Novel Zinc-Promoted Alkylation of Iminium Salts. New Synthesis of Benzylisoquinoline, Phthalidylisoquinoline, and Protoberberine Alkaloids and Related Compounds[1a]

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Received July 13, 1982

Zinc-promoted reductive coupling reaction of iminium salts with alkyl halides was found to be a successful key reaction for synthesis of a variety of alkaloids such as benzylisoquinoline, phthalidylisoquinoline, and protoberberine alkaloids. More specifically, laudanosine, cordrastine, hydrastine, narcotine, tetrahydropalmatine, and canadine were obtained. A new route for the synthesis of the emetine and yohimbine skeletons was exploited.

The synthesis of benzylisoquinoline and related compounds has been extensively studied[2] by using a variety of methods such as the Bischler–Napieralski reaction,[3] the Pictet–Spengler reaction,[4] and the Pomeranz–Fritsch reaction.[5] In some cases, drastic reaction conditions and inaccessibility of the starting materials lead to difficulties in the synthesis of benzylisoquinoline alkaloids by these routes.

Coupling a benzyl group to an isoquinoline skeleton at the C-1 position of the isoquinoline is one of the desirable patterns for the synthesis of benzylisoquinoline alkaloids. The reaction of 3,4-dihydroisoquinolines with benzylmagnesium bromide or benzyllithium is a typical reaction, although not always satisfactory.

We have already reported the synthesis of some benzylisoquinoline alkaloids using new methods which involve the electroorganic reduction of iminium salts as the key reaction.[1b] In the present study, we describe a new zinc-promoted coupling reaction of iminium salts with benzyl bromides. These reactions have considerably different character from the electroreductive method.

Results and Discussion

Reaction of 3,4-Dihydro-6,7-dimethoxy-2-methylisoquinolinium Iodide (1) with a Variety of Benzyl Bromides 2. In the presence of zinc, condensation of 1 with a variety of benzyl bromides 2 took place in acetonitrile at ~−15 °C as illustrated in Scheme I, and the results are summarized in Table I.

The reaction with benzyl bromide (**2a**) proceeded in an excellent yield. The substitution of methoxyl groups on the aromatic nucleus of benzyl bromides decreased the yields of **3** (**3b,c**). In the reaction of 3,4-dimethoxybenzyl bromide (**2c**), milder reaction conditions were essential to obtain (±)-laudanosine (**3c**), as indicated in the footnote of Table I. Although some organometallic reagents such as Grignard reagents or alkyl lithium reagents may sometimes give the same products as **3** in the reaction with **1**, the preparation of the organometallic reagents bearing an alkoxycarbonyl group or a halogen is not possible.[6] In

Scheme I

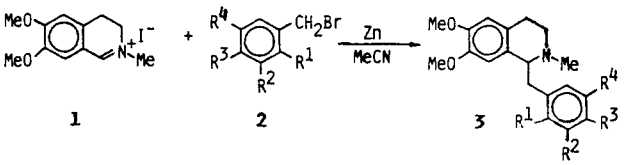

Table I. Reaction of 3,4-Dihydro-6,7-dimethoxy-2-methylisoquinolinium Iodide (1) with a Variety of Benzyl Bromides 2

benzyl bromide 2					product		
						yield,[a]	
no.	R^1	R^2	R^3	R^4	no.	%	mp, °C
2a	H	H	H	H	3a	86	oil
2b	H	H	OMe	H	3b	40	oil[63]
2c	H	OMe	OMe	H	3c	43[b,e]	113-115[c]
2d	CO_2Me	H	H	H	3d	74	oil
2e	CO_2Me	OMe	OMe	H	3e	62	oil
2f	Br	H	H	H	3f	77	66-68
2g	Br	H	OMe	OMe	3g	31	121-123[d]
2h	Br	H	CO_2Me	H	3h	61	oil

[a] Isolated yield. [b] The reaction was carried out in 20% CH_2Cl_2 in MeCN at −78 °C to room temperature. [c] Lit.[64] mp 114-115.5 °C. [d] Recrystallized from cyclohexane. [e] (±)-Laudanosine.

Table II. Reaction of 3,4-Dihydro-6,7-dimethoxy-2-methylisoquinolinium Iodide (1) with a Variety of Alkyl Halides 4

	product		
alkyl halide 4	no.	yield,[a] %	bp,[b] °C (mmHg)
i-PrI (4a)	5a	71	127 (35)
n-PrI (4b)	5b	22	148 (0.8)
CH_2=$CHCH_2Br$ (4c)	5c	60	142 (0.3)
$BrCH_2CO_2Et$ (4d)	5d	60[c] (35)	150 (0.5)
$CH_3CHBrCO_2Et$ (4e)	5e	90[d]	158 (0.5)
$BrCH_2CH$=$CHCO_2Me$ (4f)	5f	48	
$BrCH_2C(OMe)$=$CHCO_2Me$ (4g)	5g	67	
$PhCO_2CHBrPh$ (4h)	5h	39[d,e]	
$ClCH_2OMe$ (4i)	5i	27	

[a] Isolated yield. [b] Bulb to bulb distillation. [c] The reaction was carried out under reflux conditions. The yield under the usual conditions is given in parentheses. [d] A mixture of threo and erythro isomers. [e] The reaction was carried out in THF at −78 °C to room temperature.

(1) (a) The preceding paper: Shono, T.; Sasaki, M.; Nagami, K.; Hamaguchi, H. *Tetrahedron Lett.* **1982**, *23*, 97. (b) Shono, T.; Yoshida, K.; Ando, K.; Usui, Y.; Hamaguhci, H. *Ibid.* **1978**, 4819.

(2) (a) Manske, R. H. F., Ed. "The Alkaloids"; Academic Press: New York, 1950–1979; Vol. I–XVII. (b) Ito, S. "Natural Products Chemistry"; Nakanishi, K., Goto, T., Ito, S., Natori, S., Nozoe, S., Eds.; Kodansha/Academic Press: Tokyo/New York, 1974; Vol. 2, p 255. (c) Kametani, T. "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley: New York, 1977; Vol. 3, p 1. (d) Kametani, T. "The Chemistry of the Isoquinoline Alkaloids"; Hirokawa/Elsevier: Tokyo/Amsterdam, 1969.

(3) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74.

(4) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 151.

(5) Gensler, W. J. *Org. React.* **1951**, *6*, 191.

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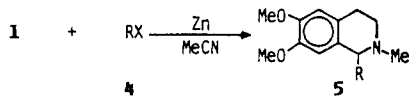
the present zinc-promoted reaction, however, the substitution of an electron-withdrawing group (CO_2Me) tended to increase the yields in contrast with the presence of electron-donating groups such as methoxyl. The presence of such groups in the products **3** supplies a further possibility for the preparation of a variety of other alkaloids.[2]

Reaction of 1 with a Variety of Alkyl Halides 4. In like fashion, reaction of **1** with a variety of alkyl halides **4** was also promoted by zinc and afforded products **5** in satisfactory yields. The results are summarized in Table II.

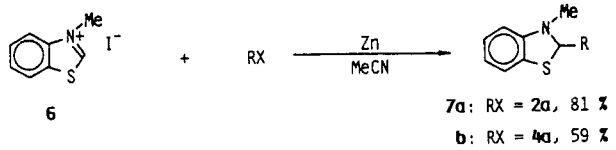


Aliphatic iodides **4a,b** also gave the expected products **5a,b**, though primary alkyl iodide **4b** seemed to have a low activity. Although the Reformatsky reaction with benzalaniline has been known to give β-lactams in low yields,[7,8] the zinc-promoted reaction of **1** with α-halo esters **4d,e** proceeded in good yields, affording the corresponding coupled products without the contamination of β-lactams. Vinylogues **4f,g** of α-halo esters gave addition products **5f,g** in which reaction took place at the γ-position exclusively, and no adducts at the α-position were obtained.[8c]

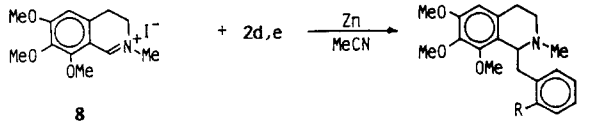
Alkyl halides containing an acetoxyl or a methoxyl group at the α-position (**4h,i**) produced the expected products **5h,i** in rather low yields.

Reaction of Other Iminium Salts. The reactions of 3-methylbenzothiazolium iodide (**6**), 3,4-dihydro-6,7,8-trimethoxy-2-methylisoquinolinium iodide (**8**), and 3,4-dihydro-2-methyl-β-carbolinium iodide (**10**) proceeded in

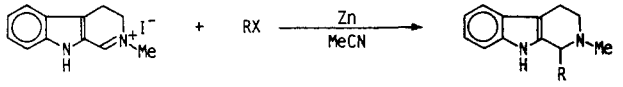
Scheme II



Scheme III



Scheme IV



(6) (a) Fieser, M.; Danheiser, R. L.; Roush, W. "Reagents for Organic Synthesis"; Wiley: New York, 1981; Vol. 9, p 5. (b) Fieser, M.; Fieser, L. F. *Ibid.* Wiley: New York, 1967; Vol. 1, p 415; 1969, Vol. 2, p 205, 1975, Vol. 5, p 321; 1977, Vol. 6, p 269; 1979, Vol. 7, p 163; 1980, Vol. 8, p 235; 1981, Vol. 9, p 229.

(7) (a) Sheverdina, N. I.; Kocheshkov, K. A. "Methods of Elemento-Organic Chemistry"; North-Holland Publishers: Amsterdam, 1967; Vol. 3. (b) Furukawa, J.; Kawabata, N. *Adv. Organomet. Chem.* **1974**, *12*, 83.

(8) (a) Gaudemar, M. *Organomet. Chem. Rev., Sect. A* **1972**, *8*, 183. (b) Shriner, R. L. *Org. React.* **1942**, *1*, 1. (c) Rathke, M. W. *Ibid.* **1974**, *22*, 423.

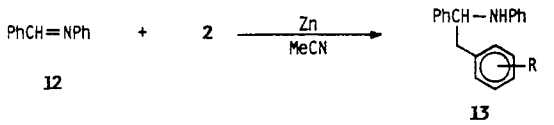
Table III. Reaction of Benzalaniline (12)

2	yield,[a] %, of 13	2	yield,[a] %, of 13
2a	96 (13a)	2d	93 (13d)
2b	80 (13b)	2f	81 (13e)
2c	18 (13c)[b]	2h	65 (13f)

[a] Isolated yield. [b] The reaction was carried out in 20% CH_2Cl_2 in MeCN at −78 °C to room temperature.

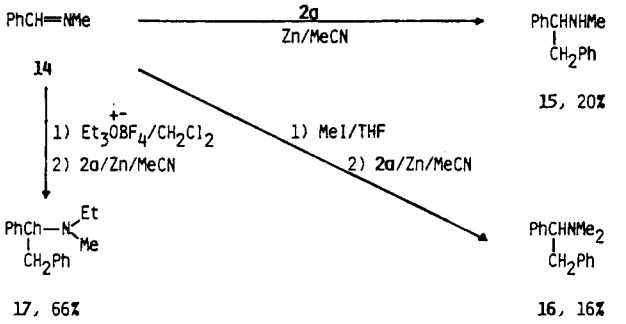
rather satisfactory yields as indicated in Schemes II–IV, respectively. In the reaction with **10**, the indolic NH group was completely inert.

Reaction of Benzalaniline (12) and Some Acyclic Imines. Although **12** did not give rise to iminium salts with alkyl halides, this zinc-promoted reaction was successful for **12** itself. The results are shown in Table III.

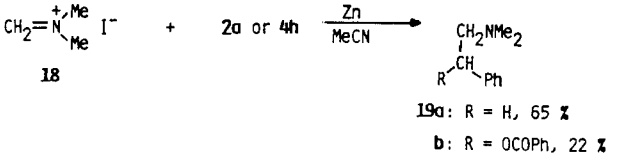


The reaction of other acyclic imines was not satisfactory. The benzylation of *N*-benzylidenemethylamine (**14**),[9] for instance, proceeded only in 20% yield, and the same reaction in the presence of methyl iodide generated *N,N*-dimethyl-1,2-diphenylethylamine (**16**) in only 16% yield (Scheme V). The less reactive imine **14**, however, was sufficiently activated through the formation of a salt with

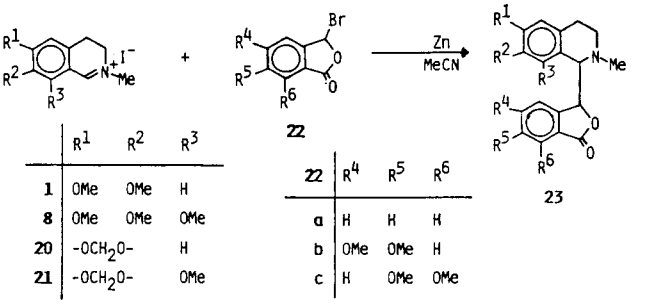
Scheme V



Scheme VI



Scheme VII



(9) The reaction of *N*-benzylidenemethylamine with benzylmagnesium chloride was reported to afford *N*-methyl-1,2-diphenylethylamine in an excellent yield: Moffett, R. B. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 605.

Table IV. Synthesis of Phthalide Isoquinoline Alkaloids 23

isoquinolinium salt	bromophthalide 22	product: yield, %, of *threo*-23	mp, °C	yield, %, of *erythro*-23	mp, °C	23
1	22a	28	163-164[a]	50	209-210[b,c]	23a
1	22b	25	oil	47	169-171[a,d]	23b[16]
1	22c	25[m]	156-157[a,e]	38[a]	205 dec[b,f]	23c[17,18]
20	22a	39	179-182[b,g]	58	210-212[b,g]	23d
20	22b	35	189-192[h]	60	164-166,[h] 184-187[b,g]	23e
20	22c	30[o]	176-179[b,g]	40[p]	138-140,[h,i] 200-202[b,g,j]	23f[13,14]
8	22a	80 (1/2)[k,l]	oil		140-141[a]	23g
8	22b	74 (5/7)[k,l]	oil		208-210[a]	23h
8	22c	76 (2/3)[k]				23i
21	22c	78[q] (2/3)[k,l]				23j[14,15]

[a] Recrystallized from methanol. [b] Picrate. [c] Recrystallized from methanol-acetone. [d] Lit.[16] mp 166-167 °C. [e] Lit.[17] mp 155-156 °C. [f] Lit.[17] mp 202 °C dec. [g] Recrystallized from THF. [h] Recrystallized from ethanol. [i] Lit.[13a] mp 132 °C. [j] Lit.[13a] mp 184 °C. [k] A mixture of two diastereoisomeric isomers, not separated. The ratio was determined by NMR. [l] Two isomers were separated by recrystallization. [m] Cordrastine I. [n] Cordrastine II. [o] α-Hydrastine. [p] β-Hydrastine. [q] β-Narcotine/α-narcotine mixture.

triethyloxonium tetrafluoroborate.[10] The salt gave **17** in 66% yield (Scheme V).

The reaction of dimethylmethyleneammonium iodide (**18**) with enolate anions or organometallic[11] reagents is known to result in condensation products. As shown in Scheme VI, reaction of **18** with **2a** was successfully promoted by zinc to afford **19a** in a satisfactory yield. Similarly, **4h** led to **19b** but in low yield.

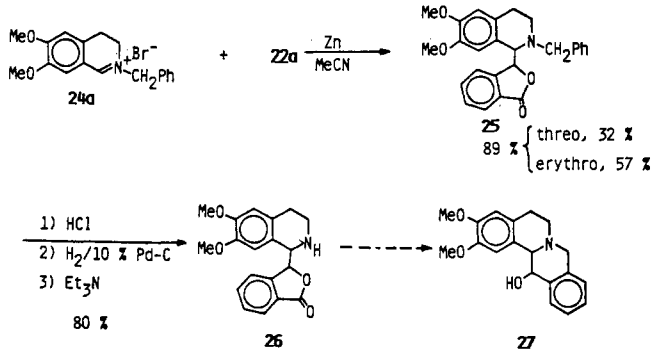
Synthesis of Phthalidylisoquinoline Alkaloids 23. As shown above, the reaction of **2d** with **1** furnished the expected product, and the presence of an alkoxycarbonyl group in the nucleus of the benzyl halide even improved the yield. Thus, the bromophthalides **22** appeared promising for the synthesis of phthalidylisoquinoline alkaloids.[12-17] The reactioin is illustrated in Scheme VII, and the results are summarized in Table IV.

As expected, the results obtained with bromophthalides **22b,c** showed that the presence of methoxyl substituents in the nuclei of bromophthalides **22** did not decrease the yield. A variety of phthalidylisoquinoline alkaloids **23**, including cordrastine (**23c**),[12] hydrastine (**23f**),[13,14] and narcotine (**23j**), were obtained in excellent yields.

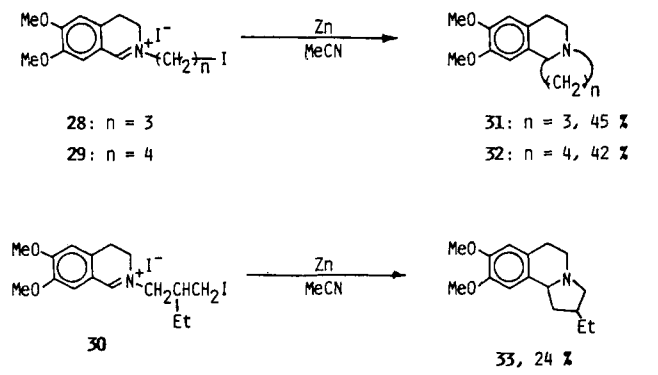
The products **23** were mixtures of two stereoisomers, which were separated by column chromatography or recrystallization. Their stereoconfigurations were determined by chromatographic and spectroscopic comparison with authentic samples.[12-18] It is noteworthy that this zinc-promoted reaction formed mainly the erythro isomers which are generally the major isomers in naturally occurring phthalide alkaloids.[13-16]

All the phthalidylisoquinoline alkaloids **23** obtained above have a methyl group on the nitrogen atom, whereas those (e.g., **26**) having a secondary amino group are useful precursors for the synthesis of 13-hydroprotoberberine **27**.[16,19] The reaction of a bromophthalide with dihydro-

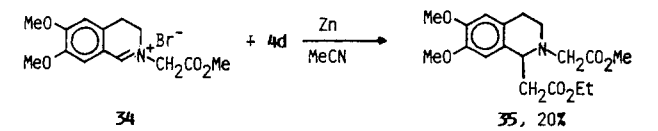
Scheme VIII



Scheme IX



Scheme X



(10) Fieser, M.; Fieser, L. F. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, p 1210; 1969, Vol. 2, p 430; 1972, Vol. 3, p 303; 1974, Vol. 4, p 527; 1977, Vol. 6, p 691; 1979, Vol. 7, p 386; 1980, Vol. 8, p 500; 1981, Vol. 9, p 482.

(11) Fieser, M.; Fieser, L. F. "Reagents for Organic Synthesis"; Wiley: New York, 1972; Vol. 3, p 114; 1974, Vol. 4, p 186; 1979, Vol. 7, p 130; 1980, Vol. 8, p 194.

(12) Kerekes, P.; Bognar, R. *J. Prakt. Chem.* **1971**, *313*, 923; *Magy. Kem. Foly.* **1971**, *77*, 655.

(13) (a) Marshall, M. A.; Pyman, F. L.; Robinson, R. *J. Chem. Soc.* **1934**, 1315. (b) Ohta, M.; Tani, H.; Morozumi, S. *Tetrahedron Lett.* **1963**, 859.

(14) (a) Ohta, M.; Tani, H.; Morozumi, S. *Chem. Pharm. Bull.* **1964**, *12*, 1072-1080. (b) Snatzke, G.; Wollenber, G.; Hrbek, Jr., J.; Santavý, F.; Bláha, K.; Klyne, W.; Swan, R. J. *Tetrahedron* **1969**, *25*, 5059. (c) Kametani, T.; Inoue, W.; Honda, T.; Sugahara, T.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 374.

(15) Battersby, A. R.; Spencer, H. *J. Chem. Soc.* **1965**, 1087.

(16) Shamma, M.; Georgiev, V. S. *Tetrahedron* **1976**, *32*, 211.

(17) Smula, V.; Cundasawmy, N. E.; Holland, H. L.; MacLean, D. B. *Can. J. Chem.* **1973**, *51*, 3287.

(18) Osmund de Silva, S.; Ahmad, I.; Sniekus, V. *Tetrahedron Lett.* **1978**, 5107.

(19) (a) Govindachari, T. R.; Rajadurai, S. *J. Chem. Soc.* **1957**, 557. (b) Govindachari, T. R.; Rajadurai, S.; Subramanian, M.; Viswanathan, N. *Ibid.* **1957**, 2943. (c) Kametani, T.; Matsumoto, H.; Satoh, Y.; Nemoto, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 376.

Scheme XI

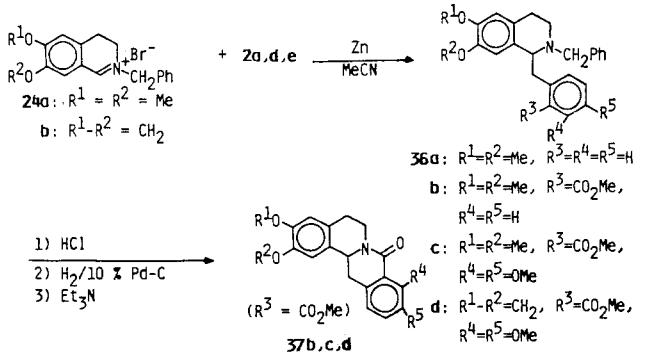


Table V. Synthesis of Protoberberine Alkaloids 37

iminium salt	benzyl bromide	% yield 36[a]	% yield 37[b]	mp, °C, of 17
24a	2a	86 (36a)		
24a	2d	93 (36b)	89 (37b)[68]	143-144[c,d]
24a	2e	93 (36c)	88 (37c)	170-171[e]
24b	2e	99 (36d)	93 (37d)	222-223[c]

[a] Isolated yield based on 24. [b] Isolated yield based on 36. [c] Recrystallized from methanol. [d] Lit.[68b] mp 141-142 °C. [e] Recrystallized from ethanol.

isoquinolinium methanesulfonate or dihydroisoquinoline itself was not successful, however, and gave only a trace amount of 1,2-diphthalidyltetrahydroisoquinoline.

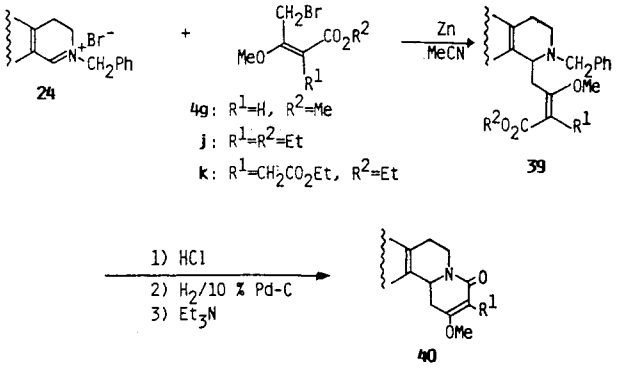
Since a benzyl group on an amino nitrogen atom is easily removable by hydrogenolysis,[20] 2-benzyl-3,4-dihydro-6,7-dimethoxyisoquinolinium bromide (**24a**) was used as the starting material. The expected product **26** was obtained in high yield through the reaction of **24a** with the bromophthalide **22a** followed by hydrogenolysis of the hydrogen chloride salt of **25** (Scheme VIII). The transformation of **26** to **27** has already been reported.[16,19]

Intramolecular Coupling Reaction and Synthesis of Protoberberine Alkaloids.[1] The intramolecular reaction of iminium salts **28–30** prepared from 3,4-dihydro-6,7-dimethoxyisoquinoline and α,ω-diiodides[21,22] gave cyclized products **31–33**, respectively, in moderate yields (Scheme IX).

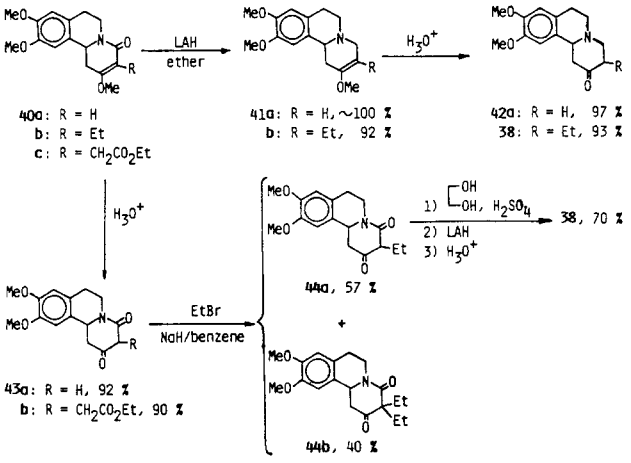
Although condensation of **35** may be promising for the synthesis of protoberberine, the reaction of the iminium salt **34** with ethyl bromoacetate (**4d**) supplied **35** only in a 20% yield (Scheme X).

As described in the synthesis of **26**, the reductive elimination of a benzyl group on a nitrogen atom is facile,[20] and the resulting secondary amino group easily forms a lactam when an alkoxycarbonyl group is suitably located. Thus, reaction of **24a,b** with benzyl bromides **2d,e** having a methoxycarbonyl group at the ortho position, followed by hydrogenolysis and neutralization with triethylamine, gave the expected 8-oxoprotoberberines **37b–d** in satisfactory overall yields (Table V, Scheme XI). In a similar way, **36a** provided the debenzylated secondary amine **37a** in a 90% yield. The transformation of **37b–d** to protoberberines such as tetrahydropalmatine[23,24] and canadine[24,25] has already been reported.

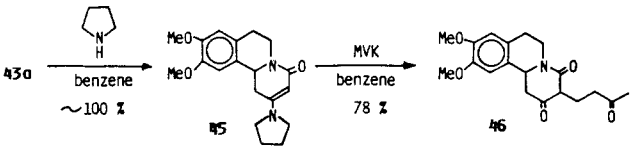
Scheme XII



Scheme XIII



Scheme XIV



Key Intermediates in the Synthesis of Emetine and Related Alkaloids.[1] In a number of studies aimed at the synthesis of emetine[26,27] and related compounds the ketone **38** is one of the most important intermediates.[28] The

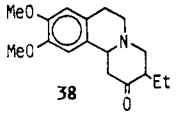


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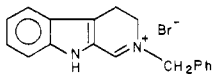
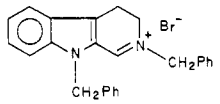
Table VI. Zinc-Promoted Alkylation and Debenzylative Cyclization

iminium salt	bromocrotonate	% yield 39[a]	% yield 40[b]	mp, °C, of 40
24a	4g	98 (39a)	95 (40a)	168.5-169.5[c]
24a	4j	91 (39b)	82 (40b)	134-136[c]
24a	4k	85 (39c)	83 (40c)	oil
 24c	4g	85 (39d)	90 (40d)	246-248[d]
 24d	4g	80 (39e)	78 (40e)	231-233[e]

[a] Isolated yield based on 24. [b] Isolated yield based on 39. [c] Recrystallized from cyclohexane-benzene. [d] Recrystallized from methanol. [e] Recrystallized from ethyl acetate.

synthesis of 38 by this new zinc-promoted condensation reaction appeared possible when reaction of 24 with bromocrotonate 4g proceeds satisfactorily, and the reductive elimination of the benzyl group was achieved without the hydrogenation of the enolic double bond (Scheme XII).

As shown in Table VI, adducts 39 were obtained in excellent yields, and the hydrogenolysis[20] of the hydrogen chloride salts of 39 followed by neutralization with triethylamine gave the enol ethers 40 of ketone 38 in high yields.

The amido groups of 40a,b were easily reduced with lithium aluminum hydride as shown in Scheme XIII, and acid hydrolysis of the enol ether 41b afforded the precursor of emetine 38[28] in excellent yield. This precursor 38 was also synthesized in a moderate yield by ethylation of the active methylene of the β-keto lactam 43a obtained through acid hydrolysis of 40a and subsequent selective reduction of the amido group (Scheme XIII).

The structure of 43a as a β-keto lactam suggested the possibility of formation of another ring on the lactam ring by the Robinson annelation.[29] Reaction of 43a with methyl vinyl ketone, however, was not successful, but the pyrrolidine enamine 45[30] supplied the uncyclized compound 46 (Scheme XIV).

The reaction of 4g with a β-carbolinium salt 24d proceeded successfully (Table VI), and the hydrolysis of the product 40e gave a new β-keto lactam 47 containing an indole moiety in high yield. If the Robinson annelation is achievable with 47, a promising key intermediate for the synthesis of yohimbine[31] and related compounds can be obtained. The annelation reaction of methyl 3-oxo-4-pentenoate with the pyrrolidine enamine of 47 gave the expected product 48 in satisfactory yield (Scheme XV). When the indolic NH group was not protected by a benzyl group, the above-described reaction was unsuccessful.

Scheme XV

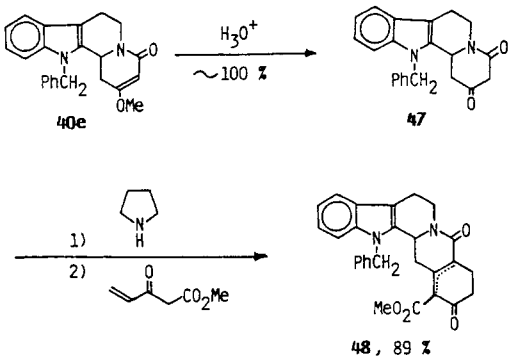


Table VII

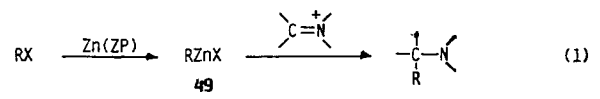
1 + 2a-c ⟶ 3a-c

2	yield, % ZP[a]	yield, % ER[b]
2a	86	65
2b	40	73
2c	43	85

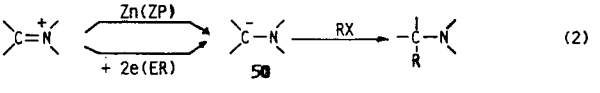
[a] Zinc-promoted reaction. [b] Electroreductive reaction.

Discussion

This zinc-promoted coupling reaction of iminium salts with alkyl halides may be explained by two different mechanisms. The first one (eq 1) is similar to the Zaitzev



(1)



(2)

reaction which involves the formation of some organozinc compound (49) from an alkyl halide and zinc. The other

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(eq 2) is the electron-transfer mechanism, which is similar to the electroreductive reaction in which two electrons are transfered to the iminium salt to form the anionic intermediate **50**.

There is no clear evidence which explains the reaction mechanism. However, the differences, exemplified below, between this zinc-promoted (ZP) reaction and the electroreductive (ER) method[1b,34-37] may suggest that this zinc-promoted reaction does not involve an electron-transfer process. (1) In the ER reaction, the presence of methoxyl groups in the nuclei of benzyl bromides increases the yields,[1b] whereas the yields decrease in the ZP reaction. The methoxyl groups increase the reactivity of benzyl bromides to carbanions (**50**) in ER reactions, while the effect of methoxyl groups is the opposite in the formation of organozinc compounds (**49**, Table VII). (2) The coupling reaction with alkyl halides such as **4a,b,g** is unsuccessful in ER[34] but satisfactory in ZP reactions. In ER reactions **4a,b,g** are reduced faster than iminium salts. If the ZP reaction involves an electron-transfer process, the reaction of **4a,b,g** must be unsuccessful also in ZP reactions (Table II). (3) Benzalaniline is inactive in ER reactions,[35] whereas satisfactory results are obtained in ZP reactions (Table III). Benzalaniline is not reducible by the electron-transfer mechanism as in ER reactions.

Experimental Section

All the products gave satisfactory analyses; infrared and ^{1}H NMR spectra were consistent with structures. Complete analytical and spectral data, which were submitted for review, are given as supplemental material (see paragraph at end of paper).

Materials. The iminium salts **1**, **6**, **8**, **10**, **20**, **21**, **24a–d**, **28–30**, and **34** were prepared from the corresponding imines and alkyl halides as described below. Into a solution of an imine (10 mmol) in 20 mL of THF was added an alkyl halide (11 mmol) at room temperature, and the solution was stirred overnight. The precipitated iminium salt was collected by filtration, washed with THF, ether, and hexane successively, and dried over silica gel under reduced pressure. The yields were usually over 90%.

The following compounds were prepared according to the reported procedures: 3,4-dihydro-6,7-dimethoxyisoquinoline,[38] 3,4-dihydro-6,7,8-trimethoxyisoquinoline,[39] 3,4-dihydro-β-carboline,[32e,32i,40] benzalaniline (**12**),[41] *N*-benzylidenemethylamine (**14**),[9] dimethylmethyleneammonium iodide (**18**),[42] 3,4-dihydro-6,7-(methylenedioxy)isoquinoline,[43] 3,4-dihydro-8-methoxy-6,7-(methylenedioxy)isoquinoline,[44] 9-benzyl-3,4-dihydro-β-carboline,[45] 1,3-diiodopropane,[46] 1,4-diiodobutane,[21,22] 2-ethyl-1,3-diiodopropane,[21,47] 4-methoxybenzyl bromide (**2b**),[48] 3,4-dimethoxybenzyl bromide (**2c**),[48] methyl α-bromo-*o*-toluate (**2d**),[49] methyl α-bromo-5,6-dimethoxy-*o*-toluate (**2e**),[50] 2,α-dibromotoluene (**2f**),[51] 2,α-dibromo-4,5-dimethoxytoluene (**2g**),[52] methyl 3,α-dibromo-*p*-toluate (**2h**),[53] methyl 4-bromo-3-methoxycrotonate (**4g**),[54] α-bromobenzyl benzoate (**4h**),[51] ethyl 4-bromo-2-ethyl-3-methoxycrotonate (**4j**),[54,55] ethyl 4-bromo-2-[(ethoxycarbonyl)-methyl]-3-methoxycrotonate (**4k**),[54,56] 3-bromophthalide (**22a**),[51c] 3-bromo-5,6-dimethoxyphthalide (**22b**),[57] 3-bromo-6,7-dimethoxyphthalide (**22c**),[58] triethyloxonium tetrafluoroborate,[59] methyl 3-oxo-4-pentenoate.[60]

Commercial 99.9% zinc powder (Institute of High Purity Chemicals, Saitama, Japan) was used without any further activation.

Zinc-Promoted Alkylation of Iminium Salts. A typical procedure is as follows.[61] In a solution of 0.667 g (2.002 mmol) of **1** in 30 mL[62] of dry acetonitrile was dissolved 1.038 g (6.068

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(61) In a large-scale preparation (more than 10-mmol scale), the whole amount of alkyl halides and zinc powder should not be added once, and the reaction time should be prolonged. For example, at the beginning, one-third of the bromide and one-fifth of the zinc powder were added at −20 °C, and the mixture was stirred at room temperature overnight. Next, one-third of the bromide and one-fifth of the zinc powder were added at −20 °C again, and the mixture was stirred at room temperature overnight. Finally, the remaining bromide and zinc powder were added at −20 °C, and the mixture was stirred at room temperature for an additional 3 days or longer. In this manner, the reaction proceeded in almost the same yields.

(62) Iminium salts should be completely dissolved before the addition of alkyl halides.

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mmol) of **2a**. Into the solution, under a nitrogen atmosphere and cooled with an ice–salt bath, was added 0.7 g (10.8 mmol) of 99.9% zinc powder. After the temperature was gradually raised to room temperature with stirring in 5 h, the stirring was continued at room temperature for 2 days. Then, the reaction mixture was poured into 50 mL of saturated aqueous sodium bicarbonate, filtered, and extracted with four 30-mL portions of methylene chloride. The combined organic solution was dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue was subjected to column chromatography (silica gel, hexane–ethyl acetate) to afford 0.513 g (1.725 mmol, 86%) of **3a**. The products **3b,d–h**, **5a–c,e–g,i**, **7a,b**, **9a,b**, **11a–d**, **13a,b,d–f**, **15**, **19a**, **23i**, **35**, **36a–d**, and **39a–e** were obtained by similar procedures, and isolated by column chromatography (silica gel or alumina, hexane–ethyl acetate) or distillation. Stereoisomers of **23a–f** and **25** were separated by column chromatography (silica gel, hexane–ethyl acetate). Separation of stereoisomers of **23g,h,j** was carried out by recrystallization from ethanol.

In the reactions of **1** with **2c**, **1** with **4h**, **12** with **2c**, and **18** with **4h**, the reaction mixtures were cooled at −78 °C in the beginning. The reaction of **1** with **4d** was carried out at reflux temperature.

2-Benzyl-2,3-dihydro-3-methylbenzothiazole (7a), bp 165 °C (0.7 mmHg; bulb to bulb).

2,3-Dihydro-2-isopropyl-3-methylbenzothiazole (7b), bp 95 °C (0.5 mmHg; bulb to bulb).

1-Benzyl-1,2,3,4-tetrahydro-6,7,8-trimethoxy-2-methylisoquinoline (9a), oil.

1,2,3,4-Tetrahydro-6,7,8-trimethoxy-1-[2-(methoxycarbonyl)benzyl]-2-methylisoquinoline (9b), oil.

1,2,3,4-Tetrahydro-1-isopropyl-2-methylpyrido[3,4-*b*]indole (11a), bp 153 °C (0.3 mmHg; bulb to bulb).

1-Benzyl-1,2,3,4-tetrahydro-2-methylpyrido[3,4-*b*]indole (11b), oil; picrate, mp 168–171 °C (from THF–cyclohexane).

1,2,3,4-Tetrahydro-1-[2-(methoxycarbonyl)benzyl]-2-methylpyrido[3,4-*b*]indole (11c), oil.

1-(2-Bromobenzyl)-1,2,3,4-tetrahydro-2-methylpyrido-[3,4-*b*]indole (11d), oil; picrate, mp 165–168 °C.

***N*-Methyl-1,2-diphenylethylamine (15)**,[9] oil.

***N*,*N*-Dimethyl-2-phenylethylamine (19a)**, bp 88 °C (11 mmHg; bulb to bulb) [lit.[65] bp 97–98 °C (22 mmHg)].

2-(Benzoyloxy)-*N*,*N*-dimethyl-2-phenylethylamine (19b), oil.

***threo*-2-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3-phthalidyl)isoquinoline (*threo*-25)**, oil.

***erythro*-2-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3-phthalidyl)isoquinoline (*erythro*-25)**: mp 134.5–136.5 °C (from methanol); picrate, mp 202.5–204.5 °C (from THF).

1-[(Ethoxycarbonyl)methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-[(methoxycarbonyl)methyl]isoquinoline (35): oil, picrate, mp 142–145 °C (from ethanol).

Reaction of 14 in the Presence of Methyl Iodide. A solution of 1.2 g (10.0 mmol) of **14** and 1.5 g (10.5 mmol) of methyl iodide in 20 mL of tetrahydrofuran was stirred at room temperature for 10 days, and it was evaporated to dryness. The reaction of the residue with 3.6 g (21.0 mmol) of **2a** and 3.0 g (46.0 mmol) of 99.9% zinc powder by the procedures described above gave 0.361 g (1.602 mmol, 16%) of ***N*,*N*-dimethyl-1,2-diphenylethylamine (16)** as an oil.

Reaction of 14 in the Presence of Triethyloxonium Tetrafluoroborate. Under a nitrogen atmosphere, 11 mL (11 mmol) of a solution of triethyloxonium tetrafluoroborate[59] in methylene chloride was added slowly into 1.194 g (10.020 mmol) of **14** at room temperature. After the mixture was stirred at room temperature overnight, the solvent was evaporated at room temperature under reduced pressure. The reaction of the residue with 3.6 mL (30.2 mmol) of **2a** and 3.3 g (50.4 mmol) of 99.9% zinc powder in 30 mL of dry acetonitrile afforded 1.586 g (6.626 mmol, 66%) of ***N*-methyl-1,2-diphenylethylamine (17)**, bp 110 °C (0.6 mmHg; bulb to bulb).

Intramolecular Coupling Reaction of Iminium Salts 28–30. By means of similar procedures, the reaction of 0.727 g (1.492 mmol) of **28** with 0.5 g (7.6 mmol) of 99.9% zinc powder in 40 mL of dry acetonitrile gave 0.155 g (0.664 mmol, 45%) of **31**. The products **32** and **33** were obtained in a similar manner.

1,2,3,5,6,10b-Hexahydro-8,9-dimethoxybenzo[*g*]indolizine (31): bp 147 °C (0.3 mmHg; bulb to bulb); mp 79–84 °C.

1,2,3,4,6,7-Hexahydro-9,10-dimethoxy-11b*H*-benzo[*a*]quinolizine (32): bp 162 °C (0.4 mmHg; bulb to bulb).

2-Ethyl-1,2,3,5,6,10b-hexahydro-8,9-dimethoxybenzo[*g*]indolizine (33): a mixture of cis and trans isomers; bp 153 °C (0.3 mmHg; bulb to bulb).

Palladium-Catalyzed Debenzylation[20] of 25, 36a–d, and 39a–e. A typical procedure is as follows. Dry hydrogen chloride was passed over a solution of 0.864 g (2.002 mmol) of **36b** in 40 mL of dry ether until precipitation of the salt ceased. The precipitate was collected by filtration, washed with 10 mL of dry ether, dried under vacuum, and dissolved into 20 mL of dry methanol. The solution was placed in a 50-mL autoclave together with 0.3 g of 10% palladium on carbon.[66] The hydrogenolysis was carried out at room temperature at a pressure of 20 kg/cm^2. After removal of the catalyst by filtration, the filtrate[67] was treated with 5 mL of triethylamine under heating for 0.5 h and concentrated to dryness. The residue was subjected to column chromatography (silica gel, ethyl acetate) to give 0.552 g (1.784 mmol, 89%) of **37b**. The products **26**, **37a,c,d**, and **40a–e** were obtained in a similar manner.

***threo*-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(3-phthalidyl)-isoquinoline (*threo*-26)**,[36] mp 145 °C dec (from methanol).

***erythro*-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(3-phthalidyl)isoquinoline (*erythro*-26)**:[36] oil, picrate, mp 131–132 °C dec (from THF).

LiAlH$_4$ Reduction[69] of 40a,b. Since the solubility of compounds **40a,b** in ether is not sufficient, the reduction was carried out by using a Soxhlet extractor in which **40a,b** were placed. When the ethereal solution of LiAlH$_4$ was refluxed under a nitrogen atmosphere, **40a,b** were gradually extracted into the ethereal solution of LiAlH$_4$ (2.6 equiv). After the usual workup, **41a,b** were obtained in almost quantitative yields.

5,6,11,11a-Tetrahydro-2,3,10-trimethoxy-8*H*-benzo[*a*]quinolizine (41a), oil.

9-Ethyl-5,6,11,11a-tetrahydro-2,3,10-trimethoxy-8*H*-benzo[*a*]quinolizine (41b), oil.

Acid-Catalyzed Hydrolysis of 40a,c,e and 41a,b. Under a nitrogen atmosphere, a solution of 0.551 g (2.001 mmol) of **41a** in 20 mL of THF and 20 mL of THF and 20 mL of 2 N hydrochloric acid was refluxed until the reactant was completely consumed (about 2 h was required). After the usual workup, 0.508 g (1.944 mmol, 97%) of **42**[70] was obtained. The products **38**, **43a,b** and **47** were obtained in a similar manner.

5,6,9,10,11,11a-Hexahydro-2,3-dimethoxy-10-oxo-8*H*-benzo[*a*]quinolizine (42a), mp 154–155 °C (from cyclohexane–ethanol) (lit.[70] mp 154–155 °C).

9-Ethyl-5,6,9,10,11,11*a*-hexahydro-2,3-dimethoxy-10-oxo-8*H*-benzo[*a*]quinolizine (38),[28,70] mp 108–110 °C (from cyclohexane) (lit.[70] mp 110–112 °C).

5,6,9,10,11,11a-Hexahydro-2,3-dimethoxy-8,10-dioxo-8*H*-benzo[*a*]quinolizine (43a): mp 158–160 °C (from ethyl acetate) (lit.[71] mp 166–168 °C).

9-[(Ethoxycarbonyl)methyl]-5,6,9,10,11,11a-hexahydro-2,3-dimethoxy-8,10-dioxo-8*H*-benzo[*a*]quinolizine (43b), oil.

12-Benzyl-1,3,4,6,7,12b-hexahydro-2,4-dioxo-2*H*-indolo-[2,3-*a*]quinolizine (47),[72] oil.

Alkylation[55] of 43a. Under an atmosphere of nitrogen, 90 mg of 60% sodium hydride in mineral oil was added into 0.425 g (1.543 mmol) of **43a** dissolved in 20 mL of dry benzene. after the mixture

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(67) Evaporation of the solvent afforded almost quantitatively 1,2,3,4-tetrahydro-6,7-dimethoxy-1-[2-(methoxycarbonyl)benzyl]isoquinoline hydrochloride as an oil.

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was refluxed for 1 h, 0.2 mL (2.6 mmol) of ethyl bromide was added at room temperature, and the mixture was gently refluxed for 5 h. After the usual workup, the products were isolated by column chromatography (silica gel, hexane–ethyl acetate) to give 0.204 g (0.615 mmol, 40%) of **44b** as the first fraction and 0.268 g (0.883 mmol, 57%) of **44a** as the second fraction.

9-Ethyl-5,6,9,10,11,11a-hexahydro-2,3-dimethoxy-8,10-dioxo-8*H*-benzo[*a*]quinolizine (44a),[73] oil.

9,9-Diethyl-5,6,9,10,11,11a-hexahydro-2,3-dimethoxy-8,10-dioxo-8*H*-benzo[*a*]quinolizine (44b), mp 135–140 °C.

Transformation of 44a to 38. Under an atmosphere of nitrogen, 0.313 g of the ethylene ketal[74] of **44a** was reduced with 50 mg (1.3 mmol) of $LiAlH_4$ in 30 mL of dry THF to yield 0.215 g of crude **9-ethyl-5,6,9,10,11,11a-hexahydro-2,3-dimethoxy-8*H*-benzo[*a*]quinolizine-10-spiro-2′-1′,3′-dioxolane,** oil.

The crude product was dissolved in 5 mL of THF and 10 mL of 10% aqueous sulfuric acid and refluxed under a nitrogen atmosphere for 8 h. After the usual workup, 0.163 g (0.563 mmol, 70% based on **44a**) of **38** was isolated by column chromatography (silica gel, ethyl acetate).

Michael Addition and Robinson Annelation[32,33,45,72,75] of 43a and 47. Under an atmosphere of nitrogen, a solution of 0.210 g (0.609 mmol) of the keto amide **47** and 0.35 mL (4.19 mmol) of pyrrolidine in 60 mL of dry benzene was refluxed for 1 h with continuous removal of water by aluminum oxide placed in a small Soxhlet extractor and concentrated to dryness to yield 0.298 g of crude **12-benzyl-1,6,7,12b-tetrahydro-4-oxo-2-(1-pyrrolidinyl)-4*H*-indolo[2,3-*a*]quinolizine** as an oil.

The crude amido-enamine and 0.1 g (0.78 mmol) of freshly prepared methyl 3-oxo-4-pentenoate were dissolved in 20 mL of dry benzene and refluxed under a nitrogen atmosphere for 4 h. Into the reaction mixture was added a solution of 10 g of sodium acetate in 20 mL of acetic acid and 20 mL of water, and the mixture was refluxed for 3 h under an atmosphere of nitrogen. After the usual workup, the crude product was subjected to column chromatography (silica gel, hexane–ethyl acetate) to afford 0.246 mmol (89%) of **$\Delta^{15,16}$- or $\Delta^{15,20}$-1-benzyl-16-(methoxycarbonyl)-17,21-dioxoyohimbane (48)** as an oil.

In a similar manner, **45** and **46** were obtained from **43a**.

5,6,11,11a-Tetrahydro-2,3-dimethoxy-8-oxo-10-(1-pyrrolidinyl)-8*H*-benzo[*a*]quinolizine (45),[76] mp 211–213 °C (from benzene).

5,6,9,10,11,11a-Hexahydro-2,3-dimethoxy-8,10-dioxo-9-(3-oxobutyl)-8*H*-benzo[*a*]quinolizine (46), oil.

(73) This compound was exactly identical with the compound obtained by acid hydrolysis of **40b**.
(74) With the usual method, 0.244 g (0.804 mmol) of **44a** gave 0.313 g of the crude ethylene ketal of **44a**.
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Acknowledgment. We thank the Ministry of Education, Science, and Culture, Japan, for a Grant-in-Aid for Developmental Scientific Research(2) (No. 56850203), and they also thank the Asahi Glass Foundation for Industrial Technology.

Registry No. 1, 30045-07-9; **2a**, 100-39-0; **2b**, 2746-25-0; **2c**, 21852-32-4; **2d**, 2417-73-4; **2e**, 76177-36-1; **2f**, 3433-80-5; **2g**, 53207-00-4; **2h**, 78946-25-5; **3a**, 47210-20-8; **3b**, 1934-93-6; **3c**, 1699-51-0; **3d**, 85222-32-8; **3e**, 85222-33-9; **3f**, 85222-34-0; **3g**, 54712-52-6; **3h**, 85222-35-1; **4a**, 75-30-9; **4b**, 107-08-4; **4c**, 106-95-6; **4d**, 105-36-2; **4e**, 535-11-5; **4f**, 1117-71-1; **4g**, 26536-93-6; **4h**, 13381-65-2; **4i**, 107-30-2; **4j**, 81701-41-9; **4k**, 81701-42-0; **5a**, 19253-43-1; **5b**, 18368-38-2; **5c**, 22191-92-0; **5d**, 70593-94-1; *erythro*-**5e**, 85222-36-2; *threo*-**5e**, 85222-38-4; **5f**, 85222-38-4; **5g**, 85222-39-5; *erythro*-**5h**, 85222-40-8; *threo*-**5h**, 85222-41-9; **5i**, 85222-42-0; **6**, 2786-31-4; **7a**, 56864-80-3; **7b**, 85222-43-1; **8**, 73554-70-8; **9a**, 29903-66-0; **9b**, 85222-44-2; **10**, 40004-92-0; **11a**, 85222-45-3; **11b**, 85222-46-4; **11b** picrate, 85222-47-5; **11c**, 85222-48-6; **11d**, 78946-26-6; **11d** picrate, 85222-49-7; **12**, 538-51-2; **13a**, 38924-78-6; **13b**, 85222-50-0; **13c**, 85222-51-1; **13d**, 76177-43-0; **13e**, 85222-52-2; **13f**, 85222-53-3; **14**, 622-29-7; **15**, 53663-25-5; **16**, 6319-84-2; **17**, 85222-54-4; **18**, 33797-51-2; **19a**, 1126-71-2; **19b**, 25314-75-4; **20**, 35287-11-7; **21**, 30936-27-7; **22a**, 6940-49-4; **22b**, 40125-46-0; **22c**, 73563-23-2; *threo*-**23a**, 73554-64-0; *erythro*-**23a** picrate, 85222-55-5; *threo*-**23b**, 55219-41-5; *erythro*-**23b**, 55563-22-9; *threo*-**23c**, 85280-87-1; *erythro*-**23c** picrate, 85280-89-3; *threo*-**23d** picrate, 85222-57-7; *erythro*-**23d** picrate, 85222-59-9; *threo*-**23e**, 85222-60-2; *erythro*--**23e**, 85222-61-3; *erythro*-**23e** picrate, 85222-62-4; *threo*-**23f** picrate, 85280-17-7; *erythro*-**23f**, 85280-18-8; *erythro*-**23f** picrate, 85280-19-9; *threo*-**23g**, 85222-63-5; *erythro*-**23g**, 85222-64-6; *threo*-**23h**, 85222-65-7; *erythro*-**23h**, 85222-66-8; *threo*-**23i**, 85222-67-9; *threo*-**23j**, 85280-20-2; **24a**, 5096-82-2; **24b**, 81701-39-5; **24c**, 81701-40-8; **24d**, 85222-69-1; *threo*-**25**, 85222-69-1; *erythro*-**25**, 85222-70-4; *erythro*-**25** picrate, 85222-71-5; *threo*-**26**, 85222-77-1; *erythro*-**26**, 85222-78-2; *erythro*-**26** picrate, 85222-79-3; **28**, 85222-80-6; **29**, 85222-81-7; **30**, 85222-72-6; **31**, 15889-93-7; **32**, 4787-30-8; *cis*-**33**, 85222-73-7; *trans*-**33**, 85222-74-8; **34**, 84690-25-5; **35** picrate, 85222-76-0; **36a**, 85222-82-8; **36b**, 81701-43-1; **36c**, 81701-44-2; **36d**, 81701-45-3; **37b**, 1876-67-1; **37c**, 81701-50-0; **37d**, 81701-51-1; **38**, 846-66-2; **39a**, 81701-46-4; **39b**, 81701-47-5; **39c**, 85222-83-9; **39d**, 81701-49-7; **39e**, 85222-84-0; **40a**, 81701-54-4; **40b**, 81701-55-5; **40c**, 81701-52-2; **40d**, 81701-53-3; **40e**, 85222-85-1; **41a**, 81701-57-7; **41b**, 81701-56-6; **42a**, 841-95-2; **43a**, 5911-65-9; **43b**, 85222-86-2; **44a**, 85222-87-3; **44b**, 85222-88-4; **45**, 85222-89-5; **46**, 81701-58-8; **47**, 85222-90-8; **48**, 85222-92-0; 12-benzyl-1,6,7,12b-tetrahydro-4-oxo-2-(1-pyrrolidinyl)-4*H*-indolo[2,3-*a*]quinolizine, 85222-93-1.

Supplementary Material Available: Full spectral and analytical data for all compounds (24 pages). Ordering information is given on any current masthead page.

Syntheses of Azolopyrimido[5,4-*e*]-*as*-triazines and Azolopyrimido[4,5-*c*]pyridazines Related to Fervenulin

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Received August 30, 1982

Syntheses of some azolopyrimido[5,4-*e*]-*as*-triazines and azolopyrimido[4,5-*c*]pyridazines, new heterocyclic systems related to the antibiotic fervenulin, are described. Synthesis of the 4-deaza analogue of the antibiotic 2-methylfervenulone (MSD-92) is also reported.

Because of the natural occurrence of the triad of antibiotics fervenulin, 2-methylfervenulone (MSD-92), and toxoflavin, the pyrimido[5,4-*e*]-*as*-triazine nucleus has aroused considerable recent attention.[1] As a part of our

0022-3263/83/1948-1628$01.50/0