FTIR Spectral Study of Intramolecular Hydrogen Bonding in Thromboxane A_2 Receptor Antagonist S-145 and Related Compounds. 3. Conformation and Activity of S-145 Analogues

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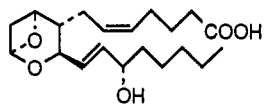
S-145, (±)-(5*Z*)-7-[3-*endo*-[(phenylsulfonyl)amino]bicyclo[2.2.1]hept-2-*exo*-yl]heptenoic acid, its chain analogues $HO_2C(CH_2)_nNHSO_2Ph$ (n = 3–8, 10, and 11) **1–8**, and (5*Z*)-9-(phenylsulfonyl)aminonon-5-enoic acid (**9**) were synthesized in order to elucidate the dependence of the conformation in solution and of the pharmacological activity on the side-chain length. Their FTIR spectra were measured in dilute CCl_4 solution. For these compounds, intramolecular hydrogen bonds similar to those observed for S-145 were found between the carboxyl and sulfonamido groups. A linear relationship was also found between the percentage (ρ) of the intramolecular hydrogen-bonded molecules and the n value. Compounds **1–9** were examined in vitro for inhibitory concentrations (IC_{50}) against U-46619- and collagen-induced aggregations for rabbit and rat washed platelets (WP), respectively, and U-46619-induced contraction for rat aorta. Three kinds of TXA_2 receptor antagonistic potencies [$\log(1/IC_{50})$] showed parabolic correlations with the n value, though the ρ value was in direct proportion to the n value. The log ($1/IC_{50}$) values for **6** (n = 8), which forms a 12-membered ring similar to the one observed for S-145, were found to be maximal values in **1–8** and were comparable to those for BM-13177. In compounds **9** (ρ = 83%) and S-145 (ρ = 89%), the IC_{50} values of 41 and 2.9 nM for rat WP were 10 and 141 times lower than that of **6** (ρ = 52%), respectively. In these compounds, which form the 12-membered ring, the inhibitory potencies increase as the ρ value increases.

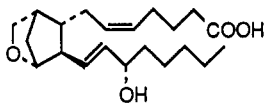
Introduction

Thromboxane A_2 (TXA_2) induces very potent vasoconstriction, platelet aggregation, and bronchoconstriction.[1] Therefore, an excess of TXA_2 has been considered to be one of the causes of cardio- and cerebrovascular diseases. In our laboratory, S-145, which was designed on the basis of the idea that U-shaped analogues of BM-13177 (sulotroban)[2] may be good TXA_2 receptor (TXA_2R) antagonists, was found to possess strong TXA_2R antagonistic properties.[3,4] Thus, we have been interested in the conformations of BM-13177 and S-145 in nonpolar solvents from the standpoint of structure-activity relationships because their conformations were anticipated to be close to those at the binding site of TXA_2R in the first approximation. On the basis of analyses of FTIR spectra of these compounds, a TXA_2R agonist U-46619,[5] and five TXA_2R antagnists in dilute CCl_4 and $CHCl_3$ solutions, we were able to establish the conformations with the large-membered ring formed by the intramolecular hydrogen bonds between a carboxyl group of the α-side chain and a functional group of the ω-side chain in these compounds, except for BM-13177.[6,7] In addition, for TXA_2 and several TXA_2R agonists, we presumed the conformation to have a 15-membered ring similar to the one observed for U-46619 and reported a geometrical resemblance among all of these compounds.[7]

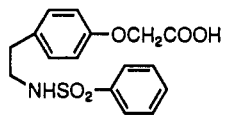
From the structural standpoint, BM-13177 cannot form the intramolecular hydrogen bonds between the carboxyl and the sulfonamido groups. This suggests that an active



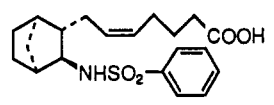
TXA_2



U-46619



BM-13177 (Sulotroban)



S-145

conformation of TXA_2R agonists and antagonists differs by the conformation with the large-membered rings formed by the intramolecular hydrogen bonds between these groups. However, the compounds examined, except for BM-13177, mainly existed in the conformation with the large-membered ring in dilute CCl_4 solution, where the environment is presumed to be similar to that of the binding site in TXA_2R[8] because the continuous dielectric constant of protein is close to that of CCl_4, as reported previously.[6,7] Therefore, it was assumed that even if the active conformation were a nonintramolecular hydrogen-bonded one, it would not greatly differ from the conformation of the large-membered ring. Based on this assumption, we examined the structure–activity relationships for S-145 and its analogues.

In dilute CCl_4 solution, S-145 and its three stereoisomers mainly existed in the conformations with the 12-membered ring as in I.[6,9] Comparison of these conformations indicated that the spatial arrangements of a bicyclo[2.2.1]-heptane ring largely deviate from each other, but we found that these compounds exhibit efficient TXA_2R antagonistic activities with roughly comparable potencies.[9] When the position of the bicyclo[2.2.1]heptane ring in the S-145 derivatives had slid to the adjacent carbon toward the carboxyl group, the TXA_2R antagonistic activity of these compounds, which are presumed to form the 12-membered

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(8) TXA_2/PGH_2 receptor (57-kDa protein) was purified from the membranes of human blood platelets, but the details of the binding site are not known yet. Ushikubo, F.; Nakajima, M.; Hirata, M.; Okuma, M.; Fujiwara, M.; Narumiya, S. *J. Biol. Chem.* **1989**, *264*, 16496.
(9) Ohtani, M.; Narisada, M. *J. Med. Chem.* **1990**, *33*, 1027.

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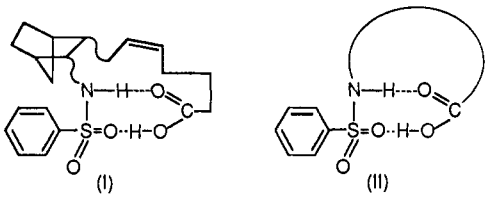
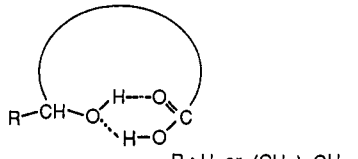


(I)

(II)

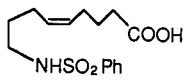


R : H or $(CH_2)_5CH_3$

(III)

$HOOC(CH_2)_nNHSO_2Ph$

1 n = 3 5 n = 7
2 n = 4 6 n = 8
3 n = 5 7 n = 10
4 n = 6 8 n = 11



9

$HOOC(CH_2)_{11}OH$

10

$HOOC(CH_2)_{10}CH(CH_2)_5CH_3$ (OH)

11

$CH_3(CH_2)_9OH$

12

$CH_3(CH_2)_4CHCH_2CH_3$ (OH)

13

ring due to the intramolecular hydrogen bonds, was little affected by the spatial arrangement of the bicyclic ring.[10] However, the introduction of a methylene group between the bicyclic ring and the (phenylsulfonyl)amino group in 7-oxabicyclo[2.2.1]heptane and 6,6-dimethylbicyclo-[3.1.1]heptane derivatives leads to a decrease of the TXA_2R antagonistic activity of these compounds which are presumed to form a 13-membered ring due to the intramolecular hydrogen bonds.[11] Furthermore, several bicyclo[3.1.0]hexane derivatives which are mimics of S-145 were found to possess strong TXA_2R antagonistic activity.[12] From these findings, it was inferred that in the S-145 analogues, the 12-membered ring structure containing the (phenylsulfonyl)amino and the carboxyl groups strongly participates in the exhibition of the TXA_2R antagonistic activity, although the effect of the bicyclic rings may not be disregarded. In order to confirm this inference experimentally, we synthesized chainlike S-145 analogues **1–9**, which seem to form various kinds of rings due to the intramolecular hydrogen bonds as in II, and obtained their FTIR spectra in dilute CCl_4 solution and their inhibitory concentrations (IC_{50}) against U-46619- and collagen-induced aggregations for rabbit and rat washed platelets (WP), respectively, and U-46619-induced contraction for rat aorta. For the chain compounds **10** and **11**, which can form the 15-membered ring due to the intramolecular hydrogen bonds (III) similar to that observed for U-46619,[6] their FTIR spectra in dilute CCl_4 solution and their IC_{50} values for rabbit WP were also measured. Full-optimization curve analysis was applied to all spectra in dilute CCl_4 solution because of a separation of overlapping absorption bands. The correlations between the number (n) of the methylene group and the percentage (ρ) of the intramolecular hydrogen-bonded molecules or the TXA_2R antagonistic potencies [$\log(1/IC_{50})$] were examined for the chainlike S-145 analogues, except for **9**.

Results and Discussion

(a) Intramolecular Hydrogen Bonding. The spectral parameters obtained for dilute CCl_4 solutions of **4–13** at concentrations below 5×10^{-5} M are listed in Table I together with the assignments of peaks and the N, the σ, and the ρ values, where N is the percentage of non-hydrogen-bonded molecules and σ is the percentage of dimers formed by the intermolecular hydrogen bonds between the carboxyl groups and those of **1–3** were not obtained because of low solubilities. The FTIR spectra of 4-8 are shown in Figure 1. In general, the formation of the hydrogen bond, XH···O=Y, causes a shift of the stretching vibration bands ν_{XH} and $\nu_{Y=O}$ to lower wavenumber.[13]

For compounds **4–8**, the intensities of the free ν_{OH} band at ca. 3532 cm^{-1} for the carboxyl group and the free ν_{NH} band at ca. 3390 cm^{-1} for the sulfonylamido group decreased and the intramolecular hydrogen-bonded ν_{OH} and ν_{NH} bands[6] appeared in the range of 3300–3200 cm^{-1}. Correspondingly, the intensity of the free $\nu_{C=O}$ band at ca. 1758 cm^{-1} for the carboxyl group also decreased and the intramolecular hydrogen-bonded $\nu_{C=O}$ band appeared in the range of 1716–1712 cm^{-1}. The changes of the intensities for all bands became larger in the order of **4–8**. In addition, compared with the antisymmetric ν_{SO_2} band at 1342 cm^{-1} observed for the sulfonylamido group of N-methyl(phenylsulfonyl)amine in dilute CCl_4 solution, its band which was shifted to a lower wavenumber was observed at 1332 cm^{-1} for **4**, 1330 cm^{-1} for **5**, 1329 cm^{-1} for **6**, and 1327 cm^{-1} for **7** and **8**.[14] From these findings, it is clear that compounds **4–8** exist in conformations with 7-12-, 14-, and 15-membered rings due to the intramolecular hydrogen bonds (II) between the carboxyl and the sulfonylamido groups as in S-145,[6] respectively. Figure 2 shows plots of the ρ values versus the n values or the size (S) of the ring formed for the hydrogen bonds. The ρ value increased linearly in proportion to the n or the S value.

For compounds **8** and **9**, the results of peak separation of the FTIR spectra are shown in Figure 3. The spectral behaviors of **9**, except for the separation into two intramolecular hydrogen-bonded $\nu_{C=O}$ bands, are similar to those of **8** as mentioned above. The antisymmetric ν_{SO_2} band for **9** was shifted to lower wavenumber by 15 cm^{-1} than that of N-methyl-(phenylsulfonyl)amine. These findings indicate that compound **9** forms the 12-membered ring in which the carboxyl and the sulfonylamido groups are joined by the intramolecular hydrogen bonds. Compound **9** gave two intramolecular hydrogen-bonded $\nu_{C=O}$ bands at 1723 and 1710 cm^{-1}, indicating that the equilibrium exists between two conformers which is attributable to the double bond as observed for S-145.[6]

In Figure 2, the ρ value was plotted against the S value in **9** and S-145, where the ρ value of S-145 is 89%.[6] The ρ values become larger in the order of **6**, **9**, and S-145, although the 12-membered ring is formed in these compounds. This suggests that the degree of freedom in the motions of the carboxyl and the (phenylsulfonyl)amino groups in these compounds becomes smaller in the order

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(14) For compounds **4–6**, free antisymmetric ν_{SO_2} bands were observed at 1344, 1343, and 1341 cm^{-1}, respectively, because their ρ values are less than 50%.

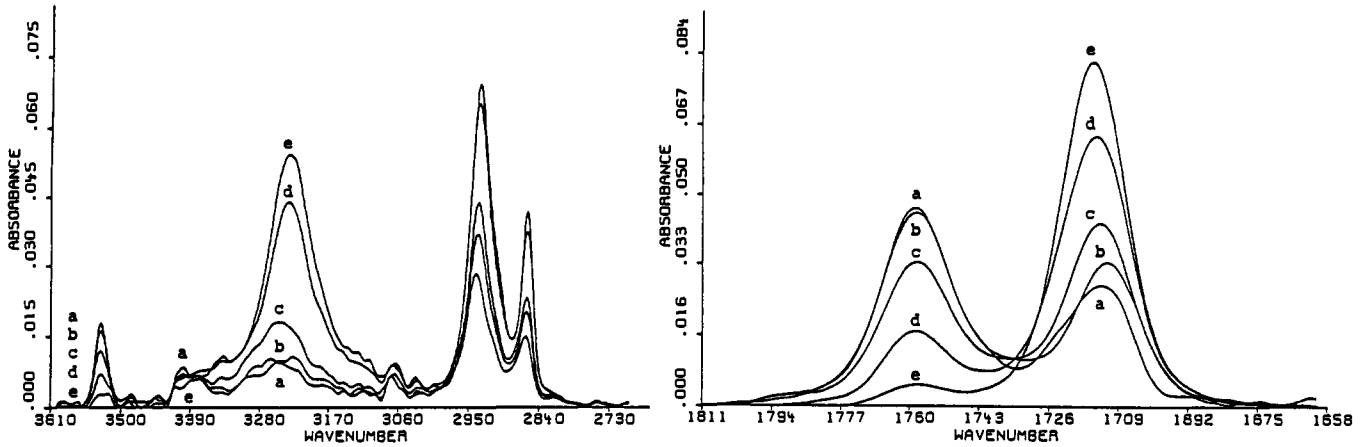

Figure 1. FTIR spectra of 4–8 in CCl_4 in 5.0-cm cell; (a) **4**, 3.0347×10^{-5} mol dm^{-3}; (b) **5**, 3.0347×10^{-5} mol dm^{-3}; (c) **6**, 3.0184×10^{-5} mol dm^{-3}; (d) **7**, 3.1159×10^{-5} mol dm^{-3}; (e) **8**, 3.0572×10^{-5} mol dm^{-3}.

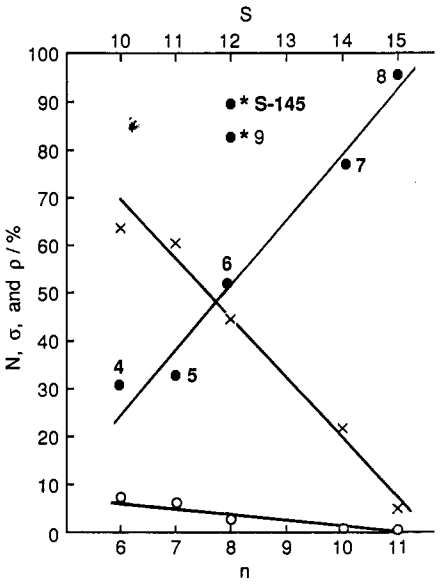

Figure 2. Variations of N (×), σ (○), and ρ (●) with chain length for $HO_2C(CH_2)_nNHSO_2Ph$ in CCl_4 at 3.01×10^{-5}–3.18×10^{-5} mol dm^{-3}, where n is the number of carbon atoms separating functional groups and S is the size of a ring formed by the intramolecular hydrogen bonds. *Plots of ρ versus S.

of **6**, **9**, and S-145, because **9** has a rigid moiety, a double bond, and S-145 has an additional one, the bicyclic ring.

The results of peak separation of the FTIR spectra in **11** are shown in Figure 4. Also, compound **10** shows spectral behavior similar to that of **11**. For compounds **10** and **11**, the intensities of the free ν_{OH} band at 3532 cm^{-1} and the free $\nu_{C=O}$ band at 1759 cm^{-1} for the carboxyl group decreased and the intramolecular hydrogen-bonded ν_{OH} and $\nu_{C=O}$ bands at 3174 and 1734 cm^{-1} appeared for **10** and 3155 and 1733 cm^{-1} for **11**, respectively. In addition, compared with the intensities of the free ν_{OH} band of the hydroxyl group in primary alcohol **12** and secondary alcohol **13**, decreases of these intensities were observed for **10** and **11**, respectively. From these findings, it is evident that compounds **10** and **11** exist in the conformation with the 15-membered ring formed by the intramolecular hydrogen bonds (III) between the carboxyl and hydroxyl groups as observed for U-46619.[6] However, the ρ values of **10** and **11** are significantly smaller than the 81% for U-46619. For compounds **10** and **11**, the $\nu_{C=O}$ band was observed at 1711 cm^{-1}, suggestive of the dimer. The σ value which was calculated from the intensity of this band agreed well with the value which was estimated from the intensity of the free $\nu_{C=O}$ band at 1759 cm^{-1}, as shown in Table I. The band at 1711 cm^{-1} was assigned to the dimer $\nu_{C=O}$ band. As mentioned above, the ring structures of **4**–**11** in dilute CCl_4 solution were revealed through the study of their FTIR spectra.

(b) Biological Activities. Compounds **1**–**11** and S-145 were examined, with a previously described procedure,[3,15] for their inhibitory activity against biological responses induced by TXA_2-related substances, as mentioned in the Introduction. Three kinds of IC_{50} values obtained for these compounds are shown in Table II, together with the physical properties of **1**–**9**. The characteristic IR frequencies of **1**–**9** are shown in Table III. The IC_{50} values for rat WP and rat aorta were corrected for the values for S-145 reported.[3]

Figure 5 shows the plots of the logarithm of the reciprocal of IC_{50} as the TXA_2R antagonistic potency against the n or the S value in the chainlike S-145 analogues **1**–**8**. The obvious effect of the chain length on these three kinds of potencies was revealed by the parabolic dependency of the $\log(1/IC_{50})$ values on the n or the S values. Three kinds of $\log(1/IC_{50})$ values for **6** (n = 8), which forms a 12-membered ring similar to that of S-145, showed the maximum value, although the compound with n = 9 is missing from these correlations. The $\log(1/IC_{50})$ values of **6** are comparable to those of BM-13177. On the other hand, the ρ value increases with an increasing n or S value in this case. These results indicate that because compound **6** does not include the bicyclic ring, the 12-membered ring structure is strongly associated with the exhibition of the TXA_2R antagonistic activity in S-145 analogues as inferred in the Introduction.

Figure 5 is a plot of the $\log(1/IC_{50})$ values of **9** and S-145 against the S value. The $\log(1/IC_{50})$ value increases as the ρ value increases in compounds **6**, **9**, and S-145 which form the 12-membered ring: their ρ values are 52, 83, and 89%, respectively. These findings indicated that the TXA_2R antagonistic potency in these compounds increases as the degree of freedom in the motions of the two functional groups decreases. In the equilibrium (free form) ⇄ (intramolecular hydrogen-bonded form), the free energy difference ΔG is approximately given by $\Delta G = -2.303RT \log(\rho/N)$. The ΔG values estimated for **6**, **9**, and S-145 are small, −0.03, −0.9, and −1.3 kcal/mol, respectively. Therefore, cleavage of the intramolecular hydrogen bonds may readily occur in these compounds. If the molecule cleaved is the active one and its conformation is similar to that of the 12-membered ring, the smaller the degree of freedom in the motions of the carboxyl and the (phe-

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Table I. FTIR Spectral Data[a] of Compounds 4–13 in CCl_4 (5-cm Cell)

compd	assign.[b]		ν, cm^{-1}	ϵ, mol^{-1} dm^3 cm^{-1}	$\Delta\nu_{1/2}$, cm^{-1}	10^8 A, cm^2 s^{-1} $molecule^{-1}$	N,[c] %	σ,[d] %	ρ,[e] %	10^5c,[f] M
4	ν_{OH}	F	3531.1	117.2	22.7	34.1				3.0347
		H	3239.0	39.7	178.7	79.0				
	$\nu_{C=O}$	F	1758.2	318.0	20.2	86.3	63.4	(6.4)	30.2	
		H	1714.5[g]	187.6	19.4	46.7				
	ν_{NH}	F	3389.1	38.4	52.8	24.6				
		H	3238.9	23.5	72.9	22.5				
5	ν_{OH}	F	3531.1	107.5	22.3	30.7				3.0662
		H	3242.7	45.7	153.8	83.0				
	$\nu_{C=O}$	F	1758.2	305.5	20.2	84.0	60.9	(5.9)	33.3	
		H	1712.1[g]	224.3	18.2	57.0				
	ν_{NH}	F	3389.5	40.9	49.3	24.7				
		H	3270.6	23.4	62.1	17.7				
6	ν_{OH}	F	3530.9	81.8	22.9	24.7				3.0184
		H	3248.6	42.2	247.1	126.5				
	$\nu_{C=O}$	F	1757.9	228.1	20.7	64.6	45.4	(3.0)	51.6	
		H	1713.9[g]	293.3	18.3	72.9				
	ν_{NH}	F	3392.3	29.2	45.1	16.1				
		H	3247.9	77.1	80.9	86.0				
7	ν_{OH}	F	3532.8[h]	38.8	24.8	9.1				3.1159
		H	3231.9	84.8	237.8	245.2				
	$\nu_{C=O}$	F	1757.7	109.2	19.7	27.2	21.8	(0.4)	77.8	
		H	1715.0	427.4	19.7	109.6				
	ν_{NH}	F	3394.4[i]	20.9	22.8	6.6				
		H	3232.1	197.8	64.8	177.8				
8	ν_{OH}	F	3532.8[h]	9.6	24.8	2.4				2.9705
		H	3225.1	129.9	212.3	337.9				
	$\nu_{C=O}$	F	1758.7	26.9	20.1	5.5	5.4	(0)	94.5	
		H	1715.4	576.6	18.1	135.9				
	ν_{NH}	F	3394.4[i]	5.2	22.8	1.6				
		H	3230.9	236.5	64.6	186.5				
9	ν_{OH}	F	3532.8[h]	30.5	24.8	7.2				3.0572
		H	3252.5	34.7	288.4	118.2				
	$\nu_{C=O}$	F	1755.1	85.8	25.7	26.9	17.1	(0.1)	82.8	
		H	1723.4	177.4	20.9	50.0				
		H	1710.2	270.8	15.3	55.7				
	ν_{NH}	F	3394.4[i]	16.4	22.8	5.7				
		H	3250.8	124.8	95.7	166.5				
10	ν_{OH}	F	3532.3	123.4	23.8	40.4				3.5153
		H[j]	3174	21	245	65				
	$\nu_{C=O}$	F	1758.6	351.7	19.6	91.2	70.1	(9.1)	20.8	
		H	1734.1	105.9	21.0	27.2				
		D	1711.1	100.7	15.4	20.8		12.2		
	ν_{OH}(12-OH)	F	3632.3	53.6	27.8	18.2				
11	ν_{OH}	F	3532.3	115.1	23.1	36.2				4.1599
		H[j]	3155	21	216	61				
	$\nu_{C=O}$	F	1758.5	332.5	19.6	87.0	66.2	(9.6)	24.2	
		H	1733.1	120.7	20.3	29.9				
		D	1711.3	102.1	16.6	22.7		12.4		
	ν_{OH}(12-OH)	F	3623.4	41.2	29.7	14.8				
12	ν_{OH}	F	3634.3	66.5	25.3	21.4				4.1899
13	ν_{OH}	F	3627.4	51.9	22.2	16.1				4.0251

[a] ν, ϵ, $\Delta\nu_{1/2}$, and A are the band frequency, the molar absorption coefficient, the band width at half-intensity, and the integrated intensity, respectively. [b] ν_{OH}, $\nu_{C=O}$, and ν_{NH} show OH, C=O, and NH stretching vibration bands, respectively, F, H, and D are free, intramolecular hydrogen-bonded, and dimer bands, respectively. [c] Percentage (N) of non-hydrogen-bonded molecules, $N = (\epsilon/501.9)100$, where 501.9 is the ϵ value of 100% free $\nu_{C=O}$ band of lauric acid in CCl_4.[6] [d] Percentage (σ) of dimers, $\sigma = (\epsilon/822.6)100$, where 822.6 is the true ϵ value per $\nu_{C=O}$ band of dimer in lauric acid in CCl_4.[6] For 4–9, the σ values given in parenthese were approximately estimated by the equations[7] $\log c_f = 0.245\sigma_o^{1/2} - 5.492$ and $\sigma = N\sigma_o/100$, where c_f is the concentration of free molecules and σ_o is the percentage of dimers at c_f, because the parameters of dimer $\nu_{C=O}$ bands were not obtained for their compounds. In order to allow comparison with the experimental value, this equation was also applied to 10 and 11 and the σ values estimated were given in parentheses. [e] Percentage (ρ) of intramolecular hydrogen-bonded molecules, $\rho = 100 - (N + \sigma)$. [f] Concentration. [g] The band is overlapped by the dimer $\nu_{C=O}$ band. [h] The parameters were estimated to be approximately N% of the parameters in lauric acid, because the band is weak and was overlapped by intramolecular hydrogen-bonded ν_{OH} and ν_{NH} bands.[6] [i] The parameters were estimated to be approximately N% of the parameters in (±)-2-*exo*-propyl-3-*endo*-(phenylsulfonyl)aminobicyclo[2.2.1]heptane because the band is weak and was overlapped by intramolecular hydrogen-bonded ν_{OH} and ν_{NH} bands.[6] [j] The band is overlapped by the intramolecular hydrogen-bonded ν_{OH} band of 12-OH group.

nylsulfonyl)amino groups is, and the more these compounds would be suitable for the binding site of TXA_2 in the receptor. This hypothesis was consistent with the observed results because the TXA_2R antagonistic potency becomes stronger in the order of 6, 9, and S-145.

Because the 15-membered ring in compounds 10 and 11 is also formed by intramolecular hydrogen bonds (III) as in U-46619, their aggregation activity for rabbit WP and their inhibitory activity against aggregation for rabbit WP induced by U-46619 were measured. However, these activities were not obtained for 10 and 11. The absence of activities for 11, which includes chains similar to the α- and the ω-side chains of U-46619, may have arisen from the small ρ value, suggesting that the degree of freedom in the motions of the functional groups is large.

Conclusion

Nine chain analogues of S-145 were synthesized in order

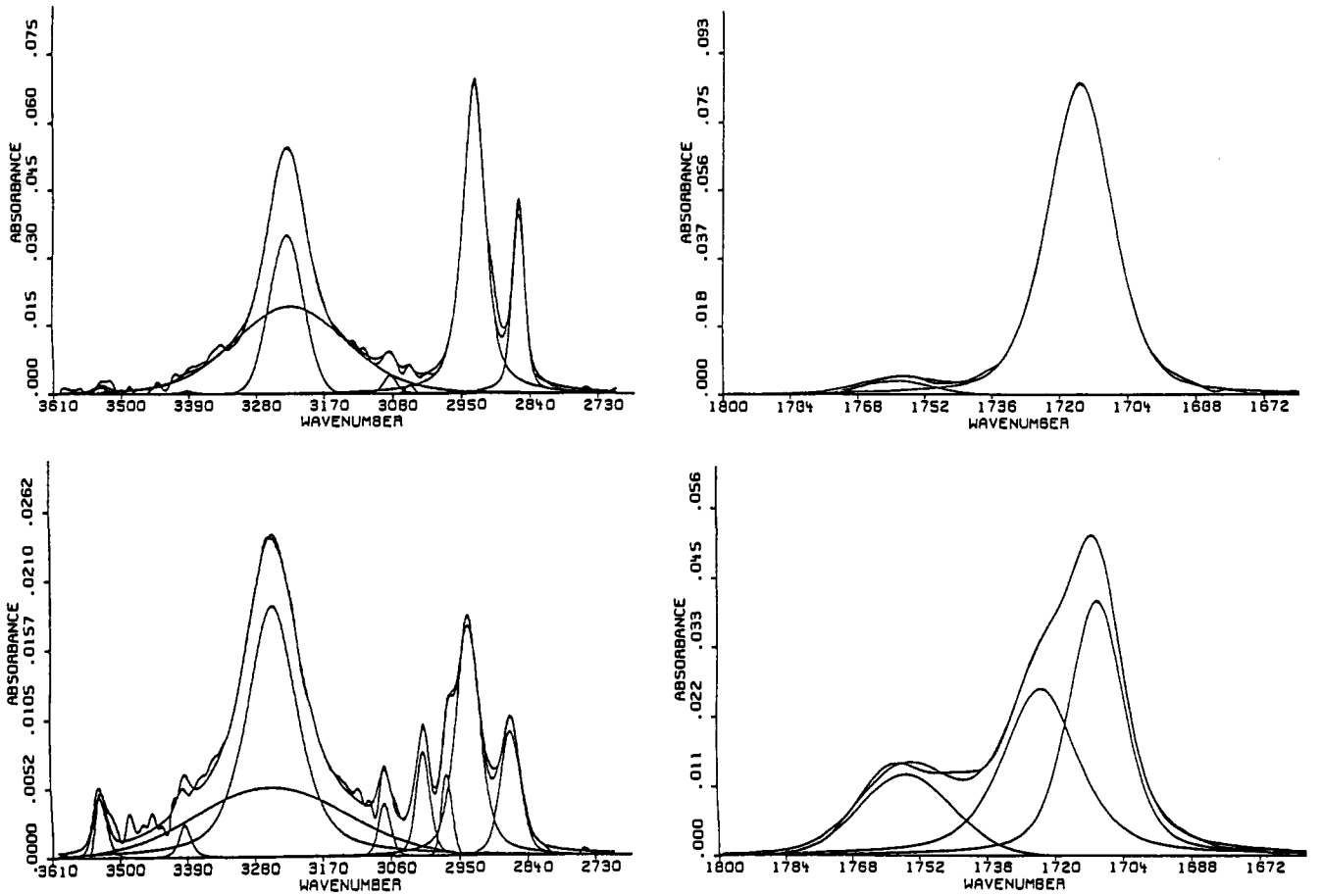

Figure 3. FTIR spectra of **8** (upper) and **9** (lower) in CCl_4 and the results of peak separations of their spectra. Spectra were obtained with a 5.0-cm cell: **8**, 2.9705×10^{-5} mol dm^{-3}, and **9**, 3.0572×10^{-5} mol dm^{-3}.

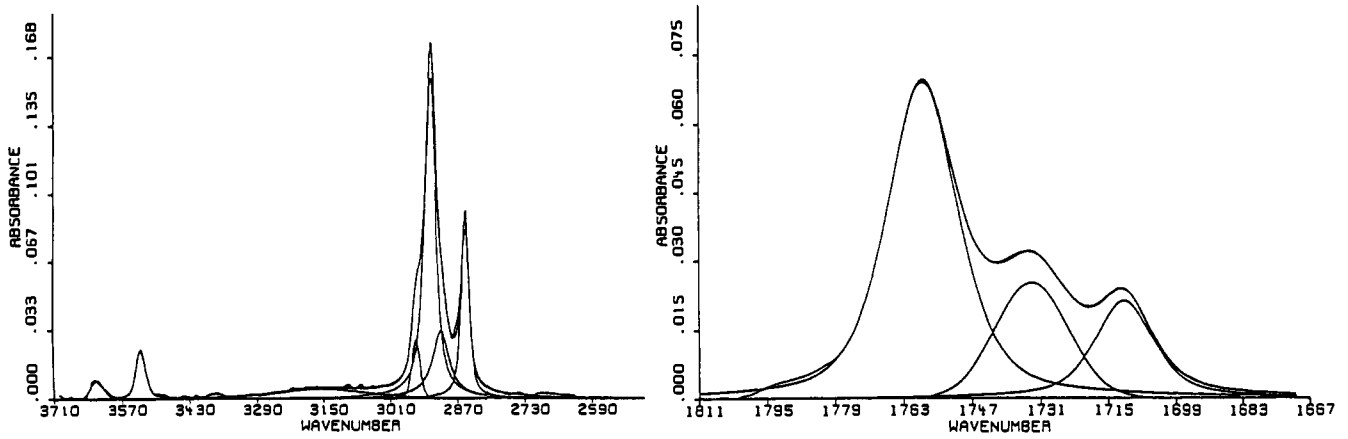

Figure 4. FTIR spectra of **11** in CCl_4 of 4.1599×10^{-5} mol dm^{-3} in a 5.0-cm cell and the results of peak separation of their spectra.

to study the structure-activity relationships. We found that the 12-membered ring structure formed by the intramolecular hydrogen bonds between the (phenylsulfonyl)amino and the carboxyl groups plays an important role in the exhibition of the TXA_2R antagonistic activities. It has been reported[3,9-11] that various kinds of bicyclic ring derivatives which mimic S-145 exhibit higher TXA_2R antagonistic activities, but some of their stereoisomers exhibit somewhat lower activities. This can be attributed to the difference of compatibilities of the (phenylsulfonyl)amino and the carboxy groups for the binding site of TXA_2 in the receptor because the relative spatial arrangement between these groups are primarily governed by the change of steric bulkiness in the bicyclic rings and the variety of dihedral angles between the α- and the ω-side chains.[16] The information obtained should be helpful for designing drugs

(16) The effects of four stereoisomers of bicyclo[2.2.1]heptane derivatives on aggregation for rat WP were roughly comparable,[9] but not in the case of 7-oxabicyclo[2.2.1]heptane ones. The latter compounds with the *exo*-(phenylsulfonyl)amino group exhibited much higher IC_{50} values than those with *endo*-ones.[11a] This may be mainly attributed to the formation of an intramolecular hydrogen bond between an NH bond of the *exo*-(phenylsulfonyl)amino group and the 7-oxygen atom in the bicyclic ring as in 2α,5α-epoxy-5α-cholestan-3α-ol[17] when these compounds do not form the intramolecular hydrogen bonds between the α- and ω-side chains.

(17) Takasuka, M.; Tanida, H. *J. Chem. Soc., Perkin Trans. 2* **1980**, 486.

Table II. Physical Properties of 1–9 and Inhibitory Concentrations (IC_{50}) of S-145, BM-13177, and 1–11

compd	formula	anal.[a]	mp, °C	S[b]	IC_{50}, nM: rabbit WP[c]	rat WP[d]	rat aorta[e]
S-145[f]				12	6	2.9[g]	1.4[g]
BM-13177					300[f]	260[h]	1800[h]
1	$C_{10}H_{13}NO_4S$	C, H, N, S	93–94	7	negative	>14500	>140000
2	$C_{11}H_{15}NO_4S$	C, H, N, S	97–98	8	negative	>14500	>140000
3	$C_{12}H_{17}NO_4S$	C, H, N, S	125–126	9	negative	>14500	>140000
4	$C_{13}H_{19}NO_4S$	C, H, N, S	80–81	10	>10000	11600	55300
5	$C_{14}H_{21}NO_4S$	C, H, N, S	84–85	11	700	290	2800
6	$C_{15}H_{23}NO_4S$	C, H, N, S	87–88	12	400	410	1600
7	$C_{17}H_{27}NO_4S$	C, H, N, S	97–98	14	ca. 10000	4350	4600
8	$C_{18}H_{29}NO_4S$	C, H, N, S	112–113	15	>10000	3480	6400
9	$C_{15}H_{21}NO_4S$	C, H, N, S	oil	12	48[f]	41	ND[i]
10[j]				15	negative	k	k
11[j]				15	negative	k	k

[a] Analyses (C, H, N, S) are within ±0.3% of the calculated values. [b] Size of a ring formed by the intramolecular hydrogen bonds. [c] Aggregation of washed platelets (WP) was induced by 1 μM U-46619. [d] Aggregation of washed platelets (WP) was induced by 4 μg/mL collagen. [e] Concentration of rat thoracic aorta induced by 30 nM U-46619. [f] Na salt. [g] Reference 3. [h] Reference 9. [i] The value was not determined. [j] Since compounds 10 and 11 were commercially available (purchased from Aldrich Chemical Co.), their physical properties are not shown in the table. [k] The value was not measured because the aggregation for rabbit WP induced by U-46619 was not observed.

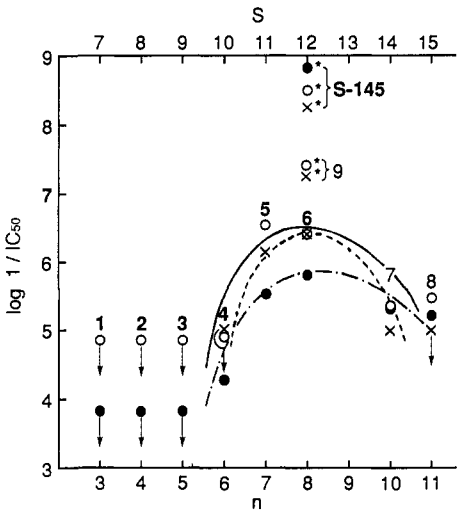

Figure 5. Parabolic dependences of log ($1/IC_{50}$) (-×- for rabbit WP, -○- for rat WP, and -●- for rat aorta) on n and S in $HO_2C(CH_2)_nNHSO_2Ph$. The arrow suggests that the true value is smaller than this value (see Table II). *Plots of log ($1/IC_{50}$) versus S.

and for confirming the structure of the binding site.

Experimental Section

General. IR spectra were recorded on a Nicolet 20SXB FTIR spectrometer. The solvent CCl_4 was dried over 4-Å molecular sieves and purified by distillation. All operations for solution were performed in a dry box filled with N_2 gas. All measurements were carried out at 27 °C. The curve-fitting calculations for peak separation of the spectra obtained in CCl_4 solution were carried out with the Nicolet FOCAS program. Since the overtone and combination bands are very weak, these bands were ignored in the calculation. Melting points were determined on a Yanagimoto apparatus and were not corrected. Proton magnetic resonance (^1H NMR) spectra were obtained on a Varian EM-390 spectrometer using deuteriochloroform unless otherwise stated, with tetramethylsilane as an internal reference. Elemental analyses were within ±0.3% of the theoretical values. Compounds 10–13 were obtained from commercial sources.

(5*Z*)-9-[(Phenylsulfonyl)amino]non-5-enoic Acid (9). To a solution of 3.09 g (30 mM) of γ-aminobutyric acid in 30 mL of 1 N KOH were added 8.33 mL (60 mM) of triethylamine, 3.83 mL (30 mM) of (phenylsulfonyl)chloride, and 10 mL of dioxane at 25 °C. The exothermic reaction was finished in a few minutes. The mixture was partitioned between AcOEt and 2 N HCl. The organic solution was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was dissolved in AcOEt and treated with diazomethane as usual. The purification of the crude product on silica gel [eluted with toluene–AcOEt (10%)] gave 2.45 g (31.8%) of γ-[(phenylsulfonyl)amino]butyric acid methyl ester (**14**) as a colorless oil. ^1H NMR ($CDCl_3$): δ 1.65–1.95 (m, 2 H), 2.35 (t, J = 7 Hz, 2 H), 3.02 (q, J = 7 Hz, 2 H), 3.64 (s, 3 H), 5.02 (t, J = 7 Hz, 1 H), 7.35–7.95 (m, 5 H).

To a solution of 2.45 g (9.5 mM) of **14** in 15 mL of toluene was added 17.1 mL (1.0 M solution in hexane) of diisobutylaluminum hydride at −78 °C. The mixture was stirred for 30 min at −78 °C, quenched with aqueous ammonium chloride, and partitioned between toluene and 2 N HCl. The organic solution was washed with water, dried over Na_2SO_4, and concentrated in vacuo to give 1.40 g (64.9%) of 1-(phenylsulfonyl)-2-hydroxypyrrolidine (**15**) as a colorless gum. Compound **15** was used for the next reaction without further purification. In a separate flask, 8.20 g (6.16 mM × 3) of (4-carboxybutyl)triphenylphosphonium bromide was suspended in 30 mL of THF, and 4.15 g (6.16 mM × 6) of potassium *tert*-butoxide was added at 25 °C. The red reaction

Table III. Characteristic Infrared Frequencies[a] (cm^{-1}) for Carboxyl and (Phenylsulfonyl)amino Groups in Compounds 1–8 (Nujol) and 9 (Neat)

compd	ν_{NH}	$\nu_{C=O}$	$\nu^{as}_{SO_2}$	$\nu^{s}_{SO_2}$	γ_{CH}	δ_{SO_2}
1	3277	1709	1323	1155	753	594
			1313		720	567
					688	
2	3282	1696	1330	1163	750	559
			1313		728	
					688	
3	3282	1710	1323	1155	749	586
					731	566
					684	
					671	
4	3287	1697	1329	1160	748	564
			1314		727	
					686	
5	3287	1707	1327	1160	755	565
			1307		723	
					689	
6	3291	1696	1328	1160	748	562
					727	
					687	
7	3293	1700	1330	1161	748	559
			1313		728	
					686	
8	3274	1708	1327	1161	758	590
		1694	1308	1147	718	569
					690	
9	3282	1707	1324	1160	756	587
					721	
					690	

[a] ν_{NH}, $\nu_{C=O}$, $\nu^{as}_{SO_2}$, $\nu^{s}_{SO_2}$ show NH, C=O, antisymmetric SO_2, and symmetric SO_2 stretching vibration bands, respectively, γ_{CH}, shows a CH out-of-plane bending vibration band of a phenyl group, and δ_{SO_2} shows a SO_2 bending vibration band.

mixture was stirred for 30 min at 25 °C. To the mixture was added a solution of 1.40 g (6.16 mM) of compound **15** in 5 mL of THF at -20 °C. The mixture was stirred for 1 h at -20 °C and partitioned between AcOEt and 2 N HCl. The organic solution was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified on silica gel [eluted with toluene–AcOEt (9:1)–(4:1)], which gave 750 mg (39.1%) of the desired acid **9** as a colorless gum. ^1H NMR ($CDCl_3$): δ 1.30–1.85 (m, 4 H), 1.85–2.20 (m, 4 H), 2.33 (t, J = 7 Hz, 2 H), 2.93 (q, J = 7 Hz, 2 H), 5.11 (t, J = 7 Hz, 1 H), 5.20–5.45 (m, 2 H), 7.40–7.98 (m, 5 H), 9.10 (br s, 1 H).

9-[(Phenylsulfonyl)amino]nonanoic Acid (6). A mixture of 50 mg of 10% palladium carbon and 311 mg (1 mM) of compound **9** in 20 mL of methanol was stirred for 1 h under hydrogen atmosphere (1 atm). After filtration, the filtrate was concentrated in vacuo to give 300 mg (95.8%) of compound **6** as colorless pillars.

4-[(Phenylsulfonyl)amino]butyric Acid (1). To a solution of 0.5 g of γ-aminobutyric acid in 10 mL of 1 N NaOH and 5 mL of water was added a solution of 1.7 mL of phenylsulfonyl chloride in 1.5 mL of dioxane at room temperature. The mixture was stirred for 2 h at the same temperature, partitioned between ether and water. The aqueous solution was acidified with 2 N HCl and extracted with AcOEt. The organic solution was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The crystalline residue was recrystallized from a mixture of CH_2Cl_2 and n-hexane, which gave 1.1 g (90%) of compound **1** as colorless needles. Compounds **2–5**, **7**, and **8** were synthesized from $H_2N(CH_2)_nCO_2H$ (n = 4–7, 10, and 11) by the same method, respectively. For **1–9**, the physical properties and characteristic infrared frequencies are given in Tables II and III, respectively.

Biology. Tests, using methods described previously,[3,15] gave the results presented in Table II.

Acknowledgment. We are grateful to Dr. M. Narisada, the Director of Shionogi Research Laboratories, Dr. H. Arita, and Dr. K. Ezumi for their helpful discussions and to Dr. K. Hanasaki and Mrs. A. Terawaki for measurements of IC_{50} values of inhibitory activities.

Naphtho and Benzo Analogues of the κ Opioid Agonist *trans*-(±)-3,4-Dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide

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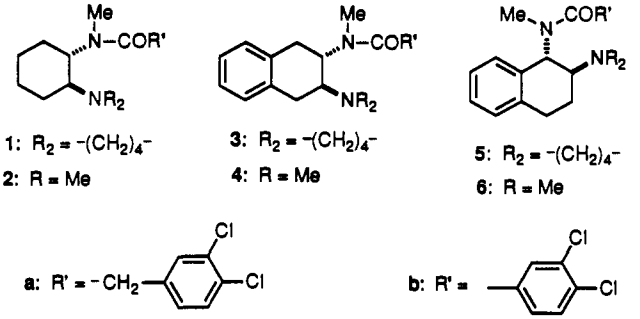
Further elaboration on the structure–activity relationships in our U-50,488 series has revealed that benzologation of this cyclohexane-1,2-diamine derivative provides compounds which either maintain the interaction with the κ receptor (e.g. compounds **3a** and **5a** in the phenylacetamido series) or eliminate the μ receptor mediated analgesia (e.g. compounds **3–6** in the benzamido series). Naphthologation also caused the elimination of μ receptor mediated analgesia (e.g. compounds **17a** and **17b**).

The disclosure[1] of a selective agonist (**1**, U-50,488) for the κ receptor in the central nervous system has triggered significant activity in the preparation of additional agonists and in the search for antagonists in this series.[2] For example, different acyl derivatives of the basic *trans*-1,2-cyclohexanediamine template have been prepared.[3] The recent disclosure[4] of 4,5- (**3a**) and 5,6- (**5a**) benzo derivatives of **1a** has stimulated us to report our efforts in this area.



Chemistry

All the compounds described below are racemic mixtures.

The benzo derivatives **3–6** were prepared by the same general route as that used for U-50,488 starting from the appropriate dihydronaphthalene as shown in Scheme I, routes A and B. Since it had been shown earlier that the 3,4-dichlorobenzamide analogue of **1a** (**2b**) was a μ agonist, these analogues (**3b–6b**) were prepared in addition to the 3,4-dichlorophenylacetamides (**3a,b**).

Finally, naphthologues **17a** and **17b** were prepared as shown in Scheme I, route C. The requisite starting material, 1,4-dihydroanthracene, was prepared as previously described[6] from acid treatment of the Diels–Alder adduct of 1,4-epoxy-1,4-dihydronaphthalene and 1,3-butadiene.

The chemistry outlined in Scheme I is straightforward except that it was found that 2,3-epoxytetralin was quite susceptible to polymerization in the absence of solvent. Thus, this intermediate was not isolated but treated di-

† The Upjohn Co., Kalamazoo, MI.

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