 3 hours at 0° the reaction mixture was washed with brine and the ether evaporated. The residue was purified by chromatography on silica gel. Elution with benzene-chloroform mixtures afforded the product (5.2 g., 45%) as an oil, homogeneous by tlc, nmr (deuteriochloroform): δ 1.83 (s, 1, OH), 3.08 (t, J = 6.5 cps, 2, CH₂CH₂OH), δ 3.92 (t, J = 6.5 cps, 2, CH₂CH₂OH), 6.4 (s, 1, β -H of furan ring), δ 7.3, m, 4, aromatic protons.

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