Synthesis and Immunological Activity of 5,6,6a,8,9,11a-Hexahydronaphth[1′,2′:4,5]imidazo[2,1-*b*]thiazoles and 5,6,6a,9,10,11a-Hexahydronaphth[2′,1′:4,5]imidazo[2,1-*b*]thiazoles

Masahiko Saito, Yasutaka Kayama, Tamaki Watanabe, Hisashi Fukushima, Takeshi Hara,*

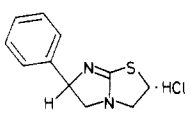
Teijin Institute for Biomedical Research, Asahigaoka, Hino, Tokyo 191, Japan

Kazuo Koyano, Akio Takenaka, and Yoshio Sasada*

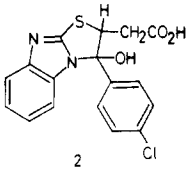
Laboratory of Chemistry for Natural Products, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 227, Japan.
Received April 24, 1980

A series of 5,6,6a,8,9,11a-hexahydronaphth[1′,2′:4,5]imidazo[2,1-*b*]thiazoles (**17** and **20**) and 5,6,6a,9,10,11a-hexahydronaphth[2′,1′:4,5]imidazo[2,1-*b*]thiazoles (**18**) has been synthesized with *cis*- and/or *trans*-1,2-diamino-1,2,3,4-tetrahydronaphthalenes (**12**) as the key intermediates and subsequently evaluated for immunological activity (effects on antibody formation and delayed-type hypersensitivity reaction). Among the compounds tested, *trans*-5,6,6a,8,9,11a-hexahydronaphth[1′,2′:4,5]imidazo[2,1-*b*]thiazole (*trans*-**17a**) and (±)-5,6,6aβ,8,9,11aα-hexahydro-8β-hydroxy-9β-methyl-8α-phenylnaphth[1′,2′:4,5]imidazo[2,1-*b*]thiazole (**20a**) showed the largest immunological activity in mice with a magnitude comparable to that of levamisole and were found to be considerably less toxic than levamisole in an acute toxicological study. The structures of **18a** and **20a** were determined by X-ray crystallography.

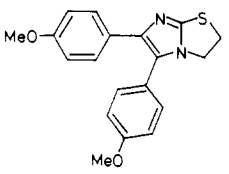
Following the discovery of an immunostimulatory activity for *dl*-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]-thiazole hydrochloride (tetramisole; *dl*-**1**) and its levarotory



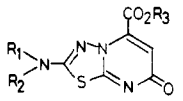
1



2



3



4

enantiomer (levamisole; *l*-**1**) by Renoux and Renoux,[1] other heterocyclic compounds having the cyclic isothioureido moiety incorporated into a fused ring system[2-5] have been synthesized and evaluated for immunological properties and related biological activities. This particular structural type of compound for which immunostimulatory or immunoregulatory activity has been reported includes 3-(*p*-chlorophenyl)-2,3-dihydro-3-hydroxythiazolo[3,2-*a*]benzimidazole-2-acetic acid (NSC 208828; **2**),[2] 2,3-dihydro-5,6-bis(*p*-methoxyphenyl)imidazo[2,1-*b*]thiazole (**3**),[3b] and alkyl 2-(substituted-amino)-7-oxo-7*H*-1,3,4-thiadiazolo-[3,2-*a*]pyrimidine-5-carboxylates (**4**).[5] The pharmacologic profile of levamisole has been studied extensively, and the present state of knowledge indicates its potential use in a broad therapeutic area in which immune suppression or imbalance is ascertained or suspected, such as cancer, rheumatoid arthritis, and recurrent and chronic infections.[6,7]

As part of our program for the search of new immunostimulatory or immunoregulatory agents, we have synthesized and studied the immunological activity of new tetracyclic compounds having an isothioureido group, hexahydronaphth[1′,2′:4,5]imidazo[2,1-*b*]thiazoles (**17a-d** and **20**) and hexahydronaphth[2′,1′:4,5]imidazo[2,1-*b*]-thiazoles (**18a-d**).

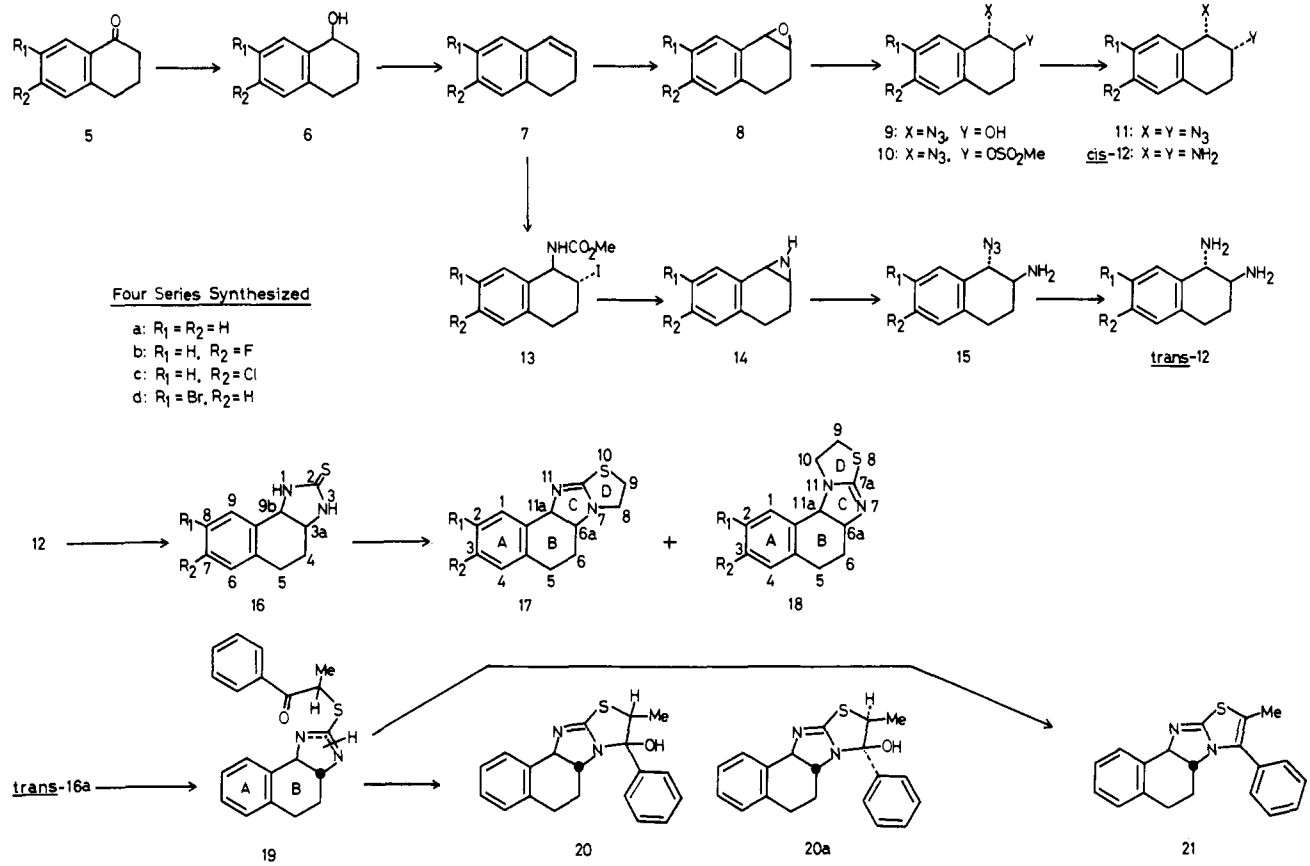
Chemistry. In planning the synthesis of **17**, **18**, and **20**, it was thought to be essential to have 1,2-diamino-1,2,3,4-tetrahydronaphthalenes (**12**) in stereochemically pure form of known geometry in order to avoid complications in synthetic steps thereafter. This was particularly so in the case of compound **20** which has substituents on C_8 and C_9, generating two additional asymmetric carbon atoms.

The cis and trans diamines (*cis*- and *trans*-**12**) were synthesized from appropriately substituted 1,2-dihydronaphthalenes **7**, employing published general methods[8] with some modifications (Scheme I). The required compounds **7** were prepared from the ketones **5**[9-11] via the

(1) G. Renoux and M. Renoux, *C. R. Hebd. Seances Acad. Sci., Ser. D*, **272**, 349 (1971).
(2) (a) C. Bell and P. H. L. Wei, *J. Med. Chem.*, **19**, 524 (1976); (b) R. L. Fenichel, F. J. Gregory, and H. E. Alburn, *Br. J. Cancer*, **33**, 329 (1976); (c) A. Tagliabue, G. Allesandri, N. Polentarutti, A. Mantovani, E. Falantano, A. Vecchi, S. Garattini, and F. Spreafico, *Eur. J. Cancer*, **14**, 393 (1978).
(3) (a) S. C. Cherkofsky and T. R. Sharpe (to Du Pont), U.S. Patent 4 064 260 (1977); (b) P. E. Bender (to SmithKline), Japanese Patent 78 40 797 (1978); (c) R. Gescheke (to Ciba-Geigy), Japanese Patent 79 16 470 (1979).
(4) A. S. Radhakrishna and K. D. Berlin, *Org. Prep. Proced. Int.*, **10**, 39 (1978).
(5) S. Herrling (to Grünenthal), German Patent 27 55 615 (1979).
(6) J. Symoens and M. Rosenthal, *J. Reticuloendothel. Soc.*, **21**, 175 (1976).
(7) For comprehensive reviews on the biological activity of levamisole, including findings in clinical studies as well as in vitro and in vivo studies, see (a) "Control of Neoplasia by Modulation of the Immune System", M. A. Chirigos, Ed., Raven Press, New York, 1977, pp 1-240; (b) "Immune Modulation and Control of Neoplasia by Adjuvant Therapy", M. A. Chirigos, Ed., Raven Press, New York, 1978, pp 1-170.
(8) (a) G. Swift and D. Swern, *J. Org. Chem.*, **32**, 511 (1967); (b) A. Hassner and C. Heathcock, *Tetrahedron*, **20**, 1037 (1964); (c) G. W. H. Potter, N. W. Coleman, and A. M. Monro, *J. Heterocycl. Chem.*, **12**, 611 (1975).
(9) N. L. Allinger and E. S. Jones, *J. Org. Chem.*, **27**, 70 (1962).
(10) A. Rosowsky, M. Chaykovsky, S. A. Yeager, R. A. St. Amand, M. Lyn, and E. J. Modest, *J. Heterocycl. Chem.*, **8**, 809 (1971).

0022-2623/80/1823-1364$01.00/0

Scheme I



alcohols **6**.[12]

The sequence of reactions for the synthesis of **11** involved epoxidation of **7**, ring opening of the epoxides **8** with sodium azide, mesylation of the azido alcohols **9**, and displacement of the methanesulfonyloxy group with the azide group. On the other hand, treatment of **7** with iodine–silver cyanate, followed by heating of the resulting iodoisocyanates in methanol, gave the iodocarbamates **13**, which were converted to the imines **14** with potassium hydroxide and then to **15** with sodium azide. The stereochemical nature of the series of reactions from **7** to **11** and **15** were verified by NMR. Observation of only one 1 H doublet for the C_1 proton of **9**–**11** and **15** indicated that these compounds were not accompanied by their geometrical isomers. The coupling constants observed for the C_1 proton signals of **11a,c,d** were 4 Hz (cis configuration), whereas those of **9**, **10**, and **15** were 7–9 Hz (trans configuration).

Lithium aluminum hydride reduction of the azide group[13] was employed to convert **11** and **15** to the diamines *cis*- and *trans*-**12**, respectively, which were, without purification, treated with carbon disulfide in refluxing aqueous ethanol to give the cyclic thioureido derivatives, *cis*- and *trans*-**16**. The configuration and conformation of these key intermediates were ascertained by the NMR C_{9b} proton chemical shifts and coupling constants (a doublet centered at δ 4.94–5.05 with J = 10 Hz in *cis*-**16** and a doublet centered at δ 4.37–4.44 with J = 12–13 Hz in *trans*-**16**). In *trans*-**16**, the C_{9b}–H bond always takes the pseudoaxial position so as to permit the formation of the five-membered imidazolidine ring including the pseudoequatorial C_{9b}–N_1 and C_{3a}–N_3 bonds. On the other hand, the C_{9b}–H bond of *cis*-**16** takes both pseudoaxial and equatorial positions. Therefore, in NMR spectroscopy the C_{9b} proton of *trans*-**16** is shielded by the benzene ring (or is deshielded less than that of *cis*-**16**), resulting in the resonance of the C_{9b} proton of *trans*-**16** at a higher magnetic field.

Treatment of **16** with 1-bromo-2-(*p*-toluenesulfonyloxy)ethane in the presence of sodium carbonate in refluxing 2-propanol afforded two isomers, **17** and **18**, which were separated by silica gel column chromatography and converted to the hydrochlorides by the standard method. The less polar isomers were assigned the structures of **17** by NMR. In the case of the cis configuration, the less polar isomers exhibit a 1 H doublet centered at δ 5.37–5.40 (J = 9 Hz) and the more polar isomers at δ 4.41–4.45 (J = 9 Hz); the former doublet is assignable to the C_{11a} proton of **17** and the latter to that of **18**. The larger δ values for the C_{11a} protons of **17** are reasonable, because C_{11a} is connected to an sp^2 nitrogen atom, whereas in **18** it is connected to an sp^3 nitrogen atom. In the case of the trans configuration, compounds **17** have a 1 H doublet (J = 12–14 Hz) assignable to the C_{11a} proton at δ 4.82–4.87, while the C_{11a}-proton doublet of **18** is obscured by other signals at δ smaller than 4.32. In the NMR spectra of the HCl salts of trans-**18a,c,d**, the C_{11a} proton signals were discernible as a doublet centered at δ 4.77–4.81 (J = 14 Hz). The structure of **18** was confirmed by an X-ray crystallo-

(11) R. W. Griffin, Jr., J. D. Gass, M. A. Berwick, and R. S. Shulman, *J. Org. Chem.*, **29**, 2109 (1964).

(12) Chizhevskaya and Idel'chick[20] described the dehydration of **6a** to **7a** with sulfuric acid in refluxing methanol in 57% yield. We are also unable to improve the yield under these conditions and found that the major byproduct was 1,2,3,4-tetrahydro-1-methoxynaphthalene. Substitution of benzene for methanol resulted in mixtures of **7a** and naphthalene. Finally, when we employed *p*-toluenesulfonic acid as the catalyst in refluxing benzene, **7a** was obtained in 93% yeild after distillation. The reaction conditions were successfully used for the conversion of **6b–d** to **7b–d**.

(13) J. H. Boyer, *J. Am. Chem. Soc.*, **73**, 5865 (1951).

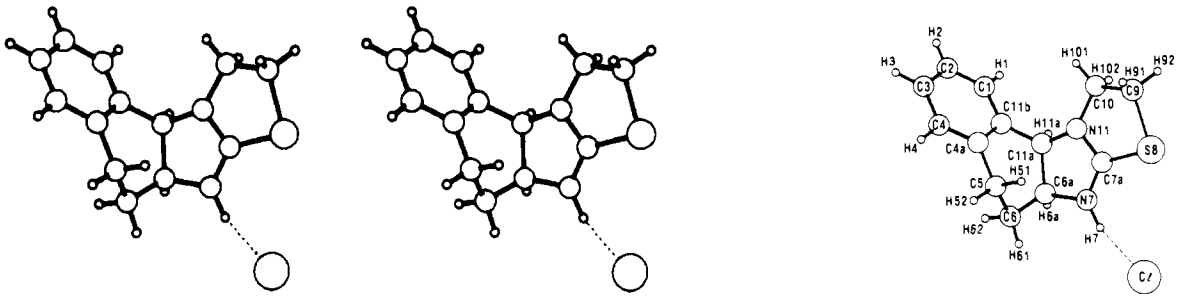


Figure 1. Stereoscopic view of one enantiomer of *cis*-**18a**·HCl.

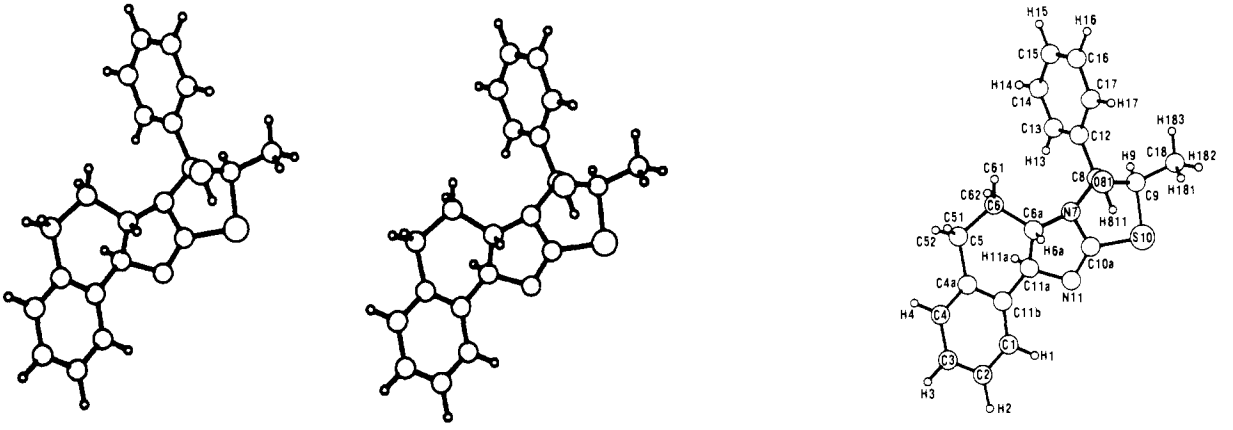


Figure 2. Stereoscopic view of one enantiomer of **20a**.

Table I. 3a,4,5,9b-Tetrahydronaphth[1,2-*d*]imidazoline-2-thiones (16)

compd	mp, °C	recrystn solvent	% yield[a]	formula	anal.[b]
cis-16a	238.5–239	acetone–EtOH	77	$C_{11}H_{12}N_2S$	C, H, N
trans-16a	258.5–259	acetone–EtOH	90	$C_{11}H_{12}N_2S$	C, H, N
trans·16b	256.5–257.5	acetone–MeCN	82	$C_{11}H_{11}FN_2S$	MS[c]
cis-16c	249–250	acetone–MeCN	71	$C_{11}H_{11}ClN_2S$	C, H, N
trans-16c	269–271	MeOH–MeCN	78	$C_{11}H_{11}ClN_2S$	C, H, N
cis-16d	247–248	MeOH–MeCN	75	$C_{11}H_{11}BrN_2S$	C, H, N
trans·16d	259.5–260.5	MeOH–MeCN	70	$C_{11}H_{11}BrN_2S$	C, H, N

[a] Yield of crude material obtained as a precipitate from the reaction mixture. [b] Analyses for the elements indicated were within ±0.4% of the theoretical values. [c] MS indicates that combustion analysis was not performed with the fluorine-containing compound but, instead, that satisfactory mass spectral data were obtained; *m/e* (relative intensity) 222 (100, M^+), 163 (48), 162 (51), 135 (32).

graphic study of *cis*-**118a**·HCl. A stereoscopic view[14] of one enantiomer of *cis*-**18a**·HCl is shown in Figure 1. N_7 is protonated, and a hydrogen bond is formed between the chlorine and N_7. From the bond lengths of C_{7a}–N_7, C_{7a}–S_8, and C_{7a}–N_{11} (Table VIc; supplementary material) the electron pair of the C_{7a}–N_7 double bond, the lone pair of N_{11}, and one of the lone pairs of S_8 are known to be delocalized over the four atoms N_7, C_{7a}, S_8, and N_{11}, the atoms constituting the isothioureido group.[15]

Next, the reaction of *trans*-**16a** with α-bromopropiophenone was studied. Whereas the reaction in boiling glacial acetic acid or ethanol gave the tetrahydronaphthimidazothiazole **21**, the reaction in *N*,*N*-dimethylformamide (DMF) or dimethyl sulfoxide (Me_2SO) at ambient temperature afforded the hexahydronaphthimidazole **20**, the precursor of **21**.

It is noteworthy that the above reactions proceed regiospecifically, in contrast to the reaction of **16**, with 1-bromo-2-(*p*-toluenesulfonyloxy)ethane; the nucleophilic ring closure takes place at N_3, but not at N_1, to give the naphth[1′,2′:4,5]imidazo[2,1-*b*]thiazole ring system. Evidence for this ring closure was provided by the NMR chemical shift of δ 4.80 and 4.98 for the C_{11a} proton of the product,[16] which is reasonable for **20** when compared with the NMR data of C_{11a} H of **17** and **18**. The regiospecificity of the reaction is probably due to the steric interference of the hydrogen atoms of the A ring and the phenyl group derived from α-bromopropiophenone in the intermediate **19**. Since compound **20** has four asymmetric carbon atoms including C_{6a} and C_{11a}, the geometry at which is fixed in trans, eight stereoisomers (four racemates) are theoretically possible. However, the NMR spectrum of the product (HBr salt) obtained in 84% yield from the reaction of *trans*-**16a** and α-bromopropiophenone exhibited only two CH_3 doublets, C*H*CH_3 quartets, and C_{11a}-H doublets in the integral ratio of 3:2. Generation of the free base **20** with aqueous NH_3, followed by three recrystallizations from methylene chloride, gave crystals which show one CH_3 doublet, C*H*CH_3 quartet, and C_{11a}-H doublet, indicating the separation of the two racemates. The ring system and the relative configuration at the asymmetric carbon atoms of this racemate (**20a**) thus obtained in pure state were

Table II. 5,6,6a,8,9,11a-Hexahydronaphth[1',2':4,5]imidazo[2,1-*b*]thiazoles (17) and 5,6,6a,9,10,11a-Hexahydronaphth[2',1':4,5]imidazo[2,1-*b*]thiazoles (18)

compd	salt	mp, °C	recrystn solvent	formula	anal.[a]
cis-17a	HCl[b]	232–235	MeOH–MeCN	$C_{13}H_{15}ClN_2S$	C, H, N
trans-17a	HCl	254–259	MeOH–MeCN	$C_{13}H_{15}ClN_2S$	C, H, N
trans-17b		165–166	CH_2Cl_2–hexane	$C_{13}H_{13}FN_2S$	MS[c,d]
cis-17c	HCl[e]	234–239	MeOH–MeCN	$C_{13}H_{14}Cl_2N_2S$	C, H, N
trans-17c	HCl[f]	275–280	MeOH–MeCN	$C_{13}H_{14}Cl_2N_2S$	H, N; C[g]
cis-17d	HCl[h]	>300	MeOH–MeCN	$C_{13}H_{14}BrClN_2S$	C, H, N
trans-17d		104.5–105.5	CH_2Cl_2–hexane	$C_{13}H_{13}BrN_2S$	C, H, N
cis-18a	HCl[i]	268–273	MeOH–MeCN	$C_{13}H_{15}ClN_2S$	C, H, N
trans-18a	HCl[j]	273–278	MeOH–MeCN	$C_{13}H_{15}ClN_2S$	C, H; N[k]
trans-18b		130–130.5	CH_2Cl_2–hexane	$C_{13}H_{13}FN_2S$	MS[c,l]
cis-18c	HCl	263–269	MeOH–MeCN	$C_{13}H_{14}Cl_2N_2S$	C, H, N
trans-18c	HCl	>300	MeOH–MeCN	$C_{13}H_{14}Cl_2N_2S$	C, H, N
cis-18d	HCl[m]	>300	MeOH–benzene	$C_{13}H_{14}BrClN_2S$	C, H, N
trans-18d		146–147	CH_2Cl -hexane	$C_{13}H_{13}BrN_2S$	C, H, N

[a] Analyses for the elements indicated were within ±0.4% of the theoretical values unless otherwise noted. [b] Base, mp 96–97.5 °C (CH_2Cl_2-hexane). Anal. ($C_{13}H_{14}N_2S$) C, H, N. [c] MS indicates that combustion analysis was not performed with the fluorine-containing compound but, instead, that satisfactory mass spectral data were obtained. [d] The mass spectral data of this compound: *m/e* (relative intensity) 248 (52, M^+), 247 (100), 220 (21), 146 (38), 135 (23), 133 (22). [e] Base, mp 95.5–96.5 °C (CH_2Cl_2-hexane). Anal. ($C_{13}H_{13}ClN_2S$) C, H, N. [f] Base, mp 171.5–173 °C (CH_2Cl_2-hexane). Anal. ($C_{13}H_{13}ClN_2S$) C, H, N. [g] C: calcd, 51.83; found, 51.32. [h] Base, mp 115–117 °C (CH_2Cl_2-hexane). Anal. ($C_{13}H_{13}BrN_2S$) C, H, N. [i] Base, mp 100–101 °C (CH_2Cl_2-hexane). Anal. ($C_{13}H_{14}N_2S$), C, H, N. [j] Base, mp 127–128.5 °C (CH_2Cl_2-hexane). Anal. ($C_{13}H_{14}N_2S$) C, H, N. [k] N: calcd, 10.50, 10.05. [l] The mass spectral data of this compound: *m/e* (relative intesity) 248 (19, M^+), 247 (17), 147 (22), 146 (100). [m] Base, mp 92.5–94.5 °C (CH_2Cl_2-hexane). Anal. ($C_{13}H_{13}BrN_2S$) C, H, N.

determined by an X-ray crystallographic study. A stereoscopic view[14] of one enantiomer of **20a** is shown in Figure 2. As can be seen from the view, the substituents at C_8 and C_9 are so arranged that C_{6a} H, C_8 OH, and C_9 CH_3 are on the same side of the hexahydroimidazo[2,1-*b*]thiazole ring system. Thus, the reaction of **16a** with α-bromopropiophenone proceeded regiospecifically and stereoselectively.

Biological Studies. In order to elucidate the immunological activity of **17**, **18**, and **20**, we have studied the effects of these compounds on humoral and cellular immune responses in mice against sheep red blood cells (SRBC) by the plaque-forming cell (PFC) method[17] and delayed-type hypersensitivity reaction (DHR) method,[18] respectively.

Compound *cis*-**17a** increased the PFC number per 10^6 spleen cells in mice. The dose–response relationship of the enhancement of the PFC response with *cis*-**17a** was similar to that obtained with levamisole (Figure 3). Compound *cis*-**17a** had optimum activity at around 3 mg/kg and levamisole at 3–12 mg/kg. With both compounds, a dose of 48 mg/kg produced little or no increase in the PFC number. Accordingly, effects of the hexahydronaphthimidazothiazoles on PFC and DHR responses were assayed at doses of 3 and 12 mg/kg, the doses chosen for the first immunological evaluation.

The results tabulated in Table III, along with the data for levamisole, show that a considerable number of the type of compounds synthesized in the present study exhibit immunological activity in mice. As for the hexahydronaphthimidazothiazoles having no substituents on the skeleton (**17a** and **18a**), no clear difference was observed between the activities of the two types of compounds having different ring systems, naphth[1',2':4,5]imidazo[2,1-*b*]thiazole and naphth[2',1':4,5]imidazo[2,1-*b*]thiazole. The compounds with trans fusion of rings A and B (*trans*-**17a** and -**18a**), however, showed a tendency of having a larger activity of enhancing the PFC response than those with cis fusion.

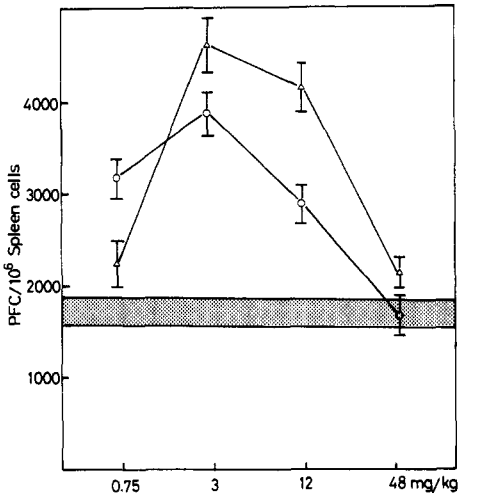


Figure 3. Dose–response relationships of the enhancement of the PFC response in ICR mice with *cis*-**17a** and with levamisole. The circles and the triangles indicate mean PFC values of four mice injected with *cis*-**17a** and levamisole, respectively. The bars indicate standard errors. The dotted area indicates the mean PFC value of four mice injected with saline as a control plus or minus the standard error.

Although the introduction of a halogen atom into the benzene ring (ring A) had little influence on the DHR-enhancing activity of the parent compounds, the influence on the PFC-enhancing activity differed, depending on the nature of the halogen atom: whereas the compounds with a fluorine atom (*trans*-**17b** and -**18b**) retain the activity, those with a chlorine or bromine atom (**17c,d** and **18c,d**) had generally only diminished or no activity of enhancing the PFC response.

Next, we studied the immunological activity of the compounds having substituents on ring D. Comparison

(14) The computer program used had been made by Takenaka and Sasada [A. Takenaka and Y. Sasada, *J. Crystallogr. Soc. Jpn.*, **22**, 214 (1980).
(15) A similar observation has been made with respect to levamisole [R. W. Baker and P. J. Pauling, *J. Chem. Soc., Perkin Trans. 2*, 203 (1973)].
(16) The C_{11a} H signal appeared as two doublets because the product contained two stereoisomeric racemates which differ from each other in the configuration at C_8 and C_9.
(17) A. J. Cunningham and A. Szenberg, *Immunology*, **14**, 599 (1968).
(18) P. H. Lagrange, G. B. Mackaness, and T. E. Miller, *J. Exp. Med.*, **139**, 1529 (1974).

Table III. Effect of 17 and 18 on PFC and DHR Responses[a]

expt no.	compd	dose, mg/kg	PFC/10^6 spleen cells[b]	ratio	expt no.	increase of foot-pad thickness,[b] mm	ratio
1	control		930 ± 90	1.00	10	0.30 ± 0.05	1.00
	cis-17a	3	1220 ± 100[c]	1.31		0.42 ± 0.04[c]	1.40
		12	860 ± 60	0.92		0.44 ± 0.06[c]	1.47
	trans-17a	3	1100 ± 100	1.18		0.57 ± 0.03[c]	1.90
		12	1500 ± 200[c]	1.61		0.42 ± 0.04[c]	1.40
	levamisole	3	1180 ± 120[c]	1.27		0.45 ± 0.03[c]	1.50
		12	1150 ± 190	1.24		0.35 ± 0.05	1.17
2	control		1500 ± 170	1.00	11	0.28 ± 0.04	1.00
	cis-18a	3	1800 ± 150[c]	1.20		0.37 ± 0.05[c]	1.32
		12	1610 ± 180	1.07		0.38 ± 0.05[c]	1.36
	trans-18a	3	2440 ± 160[c]	1.63		0.37 ± 0.06[c]	1.32
		12	2580 ± 220[c]	1.72		0.39 ± 0.04[c]	1.39
	levamisole	3	3530 ± 260[c]	2.35		0.33 ± 0.04[c]	1.18
		12	1490 ± 140	0.99		0.29 ± 0.04	1.04
3	control		1200 ± 90	1.00	12	0.25 ± 0.03	1.00
	trans-17b	3	1970 ± 140[c]	1.64		0.44 ± 0.04[c]	1.76
		12	1620 ± 110[c]	1.35		0.44 ± 0.02[c]	1.76
	trans-18b	3	2550 ± 60[c]	2.13		0.42 ± 0.04[c]	1.68
		12	2070 ± 120[c]	1.73		0.42 ± 0.03[c]	1.68
	levamisole	3	2820 ± 250[c]	2.35		0.42 ± 0.06[c]	1.68
		12	1870 ± 210[c]	1.56		0.44 ± 0.02[c]	1.76
4	control		1320 ± 180	1.00	13	0.23 ± 0.05	1.00
	cis-17c	3	1560 ± 240	1.18		0.26 ± 0.05	1.13
		12	970 ± 110[c]	0.73		0.33 ± 0.05[c]	1.43
	cis-18c	3	1880 ± 200[c]	1.42		0.27 ± 0.07	1.17
		12	1700 ± 120[c]	1.29		0.28 ± 0.02	1.22
	levamisole	3	1380 ± 160	1.05		0.27 ± 0.04	1.17
		12	1800 ± 130[c]	1.36		0.32 ± 0.04[c]	1.39
5	control		1250 ± 100	1.00	14	0.33 ± 0.02	1.00
	trans-17c	3	1530 ± 180[c]	1.22		0.50 ± 0.03[c]	1.52
		12	790 ± 150[c]	0.63		0.46 ± 0.02[c]	1.39
	trans-18c	3	1060 ± 120	0.85		0.39 ± 0.06	1.18
		12	820 ± 100[c]	0.66		0.36 ± 0.07	1.09
	levamisole	3	1330 ± 90	1.06		0.45 ± 0.03[c]	1.36
		12	1670 ± 100[c]	1.34		0.49 ± 0.06[c]	1.48
6	control		1300 ± 150	1.00	15	0.31 ± 0.02	1.00
	cis-17d	3	960 ± 100[c]	0.74		0.36 ± 0.07	1.16
		12	1495 ± 110	1.15		0.45 ± 0.02[c]	1.45
	cis-18d	3	980 ± 95[c]	0.75		0.35 ± 0.01	1.13
		12	870 ± 110[c]	0.67		0.38 ± 0.04	1.23
	levamisole	3	1850 ± 100[c]	1.42		0.20 ± 0.05[c]	0.65
		12	1330 ± 90	1.02		0.38 ± 0.03[c]	1.23
7	control		660 ± 50	1.00	16	0.26 ± 0.04	1.00
	trans-17d	3	740 ± 85	1.12		0.35 ± 0.03[c]	1.35
		12	920 ± 150[c]	1.39		0.31 ± 0.03	1.19
	trans-18a	3	1110 ± 140[c]	1.68		0.27 ± 0.07	1.04
		12	960 ± 40[c]	1.45		0.43 ± 0.04[c]	1.65
	levamisole	3	1390 ± 230[c]	2.11		0.34 ± 0.02[c]	1.31
		12	970 ± 50[c]	1.47		0.30 ± 0.04	1.15
8	control		560 ± 100	1.00	17	0.18 ± 0.10	1.00
	20a	3	550 ± 70	0.98		0.28 ± 0.05[c]	1.56
		12	1120 ± 260[c]	2.00		0.52 ± 0.05[c]	2.89
	levamisole	3	570 ± 120	1.02			
		12	1200 ± 150[c]	2.14			
9	control		640 ± 50	1.00			
	21	3	740 ± 120	1.16		0.20 ± 0.12	1.11
		12	470 ± 80[c]	0.73		0.32 ± 0.11[c]	1.78
	levamisole	3	850 ± 80[c]	1.33		0.37 ± 0.06[c]	2.06
		12	880 ± 45[c]	1.38		0.24 ± 0.04	1.33

[a] ICR mice were used in experiments 2, 3, 10, 11, 13, 15, 16, and 17, and CDF_1 (Balb/c× DBA/2Cr) mice in the other experiments. [b] Values are the averages of four mice together with the SE. [c] Values are significantly different from control values by paired Student's t test; $p < 0.05$.

of the data of **20a** with those of **21** indicates that the introduction of a double bond between C_9 and C_{10} through dehydration decreases the activity.

Since the introduction of a halogen atom into ring A of **17a** and **18a** had no beneficial effect on the immunological activity, an acute toxicological study in mice was performed with **17a**, **18a**, and **20a** (Table IV). The study indicated that *trans*-**17a** and -**20a** were considerably less toxic than levamisole. Since these two compounds, *trans*-**17a** and -**20a**, showed the largest immunological activity in mice among those determined in this study, an immunological activity of a magnitude comparable to that of levamisole

Table IV. Acute LD_{50} in Mice[a]

compd	LD_{50}, mg/kg iv[b]	LD_{50}, mg/kg sc[c]
cis-17a	27	116
trans-17a	67	320
cis-18a	20	68
trans-18a	26	190
20a	170	NE[d]
levamisole[e]	15	136

[a] CDF_1 (Balb/c × DBA/2Cr) mice were used. [b] iv, administered intravenously. [c] sc, administered subcutaneously. [d] NE indicates that no experiment was performed. [e] The LD_{50} values were reported to be 22 (iv) and 84 mg/kg (sc) in albino mice.[28]

they deserve further evaluation.

Experimental Section

Chemistry. Melting points were obtained on a Yanagimoto hot-stage apparatus and are uncorrected. Analyses were carried out by the Analytical Chemistry Laboratory of the Central Research Institute, Teijin Limited. IR spectra were recorded on a Hitachi EPI-500 spectrophotometer. NMR data were obtained on a Varian EM360A spectrometer with Me_4Si as an internal standard. Mass spectra were run on a LKB 9000 spectrometer at 70 eV unless otherwise noted. Those compounds (6–15) whose preparations are not described in this section are all obtained as a liqiud or an oil and were not subjected to combustion analysis, but structural assignments for these compounds were unambiguously confirmed by NMR and IR spectroscopies. Their spectral data are listed in Table V.[19]

7-Bromo-1,2,3,4-tetrahydro-1-naphthol (6d). To a stirred solution of 7-bromo-3,4-dihydro-1(2*H*)-naphthalenone[11] (**5d**; 9.20 g, 40.9 mmol) in a mixture of methanol (90 mL) and CH_2Cl_2 (45 mL) was added $NaBH_4$ (0.900 g, 2.38 mmol) under cooling with an ice bath. After the solution stirred at 20–23 °C for 1 h, the solvents were evaporated, and the residue was partitioned between ether (50 mL) and water (50 mL). The aqueous layer was extracted with ether (2 × 20 and 10 mL), and the combined organic layers were washed with 1 N HCl, water, saturated aqueous $NaHCO_3$ solution, and brine. The solution was dried (Na_2SO_4) and evaporated to give 9.32 g (100%) of **6d** as colorless crystals, which were employed in the next step without recrystallization: IR (KBr) 3250, 2930, 2860, 1592, 1480, 1190, 1061, 1002, 964, 884, 829, 803 cm^{-1}; NMR ($CDCl_3$) δ 1.52–2.07 [m, 5 H, CH(O*H*)-CH_2CH_2], 2.58–2.83 [**m**, 2 H, $CH(OH)CH_2CH_2CH_2$], 4.70 [m, 1 H, C*H*(OH)], 6.97 (d, 1 H, J = 8 Hz, C_5 H), 7.32 (dd, 1 H, J = 8 and 2 Hz, C_6 H), 7.62 (d, 1 H, J = 2 Hz, C_8 H). Anal. ($C_{10}H_{11}BrO$) C, H.

6-Chloro-1,2,3,4-tetrahydro-1-naphthol (6c). Crude product obtained in 98% yield was recrystallized from ether–hexane to give colorless needles: mp 66–68 °C; IR (KBr) 3270, 1599, 1483, 960, 824 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.09 [m, 4 H, CH(OH)-CH_2CH_2], 2.17 (d, 1 H, J = 6 Hz, OH), 2.59–2.76 [m, 2 H, CH-(OH)$CH_2CH_2CH_2$], 4.68 [m, 1 H, C*H*(OH)], 7.08–7.45 (m, 3 H, aromatic). Anal. ($C_{10}H_{11}ClO$) C, H.

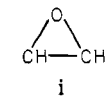
7-Bromo-1,2-dihydronaphthalene (7d). To a solution of **6d** (15.4 g, 67.8 mmol) in dry benzene (150 mL) was added *p*-toluenesulfonic acid monohydrate (0.50 g, 2.63 mmol) and the mixture was refluxed for 1.5 h with a Dean–Stark separator. The reaction mixture was cooled with an ice bath and treated with water (80 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated. The residue was distilled to give 13.8 g (97%) of **7d**: bp 83–86 °C (0.9 nm); IR (neat) 3020, 2930, 2870, 2820, 1591, 1479, 1188, 1076, 878, 837, 811, 776, 681 cm^{-1}; NMR ($CDCl_3$) δ 2.02–2.41 (m, 2 H, $=CHCH_2$), 2.58–2.87 (m, 2 H, $=CHCH_2CH_2$), 6.07 (dt, J = 10 and 4 Hz, 1 H, $=CHCH_2$), 6.37 (br d, J = 10 Hz, 1 H, $CH=CHCH_2$), 6.93 (d, J = 8 Hz, 1 H, C_5 H), 7.17–7.33 (m, 2 H, C_6 H and C_7 H). Exact mass for $C_{10}H_9Br$: calcd, 207.989; found, 207.986.

1,2-Dihydronaphthalene (7a). Compound **7a** was obtained in 93% yield after distillation: bp 101–102 °C (18 mm), lit.[20] 77 °C (5 mm).

6-Fluoro-1,2-dihydronaphthalene (7b). Compound **7b** was obtained in 94% yield after distillation: bp 96–99 °C (20 mm); IR (neat) 3030, 1612, 1584, 1492, 1243, 826 cm^{-1}; NMR δ 2.03–2.47 (m, 2 H, $CH_2CH=$), 2.63–2.93 (m, 2 H, $=CHCH_2CH_2$), 6.00 (dt, 1 H, J = 10 and 4 Hz, $=CHCH_2$), 6.44 (br d, 1 H, J = 10 Hz, $CH=CHCH_2$), 6.69–7.14 (m, 3 H, aromatic).

6-Chloro-1,2-dihydronaphthalene (7c). Compound **7c** was obtained in 94% yield after distillation: bp 66–70 °C (0.9 mm); IR 3030, 1597, 1483, 1086, 828 cm^{-1}; NMR ($CDCl_3$) δ 2.03–2.43 (m, 2 H, $=CHCH_2$), 2.63–2.93 (m, 2 H, $=CHCH_2CH_2$), 6.06 (dt, 1 H, J = 10 and 4 Hz, $=CHCH_2$), 6.43 (dt, 1 H, J = 10 and 1 Hz, $CH=CHCH_2$), 6.86–7.30 (m, 3 H, aromatic). Exact mass for $C_{10}H_9Cl$: calcd, 164.039; found, 164.041.

7-Bromo-1,2-epoxy-1,2,3,4-tetrahydronaphthalene (8d). To a stirred mixture of a solution of **7d** (11.45 g, 54.8 mmol) in CH_2Cl_2 (200 mL) and saturated aqueous $NaHCO_3$ solution (80 mL) was added *m*-chloroperbenzoic acid (80%, 12.05 g, 55.9 mmol) under cooling with an ice bath over a period of 5 min, and the mixture was stirred for an additional 8 min under cooling and for 2.5 h at room temperature. The layers were separated, and the CH_2Cl_2 layer was washed with saturated aqueous $NaHCO_3$ solution and brine and dried (Na_2SO_4). The solvent was evaporated, and the residue was chromatographed on alumina with CH_2CH_2 as eluent to give 12.3 g (99%) of **8d** as colorless crystals. Recrystallization from ether–hexane gave colorless prisms: mp 50–51 °C; IR (KBr) 2900, 1594, 1480, 1190, 1073, 936, 858, 818 cm^{-1}; NMR ($CDCl_3$) δ 1.35–2.83 (m, 4 H, $CHCH_2CH_2$), 3.53–3.77 (m, 2 H, i), 6.95 (d,



i

1 H, J = 8 Hz, C_5H), 7.35 (dd, 1 H, J = 8 and 2 Hz, C_6 H), 7.51 (d, 1 H, J = 2 Hz, C_8 H). Anal. ($C_{10}H_9BrO$) C, H.

***trans*-1-Azido-7-bromo-1,2,3,4-tetrahydro-2-naphthol (9d).** To a solution of **8d** (13.00 g, 57.8 mmol) in 80% EtOH (200 mL) were added NaN_3 (4.50 g, 69.2 mmol) and NH_4Cl (4.30 g, 80.4 mmol), and the resulting mixture was refluxed for 1.5 h. To the warm mixture was added ice–water (400 g) and then ether (100 mL). The layers were separated, and the aqueous layer was extracted with ether. The combined ether solutions were washed with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated. The residue was recrystallized from ether to give 10.74 g of **9d**, mp 88–89 °C. The material obtained on evaporation of the mother liquor was treated with ether–hexane to give 1.52 g of **9d**, mp 87.5–88.5 °C, as the second crop. The ether–hexane solution was evaporated, and the residue was chromatographed on silica gel with CH_2Cl_2 as eluent to give 2.00 g of **9d**, mp 83–86 °C, as the third crop [14.26 g in total (92%)]: IR (KBr) 3340, 2110, 1592, 1480, 1253, 1078, 1048 cm^{-1}; NMR ($CDCl_3$) δ 1.63–2.22 [m, 2 H, $CH(OH)CH_2$], 2.34 (d, 1 H, J = 4 Hz, OH), 2.83 [m, 2 H, $CH(OH)CH_2CH_2$], 3.98 [tt, 1 H, J = 8 and 4 Hz, C*H*(OH)], 4.34 (d, 1 H, J = 8 Hz, CHN_2), 7.02 (d, 1 H, J = 8 Hz, C_5 H), 7.37 (dd, 1 H, J = 8 and 2 Hz, C_6 H), 7.59 (d, 1 H, J = 2 Hz, C_8 H). Anal. ($C_{10}H_{10}BrN_3O$) C, H, N.

***trans*-1-Azido-7-bromo-1,2,3,4-tetrahydro-2-[(methanesulfonyl)oxy]naphthalene (10d).** To a stirred solution of **9d** (13.85 g, 51.7 mmol) in pyridine (25 mL) was added methanesulfonyl chloride (7.10 g, 62.0 mmol) under cooling with an ice bath over a period of 1 min, and the mixture was stirred for an additional 14 min under cooling and for 2 h at room temperature. The mixture was partitioned between AcOEt (100 mL) and water (100 mL). The aqueous layer was saturated with NaCl and extracted with AcOEt. The combined organic layers were washed with 1 N HCl, saturated aqueous $NaHCO_3$ solution, and brine, dried (Na_2SO_4), and evaporated to give 17.8 g (99%) of **10d** as colorless crystals. Recrystallization from CH_2Cl_2–hexane gave colorless needles: mp 89.5–90.5 °C; IR (KBr) 2120, 1347, 1261, 1175, 980, 966, 925, 840 cm^{-1}; NMR ($CDCl_3$) δ 2.03–2.40 [m, 2 H, $CH(OSO_2CH_3)CH_2$], 2.90 (br t, 2 H, J = 7 Hz, $CH(OSO_2CH_3)$-CH_2CH_2], 3.11 (s, 3 H, CH_3), 4.68 (d, 1 H, J = 7 Hz, CHN_3), 4.99

(19) Table V is included in the microfilm edition of this journal.
(20) I. I. Chizhevskaya and Z. B. Idel'chik, *Zh. Obshch. Khim.*, **27**, 83 (1957).

(ddd, 1 H, J = 8, 7, and 4 Hz, CH(OSO_2CH_3)], 7.10 (d, 1 H, J = 8 Hz, C_5 H), 7.45 (dd, 1 H, J = 8 and 2 Hz, C_6 H), 7.60 (d, 1 H, J = 2 Hz, C_8 H). Anal. ($C_{11}H_{12}BrN_3O_3S$) C, H, N.

***trans*-1-Azido-1,2,3,4-tetrahydro-2-[(methanesulfonyl)oxy]naphthalene (10a).** Crude product was triturated with ether and collected by filtration. The filtrate was evaporated and the residue was chromatographed on silica gel with CH_2Cl_2 as eluant to give an additional desired product (total yield, 94%). Recrystallization from ether–hexane gave colorless prisms: mp 67–67.5 °C; IR (KBr) 2100, 1354, 1179, 1169, 933 cm^{-1}; NMR ($CDCl_3$) δ 2.04–2.50 [m, 2 H, CH(OSO_2CH_3)CH_2], 2.85–3.10 [m, 2 H, CH(OSO_2CH_3)CH_2CH_2], 3.09 (s, 3 H, CH_3), 4.69 (d, 1 H, J = 6 Hz, CHN_3), 4.99 (ddd, 1 H, J = 7, 6, and 4 Hz, CH(OSO_2CH_3)]. Anal. ($C_{11}H_{13}N_3O_3S$) C, H, N.

***trans*-1-Azido-6-chloro-1,2,3,4-tetrahydro-2-[(methanesulfonyl)oxy]naphthalene (10c).** Crude product obtained in 90% yield was recrystallized from ether–hexane to give colorless needles: mp 94–94.5 °C; IR (KBr) 2100, 1350, 1333, 1180, 910 cm^{-1}; NMR ($CDCl_3$) δ 2.03–2.38 [m, 2 H, CH(OSO_2CH_3)CH_2], 2.82–3.05 [m, 2 H, CH(OSO_2CH_3)CH_2CH_2], 3.09 (s, 3 H, CH_3), 4.67 (d, 1 H, J = 7 Hz, CHN_3), 4.97 [dt, 1 H, J = 7 and 4 Hz, CH(OSO_2CH_3)], 7.20–7.34 (m, 3 H, aromatic). Anal. ($C_{11}H_{12}ClN_3O_3S$) C, H, N.

***cis*-1,2-Diazido-7-bromo-1,2,3,4-tetrahydronaphthalene (11d).** To a solution of **10d** (10.0 g, 28.9 mmol) in DMF (50 mL) was added NaN_3 (2.80 g, 43.1 mmol), and the mixture was refluxed for 3 h. The mixture was partitioned between water (250 mL) and ether (100 mL). The aqueous layer was saturated with NaCl and extracted with ether. The combined organic layers were washed with 1 N HCl, saturated aqueous $NaHCO_3$ solution, and brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel with CH_2Cl_2 as eluent to give 5.64 g (67%) of **11d** as a colorless oil, which, on standing in a refrigerator for 1 month, crystallized: mp 32–34 °C; IR (KBr) 2130, 1595, 1483, 1255 cm^{-1}; NMR ($CDCl_3$) δ 1.89–2.55 (m, 2 H, CHN_3CH_2), 2.73–3.01 (m, 2 H, $CHN_3CH_2CH_2$), 3.80 (ddd, 1 H, J = 8, 5, and 4 Hz, C$H$$N_3CH_2$), 4.55 (d, 1 H, J = 4 Hz, C$H$$N_3CHN_3CH_2$), 6.96–7.50 (m, 3 H, aromatic). Exact mass[21] for $C_{10}H_9BrN_6$: calcd, 292.007; found, 292.006.

***cis*-1,2-Diamino-7-bromo-1,2,3,4-tetrahydronaphthalene (*cis*-12d).** To a stirred suspension of $LiAlH_4$ (1.00 g, 26.4 mmol) in dry ether (120 mL) was added a solution of **11d** (5.40 g, 18.4 mmol) in dry ether (50 mL) below 10 °C under cooling with an ice bath over a period of 35 min. The mixture was stirred for an additional 40 min at room temperature and for 0.5 h at reflux. The mixture was gradually treated with saturated aqueous Na_2SO_4 solution (10 mL) under cooling with an ice bath and then with solid Na_2SO_4. The mixture was filtered, and the filtrate was evaporated to give 4.38 g (99%) of *cis*-**12d** as yellowish oil, which was used in the next step without purification: IR (neat) 3370, 3280, 2930, 1592, 1480, 1082, 821 cm^{-1}; NMR ($CDCl_3$) δ 1.37 (s, 4 H, 2 × NH_2), 1.54–1.94 [m, 2 H, CH(NH_2)CH_2], 2.67–3.21 [m, 3 H, CH(NH_2)CH_2CH_2], 3.80 [d, 1 H, J = 4 Hz, CH(NH_2)CH(NH_2)CH_2], 7.02 (d, 1 H, J = 8 Hz, C_5 H), 7.33 (dd, 1 H, J = 8 and 2 Hz, C_6 H), 7.57 (d, 1 H, J = 2 Hz, C_8 H).

***trans*-Methyl 7-Bromo-1,2,3,4-tetrahydro-2-iodo-1-naphthylcarbamate (13d).** Iodine (18.21 g, 71.7 mmol) was dissolved in a solution of **7d** (15.00 g, 71.7 mmol) in dry ether (200 mL). To the stirred resulting solution was added silver cyanate (14.97 g, 99.9 mmol) in one portion at 11 °C (under cooling with an ice bath), and the mixture was stirred under cooling for an additional 0.5 h, at room temperature overnight, and finally at reflux for 1.5 h. The mixture was filtered, and the filtrate was evaporated. The residual oil was dissolved in absolute MeOH (150 mL) and heated at reflux for 3.25 h. The mixture was concentrated to ca. 80 mL, and the precipitate (2.44 g of **13d**) was collected by filtration. The filtrate was evaporated, and the residue was chromatographed on silica gel with CH_2Cl_2–hexane (1:1–1:0) as eluent to give 11.20 g of **13d** [13.64 g (46%) in total)]. Recrystallization from MeOH–hexane gave colorless needles: mp 127.5–128.5 °C; IR (KBr) 3275, 1686, 1545, 1264 cm^{-1}; NMR ($CDCl_3$) δ 2.00–2.29 (m, 2 H, CHICH_2), 2.70–3.00 (m, 2 H, $CHICH_2CH_2$), 3.72 (s, 3 H, CH_3), 4.47–4.72 (m, 1 H, CHI), 4.92–5.26 (m, 2 H, CHNH), 7.05 (d, 1 H, J = 9 Hz, C_5 H), 7.26–7.48 (m, 2 H, C_6 H and C_8 H). Exact mass for $C_{12}H_{13}BrINO_2$: calcd, 408.918; found, 408.920.

***trans*-Methyl 1,2,3,4-Tetrahydro-2-iodo-1-naphthylcarbamate (13a).** Crude product obtained in 81% yield was recrystallized from MeOH to give colorless needles: mp 130–131.5 °C, lit.[8b] 129–131 °C.

***trans*-Methyl 6-Fluoro-1,2,3,4-tetrahydro-2-iodo-1-naphthylcarbamate (13b).** Crude product obtained in 88% yield was recrystallized from MeOH–hexane to give colorless needles: mp 131–132.5 °C; IR (KBr) 3240, 1687, 1543, 1266 cm^{-1}; NMR ($CDCl_3$) δ 1.93–2.30 (m, 2 H, CHICH_2), 2.76–3.10 (m, 2 H, $CHICH_2CH_2$), 3.71 (s, 3 H, CH_3), 4.53–4.72 (m, 1 H, CHI), 4.94–5.33 (m, 2 H, CHNH), 6.76–7.43 (m, 3 H, aromatic). Exact mass[21] for $C_{12}H_{13}FINO_2$: calcd, 348.998; found, 349.000.

***trans*-Methyl 6-Chloro-1,2,3,4-tetrahydro-2-iodo-1-naphthylcarbamate (13c).** Crude product obtained in 82% yield was recrystallized from CH_2Cl_2–MeOH to give colorless needles: mp 158.5–160 °C; IR (KBr) 3220, 1682, 1542, 1264 cm^{-1}; NMR ($CDCl_3$) δ 1.99–2.28 (m, 2 H, CHICH_2), 2.80–3.04 (m, 2 H, $CHICH_2CH_2$), 3.71 (s, 3 H, CH_3), 4.62 (m, 1 H, CHI), 4.94–5.31 (m, 2 H, CHNH), 7.09–7.28 (m, 3 H, aromatic). Anal. ($C_{12}H_{13}ClINO_2$) C, H, N.

7-Bromo-1,2-imino-1,2,3,4-tetrahydronaphthalene (14d). Compound **13d** (13.42 g, 32.7 mmol) was added to a solution of KOH (85%, 9.00 g, 136 mmol) in EtOH (110 mL), and the mixture was refluxed for 45 min and filtered. The solid collected by the filtration and the material obtained on evaporation of the filtrate were partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated to give 7.43 g (100%) of **14d** as a yellow solid, mp 78–86 °C, which was used in the next step without purification: IR (KBr) 3200, 3005, 2920, 1592, 1481, 1077, 858, 820, 767 cm^{-1}; NMR ($CDCl_3$) δ 0.97 (s, 1 H, NH), 1.55–1.88 (m, 1 H, C$H$$CH_2CH_2$), 2.08–2.97 (m, 5 H, C$HCHCH_2CH_2$), 6.96 (d, 1 H, J = 8 Hz, C_5 H), 7.35 (dd, 1 H, J = 8 and 2 Hz, C_6 H), 7.52 (d, 1 H, J = 2 Hz, C_8 H).

1,2-Imino-1,2,3,4-tetrahydronaphthalene (14a). Crude product obtained quantitatively was recrystallized from ether–hexane to give greenish prisms: mp 54.5–56.5 °C, lit.[8b] 52–52.5 °C.

6-Fluoro-1,2-imino-1,2,3,4-tetrahydronaphthalene (14b). Crude solid product obtained quantitatively was used directly in the following reaction: IR (KBr) 3220, 1497, 1237, 868, 827 cm^{-1}; NMR ($CDCl_3$) δ 0.79–1.00 (m, 1 H, NH), 1.20–3.10 (m, 6 H, $CHCHCH_2CH_2$), 6.74–7.46 (m, 3 H, aromatic).

6-Chloro-1,2-imino-1,2,3,4-tetrahydronaphthalene (14c). Crude product obtained quantitatively was recrystallized from ether–hexane to give colorless needles: mp 97.5–98.5 °C; IR (KBr) 3230, 1480, 1090, 880, 837, 825 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (br s, 1 H, NH), 1.32–3.04 (m, 6 H, $CHCHCH_2CH_2$), 7.02–7.33 (m, 3 H, aromatic). Anal. ($C_{10}H_{10}ClN$) C, H, N.

***trans*-2-Amino-1-azido-7-bromo-1,2,3,4-tetrahydronaphthalene (15d).** Compound **14d** (7.12 g, 31.8 mmol) was dissolved by warming in a mixture of EtOH (90 mL) and water (30 mL). To the resulting solution was added NaN_3 (2.70 g, 41.5 mmol) and NH_4Cl (2.70 g, 43.0 mmol), and the mixture was refluxed for 1.25 h. To the reaction mixture were added water (360 mL) and CH_2Cl_2 (100 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with brine, dried (Na_2SO_4), and evaporated to give 8.15 g (96%) of **15d** as a greenish-brown solid, mp 41–50 °C, which was used in the next step without purification: IR (KBr) 3375, 2920, 2110, 1590, 1479, 1279, 1253, 811 cm^{-1}; NMR ($CDCl_3$) δ 1.46 (s, 2 H, NH_2), 1.67–2.22 [m, 2 H, CH(NH_2)CH_2], 2.68–2.90 [m, 2 H, CH(NH_2)CH_2CH_2], 2.97–3.31 [1 H, m, CH(NH_2)], 4.12 (d, 1 H, J = 8 Hz, CHN_3), 7.02 (d, 1 H, J = 8 Hz, C_5 H), 7.40 (dd, 1 H, J = 8 and 2 Hz, C_6 H), 7.61 (d, 1 H, J = 2 Hz, C_8 H).

***trans*-1,2-Diamino-1,2,3,4-tetrahydronaphthalene (*trans*-12a).**[8c] To a stirred suspension of $LiAlH_4$ (260 mg, 6.85 mmol) in dry ether (40 mL) was added a solution *trans*-2-amino-1-azido-1,2,3,4-tetrahydronaphthalene (**15a**; 1.27 g, 6.77 mmol) in dry ether (14 mL) under cooling with an ice bath over a period of 5 min. The mixture was stirred for an additional 1.5 h at room

(21) Determined on a JEOL JMS-D300 spectrometer at 70 eV.

temperature. The mixture was gradually treated with saturated aqueous Na_2SO_4 solution (2 mL) under cooling with an ice bath and then with solid Na_2SO_4. The mixture was filtered, and the filtrate was evaporated to give 992 mg (90%) of *trans*-**12a** as yellowish oil, which was used in the next step without purification: IR (neat) 3360, 3280, 2920, 1583, 1476, 1450, 740 cm^{-1}; NMR ($CDCl_3$) δ 1.63 (s, 4 H, 2 × NH_2), 1.44–2.26 [m, 2 H, $CH(NH_2)CH_2$], 2.57–2.99 [m, 3 H, $CH(NH_2)CH_2CH_2$], 3.50 [d, 1 H, J = 8 Hz, $CH(NH_2)CH(NH_2)CH_2$], 7.05–7.63 (m, 4 H, aromatic).

***trans*-1,2-Diamino-7-bromo-1,2,3,4-tetrahydronaphthalene (*trans*-12d).** Reduction of **15d** (8.05 g, 30.1 mmol) with $LiAlH_4$ (1.16 g, 30.6 mmol) in a similar manner as for the reduction of **11d** afforded 7.02 g (97%) of *trans*-**12d** as a yellowish solid, which was used in the next step without purification: IR (KBr) 3360, 2910, 2096, 1584, 1478, 1278, 1252, 810 cm^{-1}; NMR ($CDCl_3$) δ 1.67 (s, 4 H, 2 × NH_2), 1.73–2.24 [m, 2 H, $CH(NH_2)CH_2$], 2.51–2.89 [m, 3 H, $CH(NH_2)CH_2CH_2$], 3.45 [d, 1 H, J = 9 Hz, $CH(NH_2)$-$CH(NH_2)CH_2$], 6.95 (d, 1 H, J = 8 Hz, C_5 H), 7.30 (dd, 1 H, J = 8 and 2 Hz, C_6 H), 7.70 (d, 1 H, J = 2 Hz, C_8 H).

***cis*-3a,4,5,9b-Tetrahydronaphth[1,2-*d*]imidazoline-2-thione (*cis*-16a).** To a stirred solution of *cis*-**12a** (831 mg, 5.12 mmol) in EtOH (16 mL) were added water (8 mL) and then CS_2 (0.35 mL, 5.84 mmol). The mixture was refluxed for 1.5 h and cooled with an ice bath. The precipitated *cis*-**16a** (803 mg, 77%) was collected by filtration. Recrystallization from acetone–EtOH gave colorless needles: mp 238.5–239.0 °C; IR (KBr) 3190, 1530, 1475, 1255, 1204 cm^{-1}; NMR ($CDCl_3$–Me_2SO-d_6) δ 1.69–2.09 (m, 2 H, $CHNCH_2$), 2.58–3.04 (m, 2 H, $CHNCH_2CH_2$), 4.44 (dt, 1 H, J = 10 and 4 Hz, $CHNCH_2$), 5.05 (d, 1 H, J = 10 Hz, $CHNCHNCH_2$), 7.15–7.38 (m, 4 H, aromatic), 7.79 (br s, 1 H, NH), 8.03 (br s, 1 H, NH). Anal. ($C_{11}H_{12}N_2S$) C, H, N.

***trans*-3a,4,5,9b-Tetrahydronaphth[1,2-*d*]imidazoline-2-thione (*trans*-16a).** To a stirred solution of *trans*-**12a** (14.68 g, 90.5 mmol) in EtOH (150 mL) was added CS_2 (6.0 mL, 100 mmol), and the mixture was stirred at room temperature for 17 h. After the addition of water (75 mL), the mixture was refluxed for 4.5 h and cooled with an ice bath. The precipitated *trans*-**16a** (16.6 g, 90%) was collected by filtration. Recrystallization from acetone–EtOH gave colorless prisms: mp 258.5–259 °C; IR (KBr) 3170, 1508, 1337, 1197, 742 cm^{-1}; NMR ($CDCl_3$) δ 1.63–2.64 (m, 2 H, $CHNCHNCH_2$), 2.90–3.67 (m, 3 H, $CHNCH_2CH_2$), 4.42 (d, 1 H, J = 13 Hz, $CHNCHNCH_2$), 7.13–7.50 (m, 4 H, aromatic), 8.47 (br s, 1 H, NH), 9.08 (br s, 1 H, NH). Anal. ($C_{11}H_{12}N_2S$) C, H, N.

Other tetrahydronaphthimidazolinethiones, **16**, were prepared in a similar manner from the corresponding diamines **12** (Table I).

***cis*-5,6,6a,8,9,11a-Hexahydronaphth[1′,2′:4,5]imidazo[2,1-*b*]thiazole (*cis*-17a) and *cis*-5,6,6a,9,10,11a-Hexahydronaphth[2′,1′:4,5]imidazo[2,1-*b*]thiazole (*cis*-18a).** To a solution of *cis*-**16a** (5.00 g, 24.5 mmol) in *i*-PrOH (100 mL) were added 1-bromo-2-(*p*-toluenesulfonyloxy)ethane (13.0 g, 46.6 mmol) and Na_2CO_3 (5.20 g, 49.1 mmol), and the mixture was refluxed for 14 h. The reaction mixture was evaporated, and the residue was partitioned between CH_2Cl_2 (60 mL) and water (50 mL). The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water and saturated aqueous $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel with CH_2Cl_2–MeOH (1:0–0.67) as eluent to give 0.891 g (16%) of *cis*-**17a**, 1.32 g (23%) of a mixture of *cis*-**17a** and *cis*-**18a**, and 0.921 g (19%) of *cis*-**18a**. Recrystallization of *cis*-**17a** thus obtained from CH_2Cl_2–hexane gave colorless prisms: mp 96–97.5 °C; IR (KBr) 2920, 2830, 1596, 1218, 1155, 742 cm^{-1}; NMR ($CDCl_3$) δ 1.72–2.00 (m, 2 H, $CHNCH_2$), 2.25–3.64 (m, 6 H, $CHNCHCH_2CH_2$ and SCH_2CH_2), 3.85 (dt, 1 H, J = 9 and 5 Hz, $CHNCH_2$), 5.37 (d, 1 H, J = 9 Hz, $CHNCHNCH_2$), 6.98–7.54 (m, 4 H, aromatic); MS m/e 230 (M^+). Anal. ($C_{13}H_{14}N_2S$) C, H, N. Recrystallization of *cis*-**18a** from CH_2Cl_2–hexane gave colorless needles: mp 100–101 °C; IR (KBr) 2950, 2840, 1596, 1170, 1150, 746 cm^{-1}; NMR ($CDCl_3$) δ 1.70–2.07 (m, 2 H, $CHNCH_2$), 2.58–3.65 (m, 6 H, $CHNCH_2CH_2$ and SCH_2CH_2), 4.42 (d, 1 H, J = 9 Hz, $CHNCHNCH_2$), 4.70 (dt, 1 H, J = 9 and 5 Hz, $CHNCH_2$), 6.99–7.30 (m, 4 H, aromatic); MS m/e 230 (M^+). Anal. ($C_{13}H_{14}N_2S$) C, H, N. The hydrochlorides of *cis*-**17a** and *cis*-**18a** were prepared by treating the free bases in benzene with HCl gas and HCl/*i*-PrOH, respectively.

Other hexahydronaphthimidazothiazoles, **17** and **18**, and their hydrochlorides were prepared in a similar manner from the corresponding tetrahydronaphthimidazolinethiones **16** (Table II).

***trans*-17a and *trans*-18a.** trans-**17a**: mp 121.5–122.5 °C (colorless prisms from CH_2Cl_2–hexane); IR (KBr) 1560, 1542, 1318, 1310, 1214, 1200, 1143, 1013, 745 cm^{-1}; NMR ($CDCl_3$) δ 1.69–3.99 (m, 9 H, CH_2CH_2CHN and SCH_2CH_2), 4.86 (d, 1 H, J = 14 Hz, $CHNCHNCH_2$), 7.01–7.22 (m, 3 H, aromatic), 7.45–7.73 (m, 1 H, aromatic); MS m/e 230 (M^+). *trans*-**18a**: mp 127–128.5 °C (colorless prisms from CH_2Cl_2–hexane); IR (KBr) 1565, 1322, 1167, 1123, 742 cm^{-1}; NMR ($CDCl_3$) 1.59–4.19 (m, 10 H), 7.17 (m, 4 H, aromatic); MS m/e 230 (M^+). Anal. ($C_{13}H_{14}N_2S$) C, H, N.

(±)-5,6,6a*β*,8,9,11a*α*-Hexahydro-8*β*-hydroxy-9*β*-methyl-8*α*-phenylnaphth[1′,2′:4,5]imidazo[2,1-*b*]thiazole (20a). To a solution of *trans*-**16a** (200 mg, 0.979 mmol) in DMF (1 mL) was added α-bromopropiophenone (235 mg, 1.10 mmol), and the mixture was stirred at room temperature for 21 h. After ether (8 mL) was added to the mixture, the stirring was continued for an additional 1 h. The generated precipitates were collected by filtration to give 345 mg (84%) of (±)-5,6,6a,8,9,11a-hexahydro-8-hydroxy-9-methyl-8-phenylnaphth[1′,2′:4,5]imidazo[2,1-*b*]-thiazole hydrobromide (**20**·HBr), which was found to be a 3:2 mixture of two stereoisomeric racemates from the NMR spectrum: NMR (Me_2SO-d_6) δ 1.02 and 1.35 (d, 3 H, J = 7 Hz, CH_3), 1.3–1.8 (m, 2 H, $CHNCH_2$), 2.73–3.04 (m, 2 H, $CHNCH_2CH_2$), 3.6–4.15 (m, 1 H, $CHNCH_2$), 4.52 and 4.65 (q, 1 H, J = 7 Hz, $CHCH_3$), 5.51 and 5.64 (d, 1 H, J = 14 Hz, $CHNCHNCH_2$), 7.19–8.04 (m, 9 H, aromatic).

Compound **20**·HBr (200 mg, 0.479 mmol) was suspended in CH_2Cl_2 (6 mL) and treated with concentrated NH_4OH. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was crystallized with ether (6 mL) to give 142 mg (88%) of **20**: NMR ($CDCl_3$) δ 1.04 and 1.63 (d, 3 H, J = 7 Hz, CH_3), 1.1–1.9 (m, 2 H, $CHNCH_2$) 2.5–2.9 (m, 2 H, $CHNCH_2CH_2$), 3.1–3.7 (m, 1 H, $CHNCH_2$), 3.82 and 4.22 (q, 1 H, J = 7 Hz, $CHCH_3$), 4.80 and 4.98 (d, 1 H, J = 13 Hz, $CHNCHNCH_2$), 6.84–7.90 (m, 9 H, aromatic).

The mixture of the two racemates of **20** were recrystallized three times from CH_2Cl_2 to give colorless needles of one racemate (**20a**): mp 177–178 °C; IR (KBr) 3030, 2940, 1581, 1562, 1450, 1300, 1207, 1164, 745 cm^{-1}; NMR (Me_2SO-d_6) δ 1.19 (d, 3 H, J = 7 Hz, CH_3), 1.10–1.80 (m, 2 H, $CHNCH_2$), 2.41–3.50 (m, 3 H, $CHNCH_2CH_2$), 4.17 (q, 1 H, J = 7 Hz, $CHCH_3$), 4.73 (d, 1 H, J = 13 Hz, $CHNCHNCH_2$), 6.83 (s, 1 H, OH), 7.05–7.82 (m, 9 H, aromatic). Anal. ($C_{20}H_{20}N_2OS$) C, H, N.

***trans*-5,6,6a,11a-Tetrahydro-9-methyl-8-phenylnaphth[1′,2′:4,5]imidazo[2,1-*b*]thiazole Hydrobromide (21).** A mixture of *trans*-**16a** (400 mg, 1.96 mmol), α-bromopropiophenone (460 mg, 2.15 mmol), and glacial acetic acid (8 mL) was refluxed for 1.5 h. The reaction mixture was concentrated, and crystals were collected by filtration to give 650 mg (83%) of **21**·HBr. Recrystallization from MeOH–MeCN gave colorless needles: mp 299–302 °C; IR (KBr) 2880, 1510, 1490, 1444, 1356, 750 cm^{-1}; NMR (MeOH-d_4) δ 1.67–2.20 (m, 2 H, $CHNCH_2$), 2.24 (s, 3 H, CH_3), 2.83–3.11 (m, 2 H, $CHNCH_2CH_2$), 4.13–4.64 (m, 1 H, $CHNCH_2$), 5.41 (d, 1 H, J = 14 Hz, $CHNCHNCH_2$), 7.20–7.35 (m, 4 H, C_{1-4} H), 7.62 (5 H, C_6H_5). Anal. ($C_{20}H_{18}N_2S$·HBr) C, H, N.

Compound **21**·HBr (330 mg, 0.826 mmol) was suspended in CH_2Cl_2 (15 mL) and treated with concentrated NH_4OH. The CH_2Cl_2 layer was washed with brine, dried (Na_2SO_4), and evaporated to give 261 mg (99%) of **21**. Recrystallization from CH_2Cl_2–hexane gave pale yellow needles: mp 124–125.5 °C; IR (KBr) 1615, 1548, 1346, 1320, 1178, 754, 747, 713 cm^{-1}; NMR ($CDCl_3$) δ 1.48–3.05 (m, 4 H, $CHNCH_2CH_2$), 1.97 (s, 3 H, CH_3), 3.12–3.61 (m, 1 H, $CHNCH_2$), 4.77 (d, 1 H, J = 14 Hz, $CHNCHNCH_2$), 6.90–7.88 (m, 9 H, aromatic). Anal. ($C_{20}H_{18}N_2S$) C, H, N.

X-Ray Crystallographic Studies.[22] Racemic *cis*-**18a**·HCl ($C_{13}H_{15}ClN_2S$) and **20a** ($C_{20}H_{20}N_2OS$) were recrystallized from CH_2Cl_2 and $CHCl_3$–hexane, respectively. Crystal data for racemic *cis*-18a·HCl were as follows: monoclinic; space group $P2_1/c$; a = 10.309 (2) Å; b = 11.538 (1) Å; c = 11.640 (2) Å; β = 115.66 (1)°;

(22) Values in parentheses after cell constants are standard deviations.

cell volume 1247.96 (32) Å^3 d_{measd} = 1.417 g/cm^3; d_{calcd} = 1.420 g/cm^3; Z = 4. For racemic **20a**, the corresponding data were as follows: monoclinic, space group $P2_1/c$; a = 12.886 (2) Å; b = 8.179 (1) Å; c = 17.042 (2) Å; β = 109.63 (1)°; cell volume 1691.77 (34) Å^3; d_{measd} = 1.315 g/cm^3; d_{calcd} = 1.313 g/cm^3; Z = 4.

Intensity data were collected on a Rigaku automated four-circle diffractometer in ω-2θ scan mode within the range $3 \leq 2\theta \leq 50°$ with Mo Kα radiation (λ = 0.71069 Å). Crystals were 0.4 × 0.2 × 0.4 mm in size for *cis*-**18a**·HCl and 0.3 × 0.2 × 0.5 mm in size for **20a**. Independent reflections, 2195, are obtained for *cis*-**18a**·HCl and for **20a**, 2974, of which weak 320 and 302 reflections were considered to be zero (under background in their counts). The data were corrected for Lorentz and polarization factors. The variance for each reflection was estimated by the equation $\sigma^2(|F_o|) = \sigma_p^2 + qF_o$, where σ_p is from counting statistics and q was derived from the variation among the monitered reflections;[23] q = 4.5 × 10^{-6} for *cis*-**18a**·HCl and 1.8 × 10^{-6} for **20a**.

The structures were solved by the direct method using the MULTAN program,[24] and their parameters were refined by the block-diagonal matrix least-squares method including all the hydrogen atoms. The quantity minimized was $\sum\omega(|F_o| - |F_c|)^2$, where $\omega = 1/\sigma^2(|F_o|)$. In least-squares calculations, zero reflections, except those for which $|F_c| < F_{lim}$, were included by assuming $F_o = F_{lim}$ and $\omega = \omega(F_{lim})$, where F_{lim}, an observational threshhold value, was 1.99 for *cis*-**18a**·HCl and 1.24 for **20a**. The refinement was terminated when the maximum shift of parameters of non-hydrogen atoms were 0.10σ for *cis*-**18a**·HCl and 0.67σ for **20a**. The final R values were 0.045 (0.039 for $F_o > 3/\omega$) and 0.051 (0.048), respectively. Atomic scattering factors used were taken from International Tables for X-ray Crystallography (1974).[25] Final atomic coordinates, thermal parameters, and bond lengths and angels are listed in Tables VIa-c and VIIa-c.[26]

Biological Studies. Eight to ten-week old male mice of the ICR or CDF_1 (Balb/c × DBA/2Cr) strain, purchased from Charles-River Japan, Inc., were used. Administration of the compounds to mice was performed in a saline solution for **17a**, **18a**, and levamisole and in a suspension in saline containing 1% Me_2SO for the other hexahydronaphthimidazothiazoles and **21**.

Plaque-Forming Cell (PFC) Assay. Groups of four mice were immunized intravenously with sheep red blood cells (SRBC) (1×10^8) suspended in phosphate-buffered saline (PBS; 0.1 mL). After 24 h, the test compounds were administered subcutaneously in the inguinal region. Four days after the administration, the mice were sacrificed, and hemolytic plaque-forming cells in the spleen were enumerated according to the method of Cunningham.[17]

Delayed-Type Hypersensitivity Reaction (DHR). Groups of four mice were sensitized by injection of a suspension of SRBC (1×10^8) in PBS (0.05 mL) into the footpad of one hind leg, and the test compounds were administered subcutaneously in the inguinal region. Four days later, a suspension of SRBC (1×10^8) in PBS (0.05 mL) was injected into the footpad of the other hind leg. Thickness of the hind feet was measured with a dial thickness gauge (Peacock Model G, Ikeda Rika Ltd., Tokyo) just before and 24 h after the second injection of SRBC. Increase in foot thickness was calculated in the following way: increase in foot thickness = foot thickness 24 h after injection of SRBC minus foot thickness just before injection of SRBC.

Acute Toxicity LD_{50}. The test compounds were administered intravenously or subcutaneously to groups of six mice, and the mice were observed for a period of 2 weeks. The compounds were examined at three to five dose levels selected from 400, 300, 150, 80, 40, 20, and 10 mg/kg. The LD_{50} value of each compound was calculated by the method of Litchfield-Wilcoxon.[27]

Acknowledgment. The authors thank M. Asano and S. Kimura for mass spectral measurement. Particular appreciation is expressed to S. Ishimoto and Dr. A. Mifune for their support of this investigation.

Supplementary Material Available: Physical and spectral data for compounds **6**, **8**, **9**, **11**, **12**, and **15** (Table V) and fractional coordinates, thermal parameters, bond lengths, and bond angles for *cis*-**18a**·HCl (Table VIa-c) and **20a** (Table VIIa-c) (12 pages). Ordering information is given on any current masthead page.

(23) L. E. McCandish and G. H. Staut, *Acta Crystallogr., Sect. A*, **31**, 245 (1975).
(24) G. Germain, P. Maine, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
(25) "International Tables for X-ray Crystallography", Vol. IV, J. A. Ibers and W. C. Hamilton, Eds., Kynoch Press, Birmingham, England, pp 71-147.
(26) Tables VIa-c and VIIa-c are included in the microfilm edition of this journal.
(27) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
(28) D. Thienpont, D. F. J. Vanparijs, A. H. M. Raeymaekers, J. Vanderberk, P. J. A. Demoen, F. T. Tn. Allewijn, R. P. H. Marsboon, C. J. E. Niemegeers K. H. L. Schellekens, and P. A. J. Janssen, *Nature (London)*, **209**, 1084 (1966).

Synthesis and Antiallergic Properties of Some 4*H*,5*H*-Pyrano[3,2-*c*][1]benzopyran-4-one, 4*H*,5*H*-[1]Benzothiopyrano[4,3-*b*]pyran-4-one, and 1,4-Dihydro-5*H*-[1]benzothiopyrano[4,3-*b*]pyridin-4-one Derivatives

Adolf Philipp, Ivo Jirkovsky,*

Chemistry Department

and René R. Martel

Pharmacology Department, Ayerst Laboratories, Montréal, Québec, Canada, H3C 3J1. *Received April 3, 1980*

A series of novel 2-carboxylic acids of the title ring systems has been synthesized from the corresponding 3-acetyl-4*H*-[1]benzopyran-4-one and benzothiopyran-4-one. These acids were examined for their ability to inhibit the rat passive cutaneous anaphylaxis; the pyridinone carboxylic acids **6** displayed a higher degree of iv and ip anaphylactic activities than their pyranone analogues **5**. The potassium salt **5a** (R_6 = K) was the only compound that exhibited a moderate oral activity.

The cromoglycate molecule[1,2] has become a prototype that has led to the preparation of numerous compounds embodying the chromone moiety, and pharmacological evaluation of the first generation of these analogues has

0022-2623/80/1823-1372$01.00/0