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Quinolizidines. II.[1] A Stereoselective Synthesis of Emetine[2]

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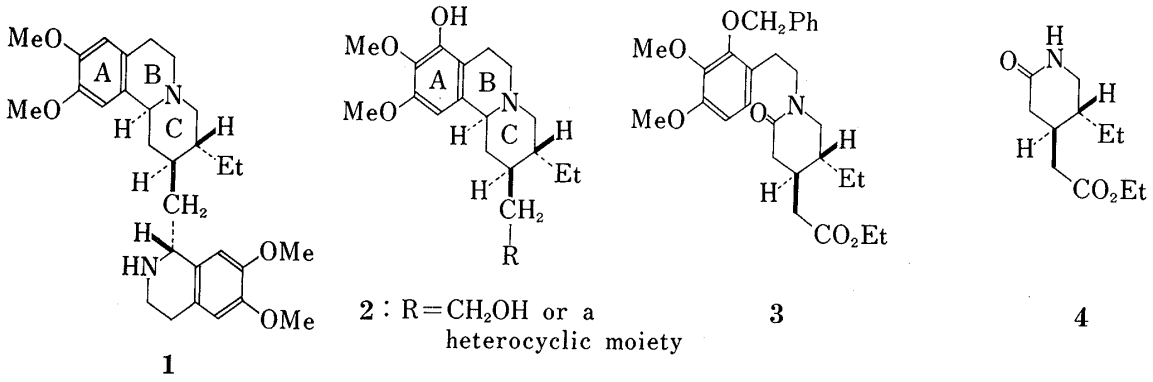
A formal synthesis of the Ipecac alkaloid emetine has been achieved in terms of the synthesis of the lactam ester **12** from ethyl *dl-trans*-5-ethyl-2-oxo-4-piperidineacetate (**4**). The steps involved are conversion of **4** into the lactim ether **5** or **6**, N-alkylation of **5** or **6** with 3,4-dimethoxyphenacyl bromide, and $NaBH_4$ reduction of the resulting lactam ketone **7**, followed by catalytic hydrogenolysis.

Keywords——lactam ester; lactim ether; N-alkylation; $NaBH_4$ reduction; catalytic hydrogenolysis; *trans* configuration; Ipecac alkaloid

A number of alkaloids structurally related to the Ipecac bases, *e.g.*, emetine (**1**), have been isolated from *Alangium lamarckii* Thw. (Alangiaceae), a medicinal plant indigenous to India.[4] The occurrence of new, highly ring-A-oxygenated benzo[*a*]quinolizidine alkaloids (type **2**) such as ankorine, alangicine, and alangimarckine in the same plant[4] offered us opportunities to establish their structures and stereochemistry by means of synthesis.[5-7] In our recent syntheses of racemic modifications of these three alkaloids,[5a,6a,7a] the *trans*-lactam ester **3** was a common key intermediate and we prepared it from ethyl *dl-trans*-5-ethyl-2-oxo-



1 **2** : R = CH_2OH or a heterocyclic moiety **3** **4**

Chart 1

1) Paper I in this series, T. Fujii, M. Nohara, M. Mitsukuchi, M. Ohba, K. Shikata, S. Yoshifuji, and S. Ikegami, *Chem. Pharm. Bull.* (Tokyo), **23**, 144 (1975).
2) A preliminary communication describing this investigation has been published.[5a]
3) Location: *13-1 Takara-machi, Kanazawa 920, Japan.*
4) For reviews, see *a*) H. T. Openshaw, "Chemistry of the Alkaloids," ed. by S. W. Pelletier, Van Nostrand Reinhold Co., New York, 1970, Chapter 4; *b*) A. Brossi, S. Teitel, and G. V. Parry, "The Alkaloids," Vol. XIII, ed. by R. H. F. Manske, Academic Press, New York, 1971, Chapter 3.
5) *a*) T. Fujii, S. Yoshifuji, and K. Yamada, *Tetrahedron Lett.*, **1975**, 1527; *b*) S. Yoshifuji and T. Fujii, *ibid*, **1975**, 1965; *c*) C. Szántay, E. Szentirmay, L. Szabó, and J. Tamás, *Chem. Ber.*, **109**, 2420 (1976).
6) *a*) T. Fujii, K. Yamada, S. Yoshifuji, S. C. Pakrashi, and E. Ali, *Tetrahedron Lett.*, **1976**, 2553; *b*) T. Fujii, S. Yoshifuji, S. Minami, S. C. Pakrashi, and E. Ali, *Heterocycles*, **8**, 175 (1977).
7) *a*) T. Fujii, S. Yoshifuji, and H. Kogen, *Tetrahedron Lett.*, **1977**, 3477; *b*) T. Fujii, H. Kogen, and M. Ohba, *ibid.*, **1978**, 3111.

4-piperidineacetate (**4**)[8] by the newly invented "lactim ether method."[9] Since one of the purposes of the above syntheses was to determine the relative stereochemistry of the new alkaloids, the *trans* configuration (in respect of the ethyl and the acetate side chains) present in **4** should have been retained throughout the synthetic schemes[5a,6a,7a] adopted. Thus, we tried to check the stereochemical outcome and synthetic generality by a parallel synthesis of emetine (**1**), a structurally analogous alkaloid of known stereochemistry.

Methylation of the N-unsubstituted lactam ester **4** with dimethyl sulfate in refluxing benzene for 3 hr furnished the O-methyllactim **5** in 73% yield. The corresponding O-ethyllactim **6** was obtained in a good yield by ethylation of **4** with triethyloxonium fluoroborate[10] as reported previously.[11] On treatment with 3,4-dimethoxyphenacyl bromide[12] at 60° for 5 hr, **5** gave the N-substituted lactam **7** in 86% yield. Replacement of the O-methyllactim **5** by the O-ethyllactim **6** in this N-alkylation improved the yield of **7** to 93%. Compound **7** was then reduced with $NaBH_4$ in EtOH, and the resulting oil, presumed to be a diastereoisomeric mixture of the lactam alcohol **8**, was hydrogenolyzed catalytically (10% Pd-C/H_2, EtOH–70% aq. $HClO_4$, 20°, 3.7 atm) to the lactam **12** in an excellent overall yield. Upon alkaline hydrolysis (50% aq. KOH–EtOH, room temp., 24 hr), the lactam ester **12** afforded the lactam acid **13**, mp 155—157°, in 90% yield. The structure and the *trans* configuration of this sample of **13** were confirmed by its identity with an authentic sample, which was prepared from **9** through **10** and **11** according to a previously reported procedure[13] but with a slight modification in the Michael addition step (**9**→**10**).

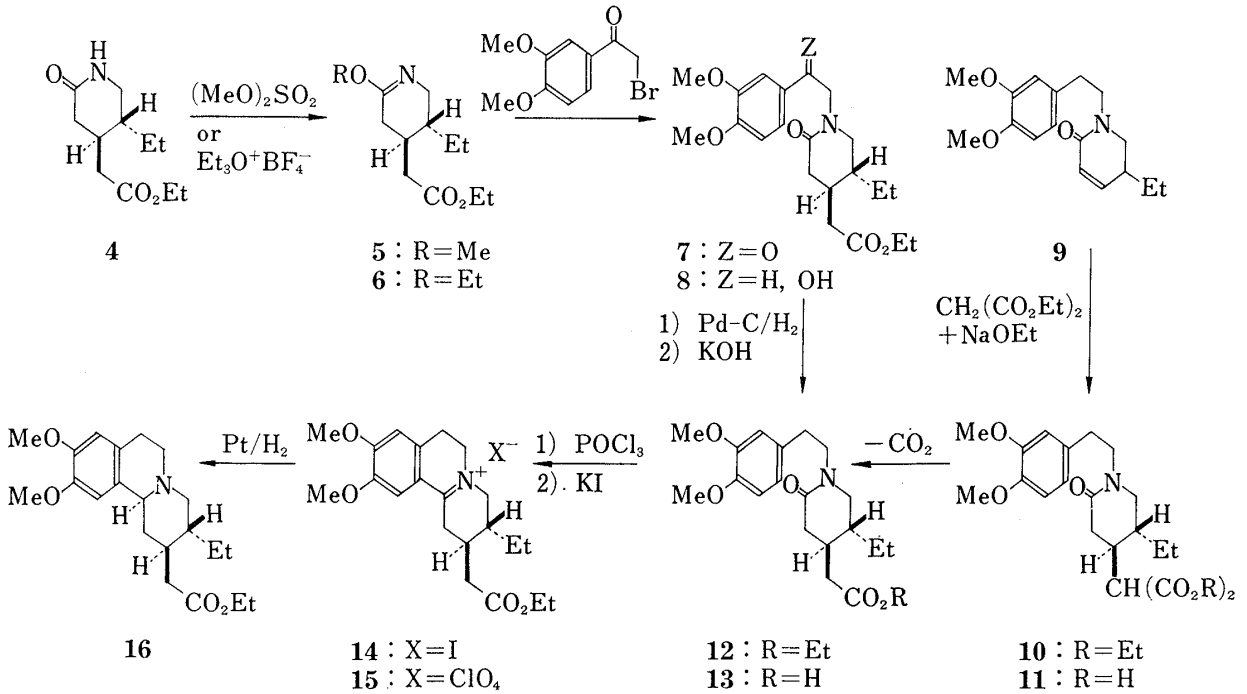


Chart 2

8) *a*) T. Fujii, S. Yoshifuji, and M. Ohba, *Chem. Pharm. Bull.* (Tokyo), **26**, 645 (1978); *b*) T. Fujii, S. Yoshifuji, and M. Tai, *ibid.*, **23**, 2094 (1975), and references cited.
9) *a*) T. Fujii, S. Yoshifuji, and K. Yamada, *Chem. Ind.* (London), **1975**, 177; *b*) *Idem*, *Chem. Pharm. Bull.* (Tokyo), **26**, 2071 (1978).
10) H. Meerwein, "Organic Syntheses," Coll. Vol. 5, ed. by H. E. Baumgarten, John Wiley and Sons, Inc., New York, 1973, p. 1080.
11) M. Uskoković, C. Reese, H. L. Lee, G. Grethe, and J. Gutzwiller, *J. Am. Chem. Soc.*, **93**, 5902 (1971).
12) *a*) C. Mannich and F. L. Hahn, *Ber. Dtsch. Chem. Ges.*, **44**, 1542 (1911); *b*) T. Fujii, S. Yoshifuji, and M. Ohba, *Chem. Pharm. Bull.* (Tokyo), **26**, 3218 (1978).
13) A. R. Battersby and J. C. Turner, *J. Chem. Soc.*, **1960**, 717.

The direct introduction of the 3,4-dimethoxyphenethyl skeleton onto the nitrogen of **4** was previously effected by the reaction of 3,4-dimethoxyphenethyl bromide with the potassium salt of **4**.[8b,14] This approach, however, provided the lactam acid **13**[15] in only 17% yield (from **4**) with recovery of 54% of **4**. Thus, the synthesis of the lactam ester **12** or the lactam acid **13** from **4** has been much improved through the above stepwise route (Chart 2), which represents an extension of our "lactim ether method"[9] for preparing N-(2-arylethyl)lactams from N-unsubstituted lactams to a complex system.

Further structural confirmation of the lactam acid **13** was achieved by its known conversion[13] into the tricycle **16** through esterification of **13** (99% yield, 10% ethanolic HCl, room temp., 48 hr)[16] and the Bischler-Napieralski cyclization of the resulting ester **12** followed by reduction (**12**→**14**→**15**→**16**). Since *dl*-**16** has been shown to lead to *l*-emetine (**1**) *via* *d*-O-methylpsychotrine,[13] the synthesis of **12** from **4** described above constitutes formal syntheses of these Ipecac alkaloids.

In conclusion, it is true that the present results have only added one more example to more than a dozen successful procedures[4,17] for the synthesis of emetine (**1**), but they have exemplified not only the correctness of the stereochemical outcome of the synthetic operations utilized in our recent syntheses[5a,6a,7a] of the *Alangium* alkaloids (type **2**) but also their potential application to the syntheses of structurally parallel indoloquinolizidine alkaloids.

Experimental

All melting points are corrected; boiling points, uncorrected. IR spectra were measured in Nujol mulls, in liquid films, or in $CHCl_3$ solutions at 0.2 M concentration. See also ref. 9*b* for details of instrumentation and measurements. The following abbreviations are used: b=broad, d=doublet, d-d=doublet-of-doublets, m=multiplet, q=quartet, s=singlet, t=triplet.

Ethyl *trans*-3-Ethyl-6-methoxy-2,3,4,5-tetrahydro-4-pyridineacetate (**5**)——A solution of **4**[8] (426 mg, 2 mmol) and dimethyl sulfate (252 mg, 2 mmol) in dry benzene (2 ml) was heated at reflux for 3 hr. The solution was ice-cooled, 50% aq. K_2CO_3 (4 ml) was added, and the resulting mixture was extracted with ether (4×10 ml). The combined ether extracts were dried over anhyd. Na_2SO_4 and evaporated *in vacuo*. Vacuum distillation of the residue gave **5** (330 mg, 73%) as a colorless oil, bp 100° (2 mmHg); IR ν_{max}^{film} cm^{-1}: 1730 (ester CO), 1691 (C=N); NMR ($CDCl_3$) δ: 0.70—1.10 (3H, unresolved t, $CCH_2\underline{Me}$), 1.27 (3H, t, J=7 Hz, $CO_2CH_2\underline{Me}$), 3.64 (3H, s, OMe), 4.16 (2H, q, J=7 Hz, $CO_2C\underline{H}_2Me$).

Ethyl *trans*-6-Ethoxy-3-ethyl-2,3,4,5-tetrahydro-4-pyridineacetate (**6**)——A solution of triethyloxonium fluoroborate[10] (950 mg, 5 mmol) and **4**[8] (532 mg, 2.49 mmol) in CH_2Cl_2 (6 ml) was refluxed for 4 hr. The solution was cooled, 10% aq. K_2CO_3 (6 ml) was added, and the resulting mixture was extracted with CH_2Cl_2 (2×15 ml). The CH_2Cl_2 extracts were dried over anhyd. Na_2SO_4 and evaporated under vacuum to leave a pale yellow oil (600 mg, 100%), shown to be homogeneous by a single spot on a thin-layer chromatography (TLC) plate. Distillation of the oil yielded **6** (488 mg, 81%) as a colorless oil, bp 116—118° (2 mmHg); IR ν_{max}^{film} cm^{-1}: 1736 (ester CO), 1687 (C=N); NMR ($CDCl_3$) δ: 0.93 (3H, t, J=6 Hz, $CCH_2\underline{Me}$), 1.24 (3H, t, J=7 Hz, $OCH_2\underline{Me}$),[18] 1.26 (3H, t, J=7 Hz, $CO_2CH_2\underline{Me}$),[18] 4.03 (2H, q, J=7 Hz, $OC\underline{H}_2Me$),[18] 4.14 (2H, q, J=7 Hz, $CO_2C\underline{H}_2Me$).[18]

Ethyl *trans*-1-(3,4-Dimethoxyphenacyl)-5-ethyl-2-oxo-4-piperidineacetate (**7**)——i) From the O-Methyllactim **5**: A mixture of **5** (227 mg, 1 mmol) and 3,4-dimethoxyphenacyl bromide[12] (259 mg, 1 mmol) was

14) T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 591 (1958).

15) A previous sample[14] of **13**, recrystallized from EtOH, melted at 151—153°. Recrystallization of that sample from 50% aq. acetone in the present work produced colorless pillars, mp 155—156.5°, identical (by mixed melting-point test and IR spectrum) with authentic **13**.[13]

16) Although the 5-ethyl-2-oxo-4-piperidineacetic acid system tends to undergo *cis*⇆*trans* isomerization under Fischer-Speier esterification conditions [T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.* (Tokyo), **26**, 2253 (1978)], we have confirmed by means of C-13 NMR spectroscopy[8b] that the *trans*→*cis* isomerization of **13** did not occur at all under these particular esterification conditions.

17) *a*) I. Ninomiya, T. Kiguchi, and T. Tada, *Heterocycles*, **6**, 1799 (1977); *b*) T. Kametani, Y. Suzuki, H. Terasawa, M. Ihara, and K. Fukumoto, *ibid.*, **8**, 119 (1977); *c*) S. Takano, M. Sasaki, H. Kanno, K. Shishido, and K. Ogasawara, *J. Org. Chem.*, **43**, 4169 (1978); *d*) S. Takano, S. Hatakeyama, and K. Ogasawara, *Tetrahedron Lett.*, **1978**, 2519.

18) The assignment of the methyl and the methylene signals was based on comparison of these with the corresponding signals of the O-methyllactim **5**.

heated at 60° for 5 hr. After cooling, the reaction mixture was dissolved in benzene (30 ml). The benzene solution was washed successively with 10% aq. Na_2CO_3 and H_2O, dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo* to leave a slightly brown oil (405 mg). Purification of the oil by column chromatography [alumina (41 g), AcOEt–hexane (1: 1, v/v), AcOEt] produced **7** (336 mg, 86%) as a colorless thick oil, MS *m/e*: 391 (M^+); IR ν_{max}^{film} cm^{-1}: 1728 (ester CO), 1687 (CO), 1643 (lactam CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (ester CO), 1685 (CO), 1631 (lactam CO); NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.25 (3H, t, J=7 Hz, $CO_2CH_2\underline{Me}$), 3.08—3.58 (2H, m, $H_{(6)}$'s), 3.94 and 4.00 (3H each, s, two MeO's), 4.19 (2H, q, J=7 Hz, $CO_2C\underline{H}_2Me$), 4.78 and 4.90 (1H each, a pair of AB type d, J=17 Hz, $COCH_2N$), 6.96 (1H, d, J=8 Hz, $H_{(5')}$), 7.58 (1H, d, J=2 Hz, $H_{(2')}$), 7.65 (1H, d-d, J=8 and 2 Hz, $H_{(6')}$).

ii) From the O-Ethyllactim **6**: A mixture of **6** (362 mg, 1.5 mmol) and 3,4-dimethoxyphenacyl bromide[12] (466 mg, 1.8 mmol) was heated at 60° for 5 hr. The reaction mixture was then worked up in a manner similar to that described above under item (i), giving **7** (546 mg, 93%) as a colorless thick oil, identical (by TLC and IR spectrum) with a sample prepared by method (i).

Ethyl *trans*-1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-5-ethyl-2-oxo-4-piperidineacetate (8)——A solution of the foregoing lactam ketone **7** (285 mg, 0.728 mmol) in EtOH (4 ml) was stirred under ice-cooling, and $NaBH_4$ (28 mg, 0.74 mmol) was added portionwise. The resulting mixture was kept stirred at room temp. for 2.5 hr. The solvent was removed from the mixture by evaporation *in vacuo* and H_2O (5 ml) was added to the residue. The aqueous mixture was extracted with $CHCl_3$ and the $CHCl_3$ solution was washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo*, leaving **8** (284 mg, 99%) as a colorless oil, which was presumed to be a mixture of the two possible diastereoisomers. The crude oil was used directly in the next hydrogenolysis step without further purification.

Ethyl *trans*-1-(3,4-Dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetate (12)——i) Hydrogenolysis of the Lactam Alcohol **8**: A solution of **8** (276 mg, 0.7 mmol) in EtOH (30 ml) containing 70% aq. $HClO_4$ (0.1 ml) was hydrogenated over 10% Pd-C (500 mg) at 20° and 3.7 atmospheres pressure for 15 hr. The catalyst was filtered off and washed with EtOH (2×5 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 over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo* to give **12** (246 mg, 93%) as a colorless oil, shown to be homogeneous by a single spot on TLC analysis; MS *m/e*: 377 (M^+); IR ν_{max}^{film} cm^{-1}: 1730 (ester CO), 1637 (lactam CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1727 (ester CO), 1625 (lactam CO); NMR ($CDCl_3$) δ: 0.84 (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), 4.16 (2H, q, J=7 Hz, $CO_2C\underline{H}_2Me$), 6.76 (3H, s, aromatic protons).

ii) Esterification of the Lactam Acid **13**: A solution of **13** (629 mg, 1.8 mmol) in 10% (w/w) ethanolic HCl (20 ml) was kept at room temp. for 48 hr. The resulting solution was concentrated *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, and dried over anhyd. Na_2SO_4. Evaporation of the solvent left **12** (676 mg, 99%) as a colorless oil,[16] identical (by TLC and IR spectrum) with a specimen prepared by method (i).

***trans*-1-(3,4-Dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid (13)**——A solution of **12** (190 mg, 0.5 mmol), obtained by the hydrogenolysis of **8**, and 50% aq. KOH (600 mg) in EtOH (1 ml) was kept at room temp. for 24 hr. Concentration of the reaction mixture under vacuum left an oil, which was dissolved in H_2O (10 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 over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo*, giving a faintly yellow solid (158 mg, 90%), mp 147—150°. Recrystallization of the solid from 50% (v/v) aq. acetone yielded **13** as colorless pillars, mp 155—157°; IR ν_{max}^{Nujol} cm^{-1}: 1706 (CO_2H), 1596 (lactam CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (CO_2H), 1601 (lactam CO); NMR ($CDCl_3$) δ: 0.82 (3H, t, J=6.5 Hz, $CCH_2\underline{Me}$), 3.87 and 3.90 (3H each, s, two MeO's), 6.76—6.96 (3H, m, aromatic protons), 8.78 (1H, b, CO_2H). This sample was identical (by mixed melting-point test and IR spectrum) with that (mp 155—156.5°) prepared by decarboxylation of **11** according to the procedure of Battersby and Turner,[13] who synthesized **11** by the Michael addition of malonate ion to the dihydropyridone **9** followed by alkaline hydrolysis of the resulting adduct **10**. In the present study, it was found that the use of a larger amount (1.5 molar equivalents) of NaOEt for their Michael addition step gave reproducible results.

***trans*-2-Ethoxycarbonylmethyl-3-ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxybenzo[*a*]quinolizinium Iodide (14)**——A solution of the foregoing lactam ester **12** (530 mg, 1.4 mmol) and $POCl_3$ (1 g, 6.5 mmol) in dry toluene (5 ml) was refluxed for 90 min. Concentration of the mixture under vacuum left an orange oil, which was dissolved in H_2O (12 ml). KI (5 g) was added to the aqueous solution and the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with 40% aq. KI (10 ml), dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo*, leaving a reddish-orange solid (640 mg, 94%), mp 126—133°. Recrystallization of the solid from EtOH–AcOEt yielded **14** as minute yellow needles, mp 169—170°[19] (lit.[20] double mp 135—140° and 167—170°); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 246 (16050), 304 (9050), 354 (9000); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1726

19) Routine C, H, N analyses agreed with the calculated values within ±0.3% for this sample.
20) M. Barash, J. M. Osbond, and J. C. Wickens, *J. Chem. Soc.*, **1959**, 3530.

(ester CO), 1647 (C=N$^+$); NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.28 (3H, t, J=7 Hz, $CO_2CH_2\underline{Me}$), 3.98 and 4.04 (3H each, s, two MeO's), 4.17 (2H, q, J=7 Hz, $CO_2C\underline{H}_2Me$), 6.92 (1H, s, $H_{(8)}$), 7.24 (1H, s, $H_{(11)}$).

***trans*-2-Ethoxycarbonylmethyl-3-ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxybenzo[*a*]quinolizinium Perchlorate (15)**——$AgClO_4$ (250 mg, 1.21 mmol) was added to a hot solution of **14** (560 mg, 1.15 mmol) in EtOH (5 ml). The resulting precipitate of AgI was filtered off while hot and washed with hot EtOH (2×10 ml). The filtrate and the washings were combined and kept in a refrigerator. The colorless needles that resulted were filtered off and dried to give **15** (470 mg, 89%), mp 115—117°. Recrystallization from EtOH produced an analytical sample,[19] mp 116—117° (lit.[13] mp 113—114°); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 246 (16800), 304 (9350), 354 (9200).

Ethyl *trans*-3-Ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-acetate (16)——The foregoing quaternary perchlorate **15** was reduced as reported previously,[13] and the free base **16** (91% yield) was isolated as colorless needles, mp 71—72°[19] (lit.[13] mp 66—66.5°); IR ν_{max}^{Nujol} cm^{-1}: 2800, 2760 (*trans*-quinolizidine), 1720 (ester CO); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2820, 2764 (*trans*-quinolizidine), 1726 (ester CO); NMR ($CDCl_3$) δ: 0.90 (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, $CO_2C\underline{H}_2Me$), 6.61 and 6.72 (1H each, s, aromatic protons).

The Perchlorate of **16**: Colorless needles (from EtOH), mp 149—150°[19] (lit.[13] mp 145—146.5°); IR ν_{max}^{Nujol} 1720 cm^{-1} (ester CO).

The Picrate of **16**: Minute yellow prisms (from EtOH), mp 166—167° (lit.[13] mp 165—166°).

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Reduction of *o*-Acylphenols through Ethyl *o*-Acylphenylcarbonates to *o*-Alkylphenols with Sodium Borohydride[1]

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It was found that the ethoxycarbonyl derivatives of *o*-acylphenols were reduced to the corresponding *o*-alkylphenols by sodium borohydride under mild conditions; the use of 3 molar equivalents of sodium borohydride was sufficient for this reduction. Various kinds of *o*-acylphenols (**1**, **3**, **5**, **7**, **9**, **11**, **13**, **15**, **17**, **19**, **21**, **23**, **25** and **27**) were reduced to the corresponding *o*-alkylphenols (**2**, **4**, **6**, **8**, **10**, **12**, **14**, **16**, **18**, **20**, **24**, **26** and **28**, respectively) in high yield by this method. *o*-Acetylphenyl acetate (**29**) afforded *o*-ethylphenol (**8**) in better yield with sodium borohydride than ethyl *o*-acetylphenylcarbonate, but *o*-acetylphenyl *p*-toluenesulfonate (**30**) did not give **8**.

Keywords——sodium borohydride reduction; *o*-acylphenols; ethyl *o*-acylphenylcarbonates; synthesis of *o*-alkylphenols; synthesis of *o*-aralkylphenols; reduction of *o*-acetylphenyl acetate

In the preceding paper[3] we reported that ethoxycarbonyl derivatives of *o*-hydroxyphenyl carboxylic acids could be reduced to the corresponding *o*-methylphenols with sodium borohydride under mild conditions.

In this paper, we wish to report the sodium borohydride reduction of *o*-acylphenols through ethyl *o*-acylphenylcarbonates, as shown in Chart 1. As described in our previous

1) This work was presented at the 98th Annual Meeting of the Pharmaceutical Society of Japan, Okayama, April 1978.
2) Location: *Koishikawa 4-6-10, Bunkyo-ku, Tokyo 112, Japan.*
3) N. Minami and S. Kijima, *Chem. Pharm. Bull.* (Tokyo), **27**, 816 (1979).