

SYNTHESES OF PYRANO[4,3-*b*]BENZODIAZEPINE AND PYRANO-
[4,3-*b*]QUINOLINE USING 4-CHLORO-3-(1-CHLOROVINYL)-6-
METHYL-2*H*-PYRAN-2-ONE AND 4-CHLORO-3-ETHYNYL-6-METHYL-
2*H*-PYRAN-2-ONE

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Abstract- Reaction of dichloropyrone (1) and chloroethynylpyrone (2) with *o*-phenylenediamine and *m*-phenylenediamine give pyranobenzodiazepine (3) and pyranoquinoline (5), respectively. Treatment of 1 and 2 with *p*-phenylenediamine yield aminoethynylpyrone (6), which is a key product in the reaction of 1 and 2 with phenylenediamines.

Moreno-Manas and his co-workers reported¹ that the reaction of 4-chloro-3-(1-chlorovinyl)-6-methyl-2*H*-pyran-2-one (1) with hydrazines gave pyranopyrazole derivatives. It seems that dichloropyrone (1) is potentially useful for the synthesis of heterocyclic compounds containing pyrane ring. Few reports, however, have been published on the reactivity of dichloropyrone (1) except their reports. In the previous papers, we reported² that dichloropyrone (1) was treated with primary and secondary amines to afford aminopyrone derivatives, and with tertiary amines to afford 4-chloro-3-ethynyl-6-methyl-2*H*-pyran-2-one (2). In the course of our continuing study, it was found that both dichloropyrone (1)³ and chloroethynylpyrone (2)⁴ were treated with phenylenediamines to afford pyrano[4,3-*b*]diazepine (3) and pyrano[4,3-*b*]quinoline (5), which is described in the communication here. These products (3 and 5) are expected to possess pharmacological activities.

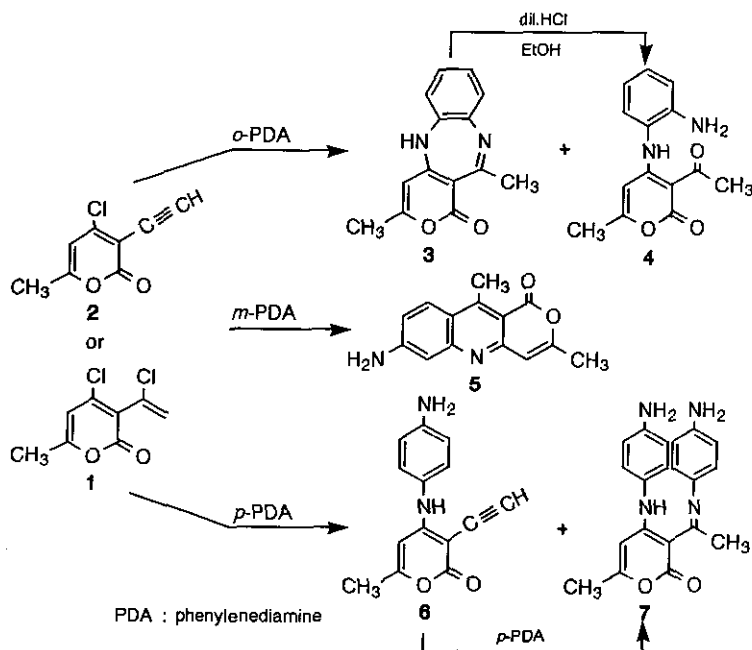
A mixture of chloroethynylpyrone (2, 5.9 mmol), *o*-phenylenediamine (6.6 mmol), and Et₃N (12.4 mmol) in 98% EtOH (50 ml) was heated under reflux for 1 h. The precipitate was collected by filtration,

Dedicated to Prof. E. C. Taylor on the occasion of his 70th birthday.

and was recrystallized from 98 % EtOH to give pyranobenzodiazepine (3) in 75 % yield, and the concentrated filtrate was purified by column chromatography on silica gel to give 3-acetyl-4-(2-aminoanilino)-6-methyl-2H-pyran-2-one (4) in 8 % yield. Pyranobenzodiazepine (3) was quantitatively converted into 4 by treatment with a small amount of 10 % HCl in EtOH.

In the same procedure as previously, the reaction of chloroethynylpyrone (2) with *m*-phenylenediamine gave pyranoquinoline (5), in 82 % yield, of which ^1H -nmr spectra showed three typical signals of a *meta*-coupled proton at 6.91 ppm, an *ortho*- and *meta*-coupled proton at 7.02 ppm, and an *ortho*-coupled proton at 8.03 ppm. Furthermore, irradiation of methyl proton at 3.27 ppm of 5 gives NOE on an *ortho*-coupled proton at 8.03 ppm.

On the other hand, a mixture of chloroethynylpyrone (2), *p*-phenylenediamine, and Et_3N in 98 % EtOH was stirred at room temperature for 30 min to afford aminoethynylpyrone (6), in 68 % yield, which was treated with *p*-phenylenediamine to give imine (7, 82 %). The structures of all products were determined by the spectral and analytical evidences (Table 1).



Scheme 1

In addition, dichloropyrone (1) also reacted with phenylenediamines in the presence of 3.5 mole eq. amount of Et_3N to yield the corresponding products (3, 4, 5, 6 and 7), respectively. In the same procedure, for example, a mixture of dichloropyrone (1, 4.9 mmol), *o*-phenylenediamine (5.9 mmol), and

Table 1. Products by reaction of 1 and 2 with phenylenediamines

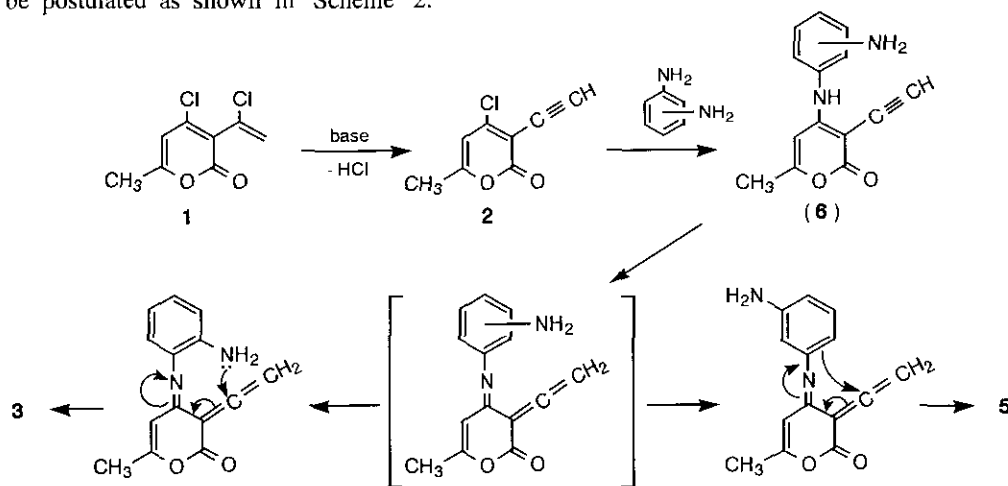
Compd. No.	Yield (%) Method A ^{a)} (Method B ^{b)})	mp (°C)	Formula	Analysis (%)			ir (KBr) cm ⁻¹	¹ H-nmr δ (ppm)
				Calcd	Found			
				C	H	N		
3	75 (58)	245 (decomp.)	C ₁₄ H ₁₂ N ₂ O ₂	70.00 (69.95)	5.00 4.94	11.67 11.60	1670	2.14 (3H, s), 2.34 (3H, s), 5.86 (1H, s), 6.64 -6.99 (4H, m), 8.06 (1H, br s)
4	8 (12)	188 – 189 (decomp.)	C ₁₄ H ₁₄ N ₂ O ₃	65.12 (65.16)	5.43 5.43	10.85 10.81	1720	2.12 (3H, s), 2.67 (3H, s), 3.87 (2H, br s), 5.66 (1H, s), 6.77 -7.20 (4H, m), 12.57 (1H, br s)
5	82 (65)	299 (decomp.)	C ₁₄ H ₁₂ N ₂ O ₂	70.00 (69.96)	5.00 4.95	11.67 11.58	1715	2.49 (3H, s), 3.27 (3H, s), 6.33 (2H, br s), 6.40 (1H, s), 6.91 (1H, d, J=2Hz), 7.02 (1H, dd, J=9 and 2Hz), 8.03 (1H, d, J=9Hz)
6	68 (3)	195 (decomp.)	C ₁₄ H ₁₂ N ₂ O ₂	70.00 (69.76)	5.00 5.01	11.67 11.72	2100, 1700	2.13 (3H, s), 3.63 (1H, s), 3.83 (2H, br s), 5.73 (1H, s), 6.60 -7.17 (4H, m), 7.09 (1H, br s)
7	60 (45)	170 – 171 (decomp.)	C ₂₀ H ₂₀ N ₄ O ₂	68.97 (68.90)	5.75 5.74	16.09 15.85	1680	2.08 (3H, s), 2.43 (3H, s), 3.73 (4H, br s), 5.87 (1H, s), 6.63 -7.05 (8H, m), 14.43 (1H, br s)

a) Method A : using chloroethynylpyrone (2)

b) Method B : using dichloropyrone (1)

Et₃N (14.7 mmol) in 98 % EtOH (50 ml) was heated under reflux for 1 h to give pyranobenzodiazepine (3) in 58% yield.

The use of chloroethynylpyrone (2) instead of dichloropyrone (1) resulted in far more yield to afford the corresponding products (Method A in Table 1). A probable route of the ring formation of pyranobenzodiazepine (3) and pyranoquinoline (5) by the reaction of 1 and 2 with phenylenediamines can be postulated as shown in Scheme 2.



Scheme 2

REFERENCES AND NOTES

1. A. Cantos, P. De March, M. Moreno-Manas, A. Pla, F. Sanchez-Ferrando, and A. Virgili, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 4425; *Idem*, *Chem. Lett.*, **1986**, 295.
2. Y. Azuma, A. Sato, K. Tanno, M. Madarame, and S. Hisamichi, *Annu. Rep. Tohoku Coll. Pharm.* 1988, **35**, 221 [*Chem. Abstr.*, 1990, **112**, 178560b]; *Idem*, *ibid.*, 1989, **36**, 219 [*Chem. Abstr.*, 1991, **114**, 143052b].
3. Preparation of **1**: A mixture of dehydroacetic acid (100 g, 0.6 mol), phosphorus pentachloride (250 g, 1.2 mol), and phosphorus oxychloride (185 g, 1.2 mol) in CHCl_3 (1000 ml) was heated under reflux for 1.5 h. The reaction mixture was slowly poured into an ice-water. The resulting mixture was neutralized with a concentrated aqueous ammonia. The organic layer was separated, and the aqueous layer was extracted with CHCl_3 . The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography on alumina with CHCl_3 elution to give a crude product (**1**), which was recrystallized from a mixture of CH_2Cl_2 -cyclohexane to afford **1** (92 g, 75 %); mp 101–102 °C (lit.,¹ mp 100 °C).
4. Preparation of **2**: A mixture of dichloropyrone (**1**, 49 g, 0.24 mol) and Et_3N (60 g, 0.6 mol) in CHCl_3 (1000 ml) was heated under reflux for 6 h. The reaction mixture was washed with 10 % HCl and water. After the solvent was removed *in vacuo*, the residue was purified by column chromatography on silica gel with CHCl_3 elution to give a crude product (**2**), which was recrystallized from Et_2O to afford **2** (37 g, 92 %); mp 145 °C (decomp.); ir (KBr) 3260, 2110, 1725 cm^{-1} ; ^1H nmr (CDCl_3): δ 2.30 (3H, s), 3.63 (1H, s), 6.19 (1H, s).

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