Reaction of Ethyl γ-Bromo-β-methoxycrotonate with Carbonyl Compounds. Synthesis of 4-Methoxy-6-substituted-5,6-dihydro-2*H*-pyran-2-ones and 3-Substituted 3-Pyrazolin-5-ones

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Ethyl β-methoxycrotonate I reacts with substituted carbonyl compounds II in benzene to give 4-methoxy-6-substituted-5,6-dihydro-2H-pyran-2-ones III. The reaction of IIIa and j with hydrazine hydrate in ethanol leads to 3-[(1'-thienyl-1-hydroxy)methyl]-5-hydroxy-1*H*-pyrazole (IVa) and 3-[(1'-styryl-1'-hydroxy)methyl]-5-hydroxy-1*H*-pyrazole (IVj) in good yields. The structure of the products were assigned and confirmed on the basis of their elemental analysis and the electronic absorption, infrared and nmr spectra.

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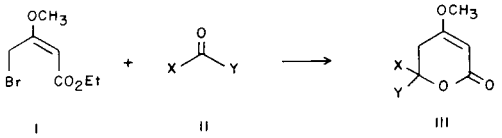
As a part of an investigation concerning the synthesis of arylidenebutenolides by ring contraction [1-4] we required the synthesis of substituted 4-methoxy-5,6-dihydro-2*H*-pyran-2-ones which would clarify the ring contraction, a presumed biosynthetic process [1-4]. Various 4-methoxy-5,6-dihydro-2*H*-pyran-2-ones were prepared [5]. The great majority of the work on the synthesis of Kawain [6] and on other related naturally occurring pyrone compounds has been reported, but at the same time no appreciable amount of work concerning the synthesis of 4-methoxy-5,6-dihydro-2*H*-pyran-2-ones having heterocyclic substituents as well as halogen-containing aromatic substituents at C-6 position have been reported. These compounds could be used as intermediate in the synthesis of natural compounds *e.g.* anibin [7] and related compounds as well as 5-arylidenbutenolide [3] by ring contraction.

Treatment of a mixture of I and II with zinc in benzene gave III within 3 hours at reflux, as a major product (followed by hplc) (Scheme 1).

Scheme 1



I II III

	X	Y
a,	2-Thienyl-	H
b,	2-ClC_6H_4-	H
c,	3-ClC_6H_4-	H
d,	2-$MeOC_6H_4$-	H
e,	3,4-$(MeO)_2C_6H_3$-	H
f,	C_6H_5-CH=C(CH_3)-	H
g,	β-Napthyl-	H
h,	2-$CH_3C_6H_4$	CH_3
i,	3-$CH_3C_6H_4$-	CH_3

Structural assignment of III was achieved on the basis of its elemental analysis and nuclear magnetic resonance (nmr) data which exhibited a characteristic H-6 and H-5 as a double doublet and a multiplet, respectively, for compounds IIIa-g while H-5 appears as a singlet for compounds IIIh and i, Table 2. The ir spectral data exhibit a strong band in the range of 1700-1710 due to pyrone carbonyl stretching (Table 1).

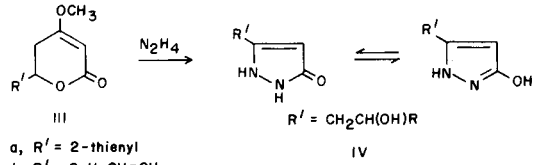
Table 1

Physical and Analytical Data of Compounds III

Compound No.	Yield %	MP	Formula	Analysis Calcd./Found % C	H
a	84	77-80	$C_{10}H_{10}O_3S$	57.14, 57.03	4.76, 4.70
b	40	110-113	$C_{12}H_{11}ClO_3$	60.50, 60.25	4.62, 4.65
c	44	80-82	$C_{12}H_{11}ClO_3$	60.50, 60.18	4.62, 4.65
d	79	115-117	$C_{13}H_{14}O_4$	66.66, 66.58	5.98, 6.05
e	83	107-108	$C_{14}H_{16}O_5$	63.63, 63.54	6.06, 6.15
f	40	123-126	$C_{15}H_{16}O_3$	73.77, 73.71	6.55, 6.71
g	70	164-167	$C_{16}H_{14}O_3$	75.59, 75.56	5.51, 5.54
h	60	110-112	$C_{14}H_{16}O_3$	72.41, 71.79	6.89, 7.01
i	58	89-92	$C_{14}H_{16}O_3$	72.41, 72.45	6.89, 6.99

Previously we reported the conversion of 4-methoxy-5,6-dihydro-2-pyrones to 3-alkyl-5-hydroxy-1*H*-pyrazoles [1]. As a continuation of this work, compound IIIa, and IIIj were selected to find the effect of substituents at the C-6 position in ring contraction.

Scheme 2



III

a, R' = 2-thienyl
j, R' = C_6H_5CH=CH-

R' = $CH_2CH(OH)R$

IV

A mixture of IIIa or j and hydrazine in methanol was heated under reflux for 90 minutes. The precipitates were filtered, washed with methanol to afford IV in high yield (Scheme 2 and Table 3). The products IVa and j gave the analytical values and the nmr spectra in full agreement with the proposed strucure.

Table 2

Spectral Data of Compounds III

Compound No.	IR Bands cm^{-1} [b]	^1H NMR [a] δ H-3	H-5	H-6	MeO	Ar-H
a [c]	1700, 1630	5.18	2.77	5.62	3.75	
b	1710, 1625	5.22	2.66	5.74	3.72	7.3
c	1710, 1630	5.18	2.60	5.34	3.72	7.3
d [d]	1710, 1635	5.18	2.66	5.71	3.75	6.8-7.5
e [e]	1710, 1630	5.20	2.65	5.36	3.75	6.81-7.2
f [f]	1710, 1630	5.18	2.56	5.32	3.72	7.2
g	1715, 1635	5.23	2.71	5.54	3.74	7.38-7.81
h [g]	1715, 1630	5.05	2.88	5.42	3.63	7.2
i [h]	1710, 1630	5.03	2.85	5.43	3.61	7.1

[a] Deutereochloroform was used as the solvent. [b] Only the lactone absorption bands were reported. [c] 7.23, m, 3H. [d] 3.73, s, 3H. [e] 3.84, s, 3H; 3.85, s, 3H (2-OCH_3). [f] 6.61, s, 1H; 1.92, s, 3H. [g] 2.32, s, 3H; 1.68, s, 3H. [h] 2.30, s, 3H, 1.68, s, 3H.

Table 3

Physical and Spectral Data of Compounds IV

Compound No.	Yield %	MP solvent	IR [b] ν cm^{-1}	NMR [a,b] H-4	H-1′	H-2′	2′-OH [c]
a	95	Ethanol	1630	5.31	2.95	5.12	6.87
j	90	Ethanol	1625	5.37	2.78	4.46	7.12

[a] Only the most important bands are reported. [b] All spectra run in D_6-DMSO. [c] Exchanged with deuterium oxide, NH and 5-OH protons are not observed for similar compounds see ref [1].

From the above reaction it is clear that the ring contraction of 6-substituted-4-methoxy-2*H*-pyran-2-ones of type III is not effected by the nature of the substituents at C-6 position 1 to give pyrazolone ring system IV.

EXPERIMENTAL

Melting points were determined on a Kofler Hot Plate and are uncorrected. Elemental analyses were performed by Alfred Bernhardt Laboratories, Ruhr, Germany. The ir absorption spectra were recorded with Perkin-Elmer Model 127 and 237 spectrophotometers. The nmr spectra were measured on a Bruker WH 90 with a deuterium internal lock.

Ethyl γ-Bromo-β-methoxycrotonate (I) [8].

This compound was prepared by the method reported [8]. Ethyl β-methoxycrotonate was heated with *N*-bromosuccinimide to give I, bp 205°, 14 mm Hg (94%) and was shown to be pure by hplc.

General Procedure for the Synthesis of 6-Substituted-4-methoxy-5,6-dihydro-2*H*-pyran-2-ones III.

Ethyl γ-bromo-β-methoxycrotonate I (2.24 g, 10 mmoles) admixed with the corresponding aldehyde or ketone II (10 mmoles) in 50 ml of dry benzene. This was slowly added to 1.5 g of industrial zinc. After initial heating the mixture was refluxed for 3 hours. It was then allowed to cool to room temperature. The entire mixture was introduced in a thin stream into a 10% hydrochloric acid solution (100 ml), and then extracted with ethyl acetate (3 × 150 ml). The combined organic layers were washed with water (2 × 100 ml), 5% sodium bicarbonate (2 × 100 ml) and water (2 × 100 ml). Drying with magnesium sulfate and evaporation of solvents at reduced pressure afforded a viscous yellow oil. The crude product was crystallized from the appropriate solvent to give the corresponding product (see Table 1 and 2).

Preparation of 3-(1′-Hydroxyalkyl)-5-hydroxy-1*H*-pyrazoles IV. General Procedure.

A solution of dihydropyrone III (0.2 mole) and hydrazone hydrate (2 g, 0.4 mole) in absolute methanol (25 ml) was heated in a steam bath for 1.5 hours. The methanol and unreacted hydrazine were removed at 100°/25 mm. The residue crystallised to a white mass on cooling. This was stirred with 10 ml of cold chloroform, filtered and crystallised once from ethanol to give the pure title compounds IVa and IVj.

Preparation of Kawain (IIIj).

This was prepared by the literature method [8].

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