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Thiazole Analogs of Benzomorphans. II.[1] Synthesis of Novel Thiazolo[5,4-*f*]morphans

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Cyanomethylation of 4,5,6,7-tetrahydro-6,6-dimethyl-7-oxobenzothiazole (VII), which was prepared from 4,4-dimethyl-1,3-cyclohexanedione (I) in several steps, afforded the cyano alcohol (VIII). Compound VIII was treated with lithium aluminum hydride and the resulting amino alcohol (IX) was converted into 7-(2-aminoethyl)-4,7-dihydro-6,7-dimethylbenzothiazole (XI) by Wagner–Meerwein rearrangement. Reaction of XI with bromine gave the salt (XII). Treatment of XII with potassium carbonate produced the bridged aziridine (XIII), which was cleaved to the thiazolo[5,4-*f*]morphan (4,5,6,7,8,9-hexahydro-5,9-methanothiazolo[4,5-*d*]azocine) derivative (XVI) by the action of benzoyl bromide. Dehydrobromination followed by hydrolysis of the benzoyl group led XVI to 5-methyl-9-methylenethiazolo[5,4-*f*]morphan (XVIII). Stereospecific hydrogenation of XVIII yielded the 9α-methyl isomer (XIX), whose *N*-methylation by the Eschweiler–Clarke method completed the synthesis of the desired thiazolo[5,4-*f*]morphan (XX). The molecular structure of the oxalate of XIX was established by X-ray analysis.

Keywords——analgesic activity; 2-aminothiazole; 7-(2-aminoethyl)-4,7-dihydro-6,7-dimethylbenzothiazole; bridged aziridine; thiazolo[5,4-*f*]morphan; X-ray analysis

It is generally accepted that a narcotic analgesic binds to its receptor at two sites; the basic nitrogen and the benzene ring possessing a phenolic hydroxyl group.[2] The role of the hydroxyl group is considered to be the formation of a hydrogen bond with a dipolar site on the receptor and to enhance the activity.[3]

In connection with the modification of the aromatic site, pyridomorphans,[4] thienomorphans[5] and pyrrolomorphans[6] have been synthesized. We have chosen to synthesize thiazolomorphans to investigate the possibility that thiazole, like the phenol group, could interact with the dipolar site on the receptor. As reported in the preceding paper, we have synthesized thiazolo[4,5-*f*]morphan derivatives, which have potent analgesic activities, comparable to that of morphine.[1] We now wish to describe the synthesis of novel thiazolo[5,4-*f*]morphans, in which the fusing mode of the thiazole ring of the above thiazolo[4,5-*f*]morphan skeleton is reversed. Belleau's approach to morphinan[7] and Shiotani's approach to 6,7-benzomorphan,[8] which started from 2,2-dialkyl-1-tetralones, provided a basis for our synthesis.

4,5,6,7-Tetrahydro-6,6-dimethyl-7-oxobenzothiazole (VII), a key intermediate for the synthesis of thiazolo[5,4-*f*]morphans, was prepared by thiazolization of 4,4-dimethyl-1,3-cyclohexanedione (I) followed by deamination of the resulting 2-aminothiazole derivative (IV). Earier workers have reported the preparation of the starting material (I) in several steps.[9] Our improved one-step preparation of I consisted of Michael condensation of methyl isopropyl ketone and ethyl acrylate in the presence of sodium ethoxide.

The diketone (I) was brominated and the reaction of the resulting bromide (II) with thiourea was examined. Treatment of II with thiourea in refluxing tetrahydrofuran, ethanol or ethyl acetate, yielded no 2-aminothiazole but gave the isothiouronium salt (III). Its infrared (IR) spectrum showed peaks at 1640, 1620 and 1595 cm^{-1} due to the enolized β-diketone and the imine groups. A 5H singlet at δ 8.57 in the nuclear magnetic resonance

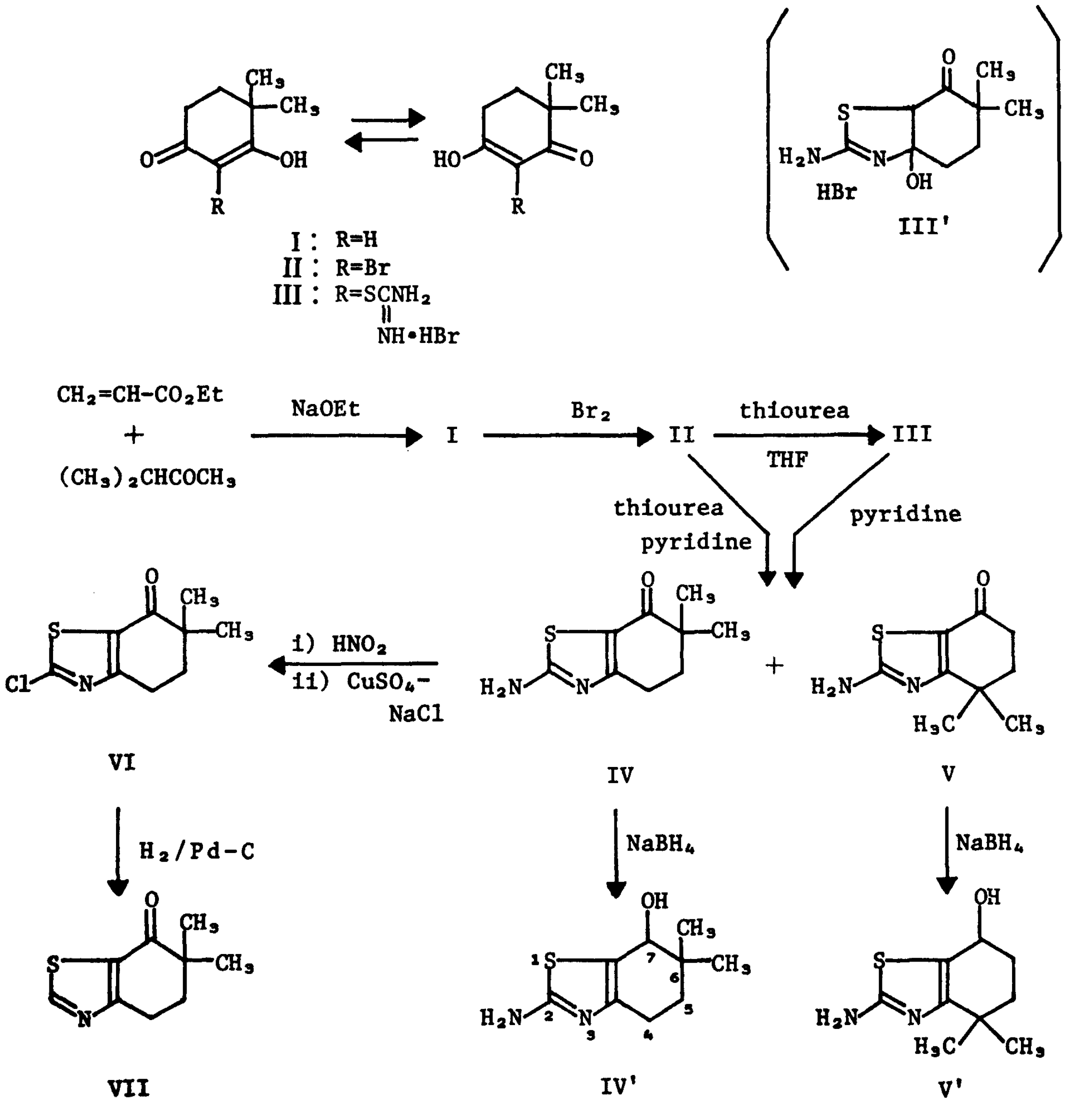


Chart 1

(^{1}H-NMR) spectrum of III was exchangeable with deuterium oxide. These spectral data indicate that compound III is not the cyclic intermediate (III') but the acyclic isothiouronium salt. In general, reaction between an α-halocarbonyl compound and thiourea to prepare 2-aminothiazole first produces an acyclic intermediate corresponding to III. This has seldom been isolated because of its great reactivity. In the case where an α-halogeno acid or ester is the reactant, this intermediate has been isolated.[10] The next step is the cyclization of this intermediate to form the second ring. This type of compound has been isolated when acyl-substituted thiourea has been used.[11] As a result, 2-aminothiazole is formed by dehydration of the second intermediate. Our isolation of the acyclic isothiouronium salt (III) is quite exceptional for the reaction between an α-haloketone and thiourea.[12]

Heating of III in pyridine gave two isomeric 2-aminothiazole derivatives, IV and V, in 68% and 20% yields, respectively. Their structures were confirmed on the basis of the ^{1}H-NMR spectra of the corresponding alcohols obtained by sodium borohydride reduction. The C_7-proton of IV', which was derived from IV, was observed at δ 4.19 as a singlet, while the corresponding proton of V' was observed at δ 4.67 as a triplet. Therefore, the major product (IV) was proved to be the desired compound. The cyclization predominantly occurred at the less

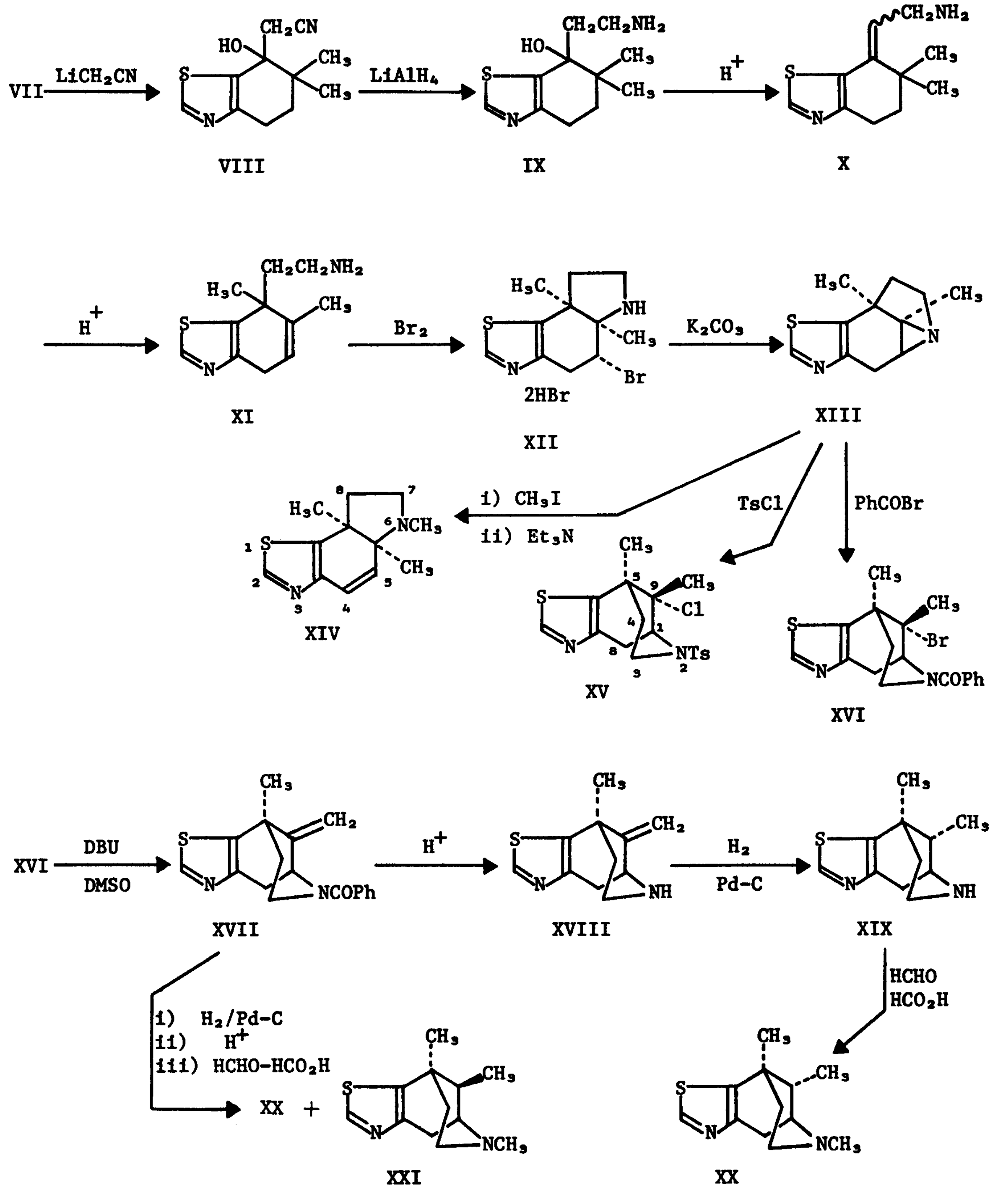


Chart 2

hindered C_1-carbonyl group. The best result was obtained when II and thiourea were heated in pyridine, and IV and V were obtained in 70% and 16% yields, respectively.

Sandmeyer reaction of IV and hydrogenolysis of the resulting chloride (VI) over palladium-carbon gave the key intermediate (VII). A characteristic signal of the C_2-proton in the thiazole ring appeared at δ 8.95 as a singlet in the ^{1}H-NMR spectrum of VII.

Transformation of VII into the thiazolo[5,4-*f*]morphan skeleton is outlined in Chart 2. Cyanomethylation of VII with lithioacetonitrile, which was prepared from acetonitrile and *n*-butyl lithium, gave VIII. Compound VIII was reduced with lithium aluminum hydride to the amino alcohol (IX) and Wagner–Meerwein rearrangement of IX was examined. On treatment with concentrated hydrochloric or hydrobromic acid at 50—60°C, IX was dehydrated to X. Its ^{1}H-NMR spectrum exhibited a 6H singlet due to two methyl groups at δ 1.16, a doublet due to the methylene group adjacent to the amine group at δ 3.66, and a triplet due to the olefinic proton at δ 5.61. When the reaction was continued at 110—120°C for ten days, X was rearranged to XI. The best result was obtained when IX was treated with 50% sulfuric acid at 110—120°C for three days, and XI was obtained in 58% yield. In its ^{1}H-NMR spectrum, two signals due to the methyl groups at δ 1.44 (s) and 1.79 (dt, $J=0.5$ and 2 Hz), a signal due to the C_4-methylene group at δ 3.42 (dq, $J=3.5$ and 2 Hz) and a signal due to the olefinic proton at δ 5.68 (tq, $J=3.5$ and 0.5 Hz) were observed. Irradiation of the signal at δ 1.79 changed the signal at δ 3.42 to a doublet ($J=3.5$ Hz) and the signal at δ 5.68 to a triplet ($J=3.5$Hz). These data indicate that XI is the expected compound, 7-(2-aminoethyl)-4,7-dihydro-6,7-dimethylbenzothiazole.

Cyclization of XI with bromine in chloroform afforded the salt (XII), consuming two equivalents of the reagent. After removal of the solvent, the product was crystallized from ethanol and acetone as the dihydrobromide in 75% yield. This suggested that one equivalent of bromine added to the olefinic group to cause the cyclization and a further one was consumed by formation of the hydrobromide perbromide, which was decomposed by the treatment with acetone. Use of one equivalent of bromine in this reaction also gave the dihydrobromide (XII), but only in 22% yield.

In order to obtain XVIII, the salt (XII) was heated with sodium bicarbonate in dimethylformamide.[7,8] However, this procedure furnished a small amount of XIII instead of XVIII. Treatment of XII with potassium carbonate in a mixture of methanol and chloroform (1: 1) also gave XIII, quantitatively. Compound XIII was relatively stable on standing, but further purification was unsuccessful. In its ^{1}H-NMR spectrum, two singlets due to the methyl groups at δ 1.37 and 1.63, and ABX-type signals at δ 2.65 (d, $J=6.5$ Hz), 3.10 (d, $J=19$ Hz) and 3.50 (dd, $J=19$ and 6.5 Hz) were observed, and there was no evidence for the presence of a secondary amine or olefin group. These data imply that the structure of XIII contains a bridged aziridine moiety.

Cleavage of the aziridine ring of XIII can give two isomeric skeletons; tetrahydrothiazolo-[5,4-*e*]indole or thiazolo[5,4-*f*]morphan. The structure of the product can be assigned with ease by analyzing ^{1}H-NMR signals of the olefin group, which resulted from fission of the C–N bond followed by elimination. Reaction of XIII with methyl iodide and treatment of the resulting quaternary ammonium salt with triethylamine caused the undesired cleavage to form XIV. Its ^{1}H-NMR spectrum revealed the signals of two olefinic protons adjacent to the thiazole ring at δ 5.86 (d, $J=10$ Hz) and 6.72 (d, $J=10$ Hz). On the other hand, reactions of XIII with acylating reagents gave the desired thiazolo[5,4-*f*]morphan derivatives (XV, XVI). In order to confirm the structures, their dehydrohalogenations were examined. Thus, on treatment of XIII with tosyl chloride, XV was obtained in 90% yield. Also on treatment with benzoyl bromide the same type of reaction led XIII to XVI in 89% yield. Heating of XVI with 1,8-diazabicyclo[5.4.0]-7-undecene in dimethyl sulfoxide afforded XVII, but XV resisted this dehydrohalogenation. On refluxing in 6 N hydrochloric acid and ethanol, XVII was hydrolyzed to 5-methyl-9-methylenethiazolo[5,4-*f*]morphan (XVIII). The ^{1}H-NMR spectrum of XV exhibited three singlets due to C_5, C_9-methyl and aromatic methyl groups at δ 1.55, 1.90 and 2.43, and ABX-type signals at δ 2.45 (d, $J=18$ Hz), 3.34 (dd, $J=6$ and 18 Hz) and 4.51 (d, $J=6$ Hz). The stereochemistry of the C_9-methyl group was anticipated on the basis of the reaction mechanism, S_N2 attack of the halogenide ion. On the other hand, the ^{1}H-NMR spectra of XVI and XVII were ambiguous, and it was considered that these compounds consisted of mixtures of rotamers involving the amido functions. Fig. 1 shows the changing of the C_9-methyl signal in the ^{1}H-NMR spectrum of XVI at various temperatures. The ^{1}H-NMR spectrum of XVIII showed a singlet due to the methyl group at δ 1.55, ABX-type signals at δ 3.09 (dd, $J=2$ and 18 Hz), 3.32 (dd, $J=6$ and 18 Hz) and 3.89 (dd, $J=2$ and 6 Hz), and two singlets due to the exomethylene group at δ 4.82 and 4.93. The methyl group at the C_9-position was apparently converted into an exomethylene group by the dehydrohalogenation of XVI to XVII. Hence, it was proved that the desired cleavage of the aziridine ring proceeded in the reaction of XIII with the acylating reagent.

Hydrogenation of XVIII over palladium-carbon yielded the 9α-methyl isomer (XIX), exclusively. In its ^{1}H-NMR spectrum, a doublet due to the 9α-methyl group appeared in high field (δ 0.85) due to the shielding effect of the thiazole ring. Finally, the desired thiazolo[5,4-*f*]-morphan (XX) was obtained by refluxing of XIX with formalin and formic acid. On the other hand, hydrogenation of XVII, in which the nitrogen atom was in the form of an amido

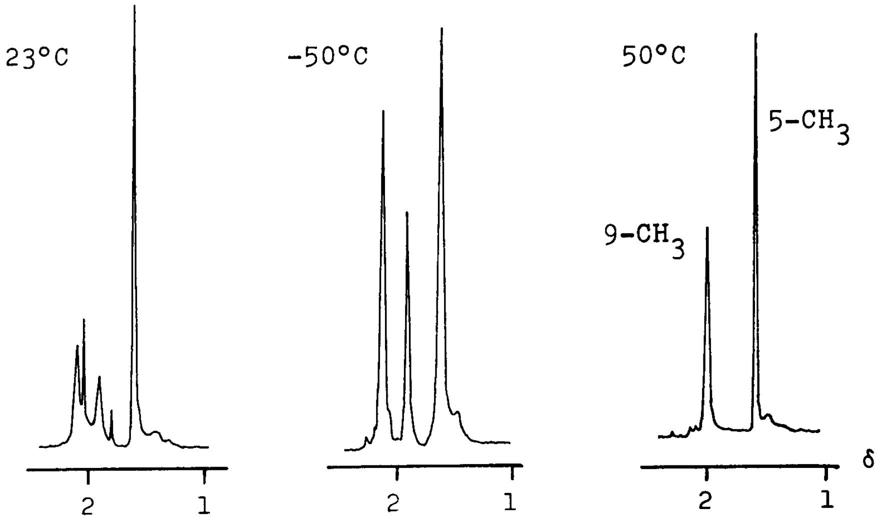


Fig. 1. Signals of Methyl Groups in the 100 MHz ^{1}H-NMR Spectra of XVI (in $CDCl_3$) at Various Temperatures

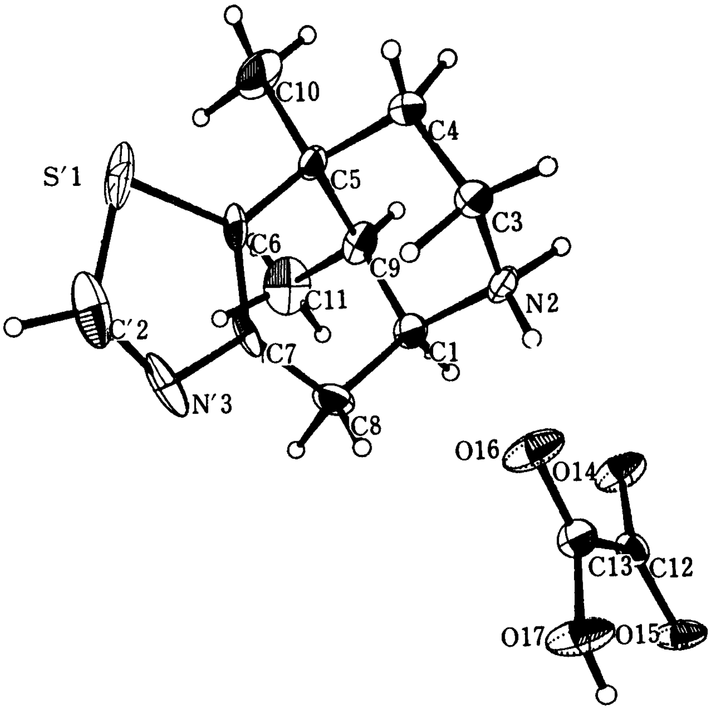
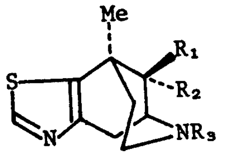


Fig. 2. Perspective drawing of the Molecular Structure of the Oxalate of XIX

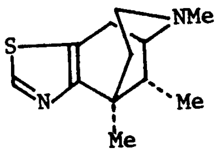
group, gave a stereoisomeric mixture. This mixture was hydrolyzed with hydrochloric acid and subsequently refluxed with formalin and formic acid. The product was chromatographed on an alumina column, and XX and the 9β-methyl isomer (XXI) were obtained in 23% and 46% yields, respectively. Therefore, the stereoselectivity in the hydrogenation of XVIII was attributed to the basicity of the nitrogen atom at the 2-position.

An X-ray analysis of XIX was carried out in order to confirm the structure. Single crystals of XIX suitable for X-ray diffraction were prepared as the oxalate. The oxalate crystallizes in the monoclinic space group $P2_1/c$ with $a=14.431(2)$ Å, $b=7.332(1)$ Å, $c=13.796(1)$ Å, $\beta=93.79(1)°$ and $Z=4$. A total of 2507 unique reflections having $Fo>3\sigma(Fo)$ was measured on a Rigaku AFC-5 diffractometer using graphite-monochromated CuKα radiation ($\lambda=1.5418$ Å) up to $2\theta_{max}=145°$. The structure was solved by direct methods using the RASA-II program package[13] provided with the diffractometer. The structure was refined by block-diagonal least-squares methods to an R factor of 0.091. Fig. 2 shows a perspective view of the oxalate of XIX.

TABLE I. Analgesic Activities of Thiazolomorphans in Mice determined by the AcOH Writhing Method



XIX : $R_1=H$, $R_2=Me$, $R_3=H$
XX : $R_1=H$, $R_2=Me$, $R_3=Me$
XXI : $R_1=Me$, $R_2=H$, $R_3=Me$



XXII

Compd.	Salt	ED$_{50}$ (mg/kg, *s.c.*)	Relative potency
XIX	Oxalate	23.3	0.2
XX	Dihydrochloride	2.82	1.9
XXI	Oxalate	6.18	0.9
XXII	Oxalate	0.48	11.3
Codeine	Phosphate	5.41	1.0

Biological Activity

The thiazolo[5,4-*f*]morphan derivatives (XIX—XXI) prepared in this study were evaluated for analgesic activity in mice by the acetic acid-induced writhing method. Thiazolo-[4,5-*f*]morphan (XXII)[1] was tested at the same time, and the results are summarized in Table I. The most effective 9α-methyl isomer (XX) was twice as potent as codeine phosphate, which was used as the standard compound. However, the activity of XX was only a sixth of that of the thiazolo[4,5-*f*]morphan (XXII). It is noteworthy that the fusing mode of the thiazole ring significantly influences the activity of thiazolomorphan.

Experimental

Melting points were measured on a Yanaco PM-S3 apparatus (a hot stage type) and are uncorrected. IR spectra were determined on a JASCO IRA-1 spectrometer. Mass spectra (MS) were recorded on a Shimadzu LKB-9000 or a JEOL 01SG spectrometer. ^{1}H-NMR spectra were taken on a JEOL PMX-60 or a JEOL PS-100 spectrometer in deuteriochloroform using tetramethylsilane as an internal standard unless otherwise stated. All organic extracts were dried over anhydrous magnesium sulfate. Concentration of all organic solutions was carried out by evaporation under reduced pressure. Column chromatography was performed with Kieselgel 60 (Merck, 230—400 mesh) or Aluminiumoxid 90 (Merck, activity II—III).

4,4-Dimethyl-1,3-cyclohexanedione (I)——Ethyl acrylate (218 ml, 2.0 mol) was added dropwise at 40—45°C to a mixture of methyl isopropyl ketone (213 ml, 2.0 mol) and NaOEt (46 g of Na in 600 ml of abs. EtOH) during 2 h. The mixture was stirred overnight, then heated to distill off 400 ml of EtOH. The residue was dissolved in water and the solution was washed with benzene, acidified with dil. HCl, and extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated. The residue was crystallized from AcOEt-hexane to give 188 g (67%) of I as colorless needles, mp 106—107°C. (lit.[9a] mp 103—105°C).

2-Bromo-4,4-dimethyl-1,3-cyclohexanedione (II)——A solution of Br_2 (70 ml, 1.36 mol) in $CHCl_3$ (200 ml) was added dropwise with vigorous stirring to an ice-cooled mixture of I (188 g, 1.34 mol), $AcONa \cdot 3H_2O$ (200 g, 1.47 mol) and $CHCl_3$ (1000 ml). After being stirred for 1 h at the same temperature, the reaction mixture was treated with water (500 ml). The crystalline precipitates were collected by filtration, then washed with water. The filtrates and the washings were combined and the organic layer was separated, washed with water, dried, and concentrated. The residue and the precipitates were combined and the mixture was recrystallized from MeOH–water to give 275 g (94%) of II as colorless prisms, mp 149.5—150.5°C. *Anal.* Calcd for $C_8H_{11}BrO_2$: C, 43.86; H, 5.06. Found: C, 43.85; H, 4.86. IR (Nujol): 1595 cm^{-1}. ^1H-NMR δ: 1.22 (6H, s), 1.86 (2H, t, $J=6$ Hz, 5-H), 2.67 (2H, t, $J=6$ Hz, 6-H), 6.78 (1H, br s, exchangeable with D_2O). MS *m/e*: 218, 220 (M^+).

2-Amino-4,5,6,7-tetrahydro-6,6-dimethyl-7-oxobenzothiazole (IV)——a) A mixture of II (72.3 g, 0.33 mol), thiourea (27.5 g, 0.36 mol) and tetrahydrofuran (THF) (600 ml) was stirred for 16 h at room temperature, then refluxed for 2 h. Filtration of the product gave 93.3 g (96%) of III as a colorless powder, mp 242—246°C (dec.). *Anal.* Calcd for $C_9H_{15}BrN_2O_2S$: C, 36.62; H, 5.12; N, 9.49. Found: C, 36.49; H, 5.00; N, 9.28. IR (Nujol): 3385, 3320, 3240, 3050, 1640, 1620, 1595 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 1.04 (6H, s, $2\times CH_3$), 1.83 (2H, t, $J=6$ Hz, 5-H), 2.72 (2H, t, $J=6$ Hz, 6-H), 8.57 (5H, br s, exchangeable with D_2O).

A mixture of III (30.7 g, 0.10 mol) and pyridine (150 ml) was refluxed for 2 h under argon. After removal of the solvent, $CHCl_3$ (100 ml) and water (100 ml) were added to the residue and the mixture was filtered to give 11.7 g (57%) of IV as a colorless powder, mp 196—203°C. Recrystallization from MeOH gave colorless prisms, mp 205—207°C. *Anal.* Calcd for $C_9H_{12}N_2OS$: C, 55.08; H, 6.16; N, 14.27. Found: C, 55.37; H, 5.98; N, 14.04. IR (Nujol): 3270, 1615 cm^{-1}. ^1H-NMR δ: 1.18 (6H, s, $2\times CH_3$), 1.95 (2H, t, $J=6$ Hz, 5-H), 2.80 (2H, t, $J=6$ Hz, 4-H), 3.24 (2H, br s, exchangeable with D_2O, $-NH_2$). MS *m/e*: 196 (M^+).

The layers of the above filtrate were separated and the organic layer was washed with water, dried, and concentrated. The residue was crystallized from MeOH to give 4.0 g (20%) of V as yellow prisms, mp 243—245°C. *Anal.* Calcd for $C_9H_{12}N_2OS$: C, 55.08; H, 6.16; N, 14.27. Found: C, 55.00; H, 5.98; N, 14.33. IR (Nujol): 3260, 1620 cm^{-1}. ^1H-NMR δ: 1.33 (6H, s, $2\times CH_3$), 1.95 (2H, t, $J=6$ Hz, 5-H), 2.59 (2H, t, $J=6$ Hz, 6-H), 3.57 (2H, br s, exchangeable with D_2O, $-NH_2$). MS *m/e*: 196 (M^+).

The mother liquor which was left after the crystallization of V from MeOH was concentrated. Crystallization the residue from pyridine–water gave an additional 2.3 g of IV as a pale yellow powder, mp 195—200°C, the total yield of IV was raised to 14.0 g (68%).

b) A mixture of II (55.0 g, 0.25 mol), thiourea (21.0 g, 0.28 mol) and pyridine (500 ml) was stirred for 18 h at room temperature, then refluxed for 1 h under argon. The reaction mixture was concentrated to one-third the initial volume and diluted with water. After cooling, the mixture was filtered to give 34.2 g (70%) of IV as pale yellow prisms, mp 195—201°C. Recrystallization from MeOH gave colorless prisms, mp 205—207°C, which were identified by comparison of the IR spectrum with that of an authentic sample and by mixed melting point determination.

The above filtrate was concentrated and the residue was crystallized from MeOH to give 7.8 g (16%) of V as orange prisms, mp 243—245°C, which were identified by comparison of the IR spectrum with that of an authentic sample and by mixed melting point determination.

$NaBH_4$ Reduction of IV——$NaBH_4$ (510 mg, 13.4 mmol) was added to a solution of IV (950 mg, 4.8 mmol) in MeOH (30 ml). After being stirred for 40 h, the reaction mixture was concentrated and the residue was diluted with water, and extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated. The residue was chromatographed on a silica gel column. The first elution with AcOEt gave 293 mg (31%) of IV (recovery yield), which was crystallized from AcOEt to give colorless prisms, mp 203—206°C. The IR spectrum was identical with that of an authentic sample.

The second elution with AcOEt gave 320 mg (33%) of IV′, which was crystallized from AcOEt to give colorless prisms, mp 160—162°C. *Anal.* Calcd for $C_9H_{14}N_2OS$: C, 54.52; H, 7.12; N, 14.13. Found: C, 54.77; H, 7.03; N, 14.11. IR (Nujol): 3460, 3420, 3280 cm^{-1}. ^1H-NMR ($CDCl_3$: $CD_3OD=4$: 1) δ: 1.00 (6H, s, $2\times CH_3$), 1.67 (2H, t, $J=6.5$ Hz, 5-H), 2.50 (2H, t, $J=6.5$ Hz, 4-H), 4.19 (1H, s, 7-H). MS *m/e*: 198 (M^+).

$NaBH_4$ Reduction of V——$NaBH_4$ (320 mg, 8.4 mmol) was added to a solution of V (816 mg, 4.2 mmol) in EtOH (30 ml). After being stirred for 15 h, the reaction mixture was concentrated and the residue was triturated with water. The crystalline material formed was collected. Recrystallization from MeOH–water gave 371 mg (45%) of V′ as colorless prisms, mp 173.5—174.5°C. *Anal.* Calcd for $C_9H_{14}N_2OS$: C, 54.52; H, 7.12; N, 14.13. Found: C, 54.55; H, 7.06; N, 14.26. IR (Nujol): 3460, 3410, 3290 cm^{-1}. ^1H-NMR ($CDCl_3$: $CD_3OD=4$: 1) δ: 1.20 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.50—2.10 (4H, m), 4.67 (1H, t, $J=5$ Hz, 7-H). MS *m/e*: 198 (M^+).

2-Chloro-4,5,6,7-tetrahydro-6,6-dimethyl-7-oxobenzothiazole (VI)——A solution of $NaNO_2$ (32 g, 0.46 mol) in water (50 ml) was added dropwise to a stirred solution of IV (82.7 g, 0.42 mol) in 40% H_2SO_4 (550 ml) at -10°C. After being stirred for 30 min at the same temperature, the diazotized solution was added to an ice-cooled solution of $CuSO_4 \cdot 5H_2O$ (170 g) and NaCl (170 g) in water (600 ml) with vigorous stirring. Stirring was continued for an additional 40 min at room temperature, then the reaction mixture was extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated. Distillation of the residual oil gave 82.4 g (91%) of VI as a pale yellow oil, bp 92—96°C (0.43 mmHg). *Anal.* Calcd for $C_9H_{10}ClNOS$: C, 50.11; H, 4.68; N, 6.49. Found: C, 50.24; H, 4.75; N, 6.50. IR ($CHCl_3$): 1665 cm^{-1}. ^1H-NMR δ: 1.22 (6H, s, $2\times CH_3$), 2.04 (2H, t, $J=6$ Hz, 5-H), 3.02 (2H, t, $J=6$ Hz, 4-H). MS *m/e*: 215, 217 (M^+).

4,5,6,7-Tetrahydro-6,6-dimethyl-7-oxobenzothiazole (VII)——A solution of VI (52.0 g, 0.24 mol) and triethylamine (34 ml, 0.25 mol) in EtOH (260 ml) was shaken with H_2 in the presence of 10% Pd-C (3.3 g) under atmospheric pressure. After removal of the catalyst and the solvent, the residue was dissolved in AcOEt. The solution was washed with water, dried, and concentrated. Distillation of the residual oil gave 41.9 g (96%) of VII as a colorless solid, bp 85—95°C (0.30 mmHg). Recrystallization from hexane gave colorless prisms, mp 105—106°C. *Anal.* Calcd for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.73. Found: C, 59.45; H, 6.10; N, 7.61. IR ($CHCl_3$): 1665 cm^{-1}. ^1H-NMR δ: 1.24 (6H, s, $2\times CH_3$), 2.06 (2H, t, $J=6$ Hz, 5-H), 3.12 (2H, t, $J=6$ Hz, 4-H), 8.95 (1H, s, 2-H). MS *m/e*: 181 (M^+).

7-Cyanomethyl-4,5,6,7-tetrahydro-7-hydroxy-6,6-dimethylbenzothiazole (VIII)——A solution of VII (59.7 g, 0.33 mol) in dry THF (100 ml) was added dropwise at -70°C under argon to a stirred suspension of $LiCH_2CN$, which had been prepared by treatment of CH_3CN (20.5 ml, 0.39 mol) in dry THF (350 ml) with a 15% solution of *n*-BuLi in hexane (250 ml, 0.39 mol). After being stirred for 35 min at the same temperature, the reaction mixture was diluted with water (100 ml) containing 23 ml of AcOH. The crystalline precipitates, the first crop of VIII, were collected by filtration. The layers of the filtrate were separated and the aqueous layer was extracted with $CHCl_3$. The organic layer and the $CHCl_3$ extract were combined, and the mixture was washed with brine, dried, and concentrated. The residue, the second crop of VIII, and the above precipitates were combined and the mixture was recrystallized from AcOEt to give 59.3 g (81%) of VIII as colorless prisms, mp 175—176°C. *Anal.* Calcd for $C_{11}H_{14}N_2OS$: C, 59.43; H, 6.35; N, 12.60. Found: C, 59.46; H, 6.23; N, 12.69. IR (Nujol): 3200, 2225 cm^{-1}. ^1H-NMR ($CDCl_3$: $CD_3OD=4:1$) δ: 1.07 (6H, s, $2\times CH_3$), 1.86 (2H, t, $J=6$ Hz, 5-H), 2.75—3.00 (4H, m), 8.70 (1H, s, 2-H). MS *m/e*: 222 (M^+).

7-(2-Aminoethyl)-4,7-dihydro-6,7-dimethylbenzothiazole (XI)——A solution of VIII (30.0 g, 0.14 mol) in dry THF (400 ml) was added dropwise during 1.5 h with stirring to an ice-cooled suspension of $LiAlH_4$ (8.58 g, 0.23 mol) in dry ether (300 ml). The reaction mixture was stirred for 2 h at the same temperature, then treated with Rochelle salt solution. The solution was separated and the aqueous layer was extracted with $CHCl_3$. The organic layer and the $CHCl_3$ extract were combined and the mixture was washed with brine, and dried. Removal of the solvent gave IX as a dark reddish oil, quantitatively. ^1H-NMR δ: 0.96 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.50—2.30 (4H, m), 2.70—3.20 (4H, m), 3.35 (3H, br s, exchangeable with D_2O, $-NH_2$ and $-OH$), 8.63 (1H, s, 2-H).

A solution of the crude amine (IX) in 50% H_2SO_4 (200 ml) was heated at 120°C under argon. After 5 h, a small portion of the reaction mixture was basified with dil. NaOH solution and extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated to give X as a pale yellow oil. ^1H-NMR δ: 1.16 (6H, s, $2\times CH_3$), 1.64 (2H, s, exchangeable with D_2O, $-NH_2$), 1.74 (2H, t, $J=6$ Hz, 5-H), 2.98 (2H, t, $J=6$ Hz, 4-H) 3.66 (2H, d, $J=6$ Hz, $-C\underline{H}_2NH_2$), 5.61 (1H, t, $J=6$ Hz, $C=C\underline{H}-CH_2NH_2$), 8.71 (1H, s, 2-H).

Heating of the above mixture was continued for an additional 3 d. The reaction mixture was basified with dil. NaOH solution and extracted with $CHCl_3$. The extract was washed with brine, dried, and concentrated. Distillation of the residual oil gave 16.3 g (58% from VIII) of XI as a pale yellow oil, bp 100—111°C (0.18 mmHg). ^1H-NMR δ: 1.19 (2H, s, exchangeable with D_2O, $-NH_2$), 1.44 (3H, s, 7-CH_3), 1.79 (3H, dt, $J=0.5$ and 2 Hz, 6-CH_3), 1.60—2.50 (4H, m), 3.42 (2H, dq, $J=3.5$ and 2 Hz, 4-H), 5.68 (1H, tq, $J=3.5$ and 0.5 Hz, 5-H), 8.67 (1H, s, 2-H).

The picrate of XI was recrystallized from EtOH to give yellow needles, mp 235—237°C (dec.). *Anal.* Calcd for $C_{17}H_{19}N_5O_7S$: C, 46.68; H, 4.38; N, 16.01. Found: C, 46.86; H, 4.32; N, 15.83.

(5*R,5a*R**,8a*S**)-5-Bromo-4,5,5a,7,8,8a-hexahydro-5a,8a-dimethyl-6*H*-thiazolo[5,4-*e*]indole Dihydrobromide (XII)**——A solution of XI (6.24 g, 30 mmol) in $CHCl_3$ (40 ml) was added dropwise with stirring to an ice-cooled solution of Br_2 (4.1 ml, 79 mmol) in $CHCl_3$ (200 ml). The reaction mixture was stirred for 1 h at room temperature, then concentrated. The residue was crystallized from EtOH-acetone to give 10.1 g (75%) of XII as a pale yellow powder, mp 216—220°C (dec.). *Anal.* Calcd for $C_{11}H_{17}Br_3N_2S$: C, 29.42; H, 3.82; N, 6.24. Found: C, 29.64; H, 3.58; N, 6.09. ^1H-NMR (CF_3CO_2H) δ: 1.92 (3H, s, CH_3), 1.95 (3H, s, CH_3), 2.55—3.00 (2H, m), 3.50—4.40 (4H, m), 5.04 (1H, dd, $J=5.5$ and 10 Hz, 5-H), 10.06 (1H, s, 2-H).

(5a*S,8a*S**)-5a,7,8,8a-Tetrahydro-5a,6,8a-trimethyl-6*H*-thiazolo[5,4-*e*]indole (XIV)**——A suspension of XII (856 mg, 1.9 mmol) and K_2CO_3 (2.0 g, 14.5 mmol) in 50 ml of $MeOH-CHCl_3$ (1:1) was stirred for 18 h. The reaction mixture was treated with water and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to give 420 mg (quantitative yield) of XIII as a yellow solid. ^1H-NMR δ: 1.37 (3H, s, CH_3), 1.63 (3H, s, CH_3), 1.83—2.14 (2H, m), 2.40—2.72 (2H, m), 2.90—3.15 (2H, m), 3.50 (1H, dd, $J=19$ and 6.5 Hz), 8.64 (1H, s).

A solution of CH_3I (0.4 ml, 6.4 mmol) in ether (10 ml) was added to a solution of the crude aziridine (XIII) in THF (20 ml). After standing for 62 h at -15°C, the reaction mixture was concentrated at below 30°C. The residue was treated with THF (30 ml) and triethylamine (4 ml), and the mixture was stirred for 21 h at room temperature, then refluxed for an additional 5 h under argon. The reaction mixture was treated with water and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated. The product was chromatographed on an alumina column. Elution with 10% AcOEt–benzene gave 79 mg (19%) of XIV as a colorless oil. High-resolution MS *m/e* Calcd for $C_{12}H_{16}N_2S$: 220.1033 (M^+). Found: 220.1036 (M^+). ^{1}H-NMR δ: 1.04 (3H, s, 8a-CH_3), 1.35 (3H, s, 5a-CH_3), 1.65—3.15 (4H, m), 2.41 (3H, s, N-CH_3), 5.86 (1H, d, J=10 Hz, 5-H), 6.72 (1H, d, J=10 Hz, 4-H), 8.53 (1H, s, 2-H).

(5*R,9*S**)-9-Chloro-5,9-dimethyl-2-(*p*-toluenesulfonyl)thiazolo[5,4-*f*]morphan (XV)**——A solution of XIII [prepared from XII (502 mg, 1.1 mmol) in a manner similar to that mentioned above] in CH_2Cl_2 (10 ml) was added to a stirred solution of *p*-TsCl (248 mg, 1.3 mmol) and triethylamine (0.1 ml) in CH_2Cl_2 (20 ml). After being stirred for 16 h, the reaction mixture was diluted with $CHCl_3$ and washed successively with 10% Na_2CO_3 solution, water, dil. HCl, and water. The solution was dried and concentrated. The residue was chromatographed on a silica gel column. Elution with AcOEt–benzene (1: 2) gave 393 mg (89%) of XV as a colorless foam. Crystallization from AcOEt–hexane gave colorless plates, mp 151.5—153°C. *Anal.* Calcd for $C_{18}H_{21}ClN_2O_2S_2$: C, 54.46; H, 5.33; N, 7.06. Found: C, 54.46; H, 5.34; N, 7.06. IR ($CHCl_3$): 1350, 1165 cm^{-1}. ^{1}H-NMR δ: 1.55 (3H, s, 5-CH_3), 1.90 (3H, s, 9-CH_3), 2.43 (3H, s, aromatic CH_3), 2.00—2.80 (2H, m), 2.45 (1H, d, J=18 Hz, 8-H), 3.34 (1H, dd, J=6 and 18 Hz, 8-H), 3.74 (1H, m), 4.51 (1H, d, J=6 Hz, 1-H), 7.30 (2H, d, J=8 Hz, aromatic protons), 7.67 (2H, d, J=8 Hz, aromatic protons), 8.57 (1H, s, 2′-H). MS *m/e*: 396, 398 (M^+).

(5*R,9*S**)-2-Benzoyl-9-bromo-5,9-dimethylthiazolo[5,4-*f*]morphan (XVI)**——A solution of XIII [prepared from XII (12.7 g, 28.0 mmol) in a manner similar to that mentioned above] in $CHCl_3$ (10 ml) was added dropwise with stirring to an ice-cooled solution of benzoyl bromide (10.1 g, 54.0 mmol) and triethylamine (2 ml) in $CHCl_3$ (80 ml). After being stirred for 6 h at room temperature, the reaction mixture was diluted with $CHCl_3$. The solution was washed successively with 10% Na_2CO_3 solution, water, dil. HCl, and water, then dried and concentrated. The residue was chromatographed on a silica gel column. Elution with AcOEt–benzene (1: 4) gave a yellow syrup. Crystallization from AcOEt–hexane gave 9.9 g (90%) of XVI as pale yellow prisms, mp162.5—164°C. *Anal.* Calcd for $C_{18}H_{19}BrN_2OS$: C, 55.25; H, 4.89; N, 7.16. Found: C, 55.25; H, 5.06; N, 6.97. IR (Nujol): 1615 cm^{-1}. ^{1}H-NMR δ: 1.61 (3H, s, 5-CH_3), 1.80—2.05 (3H, m, 9-CH_3), 2.00—4.42 (6H, m), 4.68 (1/2H, m), 5.57 (1/2H, m), 7.40 (5H, s, aromatic protons), 8.69 (1H, s, 2′-H). MS *m/e*: 390, 392 (M^+).

2-Benzoyl-5-methyl-9-methylenethiazolo[5,4-*f*]morphan (XVII)——A mixture of XVI (4.1 g, 10.5 mmol) and DBU (5.0 g, 33.1 mmol) in dry DMSO (10 ml) was heated at 120°C for 3 d under argon. After removal of the solvent, the reaction mixture was acidified with dil. HCl, and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated. The residue was chromatographed on a silica gel column. Elution with 15% AcOEt–benzene gave 3.34 g (quantitative yield) of XVII as a colorless foam. High-resolution MS *m/e* Calcd for $C_{18}H_{18}N_2OS$: 310.1139 (M^+). Found: 310.1115 (M^+). IR ($CHCl_3$): 1620 cm^{-1}. ^{1}H-NMR δ: 1.59 (3H, s, 5-CH_3), 1.90—3.60 (6H, m), 4.50—6.00 (3H, m), 7.40 (5H, s, aromatic protons), 8.65 (1H, s, 2′-H).

5-Methyl-9-methylenethiazolo[5,4-*f*]morphan (XVIII)——A solution of XVII (3.18 g, 10.3 mmol) in EtOH (40 ml) and 6 N HCl (80 ml) was refluxed for 21 h. After removal of EtOH, the resulting aqueous solution was washed with AcOEt, basified with 10% Na_2CO_3 solution, and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to give 2.07 g (98%) of XVIII as a colorless solid. IR ($CHCl_3$): 3300, 3075, 1655 cm^{-1}. ^{1}H-NMR δ: 1.55 (3H, s, 5-CH_3), 1.60—1.80 (2H, m, 4-H), 2.21 (1H, br s, exchangeable with D_2O, -NH), 2.70—2.85 (2H, m, 3-H), 3.09 (1H, dd, J=18 and 2 Hz, 8-H), 3.32 (1H, dd, J=18 and 6 Hz, 8-H), 3.89 (1H, dd, J=6 and 2 Hz, 1-H), 4.82 and 4.93 (each 1H, s, C=CH_2), 8.62 (1H, s, 2′-H). MS *m/e*: 206 (M^+).

The oxalate of XVIII was recrystallized from EtOH to give colorless prisms, mp 201—203°C. *Anal.* Calcd for $C_{13}H_{16}N_2O_4S$: C, 52.69; H, 5.44; N, 9.45. Found: C, 52.57; H, 5.34; N, 9.52.

(5*S,9*S**)-5,9-Dimethylthiazolo[5,4-*f*]morphan (XIX)**——A mixture of XVIII (2.07 g, 10.0 mmol) and 5% Pd-C (0.51 g) in EtOH (50 ml) was shaken under 4 atmospheres pressure of H_2 in a Skita apparatus. After removal of the catalyst and the solvent, the residue was chromatographed on a silica gel column. Elution with 20% MeOH–$CHCl_3$ gave 1.89 g (90%) of XIX as a colorless solid. IR ($CHCl_3$): 3310 cm^{-1}. ^{1}H-NMR δ: 0.85 (3H, d, J=7 Hz, 9α-CH_3), 1.39 (3H, s, 5-CH_3), 1.40—2.10 (3H, m), 1.99 (1H, s, exchangeable with D_2O, -NH), 2.40—3.40 (5H, m), 8.63 (1H, s, 2′-H). MS *m/e*: 208 (M^+).

The oxalate of XIX was recrystallized from EtOH to give colorless prisms, mp 222—223°C (dec.). *Anal.* Calcd for $C_{13}H_{18}N_2O_4S$: C, 52.33; H, 6.08; N, 9.39. Found: C, 52.39; H, 5.89; N, 9.27.

(5*S,9*S**)-2,5,9-Trimethylthiazolo[5,4-*f*]morphan (XX)**——A mixture of XIX (785 mg, 3.8 mmol), formic acid (30 ml) and 35% formalin (8 ml) was refluxed for 3 h. The reaction mixture was concentrated and the residue was dissolved in water. The solution was basified with 10% Na_2CO_3 solution and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated. The residue was chromatographed on an alumina column. Elution with benzene–$CHCl_3$ (3: 1) gave 768 mg (92%) of XX as a colorless oil. ^{1}H-NMR δ: 0.85 (3H, d, J=7 Hz, 9α-CH_3), 1.37 (3H, s, 5-CH_3), 1.40—2.50 (5H, m), 2.39 (3H, s, N-CH_3), 2.60 (1H, dd, J=18 and 5.5 Hz, 8-H), 3.03 (1H, dd, J=3 and 5.5 Hz, 1-H), 3.13 (1H, d, J=18 Hz, 8-H), 8.59 (1H, s, 2′-H). MS *m/e*: 222 (M^+).

The dihydrochloride of XX was crystallized from EtOH to give a colorless powder, mp 224—227°C (dec.). *Anal.* Calcd for $C_{12}H_{20}Cl_2N_2S \cdot 1/2H_2O$: C, 47.37; H, 6.96; N, 9.21. Found: C, 47.52; H, 6.88; N, 9.16.

(5*S,9*R**)-2,5,9-Trimethylthiazolo[5,4-*f*]morphan (XXI)**——A mixture of XVII (3.52 g, 11.4 mmol) and 10% Pd-C (1.18 g) in EtOH (150 ml) was shaken under 50 atmospheres pressure of H_2 at 50°C in an autoclave. After removal of the catalyst and the solvent, the residue was refluxed with 20% HCl (150 ml) and EtOH (20 ml) for 2 d. The reaction mixture was concentrated to half the initial volume. The resulting aqueous solution was washed with $CHCl_3$, basified with 10% Na_2CO_3 solution, and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated. The residue was refluxed with formic acid (50 ml) and 35% formalin (15 ml) for 3 h. The mixture was concentrated and the residue was dissolved in water. The solution was basified with 10% Na_2CO_3 solution and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated. The product was chromatographed on an alumina column. Elution with benzene gave 1.17 g (46%) of XXI as a colorless oil. ^{1}H-NMR δ: 1.24 (3H, d, $J=7$ Hz, 9β-CH_3), 1.33 (3H, s, 5-CH_3), 1.80—2.20 (4H, m), 2.34 (3H, s, N-CH_3), 2.36—2.50 (1H, m), 2.62 (1H, dd, $J=18$ and 5.5 Hz, 8-H), 3.01 (1H, dd, $J=2.5$ and 5.5 Hz, 1-H), 3.25 (1H, d, $J=18$ Hz, 8-H), 8.57 (1H, s, 2′-H). MS *m/e*: 222 (M^+).

The oxalate of XXI was recrystallized from EtOH to give colorless prisms, mp 228—230°C. *Anal.* Calcd for $C_{14}H_{20}N_2O_4S$: C, 53.83; H, 6.45; N, 8.97. Found: C, 53.67; H, 6.30; N, 9.04.

Elution with benzene–$CHCl_3$ (1: 1) gave 0.59 g (23%) of XX as a colorless oil, which was identical (by comparison of IR and ^{1}H-NMR spectra) with an authentic sample.

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