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Studies on Condensed Heterocyclic Isoquinolone Derivatives. III.[1] A Novel Oxidative Rearrangement of 11-Methyl-6-oxo-3,4-dihydro-2H,6H-1,3-thiazino[3,2-*b*]isoquinoline[2]

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The reaction of 11-methyl-6-oxo-3,4-dihydro-2H,6H-1,3-thiazino[3,2-*b*]isoquinoline (I) or the corresponding sulfone (II) with hydrogen peroxide led to a ring enlargement reaction to give a β-keto-sulfone, 1,6-methano-1-methyl-7,12-dioxo-4,5,7-trihydro-1H,3H-benzo[*g*]-1,5-thiazonine 2,2-dioxide (III), which was further converted into an enol-sulfone, 12-methyl-7-oxo-3H,7H-4,5-dihydro-2,1,4-oxathiazepino[4,3-*b*]isoquinoline 2,2-dioxide (VI), by thermal rearrangement. These ring enlargement and thermal rearrangement reactions involve intramolecular migration of the sulfonyl group. On treatment with sodium hydroxide, compound III gave 5-methyl-3,3a-dihydro-2H,5H-[2]benzothiopyrano[4,3-*b*]pyrrole 4,4-dioxide (VIII), presumably by hydrolysis and intramolecular condensation.

Reaction of compound I with chlorine in the presence of water gave 3-(4-chloro-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-2-yl)propanesulfonyl chloride (X) by ring opening, while compound II gave an additicn product, 11,11a-dichloro-11-methyl-6-oxo-3,4,11,11a-tetrahydro-2H,6H-1,3-thiazino[3,2-*b*]isoquinoline 1,1-dioxide (XIII), as the major product.

Keywords——thiazino[3,2-*b*]isoquinoline; oxidation; hydrogen peroxide; chlorine; oxidative rearrangement; thermal rearrangement; migration of sulfonyl group; ring-opening reaction

In the previous paper,[4] we reported that 11-methyl-6-oxo-3,4-dihydro-2H,6H-1,3-thiazino[3,2-*b*]isoquinoline (I) and the corresponding sulfone compound (II) exhibited strong analgesic and anti-inflammatory activity.

In the present study, we investigated the oxidation of compound I with hydrogen peroxide and with chlorine, and obtained some interesting results, including molecular rearrangements.

Oxidation of Compound I with Hydrogen Peroxide in Formic Acid

Compound II was obtained in 70% yield upon oxidation of compound I with hydrogen peroxide in acetic acid, as reported in the previous paper.[4] In order to improve the yield, the oxidation of compound I was examined in detail. The best result (88% yield) was obtained when the oxidation was carried out in dioxane in the presence of a tungsten catalyst.[5]

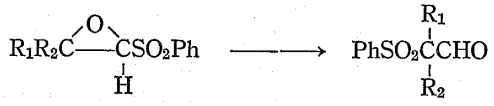
When the reaction with hydrogen peroxide was performed in formic acid, the yield of compound II was low and the formation of another substance was confirmed by thin layer chromatography. This substance was isolated in 50% yield by using excess hydrogen peroxide. The same substance was also obtained from compound II in good yield. The structure 1,6-methano 1-methyl-7,12-dioxo-4,5,7-trihydro-1H,3H-benzo[*g*]-1,5-thiazonine 2,2-dioxide (III)

1) Part II: K. Kubo, N. Ito, Y. Isomura, I. Sozu, H. Homma, and M. Murakami, *Yakugaku Zasshi*, **99**, 993 (1979).
2) This work was presented at the 99th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, 1979.
3) Location: *1-1-8, Azusawa, Itabashi-ku, Tokyo.*
4) Part I: K. Kubo, N. Ito, Y. Isomura, I. Sozu, H. Homma, and M. Murakami, *Chem. Pharm. Bull.*, **27**, 2372 (1979).
5) H.S. Shultz, H.B. Freyermuth, and S.R. Buc, *J. Org. Chem.*, **28**, 1140 (1963).

was assigned to this substance on the basis of its physical data. Mass (MS) spectral and microanalytical data indicated a molecular formula of $C_{13}H_{13}NO_4S$. Infrared (IR) spectroscopy revealed carbonyl absorptions at 1730 and 1670 cm^{-1}, which were similar to those of N-methylhomophthalimide (1705 and 1650 cm^{-1}), sulfone absorptions at 1300 and 1120 cm^{-1}, and no olefin absorption, in contrast to compound II. Proton magnetic resonance (PMR) data supported the assigned structure of compound III.

On the oxidation of 2,4-dimethyl-3-methylsulfonyl-1-oxo-1,2-dihydroisoquinoline (IV), a thiazine ring-opened analog of compound II, with hydrogen peroxide in formic acid, 2,4-dimethyl-1,3-dioxo-4-methylsulfonyl-1,2,3,4-tetrahydroisoquinoline (V) was formed through intramolecular migration similar to that observed in the oxidation of compounds I and II.

A similar rearrangement has been reported[6a,b] with $\alpha\beta$-epoxysulfones, leading to α-formyl sulfones.



Therefore, the reaction of compound II with hydrogen peroxide in formic acid probably proceeds through the formation of an epoxide, fission of the oxirane ring and intramolecular migration of the sulfonyl group.

Compound III was converted into 12-methyl-7-oxo-3H,7H-4,5-dihydro-2,1,4-oxathiazepino[4,3-*b*]isoquinoline 2,2-dioxide (VI) by heating in acetic acid under reflux, or by heating above its melting point (166°), in almost quantitative yield. In contrast, compound V was thermally stable. The molecular formula of compound VI was identical with that of compound III. The fragment ions in the MS spectrum of compound VI were the same as those of compound III, except for their intensity. The ultraviolet absorption (UV) spectrum and IR spectrum resembled those of compound II. These physical data are consistent with the above structure assigned to compound VI.

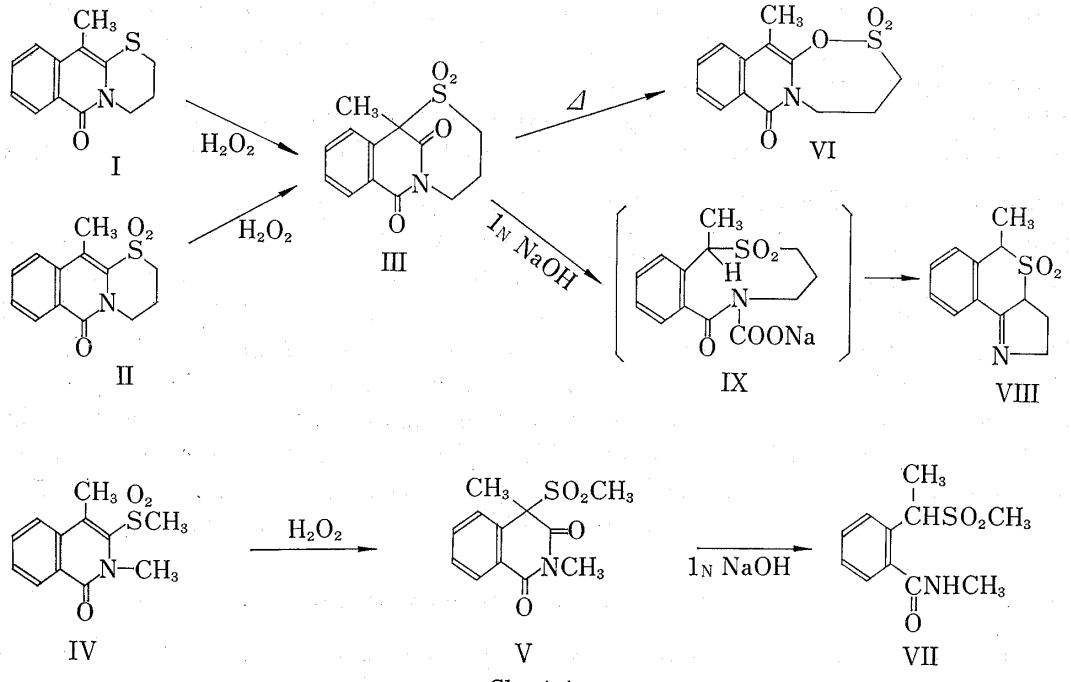


Chart 1

6) *a*) T. Durst and K.C. Tin, *Tetrahedron Lett.*, **1970**, 2369; *b*) D.F. Tavares, R.E. Estep, and M. Blezard, *Tetrahedron Lett.*, **1970**, 2373.

When compound V was treated with 1N sodium hydroxide at 50—60° for 20 hr, *o*-(1-methylsulfonylethyl)-N-methylbenzamide (VII) was obtained in 67% yield by hydrolysis of the imide group at the 3-position. A similar treatment of compound III with 1N sodium hydroxide afforded a different kind of product, 5-methyl-3,3a-dihydro-2H,5H-[2]benzothiopyrano[4,3-*b*]pyrrole 4,4-dioxide (VIII), which has the molecular formula $C_{12}H_{13}NO_2S$ and shows no IR carbonyl absorption.

This compound is a mixture of diastereomers (VIIIa and VIIIb) due to the difference in configuration of the two methines α to the sulfonyl group. The PMR spectrum indicated the presence of a methyl group, two methylene groups (δ: 2.3 and 4.0) and a methine group (δ: 5.02). The methine signal was split into a triplet by the adjacent methylene group (δ: 2.3) and the signal disappeared on addition of CD_3OD. The methyl signals appeared as two doublets (2: 1) at δ 1.68 and 1.72. Thus, the ratio of the diastereomers VIIIa and VIIIb is 2: 1, and the predominant diastereomer, $VIII_a$, was separated by recrystallization. It was observed from the PMR spectrum that compound VIIIa was converted into a mixture (2: 1) of the diastereomers VIIIa and VIIIb on standing overnight in DMSO-d_6 solution at room temperature. Thus, assignment of the structure VIII can be rationalized.

The formation of compound VIII may be explained by presuming that hydrolysis of the imide group at the 3-position of the isoquinoline ring gives an intermediate (IX), and that condensation of the methylene group α to the sulfonyl group with the carbonyl group occurs.

Oxidation of Compound I with Chlorine

When compound I was treated with chlorine in a mixture of acetic acid, chloroform and water, 3-(4-chloro-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-2-yl)propanesulfonyl chloride (X) was obtained in good yield. The chemical structure was assigned on the basis of its chemical properties and spectral data. The MS spectrum and the microanalytical data indicated a molecular formula of $C_{13}H_{13}Cl_2NO_4S$. The IR carbonyl absorptions were similar to those of compound III, although the sulfone absorptions were shifted to higher frequencies. Catalytic hydrogenation of compound X gave a product (XI) in which the chlorine atom at the 4-position of the isoquinoline ring was replaced by hydrogen. Reaction of compound XI with *p*-chloroaniline gave the corresponding sulfonanilide (XII).

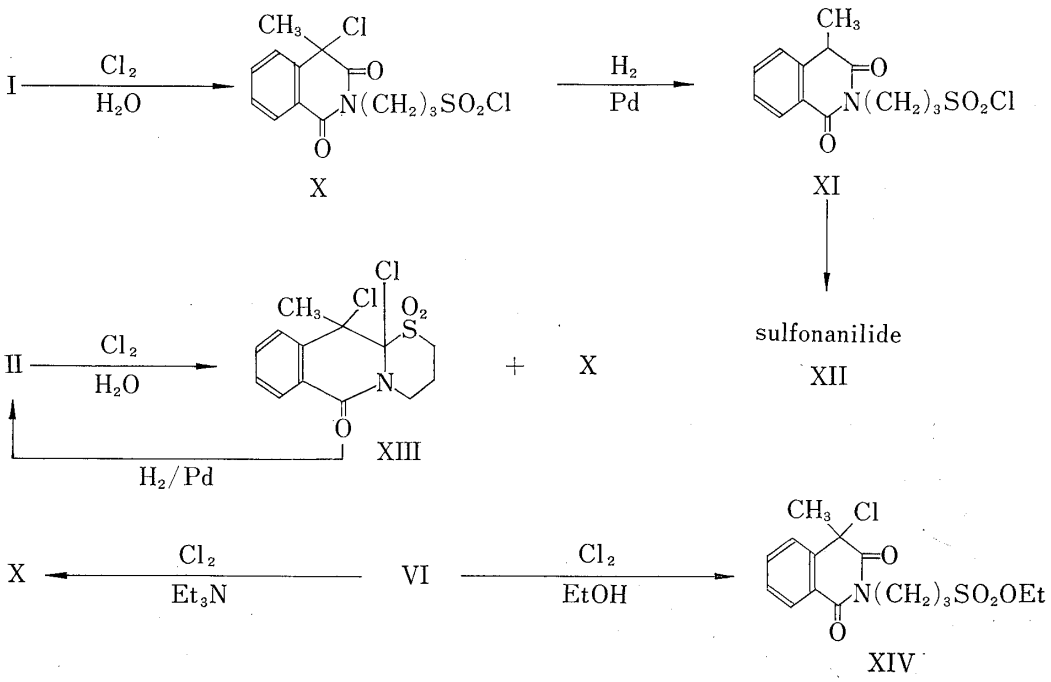


Chart 2

On the other hand, treatment of compound II with chlorine gave an addition product (XIII) together with compound X in 41% and 24% yields, respectively. Compound XIII showed IR carbonyl absorption similar to that of compound II, but gave no olefin absorption. The structure was confirmed by hydrogenation on palladium, which gave compound II.

In view of the finding that the reaction of compound II with chlorine gives compound XIII as the major product under the conditions used in the reaction of compound I, the pathway from compound I to the compound X may be rationalized by presuming that addition of chlorohydrin to the olefin bond, oxidation to sulfone and fission of the C-S bond occur successively.

Table I. IR, UV and MS Data

	IR ν_{max}^{KBr} cm^{-1}			UV λ_{max}^{MeOH} nm (log ε)	MS *m/e* (relative intensity)
	C=O	C=C	SO_2		
II	1630	1580	1290, 1125	211(4.7), 230 S (4.4), 298(4.1)	263(M^+, 100), 212(49), 198(30)
III	1730, 1670		1300, 1120	206(4.4), 273 S (3.4)	279(M^+, 25), 215(100), 187(71), 159(92)
VI	1660	1625	1365, 1155	209(4.5), 228(4.3), 282(4.0)	279(M^+, 71), 215(70), 187(81), 159(100)
VIII			1305, 1115	210(4.3), 249(4.1)	235(M^+, 4), 171(18), 156(100)
X	1720, 1670		1350, 1160	219(4.2)	349(M^+, 4), 314(36), 250(63), 215(22), 214(36), 186(22), 166(100)
XIII	1670		1330, 1130	210(4.3)	333(M^+, 3), 234(100), 206(55)

Table II. PMR Data (δ, ppm)

	Solvent	$-CH_3$	$H_3CHC<$	SO_2CH_2-, SO_2CH-	NCH_2-	Aromatic C_8-H[a]
II	DMSO-d_6	2.66(s)		3.74(2H, t) J=6 Hz	4.16(t) J=6 Hz	8.26(d) J=7 Hz
III	DMSO-d_6	1.96(s)		3.2—3.6(2H, m)	3.7—4.4(m)	8.4(m)
VI	DMSO-d_6	2.22(s)		4.3—4.5(2H, m)	4.0(t) J=6 Hz	8.22(d) J=7 Hz
VIII a	DMSO-d_6	1.68(d) J=7 Hz	4.68(q) J=7 Hz	5.02(1H, t) J=8 Hz	3.6—4.4(m)	8.06(m)
VIII b	DMSO-d_6	1.72(d) J=7 Hz	4.90(q) J=7 Hz			
X	$CDCl_3$	2.22(s)		3.7—3.9(2H, m)	4.20(t) J=7 Hz	8.20(d) J=7 Hz
XIII	$CDCl_3$	2.50(s)		3.0(1H, m), 4.9(1H, m)	3.68—4.16(m)	8.2(m)

a) C_8-H of the isoquinoline ring.

Compound X was also obtained by the reaction of compound VI with chlorine in anhydrous chloroform in the presence of triethylamine. When the reaction of compound VI with chlorine was carried out in ethanol, an ethyl sulfate (XIV) was obtained. The MS spectrum of compound XIV exhibited, besides the molecular ion, an (M^+–SO_3Et) peak and other peaks similar to those of compound X.

The IR, UV, and MS data for the above mentioned compounds are listed in Table I and the PMR data in Table II.

Experimental[7]

11-Methyl-6-oxo-3,4-dihydro-2H,6H-1,3-thiazino[3,2-*b*]isoquinoline 1,1-Dioxide (II)[4]——A tungstic acid solution (4 ml) (prepared from 20 mg of $WO_3 \cdot H_2O$ according to the literature[5]) was added to a solution of 11-methyl-6-oxo-3,4-dihydro-2H,6H-1,3-thiazino[3,2-*b*]isoquinoline[4] (I) (2.3 g) in dioxane (15 ml). The mixture was heated to 85° and then 30% hydrogen peroxide (2.8 g) was added dropwise for 2 hr at 85—90°. After heating for 2 hr, water (15 ml) was added. The precipitated crystals were collected and washed with EtOH to give 2.3 g (88%) of II, mp 184—186°.

1,6-Methano-1-methyl-7,12-dioxo-4,5,7-trihydro-1H,3H-benzo[*g*]-1,5-thiazonine 2,2-Dioxide (III)——i) Hydrogen peroxide (30%, 20 g) was added slowly to a solution of I (15 g) in 85% formic acid (50 ml) so that the temperature did not exceed 55°. When the addition was complete and the exothermic reaction subsided, more 30% hydrogen peroxide (20 g) was added and the mixture was heated at 50—55° for 8 hr. The precipitated crystals were collected and washed with EtOH to give 9.1 g (50%) of III, mp 164—166°. *Anal.* Calcd for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69, N, 5.01; S, 11.48. Found: C, 55.83; H, 4.73; N, 4.90; S, 11.60.

ii) A solution of II (10 g) in 85% formic acid (30 ml) was treated with 30% hydrogen peroxide (15 g). The mixture was heated at 50—55° for 8 hr, giving 6.4 g (60%) of III.

2,4-Dimethyl-1,3-dioxo-4-methylsulfonyl-1,2,3,4-tetrahydroisoquinoline (V)——The reaction of 2,4-dimethyl-3-methylsulfonyl-1-oxo-1,2-dihydroisoquinoline (IV) (prepared according to the literature[4]) (0.5g) with 30% hydrogen peroxide was carried out in the manner described for III-ii, giving 0.35 g (66%) of V, mp 171—173°, *Anal.* Calcd for $C_{12}H_{13}NO_4S$: C, 53.92; H, 4.90; N, 5.24; S, 11.99. Found: C, 53.63; H, 4.84; N, 5.11; S, 12.08. IR ν_{max}^{KBr} cm^{-1}: 1710, 1655 (CO), 1300, 1130 (SO_2). PMR ($CDCl_3$) δ: 2.20 (3H, s, CH_3), 3.06 (3H, s, SO_2CH_3), 3.42 (3H, s, NCH_3). MS *m/e*: 267 (M^+).

12-Methyl-7-oxo-3H,7H-4,5-dihydro-2,1,4-oxathiazepino[4,3-*b*]isoquinoline 2,2-Dioxide (VI)——i) A solution of II (2 g) in acetic acid (6 ml) was heated under reflux for 10 min. After cooling, the precipitated crystals were collected to give 1.9 g (95%) of VI, mp 246—247°. *Anal.* Calcd for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69; N, 5.01; S, 11.48. Found: C, 55.71; H, 4.62; N, 4.80; S, 11.68.

ii) Compound III was melted by heating above 170°, giving VI in quantitative yield.

O-(1-Methylsulfonylethyl)-N-methylbenzamide (VII)——A solution of V (0.1 g) in 1 N NaOH (2 ml) was heated at 50—60° for 20 hr. The precipitated crystals were recrystallized from EtOH to give 60.3 mg (67%) of VII, mp 151—152°. *Anal.* Calcd for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27; N, 5.80; S, 13.29. Found: C, 54.53; H, 6.20; N, 5.93; S, 13.13. IR ν_{max}^{KBr} cm^{-1}: 1620 (CO), 1290, 1135 (SO_2). PMR ($CDCl_3$) δ: 1.76 (3H, d, J= 7 Hz, CH_3), 2.82 (3H, s, SO_2CH_3), 2.98 (3H, d, J=5 Hz, NCH_3), 5.0 (1H, q, J=7 Hz, CH_3–CH), 6.28 (1H, br.s, NH), 7.66 (1H, m, C_8–H). MS *m/e*: 241 (M^+).

5-Methyl-3,3a-dihydro-2H,5H-[2]benzothiopyrano[4,3-*b*]pyrrole 4,4-Dioxide (VIII)——The reaction of III (3 g) in 1 N NaOH (30 ml) was carried out in the manner described above, giving 1.73 g (68%) of VIII, mp 154—155° (from EtOH). *Anal.* Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95; S, 13.63. Found: C, 61.18; H, 5.62; N, 5.97; S, 13.63.

Compound VIII (0.6 g) was recrystallized from AcOEt to give 0.3 g of a predominant diastereomer (VIIIa), mp 154—155°.

3-(4-Chloro-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-2-yl)propanesulfonyl Chloride (X)——i) A solution of I (2 g) in AcOH (8 ml), $CHCl_3$ (8 ml) and H_2O (4 ml) was bubbled through with a slow stream of chlorine for 10 min under ice cooling. The reaction mixture was poured into ice-water and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated under reduced pressure, giving 2.65 g (88%) of almost pure X, mp 83—84° (from Et_2O–hexane). *Anal.* Calcd for $C_{13}H_{13}Cl_2NO_4S$: C, 44.58; H, 3.74; Cl, 20.25; N, 4.00; S, 9.15. Found: C, 44.46; H, 3.84; Cl, 20.23; N, 4.01; S, 9.18.

ii) The reaction of VI (0.5 g) with chlorine in $CHCl_3$ (5 ml) in the presence of Et_3N (0.5 g) was carried out as described above. The crude material obtained was purified by chromatography on silica gel with $CHCl_3$ elution, giving 0.39 g (62%) of X.

11,11a-Dichloro-11-methyl-6-oxo-3,4,11,11a-tetrahydro-2H,6H-1,3-thiazino[3,2-*b*]isoquinoline 1,1-Dioxide (XIII) and Compound X——The reaction of II (0.5 g) with chlorine in a mixture of AcOH, $CHCl_3$ and H_2O was carried out as described for X-i. The reaction products were separated by chromatography on silica gel, eluting with $CHCl_3$, to give 0.26 g (41%) of XIII, mp 171—172° (from tetrahydrofuran-hexane) and 0.16 g (24%) of X. *Anal.* Calcd for $C_{13}H_{13}Cl_2NO_3S$ (XIII): C, 46.72; H, 3.92; Cl, 21.22; N, 4.19; S, 9.59. Found: C, 46.59; H, 3.87; Cl, 21.06; N, 4.14; S, 9.57.

Ethyl 3-(4-Chloro-4-methyl-1,3-dioxo-1,2,3,4-tetrahydro-2-isoquinyl)propanesulfate (XIV)——The reaction of VI (0 5 g) with chlorine in EtOH (5 ml) was carried out in the manner described for X-ii, giving 0.3 g (46%) of XIV as oil. IR ν_{max}^{KBr} cm^{-1}: 1720, 1670 (CO), 1350, 1165 (SO_2). PMR ($CDCl_3$) δ: 1 38 (3H, t, J=

7) All melting points are uncorrected. IR spectra were measured with a Hitachi 215 spectrometer and UV spectra with a Shimadzu UV-300 spectrophotometer. PMR spectra were recorded at 100 MHz with a JEOL MH100 or a JEOL FX100 spectrometer using TMS as an internal standard. MS were obtained on a Hitachi RMU-6MG double-focusing mass spectrometer.

6 Hz), 2.21 (3H, s, CH_3), 2.08—2.36 (2H, m, CH_2), 3.18 (2H, t, J=6 Hz, CH_2), 4.18 (2H, q, J=6 Hz, CH_2), 4.30 (2H, t, J=6 Hz, CH_2). MS *m/e*: 359 (M^+, 3) 250 (43), 215 (33), 214 (100), 186 (27), 166 (60).

3-(4-Methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinoline-2-yl)propanesulfonyl Chloride (XI)——Compound X (0.5 g) was hydrogenated in a solution of AcOEt (10 ml) over 5% Pd-charcoal (30 mg) for 6 hr. After removal of the catalyst, the solvent was evaporated off under reduced pressure. The residue was chromatographed on silica gel, and elution with $CHCl_3$ gave 0.29 g (64%) of XI, mp 99—100° (from isopropylether). *Anal.* Calcd for $C_{13}H_{14}ClNO_4S$: C, 49.45; H, 4.47; Cl, 11.23; N, 4.44; S, 10.15. Found: C, 49.21; H, 4.47; Cl,11.64; N, 4.49; S, 10.15. IR ν_{max}^{KBr} cm^{-1}: 1700, 1655 (CO), 1350, 1155 (SO_2). PMR ($CDCl_3$) δ: 1.68 (3H, d, J=8 Hz, CH_3), 3.96 (1H, d, J=8 Hz, $CH_3\underline{CH}$). MS *m/e*: 315 (M^+, 57), 216 (100).

3-(4-Methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-2-yl)propanesulfone-*p*-chloroanilide (XII)——Compound (X) (0.2 g) was added to an ice-cooled solution of *p*-chloroaniline (0.13 g) in pyridine (1ml). After 30 min, the reaction mixture was poured into water and extracted with $CHCl_3$. The extract was washed with dil. HCl and dried. After removal of the solvent, the residue was chromatographed on silica gel, and elution with $CHCl_3$ gave 0.16 g (31%) of XII, mp 176—177° (from EtOH). *Anal.* Calcd for $C_{19}H_{18}ClN_2O_4S$: C, 56.23; H, 4.47; N, 6.90; S, 7.90. Found: C, 55.90; H, 4.57; N, 6.86; S, 7.71. IR ν_{max}^{KBr} cm^{-1}: 1700, 1645 (CO), 1320, 1120 (SO_2). MS *m/e*: 406 (M^+, 24), 286 (100), 216 (78).

Conversion of Compound XIII into Compound II——Compound XIII (0.1 g) was hydrogenated in a solution of MeOH (20 ml) over 5% Pd-charcoal (10 mg) for 30 min. After removal of the catalyst, the solvent was evaporated off under reduced pressure. The residue was recrystallized from EtOH to give 45 mg (57%) of II.

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