(EC 6.4.1.1), and these changes are in reciprocal relation to those of glucokinase, which catalyzes the first step of glucose utilization.[7]

In the present work, particular care was taken to consider the nutritional states of rats in elucidating the effect of the ginseng saponin on serine dehydratase activity. In summary, it was found that the response of serine dehydratase activity to ginseng saponin administration is dependent on the nutritional status in rats.

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Quinolizidines. III.[1] An Improved Synthetic Route to Stereoisomers of *dl*-2,3-*cis*-Emetine[2]

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A formal synthesis of the four stereoisomers (type **2**) of *dl*-2,3-*cis*-emetine has been effected through the synthesis of the lactam acid **10** from methyl *dl*-*cis*-5-ethyl-2-oxo-4-piperidineacetate (**4**). The steps involved are conversion of **4** into the lactim ether **5** or **6**, N-alkylation of **5** or **6** with 3,4-dimethoxyphenacyl bromide, $NaBH_4$ reduction of the resulting lactam ketone **7** followed by catalytic hydrogenolysis to give the lactam ester **9**, and alkaline hydrolysis of **9**.

Keywords——lactam ester; lactim ether; N-alkylation; $NaBH_4$ reduction; catalytic hydrogenolysis; alkaline hydrolysis; *cis* configuration; *cis*-emetine isomer

The four possible stereoisomers (type **2**) of *dl*-2,3-*cis*-emetine have already been prepared[4] during the course of extensive synthetic studies of the Ipecac alkaloid emetine (**1**).[5] It is known[4d] that none of these isomers has an *in vitro* amoebicidal effect comparable to that of natural *l*-emetine (**1**) or racemic 2,3-dehydroemetine (**3**).[6] In connection with our recent studies on the anti-tumor activities of lactams and pyridones[7] and on the syntheses of the

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2) A part of this work has already been reported in a preliminary form.[8a]
3) Location: *13-1 Takara-machi, Kanazawa 920, Japan.*
4) *a*) R. P. Evstigneeva and N. A. Preobrazhensky, *Tetrahedron*, **4**, 223 (1958), and earlier references cited; *b*) M. Barash, J. M. Osbond, and J. C. Wickens, *J. Chem. Soc.*, **1959**, 3530; *c*) A. Grüssner, E. Jaeger, J. Hellerbach, and O. Schnider, *Helv. Chim. Acta*, **42**, 2431 (1959); *d*) A. Brossi and O. Schnider, *ibid.*, **45**, 1899 (1962).
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6) *a*) A. Brossi, M. Baumann, L. H. Chopard-dit-Jean, J. Würsch, F. Schneider, and O. Schnider, *Helv. Chim. Acta*, **42**, 772 (1959); *b*) D. E. Clark, P. G. Holton, R. F. K. Meredith, A. C. Ritchie, T. Walker, and K. D. E. Whiting, *J. Chem. Soc.*, **1962**, 2479.
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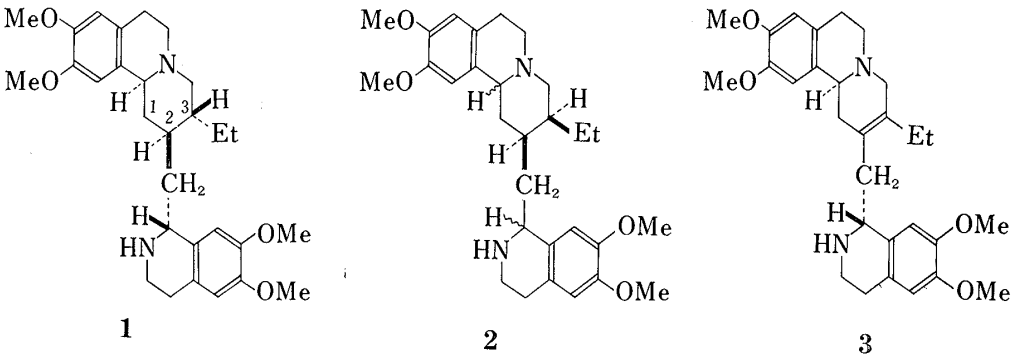

Chart 1

Ipecac and the *Alangium* alkaloids,[1,8] we had occasion to examine an improved synthetic route to racemic 2,3-*cis*-emetine isomers (type **2**) from methyl *dl*-*cis*-5-ethyl-2-oxo-4-piperidineacetate (**4**),[9] which can be synthesized readily by a previously reported procedure[9,10] or by *trans*→*cis* isomerization[9,10b,11] of an appropriate form of the corresponding *trans* synthon.[9-11] The strategic feature of the synthetic route was an application of the recently invented "lactim ether method"[12] for preparing N-(2-arylethyl)lactams from N-unsubstituted lactams; its effectiveness and usefulness have been confirmed in the above alkaloid syntheses.[1,8]

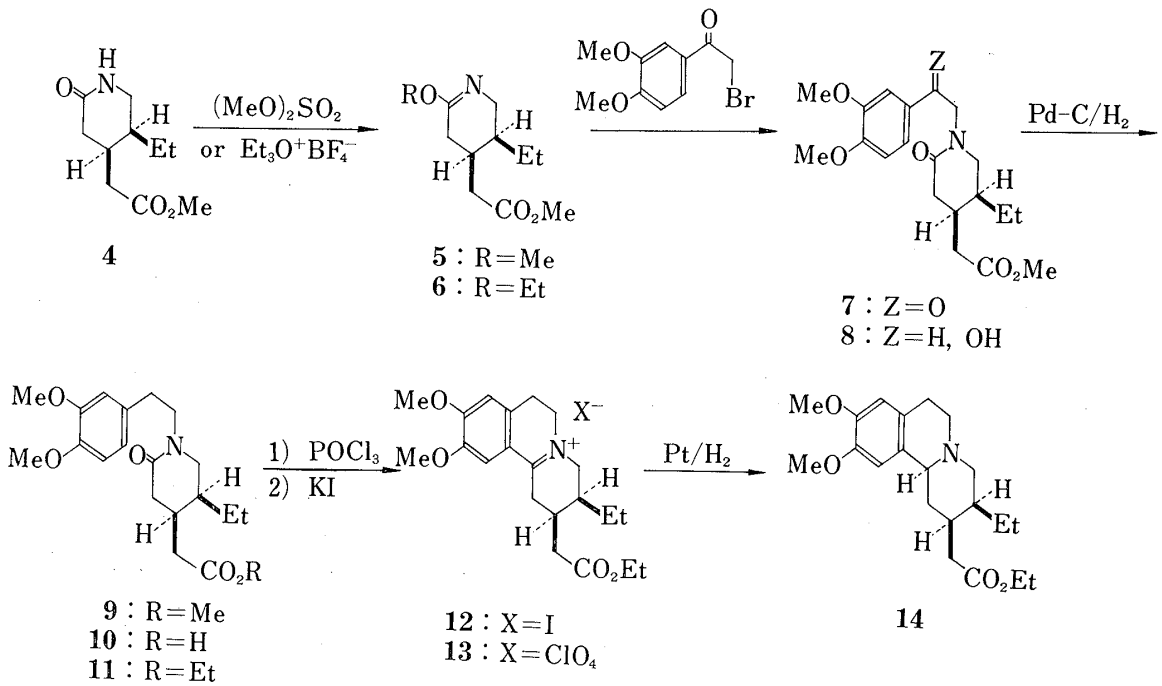

Chart 2

8) *a*) T. Fujii and S. Yoshifuji, *Tetrahedron Lett.*, **1975**, 731; *b*) T. Fujii, S. Yoshifuji, and K. Yamada, *ibid.*, **1975**, 1527; *c*) S. Yoshifuji and T. Fujii, *ibid.*, **1975**, 1965; *d*) T. Fujii, K. Yamada, S. Yoshifuji, S. C. Pakrashi, and E. Ali, *ibid.*, **1976**, 2553; *e*) T. Fujii, S. Yoshifuji, S. Minami, S. C. Pakrashi, and E. Ali, *Heterocycles*, **8**, 175 (1977); *f*) T. Fujii, S. Yoshifuji, and H. Kogen, *Tetrahedron Lett.*, **1977**, 3477; *g*) T. Fujii, H. Kogen, and M. Ohba, *ibid.*, **1978**, 3111.

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Conversion of the N-unsubstituted lactam ester **4** into the O-methyllactim **5** was effected with dimethyl sulfate as reported previously.[9] Ethylation of **4** with triethyloxonium fluoborate[13] in boiling CH_2Cl_2 for 4 hr gave the O-ethyllactim **6** in good yield. On treatment with 3,4-dimethoxyphenacyl bromide[14] at 60° for 5 hr, the lactim ether **5** or **6** produced the N-substituted lactam **7** in 83% or 86% yield. The lactam ketone **7** was then reduced with $NaBH_4$ in EtOH at 0° for 3 hr, and the resulting oil, presumed to be a mixture of the two possible diastereoisomeric lactam alcohols **8**, was catalytically hydrogenolyzed (10% Pd–C/H_2, EtOH–70% aq. $HClO_4$, 20°, 3.8 atm, 16 hr) to the lactam **9** in good yield. Alkaline hydrolysis of the methyl ester **9** (50% aq. KOH–EtOH, room temp., 24 hr) afforded the known *cis*-lactam acid **10**,[4b,15] mp 150—152°, in 90% yield (from **8**). Since the lactam acid **10** had been obtained only as a by-product in less stereoselective syntheses of the corresponding *trans*-lactam acid,[4b,15] the route to **10** from **4** above represents a considerable improvement in its synthesis.

The structure of the lactam acid **10** was confirmed by its known conversion[4b] into the tricyclic ester **14** through esterification of **10** (10% ethanolic HCl, 20°, 24 hr)[16] and the Bischler-Napieralski reaction of the resulting ester **11**, followed by reduction (**11**→**12**→**13**→**14**). The tricycle **14** has already been transformed to the four possible stereoisomers (type **2**) of *dl-cis*-emetine.[4b,d] Therefore, the acquirement of **10** by the route outlined (Chart 2) concluded a new formal synthesis of the unnatural emetine isomers.

In conclusion, the present results, together with those[1] of a parallel synthesis of natural emetine (**1**) from the *trans* isomer of **4**, have demonstrated that the operations proceeding from **4** ("lactim ether method") do not affect the stereochemical relationship already established in this intermediate. Thus, they support the correctness of the reported stereochemical outcome of similar synthetic operations utilized in our recent syntheses[8b,d,f] of the *Alangium* alkaloids, ankorine, alangicine, and alangimarckine.

Experimental

All melting points are corrected; boiling points, uncorrected. Unless otherwise stated, the organic solutions obtained after extraction were dried over anhyd. Na_2SO_4 and evaporated *in vacuo*. Infrared (IR) spectra were measured in Nujol mulls, in liquid films, or in $CHCl_3$ at 0.2 M concentration. See also ref. 12*b* for details of instrumentation and measurement. The following abbreviations are used: b=broad, d=doublet, d-d=doublet-of-doublets, m=multiplet, q=quartet, s=singlet, t=triplet.

Methyl *cis*-6-Ethoxy-3-ethyl-2,3,4,5-tetrahydro-4-pyridineacetate (6)——A solution of triethyloxonium fluoborate[13] (760 mg, 4 mmol) and **4**[9] (400 mg, 2.01 mmol) in CH_2Cl_2 (5 ml) was refluxed for 4 hr. The solution was cooled, 10% aq. K_2CO_3 (5 ml) was added, and the resulting mixture was extracted with CH_2Cl_2 (2×15 ml). The CH_2Cl_2 extracts were dried and evaporated to leave a pale yellow oil (455 mg, 100%), which was vacuum distilled to give **6** (364 mg, 80%) as a colorless oil, bp 122° (4 mmHg); IR ν_{max}^{film} cm^{-1}: 1736 (ester CO), 1680 (C=N); NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.24 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 3.69 (3H, s, CO_2Me), 4.03 (2H, q, J=7 Hz, $OC\underline{H}_2Me$).

Methyl *cis*-1-(3,4-Dimethoxyphenacyl)-5-ethyl-2-oxo-4-piperidineacetate (7)——i) From the O-Methyllactim **5**: A mixture of **5**[9] (2.68 g, 12.6 mmol) and 3,4-dimethoxyphenacyl bromide[14] (3.26 g, 12.6 mmol) was stirred at 60° for 5 hr. After cooling, the reaction mixture was dissolved in benzene (40 ml). The benzene solution was washed successively with 10% aq. Na_2CO_3 and H_2O, dried, and evaporated to leave a yellow oil (5.03 g). Purification of the oil by column chromatography [alumina, AcOEt–hexane (1: 1, v/v), AcOEt] yielded **7** (3.96 g, 83%) as a pale yellow solid, mp 118—123°. Recrystallization of the solid from

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15) E. E. van Tamelen, P. E. Aldrich, and J. B. Hester, Jr., *J. Am. Chem. Soc.*, **81**, 6214 (1959).

16) Although the 5-ethyl-2-oxo-4-piperidineacetic acid system tends to undergo *cis*⇄*trans* isomerization under Fischer–Speier esterification conditions,[11] we have confirmed by means of C-13 nuclear magnetic resonance (NMR) spectroscopy[9,11] that *cis*→*trans* isomerization of **10** did not occur at all under these particular esterification conditions.

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EtOH–hexane (1: 2, v/v) gave an analytical sample as colorless prisms, mp 122—123°; IR ν_{max}^{Nujol} cm^{-1}: 1730 (ester CO), 1687 (CO), 1638 (lactam CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}; 1730 (ester CO), 1686 (CO), 1633 (lactam CO); NMR ($CDCl_3$) δ: 0.96 (3H, t, J=6.5 Hz, $CCH_2\underline{Me}$), 2.93—3.48 (2H, m, $H_{(6)}$'s), 3.74 (3H, s, CO_2Me), 3.97 and 4.00 (3H each, s, two MeO's), 4.48 and 5.14 (1H each, a pair of AB type d, J=17.5 Hz, $COCH_2N$), 6.92 (1H, d, J=8 Hz, $H_{(5')}$), 7.57 (1H, d, J=2 Hz, $H_{(2')}$), 7.64 (1H, d-d, J=8 and 2 Hz, $H_{(6')}$). *Anal.* Calcd. for $C_{20}H_{27}NO_6$: C, 63.65; H, 7.21; N, 3.71. Found: C, 63.71; H, 7.14; N, 3.94.

ii) From the O-Ethyllactim **6**: A mixture of **6** (455 mg, 2 mmol) and 3,4-dimethoxyphenacyl bromide[14] (622 mg, 2.4 mmol) was stirred at 60° for 5 hr. The reaction mixture was then worked up in a manner similar to that described above under method (i), giving crude **7** (650 mg, 86%), mp 119—122°. Recrystallization from EtOH–hexane furnished colorless prisms, mp 122—123°, identical [by thin-layer chromatography (TLC), mixed melting-point test, and IR spectrum] with a sample obtained by method (i).

Methyl *cis*-1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-5-ethyl-2-oxo-4-piperidineacetate (8)——A solution of **7** (3.53 g, 9.35 mmol) in EtOH (100 ml) was stirred under ice-cooling and $NaBH_4$ (265 mg, 7 mmol) was added portionwise. After stirring was continued at 0° for 3 hr, acetone (1 ml) was added and the mixture was concentrated *in vacuo*. To the residue was added H_2O (20 ml) and the aqueous mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried, and evaporated to leave **8** (3.55 g, 100%) as a pale yellow oil, which was presumed to be a mixture of the two possible diastereoisomeric alcohols. The crude oil was used directly in the next hydrogenolysis without further purification.

Methyl *cis*-1-(3,4-Dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetate (9)——A solution of the foregoing lactam alcohol(s) **8** (3.55 g, 9.35 mmol) in EtOH (100 ml) containing 70% aq. $HClO_4$ (1 ml) was hydrogenated over 10% Pd–C (2 g) at 20° and 3.8 atm for 16 hr. The catalyst was removed by filtration and washed with EtOH (2×10 ml). The filtrate and the washings were combined and evaporated *in vacuo* to leave a sirup. The residue was dissolved in $CHCl_3$ and the solution was washed successively with H_2O, 5% aq. Na_2CO_3, and H_2O, dried, and evaporated to dryness to afford **9** (3.35 g, 99%) as a colorless oil, IR ν_{max}^{film} cm^{-1}: 1730 (ester CO), 1639 (lactam CO).

***cis*-1-(3,4-Dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid (10)**——A solution of the total amount of the above ester **9** and 50% aq. KOH (5 g) in EtOH (18 ml) was kept at room temp. for 24 hr. The solvent was removed by vacuum distillation and the residue was dissolved in H_2O (120 ml). The aqueous solution was washed with ether, adjusted to pH 1 with 20% aq. HCl, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried, and evaporated to give a slightly yellow solid (2.94 g, 90% yield from **8**), mp 143—146°. Recrystallization from AcOEt produced **10** as colorless prisms, mp 150—152°[17] (lit.[4b] mp 152—153°; mp 151.5—152.5°[15]); IR ν_{max}^{Nujol} cm^{-1}: 1721 (CO_2H), 1591 (lactam CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (CO_2H), 1598 (lactam CO); NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz, $CCH_2\underline{Me}$), 3.90 and 3.92 (3H each, s, two MeO's), 6.84 (3H, s, aromatic protons), 9.16 (1H, b, CO_2H). The IR and NMR (proton and C-13) spectra of this sample were different from those of the *trans* isomer (mp 155—157°).[1] Mixed melting-point comparison of the two lactam acids showed a marked depression (mp 134—135°).

Ethyl *cis*-1-(3,4-Dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetate (11)——A solution of **10** (500 mg, 1.43 mmol) in 10% (w/w) ethanolic HCl (15 ml) was kept at 20° for 24 hr. The solution was evaporated *in vacuo*, and H_2O (10 ml) was added to the residue. The aqueous mixture was extracted with $CHCl_3$, and the $CHCl_3$ solution was washed successively with H_2O, 10% aq. Na_2CO_3, and H_2O. The solution was dried and concentrated to yield **11** (525 mg, 97%) as a colorless oil, which was homogeneous on TLC analysis;[16] MS m/e: 377 (M^+); IR ν_{max}^{film} cm^{-1}: 1730 (ester CO), 1640 (lactam CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1727 (ester CO), 1624 (lactam CO); NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.5 Hz, $CCH_2\underline{Me}$), 1.26 (3H, t, J=7 Hz, $CO_2CH_2\underline{Me}$), 3.90 and 3.93 (3H each, s, two MeO's), 4.18 (2H, q, J=7 Hz, $CO_2C\underline{H}_2Me$), 6.84 (3H, s, aromatic protons).

***cis*-2-Ethoxycarbonylmethyl-3-ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxybenzo[*a*]quinolizinium Iodide (12)**——A solution of **11** (400 mg, 1.06 mmol) and $POCl_3$ (800 mg, 5.2 mmol) in dry toluene (4 ml) was heated at reflux for 90 min. Concentration of the reaction mixture under vacuum left a reddish purple oil, which was dissolved in H_2O (10 ml). To the aqueous solution was added KI (4 g) and the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with 40% aq. KI (6 ml), dried, and evaporated to dryness, giving a brown solid (500 mg, 97%), mp 139—141°. Recrystallization from EtOH–AcOEt furnished **12** as yellow prisms, mp 169—170°[17] (lit.[4b] mp 168—170°); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 246 (16100), 305 (9000), 356 (9200); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728 (ester CO), 1642 (C=N$^+$); NMR ($CDCl_3$) δ: 1.03 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.26 (3H, t, J=7 Hz, $CO_2CH_2\underline{Me}$), 4.00 and 4.04 (3H each, s, two MeO's), 4.17 (2H, q, J=7 Hz, $CO_2C\underline{H}_2Me$), 6.96 (1H, s, $H_{(8)}$), 7.28 (1H, s, $H_{(11)}$).

***cis*-2-Ethoxycarbonylmethyl-3-ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxybenzo[*a*]quinolizinium Perchlorate (13)**——The foregoing iodide **12** was treated with $AgClO_4$ as described previously[1] for the *trans* isomer, giving crude **13**, mp 164—165°, in 90% yield. Recrystallization from EtOH yielded an analytical sample as colorless prisms, mp 164—165°; UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 246 (16850), 304 (9350), 354 (9350). *Anal.* Calcd. for $C_{21}H_{30}ClNO_8$: C, 54.84; H, 6.57; N, 3.05. Found: C, 54.66; H, 6.50; N, 2.97.

Ethyl *cis*-3-Ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-acetate (14)——A solution of **13** (460 mg, 1 mmol) in 80% (v/v) aq. EtOH (24 ml) was hydrogenated over Adams catalyst (80

17) Routine C, H, N analyses agreed with calculated values within ±0.3% for this sample.

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mg) at 20° and 1 atm for 90 min. The catalyst was filtered off and the filtrate was evaporated *in vacuo* to leave **14**·$HClO_4$ (460 mg, 100%), mp 158—163°, which was dissolved in H_2O (20 ml). The aqueous solution was made basic with anhyd. K_2CO_3 and extracted with ether. The ethereal solution was dried over anhyd. K_2CO_3 and evaporated *in vacuo*, leaving the free base **14** (344 mg, 95%) as a yellow, unstable oil, IR ν_{max}^{film} cm^{-1}: 2805, 2760 (*trans*-quinolizidine), 1730 (ester CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2805, 2760 (*trans*-quinolizidine), 1722 (ester CO); NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.28 (3H, t, J=7 Hz, $CO_2CH_2\underline{Me}$), 3.88 (6H, s, two MeO's), 4.20 (2H, q, J=7 Hz, $CO_2C\underline{H}_2Me$), 6.60 and 6.72 (1H each, s, aromatic protons).

The Perchlorate of **14**: Colorless minute needles (from EtOH), mp 163—164°; IR ν_{max}^{Nujol} 1720 cm^{-1} (ester CO). *Anal.* Calcd. for $C_{21}H_{32}ClNO_8$: C, 54.60; H, 6.98; N, 3.03. Found: C, 54.86; H, 7.01; N, 2.95.

The Hydriodide of **14**: A small portion of **14**·$HClO_4$ was dissolved in hot EtOH and an equimolar amount of KI was added. The resulting precipitate was filtered off and the filtrate was concentrated *in vacuo*, leaving a solid of mp 208—211°. Recrystallization of the solid from EtOH–ether (1: 1, v/v) produced **14**·HI as faintly yellow needles, mp 211—212° (lit.[4b] mp 214.5—216.5°; mp 210—212°[4d]).

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Sustained Release of Dibucaine from Konjac Gels after Rectal Administration to Rats[1]

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The use of konjac gls as a vehicle for sustained drug release in the form of a rectal suppository was examinied in rats. Dibucaine dispersed in the konjac gels was released in the rectum at a rate predictable from *in vitro* release studies. No observable destruction of rectal mucosa was noted on microscopic observation, even after two 24 hr contacts (3-week interval) with drug-free gels.

Keywords——hydrogel; konjac gel; elastic gel; sustained release; suppository; rectal administration; dibucaine; local anesthetic

The properties of konjac gels have been studied to investigate their suitability as vehicles for the sustained release of drugs. Sustained release of dibucaine, a local anesthetic, has been obtained from konjac gels in which dibucaine base had been dispersed in the form of fine crystals.[3] A linear relationship was obtained when the cumulative amount of the drug released was plotted against the square root of time, and the release profile was in agreement with that expected from the theoretical equation.[4,5] In the present study the suitability of konjac gels for use as a rectal suppository was examined in comparison with glycerinated gelatin suppositories, whose elasticity is similar to that of the konjac gels.

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