Communications to the Editor

[Chem. Pharm. Bull. 24(7) 1679 (1976)] UDC 615.31.011.4 : 615.014

Correction of the Paper, Dissolution Behavior of Solid Drugs. VI. Determination of Transition Temperatures of Various Physical Forms of Sulfanilamide by Initial Dissolution Rate Measurements

Correction was made in the paper entitled, "Dissolution Behavior of Solid Drugs. VI. Determination of Transition Temperatures of Various Physical Forms of Sulfanilamide by Initial Dissolution Rate Measurements," published in *Chem. Pharm. Bull.* (Tokyo), **23**, 1353 (1975).

As we misunderstood reading the data quoted from the paper of Hwaing Ou Lin and J. Keith Guillory, *J. Pharm. Sci.*, **59**, 972 (1970), we would like to retract the sentence, "Although they gave figures in kcal even down to three places of decimal, the data will not be so highly reliable because of the limited accuracy of the method for quantitative application". started from the third line from the bottom on p. 1360 in our paper published in *Chem. Pharm. Bull.* (Tokyo), **23**, 1353 (1975).

We apologize to Drs. Lin and Guillory on this matter.

Kitasato University
School of Pharmaceutical Sciences
9-1 Shirokane 5-chome
Minato-ku, Tokyo, 108 Japan

Keiji Sekiguchi
Yasuyuki Tsuda
Motoko Kanke

Received February 25, 1976

[Chem. Pharm. Bull. 24(7)1679—1681(1976)] UDC 547.732.04 : 547.821.04

A Novel Ring System, α-Thieno[4,3-*f*]morphan

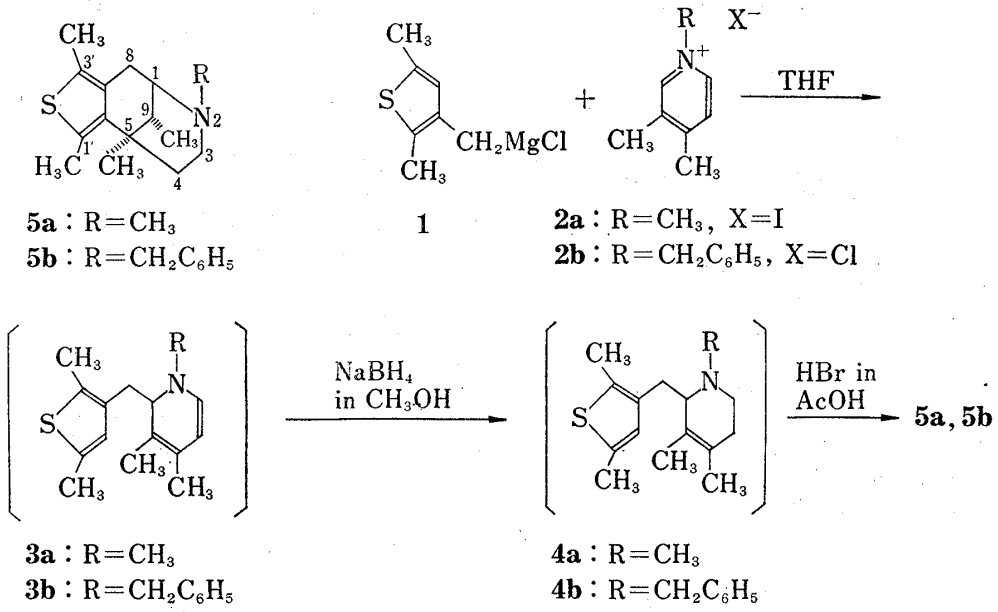
Synthesis of compounds containing a novel ring system, thieno[4,3-*f*]morphan, has been accomplished starting from 3-thenyl chloride derivative (**1**) in 3 steps.

Significant separation of analgetic activity from dependence liability has been studied with benzomorphan derivatives.[1] Quite recently, some α-thieno[2,3-*f*]morphans[2] and α-thieno[3,2-*f*]morphans,[3] replacing the benzene ring in benzomorphan with a thiophene ring, have been reported. However, the study on the title ring system has not been done.

1) *a*) E.L. May and L.J. Sargent in "Analgetics," ed. by G. de Stevens, Academic Press, New York, N.Y., 1965, Chapter IV; *b*) N.B. Eddy and E.L. May, "Synthetic Analgesics, Part IIB, 6,7-Benzomorphans," Pergamon Press, London, 1966, p. 138ff; *c*) T. Kametani, K. Kigasawa, M. Hiiragi, and N. Wagatsuma, *Heterocycles*, **2**, 79 (1974).
2) T.A. Montzka and J.D. Mariskella, *J. Heterocyclic Chem.*, **11**, 853 (1974).
3) *a*) M. Alvarez, J. Bosch, and J. Canals, *An. Quim.*, **71**, 807 (1975); *b*) J. Bosch, R. Granados, and F. Lopéz, *J. Heterocyclic Chem.*, **12**, 651 (1975); *c*) M. Ban, K. Miura, K. Suzuki, and M. Hori, A new synthetic method was presented at the 96th the Annual Meeting of the Pharmaceutical Society, Nagoya, April 7, 1976, Abstracts p. 39.

In this communication, we wish to describe the synthesis of typical thieno[4,3-*f*]morphan derivatives (**5**). The synthesis scheme of **5** is illustrated in Chart 1 and nuclear magnetic resonance (NMR) spectral data for the structural assignment of the compounds are also summarized in Table I.

1,3,4-Trimethylpyridinium iodide (**2a**) was converted into the condensation product (**3a**) by the treatment with 2,5-dimethyl-3-thenylmagnesium chloride (**1**) in tetrahydrofuran (THF) for 1.5 hr. A crude **3a** was reduced immediately without purification by $NaBH_4$ in methanol and the resulting product was purified in the form of salt such as the oxalate to give 1,2,5,6-tetrahydro-1,3,4-trimethyl-2-(2,5-dimethyl-3-thenyl)pyridine (**4a**) in 36% yield. **4a** oxalate, mp 144—146° (ethanol), *Anal.* Calcd. for $C_{15}H_{23}NS \cdot C_2H_2O_4$: C, 60.15; H, 7.42; N, 4.13. Found: C, 59.89; H, 7.42; N, 4.07. Subsequently, **4a** was successively refluxed with



5a : R=CH_3
5b : R=$CH_2C_6H_5$

1

2a : R=CH_3, X=I
2b : R=$CH_2C_6H_5$, X=Cl

3a : R=CH_3
3b : R=$CH_2C_6H_5$

4a : R=CH_3
4b : R=$CH_2C_6H_5$

Chart 1

48% HBr–AcOH (2:1) for 24 hr to give α-1′,2,3′,5,9-pentamethylthieno[4,3-*f*]morphan (**5a**), which was purified by column chromatography on silica gel (Wakogel C-200) using triethylamine-ethyl acetate–*n*-hexane (1:1:10) as an eluent in 57% yield as colorless oil. **5a** HBr, mp 272—274° (decomp.) (ethanol–acetone), *Anal.* Calcd. for $C_{15}H_{23}NS \cdot HBr \cdot 1/2H_2O$: C, 54.69; H, 7.17; N, 3.99. Found: C, 54.70; H, 7.32; N, 4.11.

Similarly, 1-benzyl-1,2,5,6-tetrahydro-3,4-dimethyl-2-(2,5-dimethyl-3-thenyl)pyridine (**4b**) was obtained by the treatment of 1-benzyl-3,4-dimethylpyridinium chloride (**2b**) with **1**, followed by $NaBH_4$ reduction, in 34% yield. **4b** oxalate, mp 167—169° (ethanol), *Anal.* Calcd. for $C_{21}H_{27}NS \cdot C_2H_2O_4$: C, 66.48; H, 7.03; N, 3.37. Found: C, 66.46; H, 7.04; N, 3.24.

TABLE I. NMR Spectral Data for the Structural Assignment of the Compounds

Compound	($CDCl_3$) δ(ppm)
4a	1.55, 1.63 (each 3H, two broad s, C_3–, C_4–CH_3 in the tetrahydropyridine), 2.37 (3H, s, N–CH_3), 2.30, 2.37 (each 3H, two s, C_2–, C_5–CH_3 in the thiophene), 6.55 (1H, broad s, C_4–H in the thiophene)
4b	1.55, 1.63 (each 3H, two broad s, C_3–, C_4–CH_3 in the tetrahydropyridine), 2.20, 2.33 (each 3H, two s, C_2–, C_5–CH_3 in the thiophene), 3.58 (2H, s, N–$C\underline{H}_2C_6H_5$), 6.30 (1H, broad s, C_4–H in the thiophene)
5a	0.85 (3H, d, J=7.0 Hz, C_9–CH_3), 1.43 (3H, s, C_5–CH_3), 2.38 (3H, s, N–CH_3), 2.24, 2.38 (each 3H, two s, C_1'–, C_3'–CH_3)
5b	0.79 (3H, d, J=7.0 Hz, C_9–CH_3), 1.41 (3H, s, C_5–CH_3), 2.25, 2.35 (each 3H, two s, C_1'–, C_3'–CH_3), 3.53, 3.68 (each H, AB type, J=14.0 Hz, N–$C\underline{H}_2C_6H_5$)

Cyclization of **4b** with 48% HBr–AcOH (2:1) gave α-2-benzyl-1′,3′,5,9-tetramethylthieno[4,3-*f*]morphan (**5b**) in 60% yield as colorless oil. **5b** HBr, mp 240—243° (decomp.) (ethanol–acetone), *Anal.* Calcd. for $C_{21}H_{27}NS \cdot HBr \cdot 1/2H_2O$: C, 61.81; H, 6.84; N, 3.28. Found: C, 62.22; H, 6.94; N, 3.31.

In the Table I, the signal for the 9-methyl group in **5a** or **5b**, respectively, appears as a diamagnetically shifted doublet, δ 0.85 or 0.79 (J=7.0 Hz) due to a position above the thiophene ring. Thus, the configuration of **5** was assessed as the α-diastereomer[4] in which both methyl groups in C_5- and C_9-positions were in a *cis* orientation.

The synthetic and biological studies of **5** and related compounds will be published in detail elsewhere in near future.

Research Laboratory
Sanwa Kagaku Kenkyusho Co., Ltd.
1212 Gejo-cho, Kasugai, 486, Japan

Masatoshi Ban
Yutaka Baba
Kenji Miura
Yasuaki Kondo
Kenji Suzuki
Mikio Hori

Gifu College of Pharmacy
5-Higashi, Mitafora, Gifu, 502, Japan

Received March 22, 1976

4) S.E. Fullerton, E.L. May, and E.D. Becker, *J. Org. Chem.*, **27**, 2144 (1962).

[Chem. Pharm. Bull. 24(7)1681—1683(1976)]

UDC 547.36.04 : 576.8.098 : 542.98

Stereochemistry in Oxidation of Primary Allylic Alcohols by Cell-free System of Callus induced from *Cannabis sativa* L.

The pro-R hydrogen from C-1 methylene of primary allylic alcohols as geraniol and *trans*-cinnamyl alcohol was abstracted in cell-free system of callus induced from *Cannabis sativa* L.

We have previously reported[1] that tetrahydrocannabinol, the other cannabinoids and essential oil which observed in the extract of original plant were not detected in the callus induced from *Cannabis sativa* L. (Moraceae). Then we have found that geraniol and nerol which are cannabinoids' precursors[2] were converted into citrals by the suspension cultures from Cannabis callus.[3] Further, without the addition of nicotinamide adenine dinucleotide (NAD) or nicotinamide adenine dinucleotide phosphate (NADP), the activity in oxidation of primary and secondary allylic alcohols, that is, geraniol, nerol, *trans*-cinnamyl alcohol, (+)-*trans*-verbenol and (−)-isophorol, was demonstrated by the cell-free system from Cannabis callus.[3]

In this paper, we report on the stereochemistry which is related to distinguish C-1 enantiomeric hydrogens of primary allylic alcohols.

1) H. Itokawa, K. Takeya, and M. Akasu, *Shoyakugaku Zasshi*, **29**, 106 (1975).
2) *a*) R. Mechoulam and Y. Gaoni, *Tetrahedron*, **21**, 1223 (1965); *b*) Y. Shoyama, M. Yagi, and I. Nishioka, *Phytochemistry*, **14**, 2189 (1975).
3) Unpublished..