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The Stevens Rearrangement of Quarternary Isoquinolinium Salts[1]

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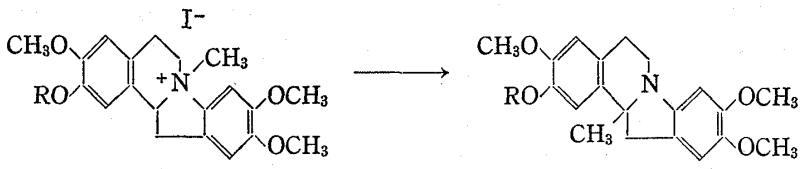
The reaction of 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(3,4-methylenedioxyphenyl)-2,2-dimethylisoquinolinium iodide (**3**) with dimsylsodium afforded the 1-methyl-1-phenylisoquinoline (**4**) and the N,N-dimethyldiphenylmethylamine (**5**). Similar reaction using the berbine methiodide (**8**), (**16**), (**17**) yielded the corresponding ochotensine type 1-spirobenzylisoquinolines (**9**), (**14**), and (**15**), respectively. The homoberbine (**20**) also gave the 1-spiroisoquinoline (**22**), however, the reaction of the homoberbine (**23**) with dimsylsodium yielded the tetrahydro-13,14-*trans*-dibenz[*c*,*g*]azacycloundecine (**28**).

Keywords——Stevens rearrangement; anionic migration; 1-spiroisoquinoline; berbine; dibenz[*c*,*g*]azacycloundecine

Previously, we reported a formation of 5,6,12,12a-tetrahydro-12a-methyldibenz[*b*,*g*]indolizines (**1**) from 5,6,12,12a-tetrahydro-N-methyl-dibenz[*b*,*g*]indolizinium salts (**2**) through the anionic migration of a methyl group at C_7 position by the action of dimsylsodium.[3] In connection with these results, dimsylsodium was found to be one of excellent reagent for the Stevens rearrangement to some quarternary isoquinolinium salts.[1] We successively investigated the similar reaction using a simple isoquinolinium salt and several kinds of polycyclic quarternary isoquinolinium salts. We wish to report these results in this paper.



2 **1**

R=CH_3, H

Chart 1

Treatment of 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-(3′,4′-methylenedioxypheny)-isoquinoline methiodide (**3**)[4] with dimsylsodium in dimethyl sulfoxide (DMSO) afforded two reaction products, 1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-1-(3′,4′-methylenedioxyphenyl)-isoquinoline (**4**) and the N,N-dimethyldiphenylmethylamine (**5**), which were separated by column chromatography on silica gel. The nuclear magnetic resonance (NMR) spectrum of the former (**4**) exhibited a singlet due to C_1–CH_3 at 1.60 ppm and NCH_3 protons resonated at 2.10 ppm. The structure of the latter (**5**) was determined by conversion to **6** by reductive deoxygenation with zinc amalgam. The NMR spectrum of **6** showed a singlet attributable to SCH_3 at 2.00 ppm. A characteristic signal due to methylene protons adjacent to two

1) A part of this work was reported in the preliminary communication, *Chem. Pharm. Bull.* (Tokyo), **23**, 1171 (1975).
2) Location: *1432–1 Horinouchi, Hachioji, Tokyo.*
3) *a*) S. Kano, T. Yokomatsu, N. Yamada, K. Matsumoto, S. Tokita, and S. Shibuya, *Chem. Pharm. Bull.* (Tokyo), **22**, 1607 (1974); *b*) S. Kano, E. Komiyama, K. Nawa, and S. Shibuya, *Chem. Pharm. Bul,.* (Tokyo), **24**, 310 (1976).
4) K. Leander and B. Luning, *Tetrahedron Lett.*, **1968**, 1393.

phenyl group was observed at 3.75 ppm. Thus, elimination of dimethylamino group was achieved during the reduction. Furthermore, desulfurization of **6** with Raney Ni catalyst yielded 4,5-dimethoxy-2-(3′,4′-methylenedioxyphenyl)phenylpropane (**7**). This anionic 1,2-shift of alkyl group was applied to a synthesis of ochotensine type 1-spirobenzylisoquinolines by the use of the methiodides of berbines and homoberbines. Several works on the Stevens rearrangement of N-methyl quarternary salts of berbines yielding 1-spirobenzylisoquinolines using strong base, lithium aluminium hydride,[5] and sodium bis-(2-methoxyethoxy)aluminium

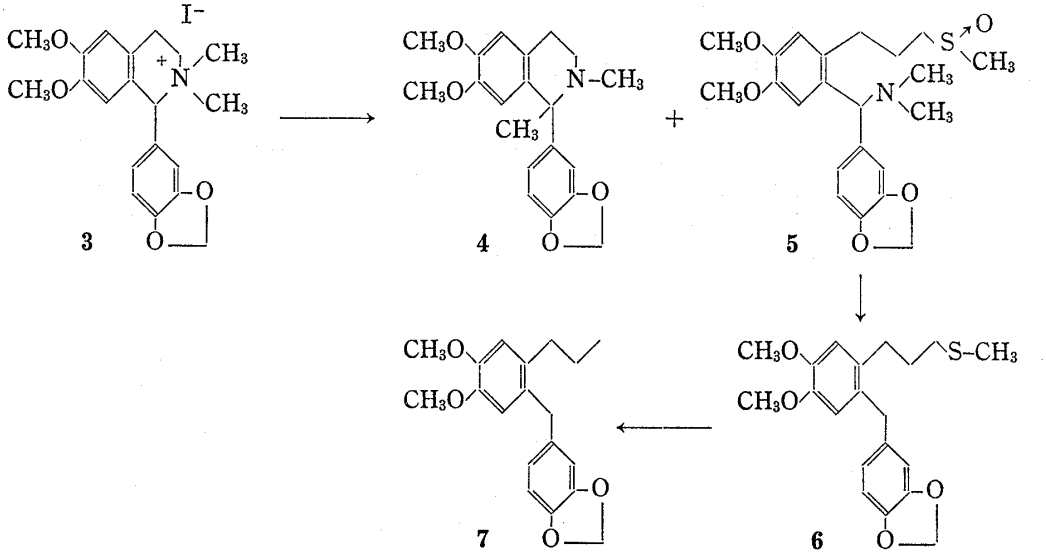


Chart 2

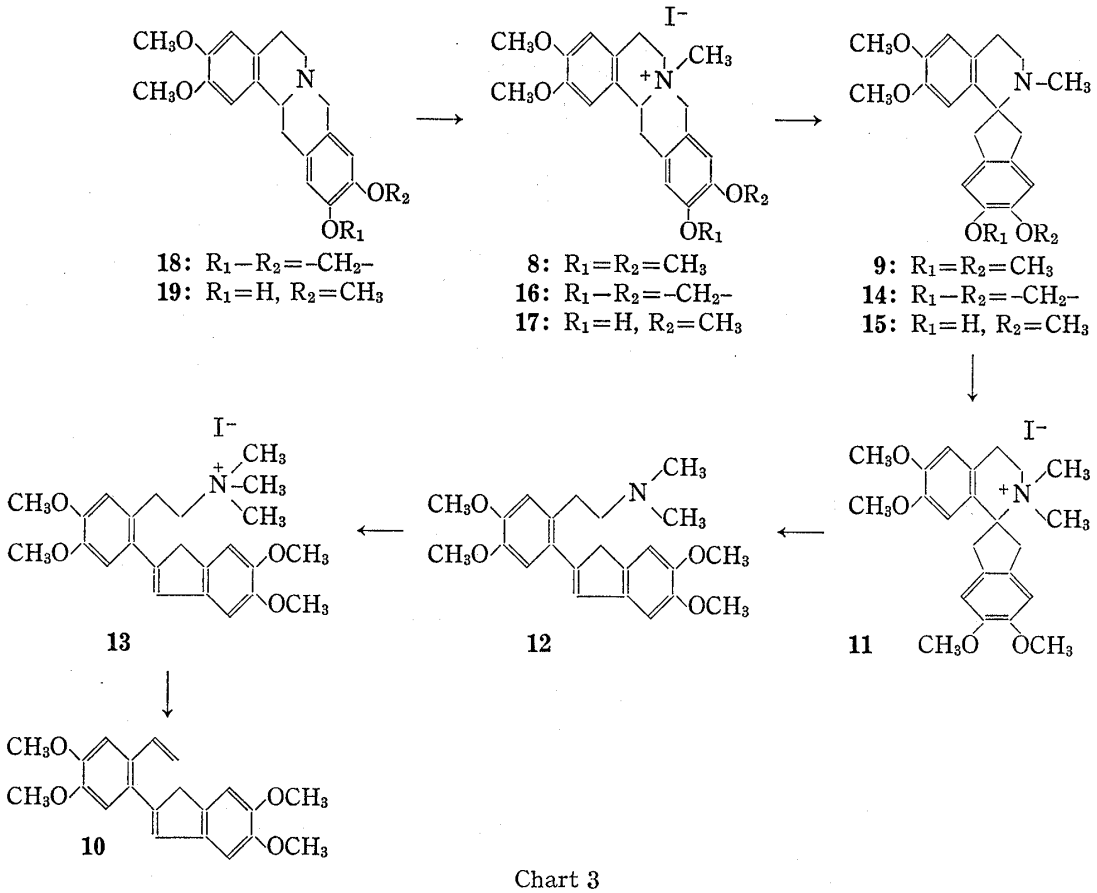


Chart 3

5) J. Imai, Y. Kondo, and T. Takemoto, *Heterocycles*, **3**, 467 (1975).

hydride[6] have been reported in addition to our initial work[1] and these anionic rearrangement was found to undergo with retention of chirality at C_{13a} position of berbines.[5,6]

The methiodide (**8**) of 2,3,10,11-tetramethoxyberbine[7] was used for our initial attempt to yield the 1-spirobenzylisoquinoline (**9**)[1] by the action of dimsylsodium. The structure of **9**, obtained from **8**, was confirmed by leading to the des N-methine (**10**) as follows. Treatment of the methiodide (**11**), prepared from **9** as usual, with dimsylsodium gave the methine base (**12**). The NMR ($CDCl_3$) spectrum of **12** showed a methylene signal at 3.67 ppm, supporting a presence of indene moiety, and olefinic and aromatic signals were observed at 6.75 (2H), 6.80 (1H), 6.92 (1H), and 7.02 (1H) ppm as singlets, respectively. The methiodide (**13**), derived from **12**, was heated in ethanolic sodium hydroxide to give the des N-methine (**10**), the structure of which was supported by a methylene signal at 3.70 ppm and two pairs of doublets, characteristic of styrenes, at 5.17 (1H, J=10, 2 Hz) and 5.53 ppm (1H, J=17, 2 Hz) exhibited in its NMR spectrum. In a similar fashion, the 1-spirobenzylisoquinolines (**14**) and (**15**) were prepared from the corresponding methiodides (**16**) and (**17**), which were obtained from the berbines (**18**)[8] and (**10**),[9] respectively.

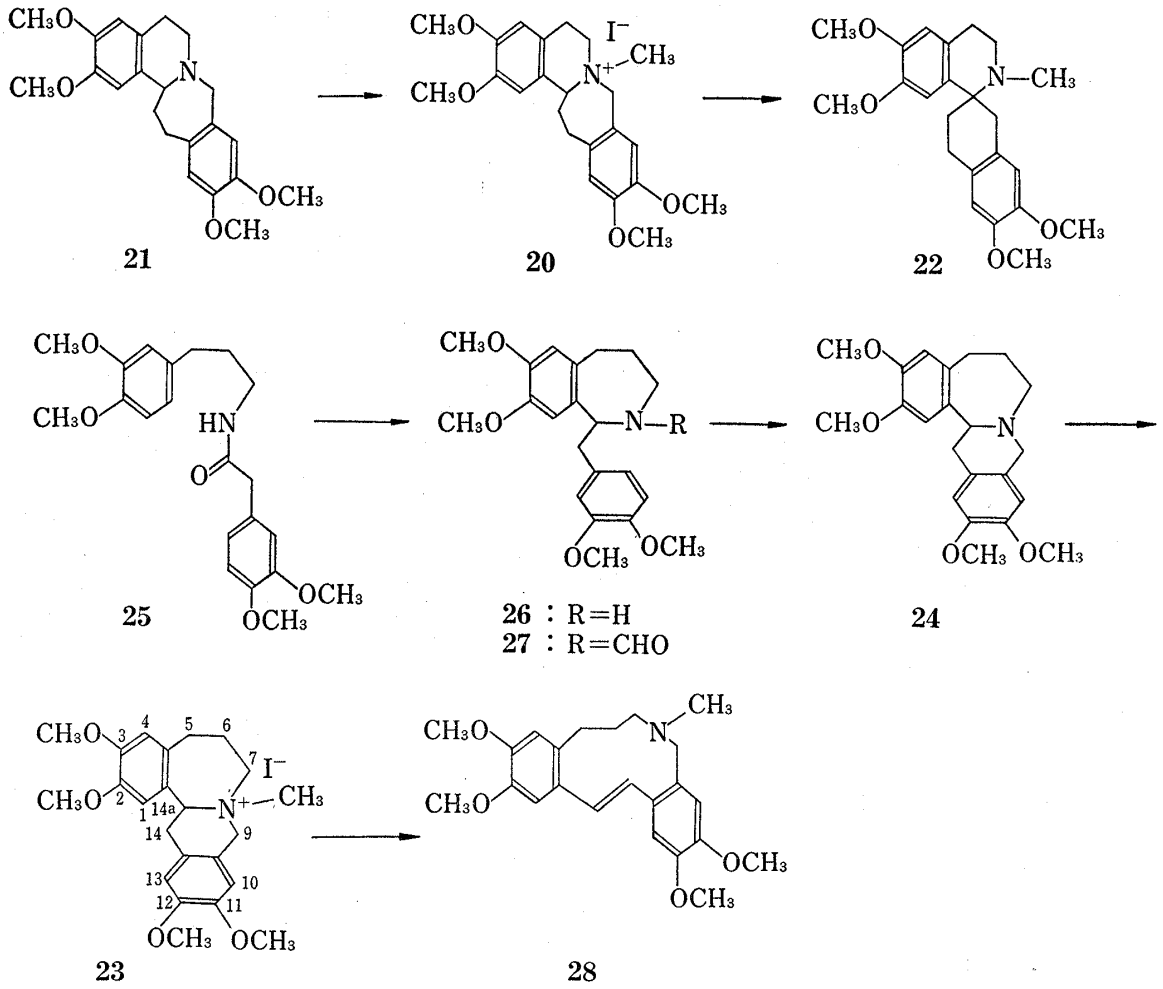


Chart 4

6) T. Kametani, S.P. Huang, A. Ujiie, M. Ihara, and K. Fukumoto, *Heterocycles*, **4**, 1223 (1976).
7) T. Kametani, "The Chemistry of The Isoquinoline Alkaloids," Hirokawa Publishing Co., Inc., 1968, p. 118. References cited therein.
8) R.D. Haworth, W.H. Perkin Jr., and J. Rankin, *J. Chem. Soc.*, **125**, 62 (1924).
9) T. Kametani, K. Fukumoto, H. Agui, H. Yagi, K. Kigasawa, H. Sugawara, M. Hiiragi, T. Hayasaka, and H. Ishimaru, *J. Chem. Soc.* (*C*), **1968**, 112.

Finally, we examined the same reaction using two kinds of methiodides of homoberbines. The reaction of the methiodide (**20**) of the tetramethoxybenz[*e*]azepino[2,1-*a*]isoquinoline (**21**)[10] with dimsylsodium afforded the expected 1-spiroisoquinoline (**22**) in 65% yield. On the other hand, different mode of reaction occurred in the case of the methiodide (**23**) of the benz[*e*]azepino[2,3-*f*]isoquinoline (**24**), prepared by the usual manner as shown in Chart 4 and the experimental section (**25**→**26**→**27**→**24**). The reaction of **23** with dimsylsodium afforded the dibenz[*c*,*g*]azacycloundecine (**28**), and formation of any rearranged product was not detected. The molecular formula of **28** was determined by microanalysis and mass spectrum (M^+, *m/e* 383) as $C_{23}H_{29}NO_4$. Its NMR spectrum showed two pairs of doublets at 6.76 (J=16 Hz) and 8.01 ppm (J=16 Hz) indicating a presence of *trans* –CH=CH– in the molecule. It would be presumed that, in the case of benz[*e*]azepino[2,3-*f*]isoquinoline system, anion formed at C_9 position abstracted hydrogen at C_{14} position, followed by Hofmann degradation to give the dibenz[*c*,*g*]azacycloundecine.

Experimental[11]

The Reaction of 1,2,3,4-Tetrahydro-6,7-dimethoxy-2-methyl-1-(3′,4′-methylenedioxyphenyl)isoquinoline Methiodide (3) with Dimsylsodium——To a stirred solution of dimsylsodium (prepared from 1.5 g of NaH and 30 ml of DMSO) was added a solution of 2 g of **3** in 35 ml of DMSO at room temperature. After the stirring had been continued for 8 hr, the mixture was poured into 200 ml of ice–H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to leave 1.5 g of pale brownish oil, which was chromatographed on 15 g of silica gel. Elution with $CHCl_3$ (100 ml) yielded 0.3 g of 1,2,3,4-tetrahydro-6,7-dimethoxy-1,2-dimethyl-1-(3′,4′-methylenedioxyphenyl)isoquinoline (**4**) as colorless needles, mp 114—116° (ether–hexane). MS *m/e*: 341 (M^+). NMR ($CDCl_3$) δ: 1.6 (3H, singlet, C_1–CH_3), 2.10 (3H, singlet, NCH_3), 3.53, 3.73 (6H, each singlet, $2\times OCH_3$), 5.87 (2H, singlet, OCH_2O), 6.10 (1H, singlet, C_8–H), 6.28 (1H, singlet, C_5–H), 6.75 (3H, multiplet, $3\times$ArH). *Anal.* Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.08; H, 6.90; N, 3.92. Elution with 2% MeOH–$CHCl_3$ afforded 1 g of the sulfoxide (**5**) as an oil. NMR ($CDCl_3$) δ: 2.20 (6H, singlet, $N<^{CH_3}_{CH_3}$), 2.43 (3H, singlet, CH_3SO), 3.77, 3.87 (6H, each singlet, $2\times OCH_3$,) 4.13 (1H, Ph_2CH–N), 5.88 (2H, singlet, OCH_2O), 6.5—6.87 (5H, multiplet, $5\times$Ar–H); this was used for the following reaction without further purification because of difficulty of crystallization.

4,5-Dimethoxy-2-(3′,4′-methylenedioxybenzyl)phenylpropyl Methyl Sulfide (6)——A mixture of 0.5 g of **5**, 30 ml of 50% AcOH–conc. HCl (1: 1) and Zn–Hg (prepared from 5 g of Zn and 0.5 g of $HgCl_2$) was heated for 1 hr on a water bath. After removal of inorganic substance, the mixture was made basic with 28% NH_4OH and extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated. The residual solid was recrystallized from ether–MeOH to give 0.4 g of **6** as colorless needles, mp 73—74°. MS *m/e*: 360 (M^+). NMR ($CDCl_3$) δ: 2.00 (3H, singlet, SCH_3), 3.75 (2H, singlet, Ph_2CH_2), 3.83 (6H, singlet, $2\times OCH_3$), 5.83 (2H, singlet, OCH_2O), 6.50—6.67 (5H, multiplet, $5\times$Ar–H). *Anal.* Calcd. for $C_{20}H_{24}O_4S$: C, 66.65; H, 6.71. Found: C, 66.97; H, 6.90.

4,5-Dimethoxy-2-(3′,4′-methylenedioxybenzyl)phenylpropane (7)——A mixture of 0.2 g of **6**, 2 ml of Raney Ni catalyst, and 70 ml of EtOH was refluxed for 14 hr. After removal of catalyst, the solvent was evaporated and remaining residue was recrystallized from ether–hexane to give 1.5 g of **7** as colorless needles,

Table I. The Methiodides of Berbines and Homoberbines

Compound	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
16	>260 (MeOH)	$C_{21}H_{24}INO_4$	52.40	5.01	2.91	52.47	5.06	2.66
17	>260 (MeOH)	$C_{21}H_{26}INO_4$	52.18	5.42	2.90	51.91	5.39	2.69
20	>260 (MeOH)	$C_{23}H_{30}INO_4$	54.01	5.91	2.74	53.75	6.07	2.52
23	208—209 (MeOH–ether)	$C_{23}H_{30}INO_4$	54.01	5.91	2.74	53.78	5.79	2.48

10) A Brossi and S. Teitel, *Helv. Chim. Acta*, **52**, 1228 (1968).

11) All melting points were uncorrected. NMR spectra were taken with a Varian T-60 spectrometer in $CDCl_3$ using TMS as an internal standard. MS were measured with a Hitachi RMU-7L spectrometer.

mp 67—68°. MS *m/e*: 314 (M^+). NMR ($CDCl_3$) δ: 0.93 (3H, triplet, $C\underline{H}_3CH_2CH_2$), 3.83 (2H, singlet, Ph_2-CH_2), 3.93 (6H, singlet, $2\times OCH_3$), 5.90 (2H, singlet, OCH_2O), 6.57—6.73 (5H, multiplet, $5\times$ Ar–H). *Anal.* Calcd. for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.58; H, 7.31.

Preparation of the Methiodides (8),[12] (16), (17), (20), and (23)——These methiodides were prepared by the usual way from the corresponding berbines and homoberbines. mp and analytical data were listed in Table I.

Synthesis of 1-Spiroisoquinolines, General Procedure——To a solution of dimsylsodium (prepared from 2.5 g of NaH and 35 ml of DMSO) was added a solution of 2.5 g of the methiodide in 35 ml of DMSO under stirring at room temperature. After the stirring had been continued for 10 hr, the mixture was poured into 300 ml of H_2O, and extracted with $CHCl_3$. For the phenolic base (**15**), the mixture was extracted after addition of excess NH_4Cl. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The remaining solid was recrystallized from the appropriate solvent.

Table II. 1-Spiroisoquinolines

Compound	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
9	80	122—123 (MeOH–ether)	$C_{22}H_{27}NO_4$	71.52	7.37	3.79	71.57	7.57	3.77
14	83	141—142 (MeOH)	$C_{21}H_{23}NO_4$	71.37	6.56	3.96	71.37	6.66	3.80
15	85	169—170 (MeOH)	$C_{21}H_{25}NO_4$	70.96	7.09	3.94	70.83	7.09	3.98
22	65	124—125.5 (MeOH–ether)	$C_{23}H_{29}NO_4$	72.03	7.62	3.65	72.12	7.82	3.44

Table III. NMR Spectra of 1-Spiroisoquinoline

Compound	NMR ($CDCl_3$): δ
9	2.22 (3H, singlet, NCH_3), 3.20, 3.33 (4H, each singlet, C_8–H_2 and C_{13}–H_2), 3.60 (3H, singlet, OCH_3), 3.83 (9H, singlet, $3\times OCH_3$), 6.43 (2H, singlet, $2\times$ Ar–H), 6.67 (2H, singlet, $2\times$ Ar–H)
14	2.27 (3H, singlet, NCH_3), 3.20, 3.30 (4H, each singlet, C_8–H_2 and C_{13}–H_2), 3.63, 3.83 (6H, each singlet, $2\times OCH_3$), 5.90 (2H, singlet, OCH_2O), 6.50 (2H, singlet, $2\times$ Ar–H), 6.67 (2H, singlet, $2\times$ Ar–H)
15	2.27 (3H, singlet, NCH_3), 3.22, 3.32 (4H, each singlet, C_8–H_2 and C_{13}–H_2, 3.62, 3.83, 3.85 (9H, each singlet, $3\times OCH_3$), 6.48, 6.51, 6.70, 6.75 (4H, each singlet, $4\times$ Ar–H)
22	2.33 (3H, singlet, NCH_3), 3.67 (3H, singlet, OCH_3), 3.83 (9H, singlet, $3\times OCH_3$), 6.60 (2H, singlet, $2\times$ Ar–H), 6.63 (2H, singlet, $2\times$ Ar–H)

N-(3′,4′-Dimethoxyphenylpropyl)-3,4-dimethoxyphenylacetamide (25)——A mixture of 5 g of 3,4-dimethoxyphenylpropylamine[13] and 5 g of 3,4-dimethoxyphenylacetic acid was heated at 180° for 1 hr. After cooling, the mixture was recrystallized from benzene to give 9 g of **25** as colorless needles, mp 104—105°. *Anal.* Calcd. for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.30; H, 7.29; N, 3.58.

1-(3′,4′-Dimethoxybenzyl)-7,8-dimethoxy-1,2,3,4-tetrahydro-5*H*-2-benzazepine (26)——A mixture of 5 g of **25**, 150 ml of CH_3CN, and 5 g of $POCl_3$ was refluxed for 4 hr. To a methanolic solution of the resulting residue, obtained after removal of the solvent, was added 3.5 g of $NaBH_4$ under stirring at room temperature. The remaining residue was suspended in H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to leave 4 g of **26** as colorless needles, mp 93—95° (ether–hexane). NMR ($CDCl_3$) δ: 3.78 (3H, singlet, OCH_3), 3.85 (9H, singlet, $3\times OCH_3$), 6.53—6.73 (5H, multiplet, $5\times$ Ar–H). *Anal.* Calcd. for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.23; H, 7.75; N, 3.90.

The Benz[*e*]azepino[2,3-*f*]isoquinoline (24)——A solution of 5 g of **26** in a mixture of 8 g of Ac_2O and 4.4 g of 99% HCOOH was heated on a water bath for 3 hr. The mixture was poured into 200 ml of H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give 4.2 g of **27** as a pale brownish oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660 (HCON); this was used for the following reaction because of difficulty of crystallization. A mixture of 4 g of **27**, 4 g of $POCl_3$, and 120 ml of CH_3CN was refluxed for 4 hr. After removal of the solvent, the remaining residue was reduced with 3 g of $NaBH_4$ in 150 ml of MeOH by the usual way to yield 2.5 g of **24** as colorless needles, mp 161—162° (MeOH–ether). MS m/e: 369 (M^+). NMR ($CDCl_3$) δ: 3.57, 3.80 (6H, each singlet, $2\times OCH_3$), 3.87 (6H, singlet, $2\times OCH_3$), 6.43,

12) H. Corrodi and E. Hardegger, *Helv. Chim. Acta*, **39**, 889 (1956).
13) I. Jirkovsky and M. Protiva, *Collect. Czech. Chem. Commun.*, **32**, 1197 (1967).

6.50, 6.60, 6.67 (4H, each singlet, 4 × Ar–H). *Anal.* Calcd. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.29; H, 7.22; N, 3.65.

The Reaction of The Methiodide (23) with Dimsylsodium——To a solution of dimsylsodium (prepared from 3.0 g of NaH and 35 ml of DMSO) was added a solution of 2 g of **23** in 30 ml of DMSO under stirring at room temperature. After the stirring had been continued for 14 hr, the mixture was worked up as usual to give 1 g of the dibenz[*c*,*g*]azacycloundecine (**28**) as colorless needles, mp 156—157° (MeOH–ether). MS *m/e*: 383 (M^+). NMR ($CDCl_3$) δ: 2.37 (3H, singlet, NCH_3), 3.90 (6H, singlet, 2 × OCH_3), 3.92 (6H, singlet, 2 × OCH_3), 6.76 (1H, doublet, J=16 Hz, olefinic H), 6.67, 6.73, 6.85, 7.08 (4H, each singlet, 4 × Ar–H), 8.01 (1H, doublet, J=16 Hz, olefinic H). *Anal.* Calcd. for $C_{23}H_{29}NO_4$: C, 72.03; H, 7.62; N, 3.65. Found: C, 72.18; H, 7.76; N, 3.37.

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