A Synthetic Route to the Morphan Ring System by Skeletal Transformation of Norbornadiene[1)]

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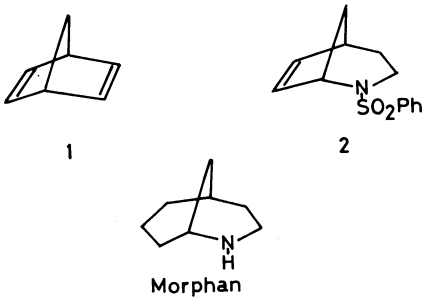
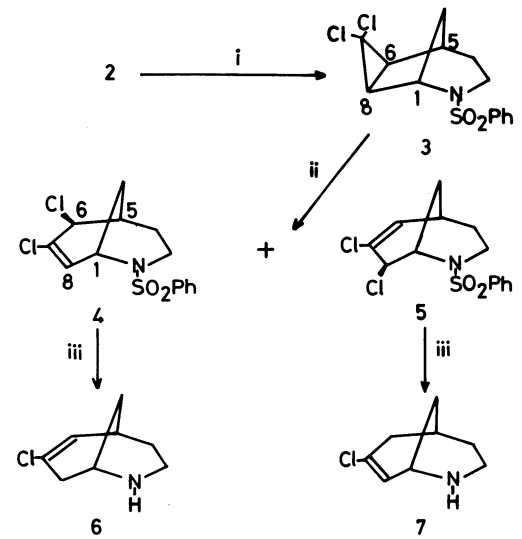
The morphan skeleton was prepared from 2-phenylsulfonyl-2-azabicyclo[3.2.1]oct-6-ene (**2**), derived from norbornadiene, through the addition of dichlorocarbene to the monoene **2** and the subsequent thermal isomerization of the adduct obtained. The isomerization products, 2-phenylsulfonyl-6,7-dichloro-2-azabicyclo-[3.3.1]non-7-ene and 2-phenylsulfonyl-7,8-dichloro-2-azabicyclo[3.3.1]non-6-ene, which are mutually convertible in the presence of lithium chloride, were converted into various morphans by reductive dechlorination and alkylation. Furthermore, the 6,7-pyridazino-annelated morphan was synthesized by the cycloaddition of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate to 2-phenylsulfonyl-2-azabicyclo[3.3.1]non-6-ene.

In the course of our studies on the reactivity of the methano-bridged azabicyclic molecules,[2)] we took an interest in the morphan ring system having pharmacological activity.[3)] The morphan ring system has been synthesized by using mostly intramolecular cyclization reactions starting from an appropriate material.[3,4)] We planned to construct the morphan skeleton by an alternative route, utilizing skeletal transformation of available bicyclic molecule such as norbornadiene (**1**). The transformation of the diene **1** to 2-phenylsulfonyl-2-azabicyclo[3.2.1]oct-6-ene (**2**) through ring expansion has already been reported.[5,6)] We examined to transform the monoene **2** to the morphan ring system and now wish to report a novel synthetic route to various morphans starting from the diene **1**.



Results and Discussion

Ring Expansion of the Monoene 2 to the Morphan Ring System. On the basis of the fact that the dichlorocarbene adduct to norbornene readily undergoes ring expansion,[7)] the ring expansion of the monoene **2** was carried out using the dichlorocarbene adduct to the monoene **2**. The cheletropic addition of dichlorocarbene to the monoene **2**, using hexadecyltrimethylammonium bromide as the phase-transfer catalyst, gave 2-phenylsulfonyl-7,7-dichloro-2-azatricyclo-[3.2.1.0.^{6,8exo}]nonane (**3**) in 56% yield (Scheme 1). During this reaction, no rearrangement occurred. The exo configuration of the adduct **3** was determined by the absence of the coupling between 1-H and 8-H. The thermal isomerization of the adduct **3** was achieved successfully by heating the adduct **3** at 130—135 °C in the absence or presence of the solvent, thus giving rise to 2-phenylsulfonyl-6,7-dichloro-2-azabicyclo[3.3.1]-non-7-ene (**4**) and its positional isomer (**5**) which can be separated readily by silica-gel chromatography (Scheme 1). The position of the double bond of **4** and **5** was determined by the fact that the doublet absorptions of vinyl protons at δ=5.37 (**4**) and 5.94 (**5**) collapse to singlet by double irradiation of 1-H of **4** and 5-H of **5** respectively. The absence of the coupling between 5-H and 6-H for **4** and between 1-H and 8-H for **5** indicated the configuration of endo 6-H for **4** and endo 8-H for **5**. The yields of **4** and **5** are shown in Table 1. The polar solvent was favorable for isomerization, although no significant solvent effect on the isomer ratio was observed. Furthermore, we found that the treatment of **4** or **5** with lithium chloride in *N*, *N*-dimethylformamide (DMF) at 50 °C for 7 h results in the migration of the double bond to give the equilibrium mixture of **4** and **5** in the ratio of 65:35, although no allylic rearrangement occurs in the absence of lithium chloride under similar conditions (Table 2). The reaction is considered to proceed through the intermediate A to give **4** and **5**.



Scheme 1. i) $|CCl_2$, r.t., 48 h; ii) 130—135 °C, 1.5 h; iii) $LiAlH_4$, THF, r.t., 30 h.

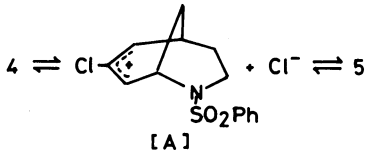


Table 1. The yields of **4** and **5** in the thermal isomerization of **3**[a)]

Solvent	Time/h	Yield/%		Recov./%
		4	**5**	**3**
None	1.5	54	43	0
m-Xylene	3.0	18	9	72
Chlorobenzene	1.5	65	33	0
DMF	1.5	56	41	0

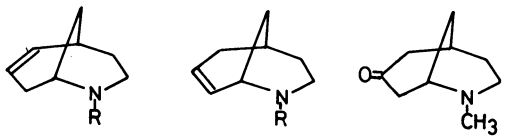
a) Temperature: 130—135 °C.

Table 2. The allylic rearrangement of **4** and **5** in the presence of lithium chloride[a)]

Substrate	Temp/°C	Time/h	Yield/%	
			4	**5**
4	50	1	84	16
4	50	3	68	32
4	50	7	65	35
4	80	15	64	35
5	50	3	58	42
5	50	7	63	37

a) Solvent: DMF.

Reductive Dechlorination of Compounds 4 and 5. The reductive cleavage of the C_6–Cl bond of **4** with lithium aluminium hydride in tetrahydrofuran (THF) at room temperature for 30 h proceeded by the S_N2' process, accompanied by the cleavage of the N–S bond, to give 7-chloro-2-azabicyclo[3.3.1]non-6-ene (**6**) in 80% yield (Scheme 1). Next, compound **6** was treated with sodium in liquid ammonia for 40 min to give 2-azabicyclo[3.3.1]non-6-ene (**8a**) in 78% yield. Attempts to undergo one-step dechlorination of **4** with sodium in liquid ammonia failed because of the destruction of the morphan skeleton. Compound **8a** was alkylated with methyl iodide and benzyl bromide to give **8b** and **8c** in 52 and 77% yields respectively.



8 9 10

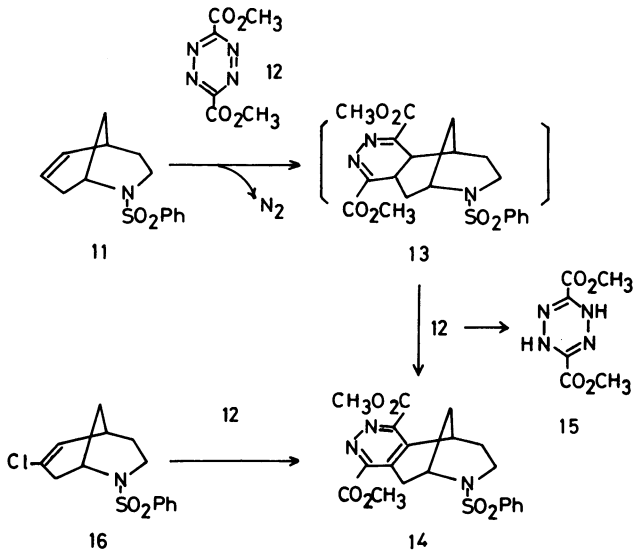
(a; R=H, b; R=CH_3, c; R=$PhCH_2$)

Compound **5** also was converted into **9a**—**c** by the steps shown in the case of **4**. The yields in the conversion of **5** into **7**, **7** into **9a**, and **9a** into **9b**, **c** were 76, 52, 36, and 70% respectively. The structure of **8b** and **9b** was established by the fact that the melting points and NMR spectra of picrates of **8b** and **9b** prepared here are identical to those of two isomers (**8b** and **9b**) prepared by an alternative route[8)] starting from 2-methyl-2-azabicyclo[3.3.1]nonan-7-one (**10**) [**8b** picrate: δ 5.84 (single multiplet, 2H, 6- and 7-H); **9b** picrate: δ 6.45 (a doublet of triplets, 1H, 7-H) and δ 5.82 (poorly resolved triplet, 1H, 8-H)].[8)] Thus, it was established that the morphan derivatives having a double bond at 6- or 7-position are synthesized from the diene **1** by skeletal transformation.

Annelation of Pyridazine Ring onto the Morphan Ring. We attempted to annelate a heterocyclic ring instead of the benzene ring of 6,7-benzomorphans. Previously it has been reported that 1,2,4,5-tetrazines undergo cycloaddition to various dienophiles to form pyridazines.[9)] To annelate a pyridazine ring onto the 6,7-position of the morphan ring, we carried out the cycloaddition of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**12**) to 2-phenylsulfonyl-2-azabicyclo-[3.3.1]non-6-ene (**11**). When a solution of a 1:2 mixture of **11** and **12** in chloroform was stirred at 50 °C for 15 h, the reaction proceeded with the evolution of nitrogen gas to give 2-phenylsulfonyl-3′,6′-bis(methoxycarbonyl)-6,7-(4′,5′-pyridazino)-2-azabicyclo[3.3.1]non-6-ene (**14**) in a quantitative yield, together with dimethyl 1H,4H-1,2,4,5-tetrazine-3,6-dicarboxylate (**15**) in nearly equimolar amounts with those of **14**. In equimolar solution of **11** and **12** in chloroform, the reaction gave **14** and **15** in 31 and 36% yields respectively. These facts indicate that the reaction proceeds by the cycloaddition of **12** to **11** to give the intermediate dihydropyridazine adduct (**13**) by release of nitrogen, followed by the dehydrogenation of **13** with **12** to give **14**, as shown in Scheme 2.

Next, we carried out the cycloaddition of **12** to 2-phenylsulfonyl-7-chloro-2-azabicyclo[3.3.1]non-6-ene (**16**) under conditions similar to those described above. The reaction proceeded through the evolution of nitrogen gas and then the dehydrochlorination of the intermediate adduct to give **14** in 37% yield. Thus, it was established that the pyridazine ring is annelated onto the morphan ring.

The above results provide a new route for the preparation of the morphan ring system from readily available diene **1**.



11 13 15 16 14

Scheme 2.

Experimental

The ^1H NMR spectra were determined on a Hitachi R-24A NMR spectrometer at room temperature with $CDCl_3$ as a solvent, using tetramethylsilane as the internal standard. The ^{13}C NMR and IR spectra were measured with a JEOL FX 90Q

Fourier transformation NMR spectrometer and a Hitachi 215 grating infrared spectrometer, respectively. All melting points were uncorrected. Compound **1** was obtained commercially and compound **2** was synthesized by the modification of the methods described in the literature.[5,6]

2-Phenylsulfonyl-7,7-dichloro-2-azatricyclo[3.2.1.0.^{6,8exo}]nonane (*3*). A 50% aqueous sodium hydroxide solution(73 g) was stirred, drop by drop, into a solution of **2** (6.6 g, 27 mmol) in chloroform (115 g) with hexadecyltrimethylammonium bromide (0.98 g) for 1 h at room temperature. After stirring for 2 d, the reaction mixture was extracted with chloroform. The chloroform solution was washed with water and dried over anhydrous magnesium sulfate. After removal of the chloroform *in vacuo*, the residue was chromatographed with a silica-gel column [chloroform–hexane (10:1) as an eluant] to give **3** (5 g, 56%), which was recrystallized from ethanol: mp 113—115 °C; IR (KBr) 1350 and 1170 cm^{-1} (SO_2); ^{1}H NMR δ=1.15—2.32 (m, 6H, 4-CH_2, 6-H, 8-H, and 9-CH_2), 2.51 (m, 1H, 5-H), 2.72—3.87 (m, 2H, 3-CH_2), 4.50 (d, 1H, J=4.7 Hz, 1-H), and 7.20—8.05 (m, 5H, aromatic). Found: C, 50.80; H, 4.62; N, 4.46%. Calcd for $C_{14}H_{15}NO_2SCl_2$: C, 50.60; H, 4.56; N, 4.22%.

Ring Expansion of 3. In the Absence of Solvent. Compound **3** (3 g, 9 mmol) was placed in a test tube and heated at 130—135 °C for 1.5 h. The mixture was cooled and chromatographed with a silica-gel column (benzene as an eluant) to give 1.62 g (54%) of **4** and 1.29 g (43%) of **5**. Compounds **4** and **5** were recrystallized from ethanol. **4**: mp 136.5—138.5 °C; IR (KBr) 1350 and 1165 cm^{-1} (SO_2); ^{1}H NMR δ=1.40—2.30 (m, 4H, 4-CH_2 and 9-CH_2), 2.45 (m, 1H, 5-H), 2.82 (m, 1H, 3-$H_{exo\ or\ endo}$), 3.60 (m, 1H, 3-$H_{exo\ or\ endo}$), 4.18 (s, 1H, 6-H), 4.48 (m, 1H, 1-H), 5.37 (d, 1H, J=6.3 Hz, 8-H), and 7.18—8.02 (m, 5H, aromatic). Found: C, 50.61; H, 4.61; N, 4.27%. Calcd for $C_{14}H_{15}NO_2SCl_2$; C, 50.60; H, 4.56; N, 4.22%. **5**: mp 108—109 °C; IR (KBr) 1340 and 1165 cm^{-1} (SO_2); ^{1}H NMR δ=1.10—2.42 (m, 4H, 4-CH_2 and 9-CH_2), 2.60 (m, 1H, 5-H), 3.00 (m, 1H, 3-$H_{exo\ or\ endo}$), 3.70 (m, 1H, 3-$H_{exo\ or\ endo}$), 3.97 (s, 1H, 8-H), 4.42 (m, 1H, 1-H), 5.94 (d, 1H, J=6.3 Hz, 6-H), and 7.25—8.00 (m, 5-H, aromatic). Found: C, 50.58; H, 4.72; N, 4.31%. Calcd for $C_{14}H_{15}NO_2SCl_2$: C, 50.60; H, 4.56; N, 4.22%.

In the Presence of Solvent. A solution of **3** (3 g, 9 mmol) in *m*-xylene, chlorobenzene, or DMF (10 cm^3) was refluxed for 1.5 h. After the removal of the solvent, the mixture was worked up as described above.

Conversion of 5 into 4. A solution of a mixture of **5** (1 g, 3 mmol) and lithium chloride (0.63 g, 15 mmol) in DMF (40 cm^3) was stirred at 50 °C for 7 h. After the removal of DMF *in vacuo*, water (20 cm^3) was added and the mixture was extracted with chloroform. The chloroform solution was washed with water, dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*. The residue was chromatographed with a silica-gel column (benzene as an eluant) to give **4** (0.63 g, 63%) with recovery of **5** (0.37 g, 37%).

7-Chloro-2-azabicyclo[3.3.1]non-6-ene (6). A solution of **4** (1.25 g, 3.8 mmol) in THF (17 cm^3) was added, drop by drop, to a suspension of lithium aluminium hydride (0.6 g, 16 mmol) in THF (43 cm^3) at room temperature. The mixture was stirred for 30 h at room temperature and water was added. After filtration of the mixture, the filtrate was extracted with chloroform. The chloroform solution was washed with water and dried over anhydrous magnesium sulfate. The removal of the solvent *in vacuo* gave **6** (0.48 g, 80%): IR (KBr) 3250 cm^{-1} (NH) and 1645 cm^{-1} (C=C); ^{1}H NMR δ=1.10—1.85 (m, 4H, 4-CH_2 and 9-CH_2), 1.90 (s, 1H, NH), 2.20—3.11 (m, 4H, 3-CH_2 and 8-CH_2), 2.55 (m, 1H, 5-H), 3.25 (m, 1H, 1-H), and 5.78 (d, 1H, J=6.7 Hz, 6-H). The treatment of **6** with hydrogen chloride in ether gave HCl salt of **6** which was recrystallized from acetonitrile: mp 216—218 °C; Found: C, 49.50; H, 6.68; N, 7.37%. Calcd for $C_8H_{13}NCl_2$: C, 49.50; H, 6.76; N, 7.22%.

7-Chloro-2-azabicyclo[3.3.1]non-7-ene (**7**) was prepared from **5** in 76% yield by procedures similar to those in the case of **6**. **7**: IR (KBr) 3250 cm^{-1} (NH) and 1645 cm^{-1} (C=C): ^{1}H NMR δ=1.10—2.10 (m, 4H, 4-CH_2 and 9-CH_2), 2.20 (s, 1H, NH), 2.20—3.20 (m, 5H, 3-CH_2, 5-H, and 6-CH_2), 3.45 (m, 1H, 1-H), and 5.66 (d, 1H, J=6.7 Hz, 8-H). HCl salt of **7**: mp 216.5—218 °C; Found: C, 49.54; H, 7.00; N, 7.21%. Calcd for $C_8H_{13}NCl_2$: C, 49.50; H, 6.76; N, 7.22%.

2-Azabicyclo[3.3.1]non-6-ene (8a). A piece of sodium was added under stirring to a solution of **6** (0.6 g, 3.8 mmol) in ether (10 cm^3) and liquid ammonia (25 cm^3) at −78 °C until the solution kept the dark blue color for about 5 min. After stirring for 40 min, ammonia was removed, methanol was added, and the resulting solution extracted with ether. The ether solution was washed with water and dried over anhydrous sodium sulfate. The removal of ether gave **8a** (0.36 g, 78%): IR (KBr) 3270 cm^{-1} (NH) and 1645 cm^{-1} (C=C); ^{1}H NMR δ=1.00—3.00 (m, 9H, 3-CH_2, 4-CH_2, 5-H, 8-CH_2, and 9-CH_2), 2.10 (s, 1H, NH), 3.10 (m, 1H, 1-H), and 5.77 (m, 2H, 6-H and 7-H). HCl salt of **8a** was recrystallized from acetonitrile: mp 278—279 °C; Found: C, 60.26; H, 9.15; N, 8.80%. Calcd for $C_8H_{14}NCl$: C, 60.17; H, 8.86; N, 8.77%.

2-Azabicyco[3.3.1]non-7-ene (**9a**) was prepared from **7** in 52% yield by the procedures being similar to those in the case of **8a**. **9a**: IR (KBr) 3260 cm^{-1} (NH) and 1615 cm^{-1} (C=C); ^{1}H NMR δ=1.20—3.10 (m, 9H, 3-CH_2, 4-CH_2, 5-H, 6-CH_2, and 9-CH_2), 2.07 (s, 1H, NH), 3.32 (m, 1H, 1-H), 5.50 (dd, 1H, J= 9.7, 6.0 Hz, 8—H),and 5.97 (dt, 1H, J=9.7, 4.0 Hz, 7-H). $(COOH)_2$ salt of **9a**: mp 210.5—212 °C; Found: C, 64.26; H, 8.59; N, 8.41%. Calcd for $C_{18}H_{28}N_2O_4$: C, 64.25; H, 8.33; N, 8.33%.

Alkylation of 8a and 9a. *With Methyl Iodide*: Sodium hydride (0.16 g, 3.2 mmol) was added to a solution of **8a** or **9a** (0.2 g, 1.6 mmol) in dimethyl sulfoxide (10 cm^3) and the mixture was stirred at 45 °C for 20 min. A solution of methyl iodide (0.71 g, 5 mmol) in dimethyl sulfoxide (5 cm^3) was added to the resulting solution. After stirring for 10 min, the mixture was poured into water (80 cm^3) and extracted with ether. The ether solution was washed with water and dried over anhydrous sodium sulfate. The removal of ether gave **8b** and **9b** in 52 and 36% yields, respectively. The melting points and NMR spectra of picrates of **8b** and **9b** were identical to those described in the literature.[9]

With Benzyl Bromide: A mixture of **8a** (0.28 g, 2.3 mmol), benzyl bromide (0.39 g, 2.3 mmol), sodium hydrogencarbonate (0.33 g, 3.9 mmol), and DMF (30 cm^3) was refluxed for 4 h. After filtration of the reaction mixture, the filtrate was evaporated and the residue was extracted with ether. The ether solution was washed with water and dried over anhydrous sodium sulfate. The removal of ether gave **8c** (0.38 g, 77%): ^{1}H NMR δ=1.50—2.05 (m, 4H, 4-CH_2 and 9-CH_2), 2.17 (m, 1H, 5-H), 2.25—2.67 (m, 4H, 3-CH_2 and 8-CH_2), 2.92 (m, 1H, 1-H), 3.49 (s, 2H, -$C\underline{H}_2$Ph), 5.72 (m, 2H, 6-H and 7-H), and 7.16 (s, 5H, aromatic). $(COOH)_2$ salt of **8c**: mp 177.5—180 °C; Found: C, 67.27; H, 7.12; N, 4.79%. Calcd for $C_{17}H_{21}NO_4$: C, 67.33; H, 6.93; N, 4.62%. Compound **9c** was prepared by the procedures being similar to those in the case of **8c**. **9c** (70% yield): ^{1}H NMR δ=1.15—2.80 (m, 9H, 3-CH_2, 4-CH_2, 5-H, 6-CH_2, and 9-CH_2), 3.12 (m, 1H, 1-H), 3.49 (s, 2H, -$C\underline{H}_2$Ph), 5.55 (m, 1H, 8-H), 6.03 (m, 1H, 7-H), and 7.18 (s, 5H, aromatic). $(COOH)_2$ salt of **9c**: mp 183—184.5 °C; Found: C, 67.18; H, 6.96; N, 4.55%. Calcd for $C_{17}H_{21}NO_4$: C, 67.33; H, 6.93; N, 4.62%.

2-Phenylsulfonyl-2-azabicyclo[3.3.1]non-6-ene (11). Benzenesulfonyl chloride (0.28 g, 1.6 mmol) was added gradually to a solution of **8a** (0.16 g, 1.3 mmol) in 2 M† sodium hydroxide (11 cm^3) and the mixture was stirred at room temperature for 5 h. The resulting solution was extracted

† 1M=1 mol dm^{-3}.

with chloroform, and the chloroform solution was washed with water and dried over anhydrous sodium sulfate. After the removal of chloroform *in vacuo*, the residue was chromatographed on a silica-gel column using benzene as the eluant to give 0.32 g (91%) of **11**, which was recrystallized from ethanol: mp 108.5—110.5 °C; IR (KBr) 1310 and 1155 cm^{-1}(SO_2); ^1H NMR δ=1.31—1.76 (m, 4H, 4-CH_2 and 9-CH_2), 1.76—2.56 (m, 3H, 5-H and 8-CH_2), 3.06 (m, 1H, 3-$H_{exo\ or\ endo}$), 3.66 (m, 1H, 3-$H_{exo\ or\ endo}$), 4.21 (m, 1H, 1-H), 5.58 (m, 2H, 6-H and 7-H), and 7.26—7.86 (m, 5H, aromatic). Found: C, 63.77; H, 6.80; N, 5.29%. Calcd for $C_{14}H_{17}NO_2S$: C, 63.84; H, 6.52; N, 5.32%.

2-Phenylsulfonyl-7-chloro-2-azabicyclo[3.3.1]non-6-ene (16) was prepared from **6** by procedures similar to those used in the case of **11**. **16**: mp 124—126 °C; IR (KBr) 1350 and 1170 cm^{-1} (SO_2); ^1H NMR δ=1.40—2.05 (m, 4H, 4-CH_2 and 9-CH_2), 2.05—2.95 (m, 3H, 5-H and 8-CH_2), 3.03 (m, 1H, 3-$H_{exo\ or\ endo}$), 3.72 (m, 1H, 3-$H_{exo\ or\ endo}$), 4.33 (m, 1H, 1-H), 5.76 (d, 1H, J= 6.0 Hz, 6-H), and 7.30—7.95 (m, 5H, aromatic). Found: C, 56.22; H, 5.40; N, 4.79%. Calcd for $C_{14}H_{16}NO_2ClS$: C, 56.46; H, 5.43; N, 4.70%.

2-Phenylsulfonyl-3',6'-bis(methoxycarbonyl)-6,7-(4',5'-pyridazino)-2-azabicyclo[3.3.1]non-6-ene (14). A solution of a mixture of **11** (0.1 g, 0.38 mmol) and **12** (0.15 g, 0.76 mmol) in chloroform (10 cm^3) was stirred at 50 °C for 15 h. After the removal of chloroform *in vacuo*, the residue was chromatographed on a silica-gel column using chloroform as the eluant to give **14** (0.18 g, 91%) and **15** (0.11 g, 57%). Compound **14** was recrystallized from chloroform–benzene and **15** from chloroform–hexane. **14**: mp 197—199 °C; IR (KBr) 1735 cm^{-1} (CO); ^1H NMR δ=1.50—3.70 (m, 9H, 3-CH_2, 4-CH_2, 5-H, 8-CH_2, and 9-CH_2), 3.86 (s, 3H, -CO_2Me), 3.92 (s, 3H, -CO_2Me), 4.52 (m, 1H, 1-H), and 7.30—7.85 (m, 5H, aromatic); ^{13}C NMR δ=27.1, 29, 29.8, and 30.3 (4-, 5-, 8-, and 9-C), 37.7 (t, 3-C), 45.7 (d, 1-C), 53.1 and 53.3 (OMe), 127, 129.3, and 132.7 (aromatic), 137.6 and 140 (s, 6- and 7-C), 151.2 and 152 (s, 3'- and 6'-C), and 164.5 and 164.7 (s, CO). Found: C, 55.38; H, 4.77; N, 9.70%. Calcd for $C_{20}H_{21}N_3O_6S$: C, 55.67; H, 4.92; N, 9.74%. **15**: mp 174.5—175.5 °C; IR (KBr) 1728 cm^{-1} (CO); ^1H NMR 3.83 (s, 6H, -CO_2Me), and 7.42 (brs, 2H, NH). Found: C, 35.99; H, 4.04; N, 27.99%. Calcd for $C_6H_8N_4O_4$: C, 36.08; H, 4.00; N, 27.75%.

Reaction of 16 with 12. A solution of a mixture of **16** (0.1 g, 0.34 mmol) and **12** (0.13 g, 0.68 mmol) in chloroform (5 cm^3) was stirred at 50 °C for 15 h. The reaction mixture was worked up as described in the case of **11**.

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