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Spirocyclopropane Compounds. V.[1] One-Step Synthesis of 5-Acetylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one

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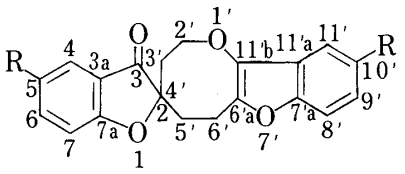
5-Acetylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (**3a**, AG-629), previously found to be the most potent antiulcer compound in a series of spirocyclopropanes, was obtained by one-step synthesis starting from methyl 5-acetyl-2-[(tetrahydro-2-oxo-3-furanyl)oxy]benzoate (**1a**). In this reaction, 5,10′-(diacetyl-5′,6′-dihydrospiro[benzofuran-2(3*H*),4′(3′*H*)-[2*H*]oxocino[3,2-*b*]-benzofuran]-3-one (**5a**), which has a new ring system, and 1*H*,3*H*-8-acetyl-4,5-dihydronaphtho[1,2-*c*:4,3-*b*′]difuran-1-one (*6*) were isolated as by-products. A possible reaction mechanism is presented.

Keywords——AG-629; one-step synthesis; Dieckmann reaction; reaction mechanism; new ring system

5-Acetylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (**3a**, AG-629) shows prominent prophylactic and curative effects on various experimental ulcers in animals.[2] This antiulcer activity does not appear to result from inhibition of gastric secretion, since the antisecretory activity of **3a** was not significant at the dose producing antiulcer activity. Compound **3a** thus appears to be an antiulcer agent of a new structural type. This report describes a one-step synthesis of **3a** starting from methyl 5-acetyl-2-[(tetrahydro-2-oxo-3-furanyl)oxy]benzoate (**1a**). The structures of the by-products isolated and the reaction mechanisms involved are also discussed.

Our previous report[3] described the stepwise synthesis of spiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (**3b**) and its derivatives *via* **2b** from **1b** (ref. Chart 1). However, a larger-scale and easier preparation was required, and therefore a one-step synthesis of **3b** was developed. Dieckmann condensation of **1b** with triethylamine in *N,N*-dimethylformamide directly afforded the desired **3b** in 29% yield. In this reaction, 2-(2-hydroxyethyl)-3(2*H*)-benzofuranone (**4**) and a dimeric product (**5b**) were obtained in 17 and 14% yields, respectively. The structure of **5b** was confirmed on the basis of its spectral data. That is, compound (**5b**) showed the molecular ion peak at *m/e* 320 and the base peak at *m/e* 160 in the mass spectrum, suggesting that **5b** is dimeric. The infrared (IR) spectrum showed a carbonyl absorption band at 1710 cm^{-1} and the proton nuclear magnetic resonance (^{1}H-NMR) spectrum exhibited couplings between 2.04 (2H, q) and 4.45 (2H, m) and between 2.53 (2H, t) and 3.22 ppm (2H, m). Twenty signals in the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum (Table I) suggested that **5b** is an unsymmetrical dimer. Thus, the structure of **5b** was determined to be 5′,6′-dihydrospiro[benzofuran-2(3*H*),4′(3′*H*)-[2*H*]oxocino[3,2-*b*]benzofuran]-3-one. Dieckmann reaction of **1b** using a catalytic amount of 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) instead of triethylamine gave **2b** in 49% yield. The use of a longer reaction time did not increase the yield of **2b** and the starting **1b** was recovered. Addition of sodium chloride to the reaction mixture gave a good yield of **3b** in a one-pot reaction. In the same way, **3a** was obtained from **1a**. This reaction appears to proceed through

TABLE I. ^{13}C-NMR Spectral Data for 5′,6′-Dihydrospiro[benzofuran-2(3*H*),4′(3′*H*)-[2*H*]oxocino[3,2-*b*]benzofuran]-3-one (**5b**) and 5,10′-Diacetyl Derivative (**5a**) in $CDCl_3$ (δ, ppm)



5a: R = $COOCH_3$
5b: R = H

Compd. No.	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	C-2′	C-3′
5a	90.5	201.4	119.1	126.0	131.5	137.8	113.7	172.9	67.1	29.8
5b	89.0	202.6	119.3	124.8	117.2	137.9	113.4	170.5	67.1	21.4

Compd. No.	C-5′	C-6′	C-6′a	C-7′a	C-8′	C-9′	C-10′	C-11′	C-11′a	C-11′b
5a	29.8	29.8	147.8	154.5	110.9	118.4	132.1	118.4	124.4	134.4
5b	21.4	21.4	146.4	152.2	110.9	122.2	121.8	123.6	124.6	134.1

nucleophilic attack of the chloride anion on the 5′-carbon of **2b** (B_{AL} route), followed by decarboxylation, and subsequent intramolecular cyclization of the intermediary carbanion (**a**) to form a spirocyclopropane ring. The base-catalyzed decarboxylation (B_{AC} route) through **b** and **c** yielded **4** and **5a**, **b**. When crude **1a** was used for the one-step synthesis of **3a**, a small amount of a by-product (**6**) was isolated. Compound **6** was hardly soluble in organic solvents and its ^{13}C-NMR spectrum could not be measured. Its structure was established by X-ray crystallographic analysis as 1*H*,3*H*-8-acetyl-4,5-dihydronaphtho-[1,2-*c*:4,3-*b*′]difuran-1-one. The IR and ^{1}H-NMR spectra of **6** were consistent with this structure. A possible reaction mechanism for the formation of **6** is shown in Chart 1. Base-catalyzed condensation of the ester (**1a**) with γ-butyrolactone yields **d**. Decarboxylation of **d** to dihydrofuran (**e**), followed by base-catalyzed Wittig-type rearrangement to **f**, and subsequent dehydration affords the triene (**g**). Isomerization of **g** by valence tautomerization followed by dehydrogenation produces **6**. This reaction mechanism for the formation of **6** is supported by the fact that **6** was not detected in the one-step synthesis of **3a** from **1a** in the absence of γ-butyrolactone.

Experimental

All melting points are uncorrected and were taken on a Yanagimoto micromelting point apparatus. IR spectra were taken on a Hitachi 260-10 infrared spectrophotometer. NMR spectra were obtained on Varian EM-360 60 MHz and XL-100A spectrometers with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given as δ values (ppm): s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; br, broad; m, multiplet.

One-Step Synthesis of 5-Acetylspiro[benzofuran-2(3*H*),1′-cyclopropan]-3-one (3a)——A solution of methyl 5-acetyl-2-[(tetrahydro-2-oxo-3-furanyl)oxyl]benzoate (**1a**) (278 g, 1 mol) in dimethylformamide (DMF) (1.8 l) was added dropwise to a mixture of DBU (4.17 g), NaCl (67 g) and DMF (1 l) under stirring at 150 °C over a period of 2 h. The whole was stirred for an additional 2 h, then the solvent was removed *in vacuo* and the residue was diluted with H_2O. The aqueous solution was extracted with CH_2Cl_2. The extract was washed, dried and decolorized by passing it through silica gel. The CH_2Cl_2 solution was concentrated *in vacuo* and the resulting crystals were recrystallized from EtOH to afford **3a** (136 g, 67%), mp 106—107 °C. IR ν_{max}^{KBr} cm^{-1}: 1710 (CO), 1675 ($COCH_3$). ^{1}H-NMR ($CDCl_3$): 1.70

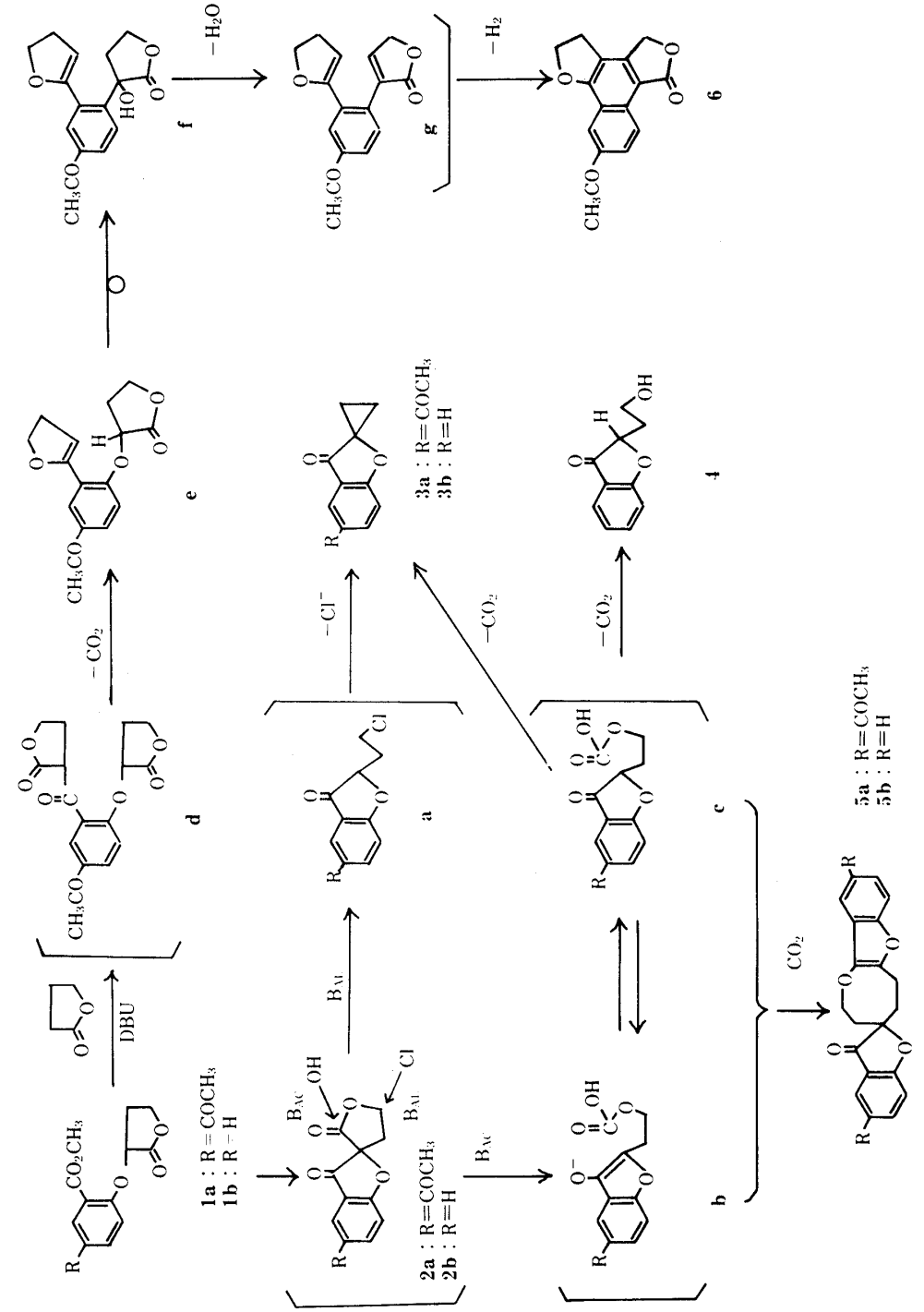


Chart 1

(4H, m, CH_2), 2.62 (3H, s, $COCH_3$), 7.23 (1H, d, $J=9$ Hz, 6-aromat. H), 8.33 (2H, m, 4- and 7-aromat. H). *Anal.* Calcd for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.29; H, 4.89.

The mother liquor was concentrated *in vacuo* and the resulting crystals were dissolved in EtOH. The EtOH-insoluble crystals were recrystallized from $CHCl_3$–acetone to afford 5,10′-diacetyl-5′,6′-dihydrospiro[benzofuran-2(3*H*),4′(3′*H*)-[2*H*]oxocino[3,2-*b*]benzofuran]-3-one (**5a**) (6.5 g, 3%), mp 205—207 °C. IR ν_{max}^{KBr} cm^{-1}: 1720 (CO), 1680 ($COCH_3$). ^{1}H-NMR ($CDCl_3$): 2.17 (2H, t, $J=5$ Hz, 3′-CH_2), 2.4—2.9 (2H, m, 5′-CH_2), 2.67 (3H, s, $COCH_3$), 2.73 (3H, s, $COCH_3$), 3.28 (2H, q, $J=4$ Hz, 6′-CH_2), 4.57 (2H, t, $J=5$ Hz, 2′-CH_2). ^{13}C-NMR: see Table I. *Anal.* Calcd for $C_{24}H_{20}O_6$: C, 71.28; H, 4.99. Found: C, 71.11; H, 4.86.

1*H*,3*H*-8-Acetyl-4,5-dihydronaphtho[1,2-*c*:4,3-*b*′]difuran-1-one (6)——The crude product (**1a**) obtained by the reaction of methyl 5-acetylsalicylate with α-bromo-γ-butyrolactone was used for the one-step synthesis of **3a**. The crystals obtained from the mother liquor of recrystallization of **3a** were recrystallized from $CHCl_3$ to afford **6**, mp 244—245 °C. IR ν_{max}^{KBr} cm^{-1}: 1740 (γ-lactone), 1680 ($COCH_3$). ^{1}H-NMR ($CDCl_3$): 2.72 (3H, s, $COCH_3$), 3.38 (2H, t, $J=9$ Hz, 4-CH_2), 5.00 (2H, t, $J=9$ Hz, 5-CH_2), 5.26 (2H, s, 3-CH_2), 8.18 (1H, dd, $J=2$ and 9 Hz, 9-aromat. H), 8.60 (1H, d, $J=2$ Hz, 7-aromat. H), 8.94 (1H, d, $J=9$ Hz, 10-aromat. H). *Anal.* Calcd for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51. Found: C, 71.72; H, 4.57.

X-Ray Crystallographic Analysis of 6——All the measurements were performed on a Rigaku AFC-5 four-circle diffractometer using graphite-monochromated Mo-*Kα* radiation ($\lambda=0.7107$ Å). Columnar crystals obtained from $CHCl_3$ solution belonged to the monoclinic system, space group $P2_1/c$. Cell constants were determined to be $a=7.821$ (2), $b=15.016$ (3), $c=10.706$ (3) Å and $\beta=99.97$ (2)° from the least-squares fit of 25 reflections in the range $31° < 2\theta < 37°$. Among 2282 independent reflections measured up to $2\theta=50°$, 1578 having $F_o > 3\sigma(F_o)$ were used for calculations. The structure was solved by the direct methods[4] and refined by the block-diagonal least-squares method[5] using unit weights. Refinement of C and O atoms by applying anisotropic thermal parameters revealed all H

Table II. Atomic Coordinates and Their Standard Deviations in Parentheses

Atom	*x/a*	*y/b*	*z/c*
C(1)	0.6799 (5)	0.5797 (3)	0.4005 (3)
C(2)	0.5744 (5)	0.5985 (3)	0.2823 (4)
C(3)	0.4885 (5)	0.5310 (3)	0.2111 (4)
C(4)	0.5050 (6)	0.4423 (3)	0.2564 (4)
C(5)	0.6063 (5)	0.4223 (3)	0.3703 (4)
C(6)	0.6974 (5)	0.4905 (3)	0.4459 (4)
C(7)	0.8032 (5)	0.4764 (2)	0.5665 (4)
C(8)	0.8867 (5)	0.5444 (3)	0.6376 (4)
C(9)	0.8716 (5)	0.6323 (3)	0.5936 (4)
C(10)	0.7700 (5)	0.6474 (3)	0.4784 (4)
O(11)	0.7594 (4)	0.7342 (2)	0.4433 (3)
C(12)	0.8792 (6)	0.7838 (3)	0.5407 (4)
C(13)	0.9425 (6)	0.7196 (3)	0.6493 (4)
C(14)	0.9815 (6)	0.5073 (3)	0.7604 (4)
O(15)	0.9422 (4)	0.4130 (2)	0.7516 (3)
C(16)	0.8383 (6)	0.3935 (3)	0.6381 (4)
O(17)	0.7924 (5)	0.3185 (2)	0.6126 (3)
C(18)	0.3738 (5)	0.5497 (3)	0.0860 (4)
C(19)	0.3606 (6)	0.6431 (3)	0.0359 (4)
O(20)	0.2928 (4)	0.4892 (2)	0.0279 (3)
H(C2)	0.573 (5)	0.659 (3)	0.254 (4)
H(C4)	0.438 (6)	0.398 (3)	0.205 (4)
H(C5)	0.614 (6)	0.362 (3)	0.402 (4)
H(C12)	0.819 (6)	0.832 (3)	0.560 (5)
H(C12)′	0.983 (6)	0.802 (3)	0.496 (4)
H(C13)	0.873 (6)	0.734 (3)	0.728 (5)
H(C13)′	1.076 (6)	0.718 (3)	0.665 (4)
H(C14)	0.932 (6)	0.533 (3)	0.840 (4)
H(C14)′	1.112 (6)	0.516 (3)	0.761 (4)
H(C19)	0.297 (6)	0.643 (3)	−0.043 (4)
H(C19)′	0.302 (6)	0.678 (3)	0.094 (4)
H(C19)″	0.473 (6)	0.672 (3)	0.031 (4)

atoms on a differential electron density map. Further refinement including H atoms with isotropic thermal parameters reduced the residual to a final unweighted R value of 0.055. Atomic coordinates are listed in Table II.

Spiroannelation of Methyl 2-[(Tetrahydro-2-oxo-3-furanyl)oxy]benzoate (1b)——A solution of **1b** (23.6 g, 100 mmol) in Et_3N (40 ml) and DMF (230 ml) was refluxed for 7 h. After removal of the solvents *in vacuo*, the residue was diluted with H_2O. The aqueous solution was acidified with AcOH and extracted with AcOEt. The extract was washed, dried and concentrated *in vacuo*. The residue was crystallized from EtOH to afford **3b** (3.6 g, 29%), mp 89—92 °C. The spectral data were identical with those of the product described in the previous report.[3] The mother liquor was concentrated *in vacuo* and the residue was crystallized from MeOH to afford 5′,6′-dihydrospiro[benzofuran-2(3*H*),4′(3′*H*)-[2*H*]oxocino[3,2-*b*]benzofuran]-3-one (**5b**) (2.2 g, 14%), mp 123—126 °C. IR ν_{max}^{KBr} cm^{-1}: 1720, 1710 ($COCH_3$ and CO). ^{1}H-NMR ($CDCl_3$): 2.04 (2H, q, J=4 Hz, 3′-CH_2), 2.53 (2H, t, J=5 Hz, 5′-CH_2), 3.22 (2H, m, 6′-CH_2), 4.45 (2H, m, 2′-CH_2). ^{13}C-NMR: see Table I. MS *m/e*: 320 (M^+), 160. *Anal.* Calcd for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 74.87; H, 4.93. The mother liquor was concentrated *in vacuo*, the residue was chromatographed on silica gel, and the resulting crystals were recrystallized from AcOEt–hexane to afford 2-(2-hydroxyethyl)-3(2*H*)-benzofuranone (**4**) (3 g, 17%), mp 41—44 °C. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1700 (CO). ^{1}H-NMR ($CDCl_3$): 2.10 (2H, m, $C\underline{H}_2CH_2OH$), 3.25 (1H, br, OH), 3.88 (2H, t, J=5 Hz, $CH_2C\underline{H}_2OH$), 4.73 (1H, q, J=5 Hz, CH). *Anal.* Calcd for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66. Found: C, 67.66; H, 5.47.

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