

Studies on the Alkaloids of *Thalictrum Thunbergii* DC. (XV)*

The Identity of Thalictine with Aromoline

Eiichi FUJITA^{*2}, Toshiaki TOMIMATSU^{*3} and Yoko KITAMURA^{*3}

(Fujita Laboratory)

Received May, 8, 1964

The detailed investigation on the structures of thalictine and homothalictine has resulted in the revision of the tentatively proposed structures for thalictine and homothalictine. Thalictine was proved to be identical with aromoline(6) itself. Homothalictine is 0-methylaromoline(7).

The authors, therefore, suggest that the name "thalictine" will be cancelled and "homothalictine" should be changed to "homoaromoline".

The authors have studied the structures of thalictine and 0-methylthalictine, the main alkaloids of the stems and leaves of *Thalictrum Thunbergii* DC. (Ranunculaceae), and established their structures to be formulated as 1 and 2, respectively.¹⁾

The authors also separated thalictine and homothalictine, the bisbenzylisoquinoline type alkaloids, from the underground part of the plant and proposed the tentative structural formulas 3 and 4 to them from the results of the cleavage reaction with sodium in liquid ammonia.²⁾

Now, they tried to examine in detail the proposed formulas 3 and 4, and found that they should be revised to 6 (aromoline) and 7 for thalictine and homothalictine, respectively.

As shown in the previous papers²⁾ thalictine was methylated with diazomethane for two days to form homothalictine which still contained a cryptophenolic hydroxyl group. The latter was allowed to react with diazomethane for two weeks to afford 0,0-dimethylthalictine (0-methylhomothalictine), a non-phenolic base. The free base resisted to be crystallized. The crystalline dimethiodide was converted to dimethochloride, the Hofmann degradation of which yielded a methyl methine base monohydrate, m.p. 98°. The base was identified with 0-methoxyacanthine methyl methine (11),³⁾ m.p. 98~99°, which was derived from 0-methoxyacanthine (9) through the similar way, by the mixed melting point test and the comparison of their infrared spectra. The identity was proved also with their oxalates and dimethiodides, respectively.

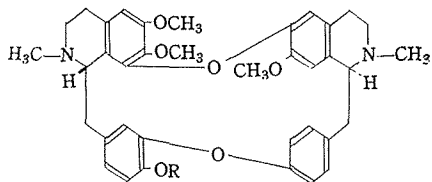
The ozonolysis of 0,0-dimethylthalictine methyl methine (11) gave 4-methoxy-3,4'-oxydibenzaldehyde (12), a mixture of the carboxylic aldehydes (13) and a diamino dialdehyde derivative (14). The latter was isolated as a crystalline dimethiodide, m.p. 245° (decomp.), the infrared spectrum of which was completely superimposable with that of the diamino dialdehyde dimethiodide, m.p. 245° (decomp.)⁴⁾ afforded by the ozonolysis of 0-methoxyacanthine methyl methine, whilst it apparently differed from that of the

* Part XIV: *Yakugaku Zasshi*, **83**, 159 (1963).

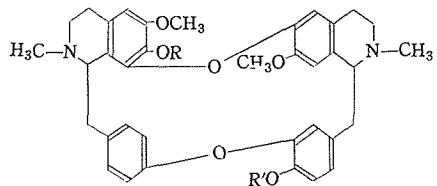
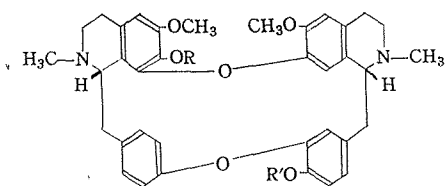
^{*2} 藤田 栄一 ^{*3} 富松 利明, 北村 蓉子

^{*3} Faculty of Pharmacy, Tokushima University.

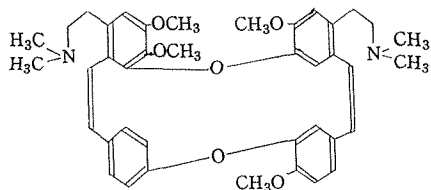
Chart 1.



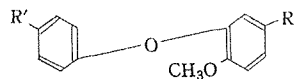
1: R=H
2: R=CH₃


$$\begin{aligned} 3: R=R'&=H \\ 4: R=H, R'&=CH_3 \\ 5: R=R'&=CH_3 \end{aligned}$$


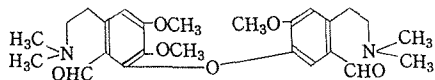
- 6: $R=R'=H$
- 7: $R=H, R'=CH_3$
- 8: $R=CH_3, R'=H$
- 9: $R=R'=CH_3$
- 10: $R=CH_3, R'=C_2H_5$



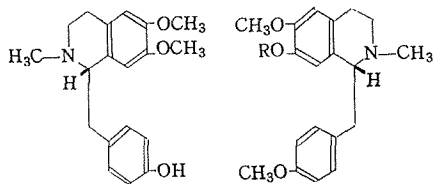
11



12: $R=R'=CHO$
13: $R=CHO, R'=COOH$
or $R=COOH, R'=CHO$

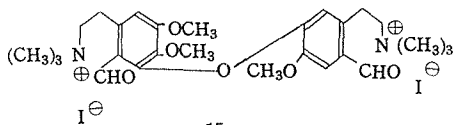


14

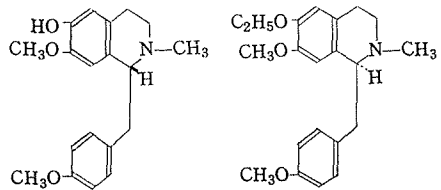


16

17: R=H
18: R=C₂H₅



15



19

20

dimethiodide (15), m.p. 235° (decomp.), of the corresponding diamino dialdehyde compound similarly derived from 0-methylthalicberine methyl methine. If 0,0-dimethylthalicrine has the structure 5, the methiodide of the diamino dialdehyde compound obtained by ozonolysis of its methyl methine should be formulated as 15. Thus, the postulated formulas 3 and 4 for thalicrine and homothalicrine were denied, and it was clarified that they have the oxyacanthine type structures.

The cleavage reaction of 0,0-dimethylthalicrine with sodium in liquid ammonia was re-examined. The usual treatment of the reaction mixture gave a couple of phenolic bases. The one was easily confirmed to be the well-known L-(*d*)-armepavine (16).^{2b)} The other was not crystallized as a free base, but the picrate, m.p. 135°, and the methiodide, m.p. 163°, were isolated as the pure crystals, and identified as D-(*l*)-1-(4-methoxybenzyl)-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (17) picrate, m.p. 136°,⁵⁾ and methiodide, m.p. 163°, respectively. In this connection, the picrate of the corresponding 6-hydroxy-7-methoxy compound (19) showed m.p. 191° (decomp.)⁶⁾, and the infrared spectrum was different from that of 17 picrate.

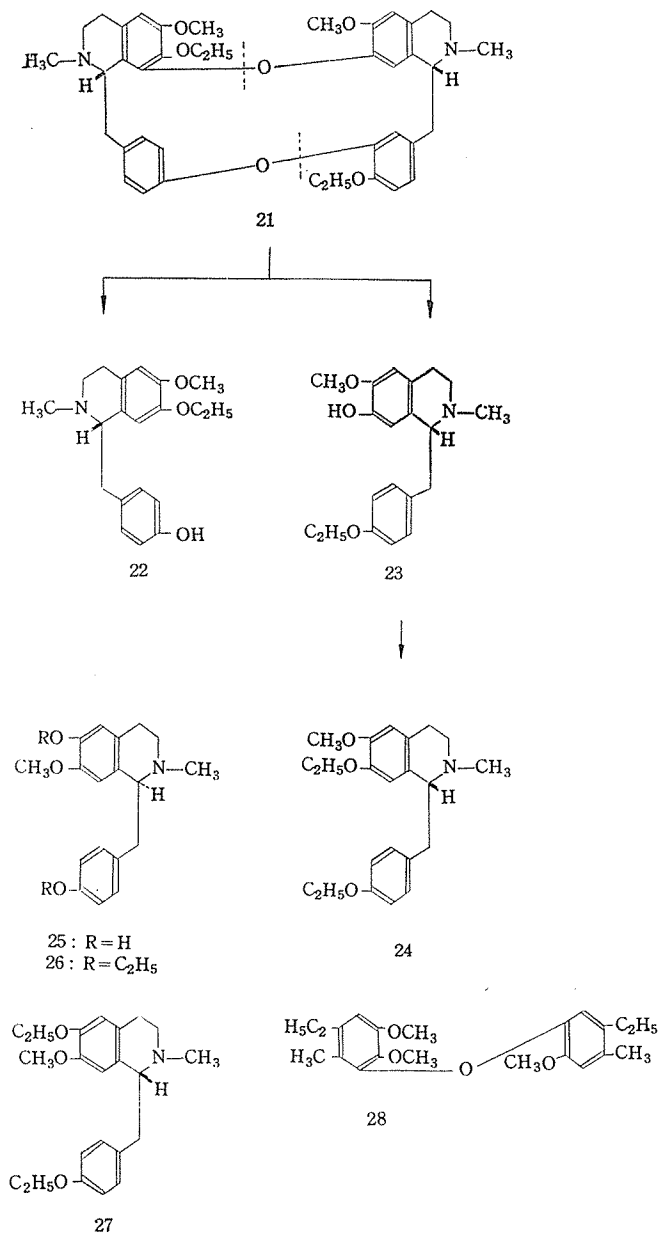
In the previous paper,^{2a)} the authors compared the infrared spectra of the oxalate of the compound 18 with that of the oxalate of the compound 20^{1b)} which was obtained from the first sodium-liquid ammonia cleavage of thalicberine (1) followed by 0-ethylation, the second cleavage, and 0-methylation, and regarded them by mistake as the enantiomers. In the detailed examination of these two spectra, their slight differences were found in the regions of 1020~1030, 1135~1140, and 1415~1425 cm⁻¹. Moreover, the difference of the melting point was recognized between these oxalates. (18 oxalate: m.p. 168°; 20 oxalate: m.p. 145°).

The cleavage of 0,0-diethylthalicrine (21) with sodium in liquid ammonia was again carried out. L-(*d*)-1-(4-Hydroxybenzyl)-2-methyl-6-methoxy-7-ethoxy-1,2,3,4-tetrahydroisoquinoline (22) was yielded as one of the bisected products. Another product was ethylated by diazoethane to give an amorphous 0-ethyl derivative, the oxalate of which had m.p. 177~178°. The infrared spectrum of this oxalate in nujol was different from that of oxalate, m.p. 181~183°, of L-(*d*)-N-methylisococlaurine 0,0-diethyl ether (26), which was obtained by the cleavage of 0-methylthalicberine (2) with sodium in liquid ammonia, followed by ethylation. The former was also apparently different from the infrared spectrum of the oxalate of the compound 27⁷⁾, the antipode of 26.

On the other hand, the infrared spectrum of the oxalate, m.p. 177~178°, in nujol was completely superimposable with the spectrum of the oxalate, m.p. 177~178°, of the compound 24, which was derived from 0-ethyloxyacanthine (10) by the similar way.

Meanwhile, the infrared spectra in chloroform, of the amorphous compounds 26 and 24 were compared and re-examined in detail, and now, very slight differences were recognized, although the authors had misunderstood both spectra to be completely identical in the previous paper.^{2b)} The spectrum of 26 showed that the intensities of the absorption at 1120 cm⁻¹ and 1470 cm⁻¹ are stronger than those at 1105 cm⁻¹ and 1480 cm⁻¹ respectively, while the spectrum of 24 showed the reverse intensity-inter-relationships.

Chart 2.



The above-mentioned experimental results established that 0,0-dimethylthalicrine was completely identical with 0-methoxyxyacanthine including the stereochemistry of a couple of asymmetric centers.

So, a crystal of obaberine⁸⁾ (identical with 0-methoxyxyacanthine) was seeded into amorphous 0,0-mdiethylthalicrine to be crystallized. The crystal thus obtained was recognized to be identical with 0-methyl oxyacanthine by the mixed melting point test and the infrared spectra.

Consequently, thalictine must be identical with aromoline⁹⁾ (6), although their melting points are different on the references (aromoline: m.p. 175^{ca)}; thalictine: m.p. 221~222^{ca)}), presumably due to the addition of solvent (chloroform) to aromoline. The direct comparison of thalictine and aromoline could not be realized, because of no available sample of aromoline. Nevertheless, the name "thalictine" should be cancelled, and "homothalictine" should be changed to "homoaromoline."

In connection with this revision, it appears necessary to emphasize that the structures 1 and 2 established for thalictberine and 0-methylthalictberine are correct. The fact that the dimethiodide (15) of the diaminodialdehyde derivative which is obtained from the methine base, a product of Hofmann degradation of 0-methylthalictberine, by ozonolysis, is apparently different from the dimethiodide of the corresponding diaminodialdehyde compound (14) derived from 0-methyloxyacanthine through the analogous course, and especially the identification of compound 28 derived from 15 by the total synthesis^{1e)} have demonstrated that the structures 1 and 2 are completely correct. The further evidence is now brought by n.m.r. spectra.

The comparison of n.m.r. spectra of 0-methylthalictberine (2) and tetrandrine (29) seemed very interesting. The n.m.r. spectrum^{*4} of tetrandrine (29) had the singlet signals at 6.10 (6.10), 6.28 (6.27), 6.66 (6.65) and 6.83 (6.82) for 0-methyl protons, and 7.40 (7.41) and 7.69 (7.70) for N-methyl protons. The data in the parentheses show those reported by Bick *et al.*^{10)*5} On the contrary, the n.m.r. spectrum of 0-methylthalictberine (2) had the singlet signals at 6.12, 6.15, 6.25 and 6.36 for methoxyl protons, and at 7.45 and 7.90 for N-methyl protons.

In general, the protons of a methoxyl group which lies on the plane of a benzene ring have their chemical shift at the lower magnetic field than the protons of a methoxyl group which takes its position over or under a benzene ring, due to the magnetic anisotropy of benzene ring. The assignment of the chemical shifts (see Table 1) by Bick *et al.*¹⁰⁾ to each methoxyl group of tetrandrine is recognized to be reasonable, when the stereo model is examined. The methoxyl group at position 7 in 29 is subject to the anisotropic effect of rings B and C, and will have the chemical shift at the higher magnetic field than the methoxyl at position 6' which gets only an effect of ring A.

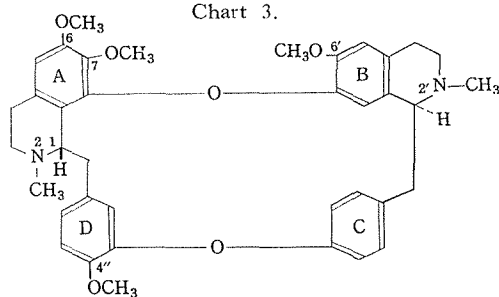
Each signal of the methoxyl and N-methyl protons in 0-methylthalictberine was assigned as shown in Table 1. The methoxyl group at position 7 in 2 is only subject to the effect of ring B, while one at 7' can easily take the conformations which are favorably located over the rings A, C and D. The latter was, therefore, assigned to the chemical shift in the higher magnetic field.

Generally, the difference of the relative shift among the chemical shifts of the methoxyl groups in 0-methylthalictberine (2) is smaller than that in tetrandrine and the signals appear in the lower magnetic field. Tetrandrine contains a 18-membered ring, while 0-methylthalictberine does a 19-membered ring. As their models show, the

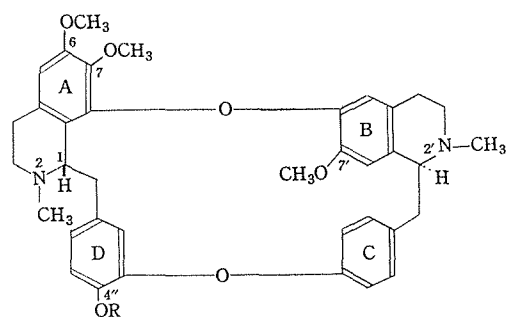
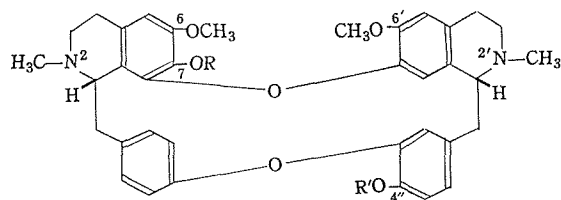
*4 The spectra herein were taken with a Varian A-60 analytical NMR spectrometer system at 60 Mc. in deuteriochloroform containing tetramethylsilane as an internal reference. Chemical shifts are expressed on τ -scale.

*5 The measurements were made at 40 Mc. sec⁻¹ with a Varian Associates 12" electromagnet and a V-4300B spectrometer.

Chart 3.



29


 1: R=H
 2: R=CH₃

 6: R=R'=H
 7: R=H, R'=CH₃
 9: R=R'=CH₃

former has more crowded stereochemistry than the latter. In other words, there is more space between each methoxyl and each benzene ring in the latter, and the grade of their approach is not so close as in the case of the former. The probability of the conformation where a methoxyl group is favorably located just close to the upside or the back side of a benzene ring is smaller in 0-methylthalicberine than in tetrandrine, hence the chemical shift which appears as an average taken on the various orientations of methoxyl group regards to benzene rings moves to the lower magnetic field in the former than in the latter. These observations will give another evidence for the correct structure of 2 for 0-methylthalicberine.

The N-methyl group protons in position 2' of 0-methylthalicberine (2) show the

Table 1. Chemical Shift Data for Several Alkaloids in τ -value.

Name	Formula (chart 3)	O-Me					N-Me	
		4''	6	6'	7	7'	2'	2
Tetrandrine	29	6.10 (6.10)	6.28 (6.27)	6.66 (6.65)	6.83 (6.82)	—	7.40 (7.41)	7.69 (7.70)
O-Methylthalicberine	2	6.12	6.15	—	6.25	6.36	7.45	7.90
Thalicberine	1	—	6.15	—	6.25	6.38	7.45	7.91
Thalicrine	6	—	6.23	6.44	—	—	7.48	7.53
Aromoline	6	—	(6.23)	(6.44)	—	—	(7.51)	(7.51)
Homothalricrine (=Homoaromoline)	7	6.13	6.27	6.42	—	—	7.47	7.56
O,O-Dimethylthalicrine	9	6.12	6.22	6.38	6.82	—	7.34	7.43
O-Methyl-oxyacanthine	9	6.12 (6.10)	6.22 (6.21)	6.38 (6.40)	6.82 (6.80)	—	7.34 (7.35)	7.43 (7.45)

signal at a slightly higher field than the corresponding protons of tetrandrine (29), while the same group protons at position 2 of 2 show their signal at 0.2 ppm higher field than those of 29. The models tell that the N-methyl group in position 2 of 0-methylthalicberine is more favored to be located for getting the + effect of D ring than the corresponding group in tetrandrine.

Finally, n.m.r. spectra of thalicrine and aromoline, and those of 0,0-dimethylthalicrine and 0-methyloxyacanthine were found to be identical, respectively. The signals of their methoxyl and N-methyl protons, together with those of homothalricrine, were summarised in Table 1.

EXPERIMENTAL *6

0,0-Dimethylthalicrine To the solution of thalicrine (1.2 g.) of m.p. 221° in chloroform was added diazomethane-ether solution prepared from nitrosomethylurea (5g.). The reaction mixture was allowed to stand for two weeks. During the time freshly prepared diazomethane-ether solution was added three times. Ether and excess diazomethane were distilled off. The residue was dissolved in 5% acetic acid, made alkaline with a dilute sodium hydroxide solution, extracted with ether, dried over anhydrous potassium carbonate and evaporated to leave a pale yellow amorphous residue (1.25 g.). Hydrobromide: Colorless needles, m.p. 265° (decomp.), from ethanol. *Anal.* Calcd. for $C_{38}H_{42}O_6N_2 \cdot 2 HBr \cdot 2 H_2O$: C, 55.62; H, 5.90; N, 3.41. Found: C, 55.20, 55.25; H, 6.38, 6.14; N, 3.50, 3.48. The infrared spectrum in nujol was identical with the spectrum of 0-methyloxyacanthine hydrobromide. The free base obtained from the hydrobromide by the usual treatment was crystallized by seeding a crystal of obaberine. Colorless needles, m.p. 142° from ether. *Anal.* Calcd. for $C_{38}H_{42}O_6N_2$: C, 73.29; H, 6.80; N, 4.50. Found: C, 72.99; H, 6.83; N, 4.47. The melting point was not depressed, on admixture with obaberine (m.p. 142°). The infrared spectra (KBr) were completely superimposable.

*6 All melting points are uncorrected.

0,0-Dimethylthalicrine methyl methine 0,0-Dimethylthalicrine dimethiodide (1.5 g.) was dissolved in aqueous methanol (1 : 1 by volume; 20 ml.). The treatment of the solution with freshly made silver chloride gave dimethochloride, which was heated with 30 % aqueous potassium hydroxide solution in a water-bath for two hours. The reaction mixture was extracted with ethyl acetate, followed by extraction of the extract with 5 % acetic acid. The acidic extract was made alkaline with dil. sodium hydroxide solution, and the precipitated methine base was extracted with ether. The usual treatment of the ethereal extract gave colorless amorphous substance (0.8 g.). Oxalate was crystallized by the usual treatment of the substance with ethanolic solution of oxalic acid. Colorless small needles of m.p. 210° (decomp.). *Anal.* Calcd. for $C_{40}H_{46}O_6N_2 \cdot (COOH)_2 \cdot 4\frac{1}{2}H_2O$: C, 61.37; H, 6.99. Found: C, 61.29; H, 7.01. The infrared spectrum of the oxalate in nujol was identical with the spectrum of 0-methoxyacanthine methyl methine oxalate. Oxalate was dissolved in warm water and made free with dil. sodium hydroxide solution. Extraction with ether and the usual treatment of the ethereal extract yielded crystalline free base, which was recrystallized from acetone-petroleum ether to give the colorless needles of m.p. 98° . $[\alpha]_D^{22} \pm 0^{\circ}$. *Anal.* Calcd. for $C_{40}H_{46}O_6N_2 \cdot 3H_2O$: C, 68.16; H, 7.44. Found: C, 68.41, 68.28; H, 7.54, 7.42. On admixture with 0-methoxyacanthine methyl methine m.p. 98° , the melting point was not depressed. Moreover, the infrared spectra of both substances in nujol were quite identical. The dimethiodide was prepared by refluxing of the methine base with methyl iodide in methanol for three hours on a water bath. The pale yellow crystal of m.p. $233\sim 234^{\circ}$ (decomp.) was obtained after recrystallization from methanol. *Anal.* Calcd. for $C_{42}H_{52}O_6N_2I_2 \cdot 5H_2O$: C, 49.22; H, 6.10. Found: C, 49.27; H, 6.28. The infrared spectrum in nujol was identical with the spectrum of 0-methoxyacanthine methyl methine dimethiodide.

Ozonolysis of 0,0-dimethylthalicrine methyl methine The methine base (1 g.) was dissolved in 1.5 % acetic acid solution (40 ml.), which was cooled in ice water. Through this cold solution, oxygen which contained ca. 3% of ozone was passed at the velocity of ca. 1 ml. per second. After about nine hours, extraction of the separated substance with ether was done and the remaining acetic acid solution was again ozonized. Repeated extraction and ozonization were carried out. After 14 hours, no precipitate appeared when a little sample of the acidic solution was made alkaline with ammonium hydroxide. At this point the reaction was finished. From the ethereal extract, crude acidic (0.2 g.) and neutral substances (0.1 g.) were separated. These compounds were treated in the same way as described in a previous paper^{1d}). To the acetic acidic mother liquor was added platinum black to decompose ozone and hydrogen peroxide. After over-night standing, the catalyst was filtered off and catalytic reduction with palladium-charcoal was carried out to convert amine oxide to amine. (10 ml. of H_2). The filtrate freed from catalyst was concentrated to about 30 ml. under reduced pressure. Fifty per cent potassium hydroxide solution (10 ml.) was added to separate a substance which was extracted with ether. The extract was treated as usual to give a pale yellow viscous oil (0.1 g.). Dimethiodide was crystallized from methanol to give pale yellow needles of m.p. 245° (decomp.) (0.1 g.). *Anal.* Calcd. for $C_{27}H_{40}O_6-$

$N_2I_2 \cdot H_2O$: C, 42.64; H, 5.57. Found: C, 42.93; H, 5.91. The infrared spectrum in nujol of this compound was completely identical with that of the diamino dialdehyde dimethiodide of m.p. 245° (decomp.) prepared from 0-methyloxyacanthine methine by ozonolysis, while it apparently differed from that of the corresponding diamino dialdehyde dimethiodide of m.p. 235° (decomp.) prepared from 0-methylthalicberine methyl methine by ozonolysis.

Cleavage of 0,0-dimethylthalicrine with sodium in liquid ammonia

0,0-Dimethylthalicrine (0.65 g.; m.p. 142°) was dissolved in tetrahydrofuran (50 ml.), and this solution was added dropwise into liquid ammonia (500 ml.) under vigorous stirring. At the same time, sodium (1.0 g.) was added piece by piece. The temperature was kept at $-40 \pm 5^\circ$. After the reaction was finished (ca. 3 hours), the reaction mixture was allowed to stand overnight, and ammonia was evaporated to give a viscous residue. The latter was dissolved in 5% acetic acid, made alkaline with ammonium hydroxide and extracted with ether. The ethereal solution was extracted with 5% sodium hydroxide solution to dissolve phenolic base. The sodium hydroxide solution was acidified with acetic acid and again made alkaline with ammonium hydroxide to precipitate the phenolic base, which was extracted with ether. The usual treatment of the ethereal extract gave a crude phenolic base mixture (0.6 g.). On the other hand, ethereal solution which was free from phenolic base by extraction with dil. sodium hydroxide solution gave only traces of residue after evaporation of solvent.

The above described crude phenolic base was dissolved in a small amount of ethanol and to this solution was added dropwise a saturated solution of oxalic acid in ethanol. The precipitated colorless fine needles of m.p. $192\sim 193^\circ$ (0.3 g.) were identified with L-(d)-armepavine oxalate. The filtrate was evaporated to give a residue which was dissolved in water, made alkaline with ammonium hydroxide and extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate and evaporated to yield a pale yellowish amorphous residue (0.2 g.) which resisted to be crystallized. The substance (0.05 g.) was dissolved in a small amount of ethanol and to this solution was added a saturated solution of picric acid in ethanol. Within a short time the crystals were separated. Recrystallization from methanol gave the orange yellow needles of m.p. 135° . *Anal.* Calcd. for $C_{19}H_{23}O_3N \cdot C_6H_3O_7N_3$: C, 55.35; H, 4.83; N, 10.33. Found: C, 55.61; H, 5.00; N, 10.35. The compound did not show the depression of the melting point when admixed with the substance of m.p. 136° which was obtained by the similar reactions with 0-methyloxyacanthine. The infrared spectra (KBr) of both compounds were completely identical.

The crude free base (0.15 g.) was dissolved in a small amount of methanol and to this solution was added methyl iodide (1 ml.). The solution of the mixture was heated on a water bath under refluxing for three hours. The precipitated crystals were recrystallized from methanol to give colorless plates (0.1 g.) of m.p. 163° . *Anal.* Calcd. for $C_{19}H_{23}O_3N \cdot CH_3I$: C, 52.95; H, 5.76; N, 3.07. Found: C, 53.04; H, 6.03; N, 3.33. The comparison of the infrared spectrum (in nujol) of this compound with that of the methiodide which was derived by the same way from 0-methyloxyacanthine showed a complete identity.

Cleavage of 0,0-diethylthalicrine with sodium in liquid ammonia. 0,0-Diethylthalicrine (0.88 g.) was dissolved in a mixture of equal volume of tetrahydrofuran and ether. The solution was added dropwise to vigorously stirred liquid ammonia (500 ml.) and at the same time sodium (1.5 g.) was thrown into the latter piece by piece. The reaction time was $1\frac{3}{4}$ hours. The temperature was kept at $-45\sim-50^\circ$. The usual treatment gave only phenolic basic products (0.5 g.). The less soluble oxalate was recrystallized to give colorless needles of m.p. 204° (0.3 g.) which were proved to be L-(*d*)-1-(4-hydroxybenzyl)-2-methyl-6-methoxy-7-ethoxy-1,2,3,4-tetrahydroisoquinoline oxalate. The usual treatment of the filtrate gave another phenolic crude base (0.3 g.) which was ethylated for two days by diazoethane prepared from nitrosoethylurea (5 g.) and alkali. The ethylated non-phenolic base (0.2 g.) resisted to be crystallized, so its oxalate was prepared. Colorless needles of m.p. $177\sim178^\circ$ were obtained after purification by recrystallization from ethanol. *Anal.* Calcd. for $C_{22}H_{29}O_3N(COOH)_2$: C, 64.70; H, 7.01; N, 3.14. Found: C, 65.18; H, 7.04; N, 3.69. The infrared spectrum of this compound in nujol was completely superimposable with the spectrum of the oxalate, m.p. $177\sim178^\circ$, of the compound which was obtained by sodium-liquid ammonia cleavage of 0-ethyloxyacanthine, followed by 0-ethylation of another phenolic base product which was different from L-(*d*)-armepavine.

0-Methyloxyacanthine. Oxyacanthine (0.6 g.) was methylated with diazomethane-ether solution by the usual way to yield an amorphous non-phenolic base, to which a crystal of obaberine was seeded. The crystalline 0-methyloxyacanthine was recrystallized from ether to give colorless needles (0.5 g.) of m.p. 142° . *Anal.* Calcd. for $C_{38}H_{42}O_6N_2$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.58; H, 7.05; N, 4.68.

0-Methyloxyacanthine methyl methine. Colorless plates; m.p. $98\sim99^\circ$. $[\alpha]_D^{30} \pm 0^\circ$ (c 0.4; methanol). *Anal.* Calcd. for $C_{40}H_{46}O_6N_2 \cdot 3H_2O$: C, 68.16; H, 7.44. Found: C, 67.92; H, 7.73. Oxalate: colorless needles. m.p. 205° (decomp.). *Anal.* Calcd. for $C_{40}H_{46}O_6N_2(COOH)_2 \cdot 4\frac{1}{2}H_2O$: C, 61.37; H, 6.99; N, 3.41. Found: C, 61.51; H, 7.05; N, 3.83. Dimethiodide: pale yellow crystals. m.p. 240° (decomp.). *Anal.* Calcd. for $C_{42}H_{52}O_6N_2I_2 \cdot 4\frac{1}{2}H_2O$: C, 50.82; H, 6.19; N, 2.85. Found: C, 50.75; H, 6.07; N, 3.00.

Cleavage of 0-methyloxyacanthine with sodium in liquid ammonia.

The solution of 0-methyloxyacanthine (0.6 g.) in tetrahydrofuran (50 ml.) was allowed to react with sodium (1.5 g.) in liquid ammonia (500 ml.) by the above-mentioned way. The temperature was kept at $-45\sim-50^\circ$. The cleavage products consisted of phenolic bases only. Less soluble oxalate of L-(*d*)-armepavine, m.p. 200° , (0.3 g.) was removed by filtration, and from the mother liquor another kind of phenolic base was obtained. The free base could not be crystallized. Picrate was yellow needles of m.p. 136° . *Anal.* Calcd. for $C_{19}H_{23}O_3N \cdot C_6H_3O_7N_3$: C, 55.35; H, 4.83; N, 10.33. Found: C, 55.76; H, 5.08; N, 10.47. Methiodide: colorless plates of m.p. 163° . *Anal.* Calcd. for $C_{19}H_{23}O_3N \cdot CH_3I$: C, 52.95; H, 5.76; N, 3.07. Found: C, 53.45; H, 5.91; N, 3.14.

Cleavage of 0-ethyloxyacanthine with sodium in liquid ammonia.

0-Ethoxyacanthine (1.15 g.) was dissolved in a mixture of tetrahydrofuran and ether (1 : 1 by volume; 20 ml.). The solution was treated with sodium in liquid ammonia as usual. The temperature was kept at $-45\sim-50^{\circ}$. The reaction mixture was treated by the same way as mentioned above to give L-(d)-armepavine oxalate of m.p. 205° (0.32 g.). Another phenolic product was a viscous substance, which was ethylated by diazoethane to give an amorphous 0-ethylated base (0.18 g.). The oxalate of the latter was obtained as colorless needles (0.1 g.) of m.p. $177\sim178^{\circ}$. *Anal.* Calcd. for $C_{22}H_{29}O_3N(COOH)_2$: C, 64.70; H, 7.01; N, 3.14. Found: C, 64.14; H, 7.16; N, 3.46.

ACKNOWLEDGEMENT

The authors are indebted to Prof. M. Tomita for his kind supply of the samples, obaberine and 19 picrate, and to Mr. T. Ibuka for the sample of 27 oxalate. Their thanks are also due to Mr. T. Shingu in the Faculty of Pharmaceutical Sciences, Kyoto University, and Dr. K. Tori in Shionogi & Co., Ltd. for their n. m.r. spectral measurements. Microanalyses were carried out by Dr. K. Konobu and members in Elementary Analytical Center of Kyoto University and Mrs. Ikegami in this Institute, to whom the authors wish to express their thanks.

REFERENCES

- (1) a) E. Fujita and T. Tomimatsu: *Yakugaku Zasshi*, **79**, 1256, 1260 (1959); b) T. Tomimatsu, *Ibid.*, **79**, 1380 (1959); c) E. Fujita, T. Tomimatsu, and Y. Kano, *Ibid.*, **80**, 1137 (1960); d) T. Tomimatsu and Y. Kano, *Ibid.*, **83**, 153 (1963); e) E. Fujita, T. Tomimatsu, and Y. Kano, *Ibid.*, **83**, 159 (1963).
- (2) a) E. Fujita, T. Tomimatsu, and Y. Kano, *Ibid.*, **82**, 311 (1962); b) T. Tomimatsu and Y. Kano, *Ibid.*, **82**, 315, 320 (1962).
- (3) E. Späth and J. Pikl, *Ber.*, **62**, 2251 (1929); F. v. Bruchhausen and H. Schultze, *Arch. Pharm.*, **267**, 617 (1929). They gave m.p. $152\sim153^{\circ}$ or m.p. 152° for the anhydrous compound.
- (4) F. v. Bruchhausen and P. H. Gericke, *Arch. Pharm.*, **269**, 123 (1931) gave m.p. 259° (decomp.), while H. Kondo and K. Yano, *Yakugaku Zasshi*, **52**, 827 (1932) gave dec. 250° for the same compound.
- (5) M. Tomita and Y. Sasaki, *Pharm. Bull.*, **2**, 375 (1954); E. Fujita, *Ibid.*, **2**, 378 (1954).
- (6) M. Tomita and Y. Kondo, *Yakugaku Zasshi*, **77**, 1021 (1957).
- (7) M. Tomita and T. Ibuka, *Ibid.*, **83**, 940 (1963).
- (8) T. Kugo, M. Tanaka, and T. Sagae, *Ibid.*, **80**, 1425 (1960).
- (9) I. R. C. Bick, E. S. Ewen and A. R. Todd, *J. Chem. Soc.*, **1949**, 2767.
- (10) I. R. C. Bick, J. Harley-Mason, N. Sheppard, and M. J. Vernengo, *Ibid.*, **1961**, 1896.