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# Heteroaromatic Analogs of Benzomorphan. Synthesis of Novel Thiazolo[4,5-*f*]morphans

Monothiazolization of ethyl 2-methyl-1,3-dioxo-2-cyclohexaneacetate (I) afforded 2-aminothiazole derivative (IIa) corresponding to tetralone. In several steps, IIa was converted to some thiazolo[4,5-*f*]morphans (X) *via* 9-oxothiazolo[4,5-*f*]morphan (VIII).

**Keywords**——analgesic activity; 2-aminothiazole; 9-oxothiazolo[4,5-*f*]morphan; Wittig reaction; Wolff–Kishner reduction; thiazolo[4,5-*f*]morphan

Concerning structure-activity relationship especially the influence of the aromatic ring, it has been interested in the analgesic and antagonist activity of benzomorphan analogs in which the benzene ring is replaced by a heteroaromatic ring. In this sense, pyridomorphans[1] and thienomorphans[2] have been synthesized. The characteristic structure of thiazole that has both of electron-rich and electron-poor site and $\pi$ excessive property as a whole, has led us to attempt the synthesis of thiazolomorphan.

Grewe cyclization[3] by which thienomorphans were synthesized does not appear to be suitable for our purpose, in view of the weak nucleophilicity of thiazole. Hence in order to synthesize 9-oxothiazolo[4,5-*f*]morphan (VIII) as a key intermediate, we have applied a sequence of reactions used in the tetralone route by which Kavadias prepared 9-oxobenzomorphans[4] and as a result novel thiazolo[4,5-*f*]morphan derivatives were obtained from this intermediate.

Treatment of ethyl 2-methyl-1,3-dioxo-2-cyclohexaneacetate (I)[5] with an equivalent of bromine in acetic acid followed by the action of thiourea in tetrahydrofuran, led to IIa [mp 160—162°; MS *m/e*: 268 ($M^+$); PMR $\delta$ ($CDCl_3$): 1.13 (3H, t, $J$=7 Hz), 1.30 (3H, s, 4-$CH_3$), 2.63—3.20 (6H, m), 4.00 (2H, q, $J$=7 Hz), 5.37 (2H, br, s, –$NH_2$)] and IIIa [MS *m/e*: 324 ($M^+$)] in 63% and 11% yields, respectively. The insoluble dithiazole (IIIa) was acetylated and the structure of the acetate (IIIb) was confirmed.[6] [mp>350°; MS *m/e*: 408 ($M^+$); PMR $\delta$ (DMSO-$d_6$): 0.83 (3H, t, $J$=7 Hz), 1.53 (3H, s, 4-$CH_3$), 2.13 (6H, s, $2\times CO\underline{CH_3}$), 2.93 (2H, br s, –$\underline{CH_2}CO_2Et$), 3.70 (2H, q, $J$=7 Hz), 3.97 (2H, s, 8-H)].

By Sandmeyer reaction (diazotization in 40% $H_2SO_4$ and subsequent treatment with $CuSO_4$–NaCl), IIa was converted to IIb [mp 63.5—64.5°; MS *m/e*: 287, 289 ($M^+$)] in 64% yield. Compound (IIb) was then hydrogenated over 10% Pd-C in the presence of triethylamine to IIc [bp 113—114° (0.15 mmHg); PMR $\delta$ ($CDCl_3$): 8.65 (1H, s, 2-H)] quantitatively. Treatment of IIc with methanolic methylamine solution afforded IV (mp 217.5—219°) in 78% yield, whose IR [$\nu$ (Nujol): 3320, 1680 $cm^{-1}$] indicated the formation of five-membered lactam. The hydroxy lactam (IV) was dehydrated to V [mp 156—161°; IR $\nu$ ($CHCl_3$): 1720, 1670 $cm^{-1}$; PMR $\delta$ ($CDCl_3$): 1.40 (3H, s, 8a-$CH_3$), 2.83 (2H, s, 8-H), 3.05 (3H, s, N–$CH_3$), 3.60 (2H, d, $J$=4 Hz, 4-H), 5.15 (1H, t, $J$=4 Hz, 5-H), 8.70 (1H, s, 2-H)] with *p*-toluenesulfonic acid in toluene in 88% yield. Lithium aluminum hydride reduction of V in refluxing ether and subsequent treatment of the resulting enamine (VI) [IR $\nu$ ($CHCl_3$): 1660 $cm^{-1}$] with bromine in dichloromethane at −60° afforded the immonium salt (VII) [perchlorate: mp 150—152.5°; IR $\nu$ (Nujol): 1680 $cm^{-1}$] quantitatively. On treatment with aqueous ammonium bicarbonate solution in 95% ethanol, VII was hydrolyzed and rearranged to 2,5-dimethyl-9-oxothiazolo[4,5-*f*]morphan (VIII) [mp 122.5—125.5°; IR $\nu$ ($CHCl_3$): 1735 $cm^{-1}$; PMR $\delta$ ($CDCl_3$): 1.58 (3H, s, 5-$CH_3$), 2.45 (3H, s, N–$CH_3$), 8.72 (1H, s, 2′-H)] in 72% yield.

Heating of VIII with hydrazine and potassium hydroxide in diethylene glycol at 170° furnished 2,5-dimethylthiazolo[4,5-*f*]morphan (Xa) [PMR $\delta$ ($CDCl_3$): 1.48 (3H, s, 5-$CH_3$), 2.40 (3H, s, N–$CH_3$), 8.58 (1H, s, 2′-H); oxalate: mp 233.5—234° (dec.)] in 49% yield. To introduce 9-methyl group, the ketone function of VIII was converted to exomethylene and to

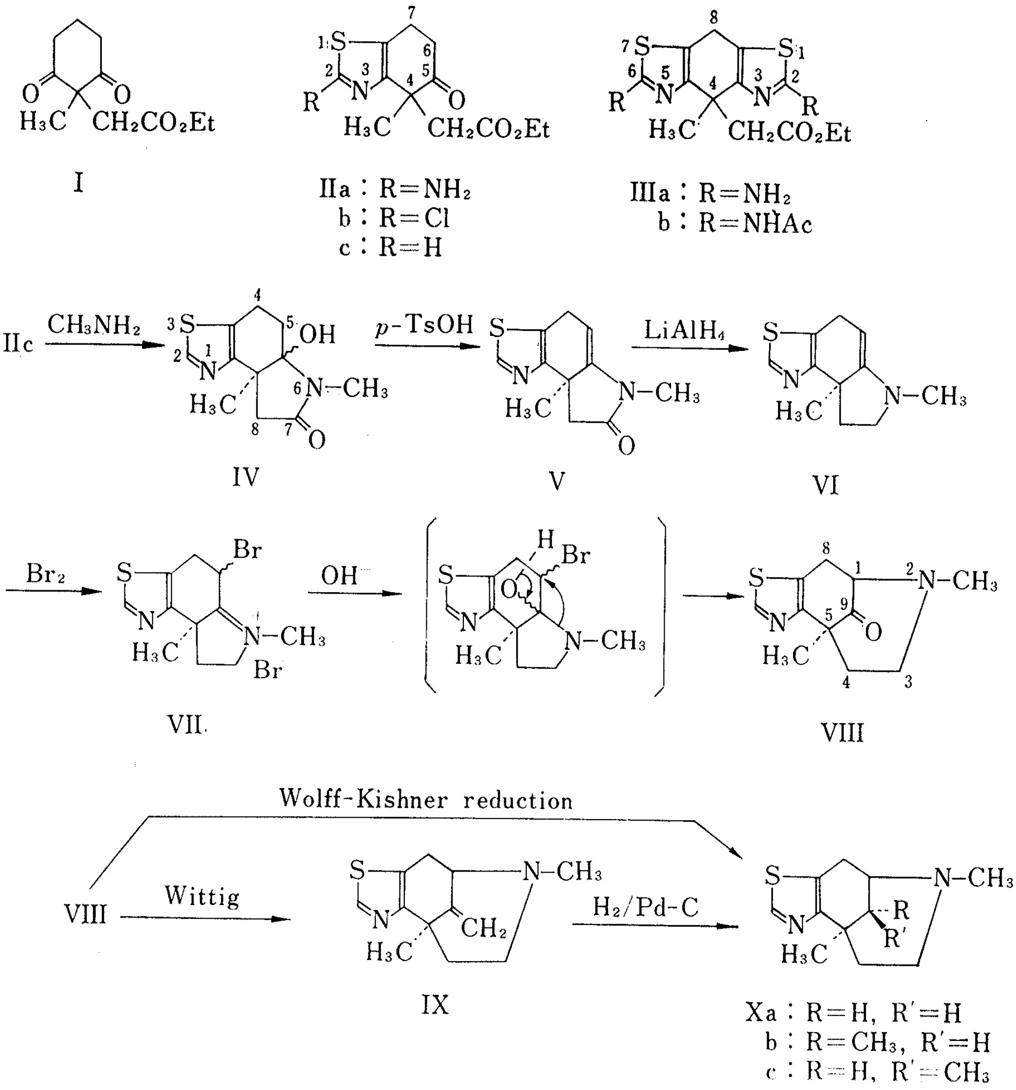

Chart 1

methyl group by the subsequent hydrogenation in the following manner. Thus, Wittig reaction between VIII and methyltriphenyl phosphonium iodide in the presence of *n*-butyl lithium in dry tetrahydrofuran produced the exomethylene compound (IX) [PMR $\delta$ ($CDCl_3$): 1.67 (3H, s, 5-$CH_3$), 3.43 (3H, s, N-$CH_3$), 4.94 (2H, s, C=$CH_2$), 8.62 (1H, s, 2'-H); oxalate: mp 243.5—244° (dec.)] in 83% yield. Although IX appreciably resisted to hydrogenation over $PtO_2$ under various conditions, reduction of IX was completed over 10% Pd-C at 5 atmospheric pressure. The resultant mixture was separated by chromatography on silica gel and 2,5,9$\alpha$-trimethylthiazolo[4,5-*f*]morphan (Xb) and 2,5,9$\beta$-trimethylthiazolo[4,5-*f*]-morphan (Xc) were obtained in 75% and 9% yields, respectively. [PMR $\delta$ ($CDCl_3$): 0.85 (3H, d, $J$=7 Hz, 9$\alpha$-$CH_3$), 1.45 (3H, s, 5-$CH_3$), 2.37 (3H, s, N-$CH_3$), 8.58 (1H, s, 2'-H) for Xb and 1.24 (3H, d, $J$=7 Hz, 9$\beta$-$CH_3$), 1.45 (3H, s, 5-$CH_3$), 2.33 (3H, s, N-$CH_3$), 8.53 (1H, s, 2'-H) for Xc; oxalate of Xb: mp 213—214°; oxalate of Xc: mp 213.5—215.5°]. The configurations of 9-methyl groups in Xb and Xc were established from PMR spectra. The doublet signal of Xc was observed at $\delta$ 1.24, while the signal of Xb (9$\alpha$-$CH_3$) shifted up to $\delta$ 0.85 due to the shielding effect of thiazole ring. The observed stereoselectivity in this hydrogenation reaction has ample precedent in benzomorphan series.[3b)]

Thiazolo[4,5-*f*]morphans prepared in this study were evaluated for analgesic activity by the acetic acid induced mouse writhing method. The $ED_{50}$'s (subcutaneous injection) for the oxalates of Xa, Xb and Xc were 5.28, 1.16 and 4.22 mg/kg, respectively, and the most effective compound (Xb) was over 10 times more potent than codeine phosphate (13.1 mg/kg) used as the standard compound. The further pharmacological studies are in progress and will be published in detail elsewhere.

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### References and Notes

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# Odorous Metabolites of a Fungus, *Chaetomium globosum* Kinze ex Fr. Identification of Geosmin, a Musty-smelling Compound[1)]

Geosmin, an earthy-musty smelling compound, and 2-phenylethanol were detected by gas chromatography and mass spectrometry combined with gas chromatography from the volatile metabolites of *Chaetomium globosum* Kinze ex Fr., a fungus isolated from the soil at Sugadaira, Nagano Prefecture. It was suggested that fungi are partly responsible for the unpleasant earthy-musty odor and taste in public water supplies.

**Keywords**——geosmin; 2-phenylethanol; fungi; *Chaetomium globosum*; earthy-musty odor; odorous metabolite; public water supplies; water pollution

Unpleasant earthy-musty odor and taste occurred in public water supplies in recent years have been attributed mainly to geosmin (I)[2)] and 2-methylisoborneol[3)] which are produced by several actinomycetes and blue-green algae.[4)] In connection with the study on the causal agents of odors and tastes in water supplies, we previously reported the isolation and identification of 6-pentyl-$\alpha$-pyrone from two strains of fungi, *Trichoderma* and *Aspergillus* species,[5)] and also the identification of 2-phenylethanol and phenylacetaldehyde from several fungi, such as *Chaetomium*, *Penicillium*, and *Robillarda* species, obtained from the bottom deposits of Sengari reservoir, Kobe City Water Supply Bureau.[4d)] However, these compounds have