Cyclic Isothioureido Compounds. II (1). Reaction of *trans*-3a,4,5,9b-Tetrahydronaphth[1,2-*d*]-imidazoline-2-thiones with α-Bromoketones

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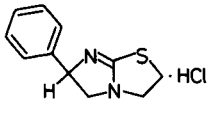
Received February 23, 1981

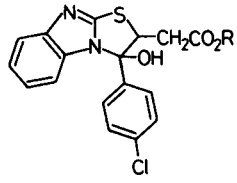
The reaction of *trans*-3a,4,5,9b-tetrahydronaphth[1,2-*d*]imidazoline-2-thiones (**8**) with α-bromoketones gave, depending upon the structure of the α-bromoketones, reaction solvent and reaction temperature, the hydrobromides of tetrahydronaphth[1,2-*d*]imidazolin-2-ylthiomethyl ketone (**10**), hexahydro-8-hydroxynaphth[1′,2′:4,5]imidazo[2,1-*b*]thiazoles (**5**, **11**, **19** and **20**) or tetrahydronaphth[1′,2′:4,5]imidazo[2,1-*b*]-thiazoles (**12** and **16**). Structural determinations based on ir and nmr spectroscopies are discussed.

J. Heterocyclic Chem., **18**, 1089 (1981).

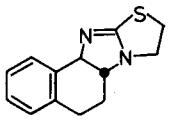
Tetra- or dihydroimidazo[2,1-*b*]thiazole derivatives **1** (levamisole) (2-5) and **2a** (NSC 208828) (6) are known to possess immunoregulatory or immunostimulatory activity, a characteristic which shows the potential utility of these compounds in therapy of autoimmune diseases and cancers. Previously we reported the synthesis of



1



2a, R = H
b, R = C_2H_5



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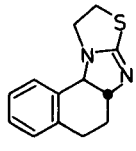

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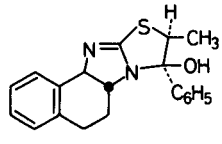
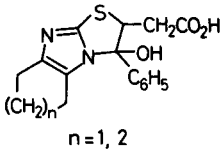
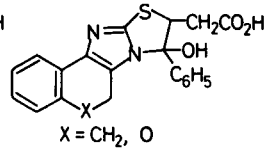


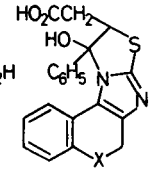
5a



n = 1, 2
6



X = CH_2, O
7a



7b

5,6,6a,8,9,11a-hexahydronaphth[1′,2′:4,5]imidazo-[2,1-*b*]thiazoles **3** and **5a** and 5,6,6a,9,10,11a-hexahydronaphth[2′,1′:4,5]imidazo[2,1-*b*]thiazole **4**, as the potentially immunologically active compounds structurally related to **1** and **2a**, by the reaction of *trans*-3a,4,5,9b-tetrahydronaphth[1,2-*d*]imidazoline-2-thione (**8a**) with 1-bromo-2-(*p*-toluenesulfonyloxy)ethane or with α-bromopropiophenone. Radhakrishna and Berlin reported (7), during our work described herein, the synthesis of the tricyclic and the tetracyclic thiazoloimidazoles **6** and **7a** (or **7b**), also structurally related to **1** and **2a**. As a continuation of our study, we have studied the reaction of **8** with α-bromoketones in some detail and the result is the subject of this paper.

The products of the reaction of **8** with α-bromoketones under various conditions are shown in Scheme I and Table I. When the imidazoline-2-thione **8a** was allowed to react with α-bromoacetophenone (**9**) in boiling acetic acid, the product was the tetrahydronaphth[1′,2′:4,5]imidazo-[2,1-*b*]thiazole hydrobromide **12** hydrobromide (run 3). The observation of the nmr signal for the C-11a methine proton at δ 5.50 favored the naphth[1′,2′:4,5]imidazo-[2,1-*b*]thiazole ring system over the alternative, naphth[2′,1′:4,5]imidazo[2,1-*b*]thiazole ring system; in the latter case the signal is expected to appear in a higher magnetic field based on the nmr spectral data of compounds **3** hydrochloride and **4** hydrochloride (C-11a methine proton signal: **3** hydrochloride, δ 5.29; **4** hydrochloride δ 4.83). The final structure determination was made based on the good agreement of the chemical shift (δ 4.77) of the C-11a methine proton of the hexahydro-8-hydroxynaphthimidazothiazole **11**, the hydrobromide of which was the precursor of **12** hydrobromide to that (δ 4.73) of **5a** whose structure had been determined by X-ray crystallography (1).

The product of the reaction of **8** with **9** varies according to the solvent and the temperature employed: while the reaction in boiling ethanol gave the phenyl thiomethyl ketone hydrobromide **10** hydrobromide (run 1), the reaction in *N,N*-dimethylformamide (DMF) at room temperature afforded **11** hydrobromide (run 2). The free base **11** and **12** were obtained from **11** hydrobromide and **12** hydrobromide, respectively, by a standard method. Structural assignments of the closed tetracyclic form (**11** hydrobromide and the corresponding free base) and the open form (**10** hydrobromide) are supported by the absence and the presence of the carbonyl absorption in the ir spectrum (potassium bromide), respectively.

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Scheme I

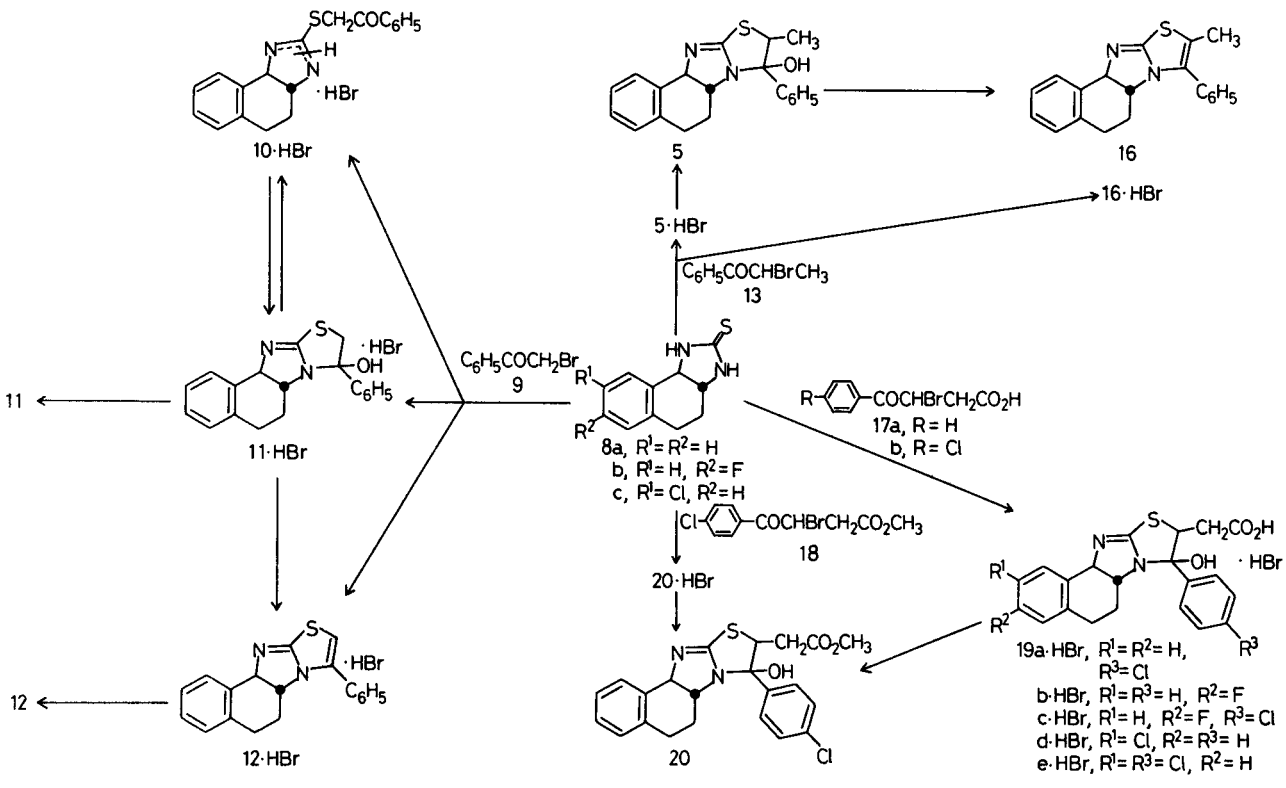


Table I

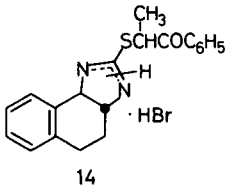
Reaction of theThioureido Compounds **8** and **22** with α-Bromoketones

Run	Thioureido Compound	α-Bromo-ketone (a)	Reaction Conditions: Solvent	Temperature	Period (hours)	Product	Yield (b) (%)
1	**8a**	**9**	ethanol	reflux	3	**10**•HBr	95
2	**8a**	**9**	DMF (c)	room temperature	27	**11**•HBr	96
3	**8a**	**9**	acetic acid	reflux	2	**12**•HBr	85
4 (d)	**8a**	**13**	DMF	room temperature	21	**5**•HBr	84
5	**8a**	**13**	DMSO (e)	room temperature	2	**5** (f)	81
6 (d)	**8a**	**13**	acetic acid	reflux	1.5	**16**•HBr	83
7	**8a**	**17b**	ethanol	reflux	2	**19a**•HBr	95
8	**8a**	**17b**	acetic acid	90°	4	**19a**•HBr	92
9	**8a**	**18**	ethanol	reflux	1.5	**20**•HBr	87
10	**8a**	**18**	acetic acid	90°	3	**20**•HBr	89
11	**8b**	**17a**	acetic acid	90°	0.75	**19b**•HBr	79
12	**8b**	**17b**	acetic acid	90°	2.8	**19c**•HBr	86
13	**8c**	**17a**	acetic acid	90°	1	**19d**•HBr	60
14	**8c**	**17b**	ethanol	reflux	3	**19e**•HBr	56
15	**8c**	**17b**	acetic acid	90°	2	**19e**•HBr	72
16	**21**	**17b**	ethanol	reflux	4	**23**•HBr	91

(a) α-Bromoketone was used in a stoichiometric amount or in a small excess (1.00-1.13 equivalent) to thioureido compound. (b) Yield of crude material identified by ir and nmr spectroscopies. (c) DMF = *N,N*-dimethylformamide. (d) Reported in reference 1. (e) DMSO = dimethyl sulfoxide. (f) Isolated as the free base after treating of the reaction mixture by aqueous ammonia.

Interestingly, when the nmr spectra of **10** hydrobromide and of **11** hydrobromide were determined in DMSO-d_6, there resulted essentially identical spectra showing two sets of signals assignable to the SCH_2 and the $CH_2CHNCHN$ protons of **10** hydrobromide and **11** hydrobromide (see Experimental), indicating that the open from **10** hydrobromide and the closed from **11** hydrobromide entered into an equilibrium with each other in DMSO. However, the nmr spectrum in DMSO-d_6 of the free base **11** indicated that it existed solely as the closed tetracyclic form in DMSO. The characteristic observations which enabled the structural assisgnment of **11** in DMSO were: 1) the SCH_2 signal as AB-quartet; 2) the OH singlet at δ 6.84 (extinguishable with added deuterium oxide); and 3) doublet of the C-11a methine proton at δ 4.77, in a good agreement with the chemical shift (δ 4.86) of the C-11a methine proton of **3**.

We reported previously that the reaction of **8a** with α-bromopropiophenone (**13**) in DMF gave a mixture of two products (the major one being **5a**) discernible in the nmr spectrum exhibiting two sets of signals with respect to the hydroxyl, methyl, C-9 methine and C-11a methine protons. The same mixture was obtained in the reaction in DMSO (run 5). It should be noted that the minor product (**5b**) is a stereoisomer which differs in the configuration at C-8 and C-9 as supported by: 1) the absence of the carbonyl absorption in the ir spectrum; 2) the observation of the hydroxyl signal in the nmr spectrum; 3) the chemical shift of the C-9 methine ($CHCH_3$) proton, hydrobromide salt, δ 4.52; free base, δ 3.82 — smaller values than those of the **5a** hydrobromide and **5a**; and 4) the chemical shift of the C-11a methine ($CH_2CHNCHN$) proton, hydrobromide salt, δ 5.64; free base, δ 4.98 — larger values than those of **5a** hydrobromide and **5a**, excluding the possibility of its being the open form, tricyclic compound **14** or another closed form, tetracyclic compound **15**. As for the $CHCH_3$



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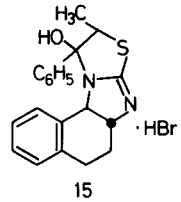

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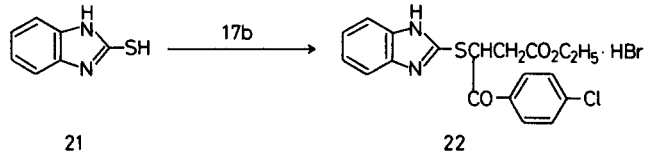
signal in nmr, **14** would have the signal of δ value larger than that of **5a**. And **14** and **15** would have the $CH_2CHNCHN$ signal of δ value smaller than that of **5a**. Heating a mixture of **5a** and **5b** at reflux in acetic acid gave a single compound **16** in a high yield.

Finally we studied the reaction of **8** with the bromoketoacids **17** and the bromoketoester **18**. The reaction in boiling ethanol (runs 7, 9 and 14) or at 90° in acetic acid (runs 8, 10-13 and 15) afforded the hexahydronaphthimidazothiazoles **19** hydrobromide and **20** hydrobromide in high yields. The free base **20** was generated from **20** hydrobromide and later prepared by treatment of **19a** hydrobromide with excess diazomethane. The structural determination is again based on ir (no ketone carbonyl absorption) and nmr (C-9 methine proton signal at around δ 4.76-4.83 for **19** hydrobromide and **20** hydrobromide and δ 4.42 for **20**; C-11a methine proton doublet at δ 5.45-5.52 for **19** hydrobromide and **20** hydrobromide and δ 4.74 for **20**) spectroscopies as well as combustion analysis.

For comparison, we run the reaction of 2-mercaptobenzimidazole (**21**) with the bromoketoacid **17b** in boiling ethanol, and, contrary to the case of **8a**, obtained the open form compound, benzimidazolylthioketoester hydrobromide **22**. Another point of difference, compared to the case of **8a**, is the esterification which took place with the aid of hydrogen bromide generated in situ.

Scheme II



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Our observation that in a DMSO solution, **11** and **20** exist as the closed tetracyclic form and **11** hydrobromide as an equilibrium mixture of the closed and the open forms is interesting compared with the observations of Bell and Wei (6) on **2** and of Radhakrishna and Berlin (7) on **6** and **7a** (or **7b**); the formers stated that **2a** and **2b** existed as the open form at neutral and high *p*H and as the closed form in acid medium, and the latters observed **6** and **7a** (or **7b**) in DMSO as their open forms. It should be noted that introduction of a substituent at C-9 (**5**, **19** and **20**) makes even the hydrobromides of the compounds exist as the closed forms in DMSO.

Although inspection of the nmr spectra of **19** hydrobromide, **20** hydrobromide and **20** suggests that the reaction of **8** with **17** or **18** may be more stereoselective with respect to the configuration at C-8 and C-9 than the reaction with **13**, an additional study including X-ray analysis is necessary for clarification of this point.

EXPERIMENTAL

Melting points were taken on a Yanagimoto hot-stage apparatus and are uncorrected. Combustion analyses were carried out by the Analytical Chemistry Laboratory of the Central Research Institute, Teijin Ltd. Infrared spectra were recorded on a Hitachi EPI-S2 spectrophotometer. Nmr spectra were obtained on a Varian EM360A spectrometer unless otherwise noted with tetramethylsilane as an internal standard. Mass spectra were run on a LKB 9000 spectrometer at 70 eV. Reactions of *trans*-3a,4,5,9b-tetrahydronaphth[1,2-*d*]imidazoline-2-thiones (**8**) with α-bromoketones are exemplified by the following, first three experiments described in detail. For other reactions see Tables I-III.

trans-Phenyl 3a,4,5,9b-Tetrahydronaphth[1,2-*d*]imidazolin-2-ylthiomethyl Ketone Hydrobromide (**10**·HBr).

To a stirred suspension of *trans*-3a,4,5,9b-tetrahydronaphth[1,2-*d*]imidazoline-2-thione (**8a**, 428 mg, 2.10 mmoles) in ethanol (10 ml) was added α-bromoacetophenone (**9**, 440 mg, 2.21 mmoles), and the mixture was refluxed for 3 hours. The solvent was evaporated, the residue was triturated with ether (8 ml), and the solid was collected by filtration to give 801 mg (95%) of **10** hydrobromide. Recrystallization from acetonitrile-methanol gave colorless leaflets, mp 258-268° dec; ir (potassium bromide): 3050, 1674, 1519, 1493, 1325, 1200, 749 cm^{-1}.

Anal. Calcd. for $C_{19}H_{19}BrN_2OS$: C, 56.58; H, 4.75; N, 6.95. Found: C, 56.57; H, 4.51; N, 6.85.

trans-6a,5,6,6a,8,9,11a-Hexahydro-8-hydroxy-8-phenylnaphth[1',2':4,5]-imidazo[2,1-*b*]thiazole (**11**).

To a stirred solution of **6a** (200 mg, 0.979 mmoles) in DMF (1.5 ml) was added **9** (220 mg, 1.11 mmoles), and the mixture was stirred at room temperature for 27 hours. Ether (10 ml) was added to the reaction mixture, and the solid was collected by filtration to give 379 mg (96%) of **11** hydrobromide; ir (potassium bromide): 3440, 3140, 1548, 1457, 1180, 1059 cm^{-1}; nmr (8) (DMSO-d_6): 1.33-2.40 (2H, m, C*H*$_2$CHN), 2.73-3.17 (2H, m, C*H*$_2$CH$_2$CHN), 3.64-3.98 (1H, m, CH$_2$C*H*N), 4.06 (H-A) and 4.19 (H-B) (1.2H, AB quartet, SCH$_2$ of **11**·HBr), 4.94 (0.4H, d, J = 15 Hz, CH$_2$CHNC*H*N of **10**·HBr), 5.39 (0.8H, s, SCH$_2$ of **10**·HBr), 5.47 (0.6H, d, J = 15 Hz, CH$_2$CHNC*H*N of **11**·HBr), 7.08-8.14 (9H, m, aromatic). In order to obtain an analytical sample, recrystallization of a portion of **11** hydrobromide thus obtained was performed from acetonitrile-methanol to give colorless leaflets, mp 258-268° dec, whose ir spectrum (potassium bromide) was identical to that of **10** hydrobromide obtained by the above-described reaction of **8a** with **9** in boiling ethanol, showing the isomerization of **11** hydrobromide to **10** hydrobromide.

Anal. Calcd. for $C_{19}H_{19}BrN_2OS$: C, 56.58; H, 4.75; N, 6.95. Found: C, 56.56; H, 4.67; N, 6.90.

A suspension of **11** hydrobromide (333 mg, 0.826 mmoles) in methylene chloride (20 ml) was treated with 5% aqueous ammonia (10 ml), and the organic layer was washed with brine (3 x 10 ml), dried over anhydrous sodium sulfate and evaporated to give 244 mg (92%) of **11**. Recrystallization from methylene chloride gave colorless prisms, mp 151-152°; ir (potassium bromide): 1578, 1561, 1446, 1195, 1181 cm^{-1}; nmr (DMSO-d_6): δ 1.26-1.82 (2H, m, C*H*$_2$CHN), 2.41-3.59 (3H, m, C*H*$_2$CH$_2$C*H*N), 3.48 (H-A) and 3.84 (H-B) (2H, AB quartet, J = 12 Hz, SCH$_2$), 4.77 (1H, d, J = 14 Hz, CH$_2$CHNC*H*N), 6.84 (1H, s, OH), 7.03-7.83 (9H, m, aromatic); ms: exact mass calcd. for $C_{19}H_{18}N_2OS$, 322.114; found, 322.115.

Anal. Calcd. for $C_{19}H_{18}N_2OS$: C, 70.78; H, 5.63; N, 8.69. Found C, 70.50; H, 5.52; N, 8.59.

trans-5,6,6a,11a-Tetrahydro-8-phenylnaphth[1'2':4,5]imidazo-[2,1-*b*]thiazole (**12**).

A mixture of **8a** (400 mg, 1.96 mmoles), **9** (410 mg, 2.06 mmoles), and acetic acid (8 ml) was refluxed for 2 hours. The solvent was evaporated, the residue was triturated with methanol (4 ml)-ether (6 ml), and the solid was collected by filtration to give 644 mg (85%) of **12** hydrobromide. Recrystallization from methanal-acetonitrile gave colorless prisms, mp 293-295° dec; ir (potassium bromide): 1500, 1345, 749, 731 cm^{-1}; nmr (DMSO-d_6): δ 1.78-2.16 (2H, m, C*H*$_2$CHN), 2.85-3.08 (2H, m, C*H*$_2$CH$_2$CHN), 4.38-4.89 (1H, m, CH$_2$C*H*N), 5.50 (1H, d, J = 14 Hz, CH$_2$CHNC*H*N), 7.14 (1H, s, SCH), 7.20-7.35 (4H, m, C_{1-4} H), 7.56-7.60 (5H, m, C_6H_5).

Anal. Calcd for $C_{19}H_{17}BrN_2S$: C, 59.23; H, 4.45; N, 7.27. Found: C, 59.18; H, 4.28; N, 7.17.

The free base **12** was obtained from **12** hydrobromide by treatment with aqueous ammonia. Recrystallization from ether-hexane gave colorless prisms, mp 153.5-155°; ir (potassium bromide): 1592, 1548, 1343, 742, 698 cm^{-1}; nmr (deuteriochloroform): δ 1.86-3.04 (4H, m, C*H*$_2$C*H*$_2$CHN), 3.23-3.73 (1H, m, CH$_2$C*H*N), 4.88 (1H, d, J = 14 Hz, CH$_2$CHNC*H*N), 5.72 (1H, s, SCH), 6.99-7.77 (4H, m, C_{1-4} H), 7.43 (5H, s, C_6H_5).

Anal. Calcd. for $C_{19}H_{16}N_2S$: C, 74.97; H, 5.30; N, 9.20. Found: C, 75.08; H, 5.19, N, 9.31.

trans-5,6,6a,11a-Tetrahydro-9-methyl-8-phenylnaphth[1'2':4,5]-imidazo[2,1-*b*]thiazole (**16**).

A stirred solution of (±)-5,6,6aα,8,9,11aβ-hexahydro-8-hydroxy-9-methyl-8-phenylnaphth[1'2':4,5]imidazo[2,1-*b*]thiazole (**5**); 3:2 mixture of two stereoisomeric racemates, 202 mg, 0.600 mmoles) in acetic acid (2 ml) was refluxed for 2 hours. The solvent was evaporated, and the residue was dissolved in methylene chloride (10 ml) and treated with 5% aqueous ammonia (10 ml). The layers were separated, and the aqueous layer was extracted with methylene chloride (2 × 4 ml). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was crystallized with ether to give 181 mg (94%) of **16**. Recrystallization from methylene chloride-hexane gave pale yellow needles, mp 124-125.5°. The ir and nmr spectra were identical with those of 16 prepared from **16** hydrobromide obtained directly by the reaction of **8a** with α-bromopropiophenone (**13**) in refluxing acetic acid (1).

Anal. Calcd. for $C_{20}H_{18}N_2S$: C, 75.43; H, 5.70; N, 8.80. Found: C, 75.37; H, 5.62; N, 8.67.

Esterification of (±)-5,6,6aα,8,9,11aβ-Hexahydro-8-hydroxy-8-(*p*-chlorophenyl)naphth[1'2':4,5]imidazo[2,1-*b*]thiazole-2-acetic Acid Hydrobromide (**19a**·HBr).

To a stirred solution of **19a** hydrobromide (51 mg, 0.130 mmoles) in absolute methanol (4 ml) was added excess ethereal solution of

Table II

Physical and Analytical Data for Hexahydronaphth[1',2':4,5]imidazo[2,1-*b*]thiazoles (**19**).

Compound No.	Mp (°C) (a)	Recrystallization Solvent	Formula	Anal.	C (%)	H (%)	N (%)
19a·HBr	222-225	methaol-acetonitrile	$C_{21}H_{20}BrClN_2O_3S$	Calcd.	50.87	4.07	5.65
				Found	50.99	4.07	5.68
19b·HBr	208-221	methanol-ethyl acetate	$C_{21}H_{20}BrFN_2O_3S$	Calcd.	52.62	4.21	5.84
				Found	52.46	4.30	5.68
19c·HBr	226-230	methanol-ethyl acetate	$C_{21}H_{19}BrClFN_2O_3S$	Calcd.	49.09	3.73	5.45
				Found	48.93	3.87	5.39
19d·HBr	218-223	methanol-benzene	$C_{21}H_{20}BrClN_2O_3S$	Calcd.	50.87	4.07	5.65
				Found	50.93	4.20	5.72
19e·HBr	250-255	methanol-acetonitrile	$C_{21}H_{19}BrCl_2N_2O_3S$	Calcd.	47.57	3.61	5.28
				Found	47.45	3.73	5.35

(a) Decomposition.

Table III

Spectral Data for Hexahydronaphth[1′,2′:4,5]imidazo[2,1-*b*]thiazoles (**19**)

Compound No.	^{1}H NMR Spectral Data (a)	IR Spectral Data (b)
19a·HBr	1.35-2.13 (2H, m, C*H*$_2$CHN), 2.63-3.11 (4H, m, C*H*$_2$CH$_2$CHN and CH$_2$CO), 3.54-4.08 (1H, m, CH$_2$C*H*N), 4.76 (1H, dd, J = 10 and 5 Hz, SCH), 5.46 (1H, d, J = 14 Hz, CH$_2$CHNC*H*N), 7.05-7.40 (5H, m, C$_{1-4}$ H and OH), 7.58 (2H, broad d, J = 8 Hz, C-2′ and C-5′ of C$_6$H$_4$Cl), 7.80 (2H, broad d, J = 8 Hz, C-3′ and C-4′ H of C$_6$H$_4$Cl), 8.13 (1H, broad s, CO$_2$H)	3230, 1733, 1548, 1452, 1400, 1145, 1094
19b·HBr	1.17-2.14 (2H, m, C*H*$_2$CHN), 2.70-3.00 (4H, m, C*H*$_2$CH$_2$CHN and CH$_2$CO), 3.56-4.07 (1H, m, CH$_2$C*H*N), 4.63-4.89 (1H, m, SCH), 5.45 (1H, d, J = 14 Hz, CH$_2$CHNC*H*N), 6.98-8.13 (10H, m, OH, aromatic and CO$_2$H).	3450, 3205, 3070, 1721, 1536, 1254, 1151
19c·HBr	1.31-2.02 (2H, m, C*H*$_2$CHN), 2.80-3.03 (4H, m, C*H*$_2$CH$_2$CHN and CH$_2$CO), 3.60-4.11 (1H, m, CH$_2$C*H*N), 4.83 (1H, dd, J = 11 and 5 Hz, SCH), 5.48 (1H, d, J = 15 Hz, CH$_2$CHNC*H*N), 6.99-7.96 (7H, aromatic)	3410, 3190, 1720, 1533, 1150
19d·HBr	1.22-2.21 (2H, m, C*H*$_2$CHN), 2.75-3.04 (4H, m, C*H*$_2$CH$_2$CHN and CH$_2$CO), 3.57-4.16 (1H, m, CH$_2$C*H*N), 4.82 (1H, dd, J = 11 and 5 Hz, SCH), 5.52 (1H, d, J = 14 Hz, CH$_2$CHNC*H*N), 7.36-8.13 (10H, m, OH, aromatic and CO$_2$H)	3390, 3200, 3050, 1721, 1543, 1158
19e·HBr	1.24-2.23 (2H, m, C*H*$_2$CHN), 2.64-3.26 (4H, m, C*H*$_2$CH$_2$CHN and CH$_2$CO), 3.53-4.11 (1H, m, CH$_2$C*H*N), 4.78 (1H, dd, J = 10 and 5 Hz, SCH), 5.47 (1H, d, J = 14 Hz, CH$_2$CHNC*H*N), 7.33-8.40 (9H, m, OH, aromatic and CO$_2$H)	3400, 3200, 3060, 1720, 1531, 1405, 1149

(a) The spectrum of **19c**·HBr was recorded in DMSO-d$_6$-methanol-d$_4$ (2:1). Other spectra were recorded in DMSO-d$_6$. (b) All spectra were recorded in potassium bromide.

diazomethane under cooling with an ice bath. After the addition, the mixture was stirred for a further 15 minutes and evaporated. The residue was dissolved in methylene chloride (10 ml), washed with brine, dried over anhydrous sodium sulfate, evaporated and crystallized with ether to give 47 mg (quantitative) of (±)-methyl 5,6,6aα,8,9,11aβ-hexahydro-8-hydroxy-8-(*p*-chlorophenyl)naphth[1′,2′:4,5]imidazo[2,1-*b*]-thiazole-2-acetate (**20**). Recrystallization from methylene chloride-hexane gave colorless plates, mp 117-118°; ir (potassium bromide): 1740, 1580, 1562, 1202, 1171, 1090 cm^{-1}; nmr (deuteriochloroform): δ 1.05-1.66 (2H, m, C*H*$_2$CHN), 2.04-3.66 (5H, m, C*H*$_2$CH$_2$C*H*N and CH$_2$CO), 3.60 (3H, s, CH$_3$), 4.42 (1H, dd, J = 9 and 5 Hz, SCH), 4.45 (1H, broad s, OH), 4.74 (1H, d, J = 14 Hz, CH$_2$CHNC*H*N), 6.88-7.84 (8H, m, aromatic).

Anal. Calcd. for C$_{22}$H$_{21}$ClN$_2$O$_3$S: C, 61.60; H, 4.93; N, 6.53. Found: C, 61.60; H, 4.86; N, 6.46.

Ethyl 3-(Benzimidazol-2-ylthio)-3-(*p*-chlorobenzoyl)propionate Hydrobromide (**22**).

A solution of 2-mercaptobenzimidazole (**21**, 100 mg, 0.666 mmoles) and **17b** (195 mg, 0.666 mmoles) in ethanol (3 ml) was refluxed for 4 hours. The solvent was evaporated, the residue was crystallized with ether, and the solid was collected by filtration to give 284 mg (91%) of **22**. Recrystallization from ethanal-hexane gave colorless prisms, mp 166-168° [Lit **6a** mp 168-170°]; ir (potassium bromide): 2810, 1740, 1687, 1212, 1182, 1171, 930, 739 cm^{-1}; nmr (DMSO-d$_6$): δ 1.07 (3H, t, J = 7 Hz, CH$_3$), 2.93-3.43 (2H, m, CH$_2$CO), 4.00 (2H, q, J = 7 Hz, C*H*$_2$CH$_3$), 5.82 (1H, t, J = 7 Hz, SCH), 7.13-8.21 (8H, m, aromatic).

Acknowledgement.

The authors thank Dr. Y. Kato for valuable discussion and Miss A. Mineo for 100 MHz nmr spectral determination on a JEOL spectrometer.

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