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Studies on the Synthesis and Anti-Inflammatory Activity of 2,6-Di-*tert*-butylphenols with a Heterocyclic Group at the 4-Position. I

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A number of 2,6-di-*tert*-butylphenols with a heterocyclic group at the 4-position were prepared. The heterocyclic groups were as follows: benzoxazole, benzothiazole, benzimidazole, indole, imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine. Anti-inflammatory activity of these compounds was examined by using the adjuvant-induced arthritis (A.A) assay. Some compounds were further tested in carrageenin-induced rat paw edema (CIPE) assay and AcOH-induced writhing (AIW) assay in mice. The anti-inflammatory activity was greatly dependent on the value of the heterocyclic group. Among these compounds, 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-benzoxazole (IIa) and 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)indole (Xg) showed very potent activity. Both IIa and Xg had a minimum effective dose of 5 mg/kg (*p.o.*) in A.A assay and showed stronger activity than phenylbutazone in CIPE assay but weaker analgesic activity than aminopyrine in AIW assay.

Keywords——anti-inflammatory activity; 2,6-di-*tert*-butylphenol; heterocyclic group; analgesic activity; indole; benzoxazole; benzimidazole; benzothiazole

A number of nonsteroidal anti-inflammatory drugs (NSAID) have been used in the treatment of rheumatoid arthritis. Although these drugs ameliorate the arthritic condition, they are not curative and have side effects, largely gastrointestinal disturbances. These side effects are closely related to their mode of action, namely inhibition of prostaglandin synthesis. Thus, there has been continuing interest in the development of a more efficacious anti-inflammatory agent with reduced side effects. Recent studies[1] of inflammation suggest that oxygen-derived radicals play important roles in the inflammatory site, and superoxide dismutase (SOD)[2] which has radical-scavenging activity showed clinical effect in patients with rheumatoid arthritis. Its mode of action is very different from that of most NSAID. Moreover, some antioxidants such as α-tocopherol[3] and 2,6-di-*tert*-butylphenols[4] have been reported to have anti-inflammatory activity. These facts suggested that compounds with antioxidant activity might be a new type of anti-inflammatory agent. In this paper, we describe the synthesis and anti-inflammatory activity of 2,6-di-*tert*-butylphenols with a heterocyclic moiety at the 4-position.

Synthesis

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)benzoxazole (IIa) and oxazolopyridine analogues (IIh, i) were easily prepared by reacting 3,5-di-*tert*-butyl-4-hydroxybenzoyl chloride (I) with *o*-aminophenol or *o*-hydroxyaminopyridines under heating in pyridine. While the reaction of I with *o*-phenylenediamine yielded only the diacyl compound, 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)benzimidazoles (IIIa, b) were prepared in poor yields by reacting 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde with *o*-phenylenediamines in EtOH. 2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)benzothiazole (IV) was prepared by reacting I with *o*-aminothiophenol in the

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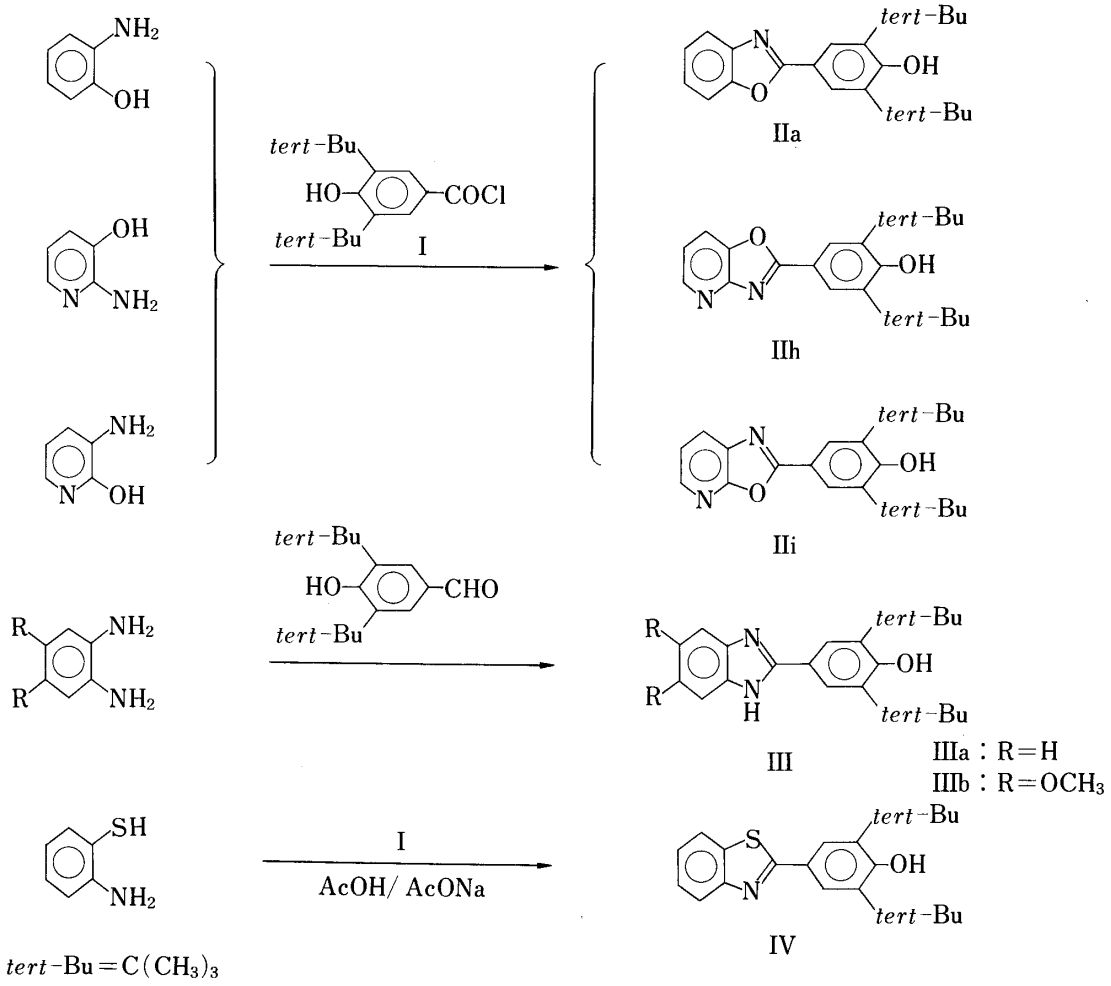

Chart 1

presence of sodium acetate in AcOH.

Since compounds IIa and IIh showed potent anti-inflammatory activity, derivatives of IIa and 2,6-di-*tert*-butylphenols with other heterocyclic compounds were prepared to find more potent compounds. Compounds IIb—g were prepared from *o*-aminophenol derivatives and compound I. Compound IIa was converted to the acyl derivative (V) by acylation with acetyl chloride. Compound IIc was converted to the amino derivative (VI) by catalytic reduction, then converted to the dimethylamino derivative (VII) by reductive alkylation.

Though preparation of 2- or 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)indoles (X, XI) using the Fisher indole synthesis procedure[5] was unsuccessful, compounds X, XI were prepared in unsatisfactory yields by using the Bishler indole synthesis.[5] Reaction of 4-(2-bromopropionyl)-2,6-di-*tert*-butylphenol (IXb)[6] and aniline (VIIIa) yielded compound Xa as the main product and compound XIa as a minor product. However, reaction of 4-(2-bromoacetyl)-2,6-di-*tert*-butylphenol (IXa) with *N*-methylaniline (VIIIb) yielded compound Xb as a minor product and compound XIb as the main product. Reaction of IXb with *m*-methoxyaniline (VIIIc) also yielded two compounds, Xc and XIc, and Xc was the main product. However, reaction of IXa or IXb with anilines (VIIIa, d, e, f) yielded only the corresponding compounds Xd—g, respectively.

The structures of these compounds Xa—g, XIa—c were determined by comparing the ^{1}H- or ^{13}C-nuclear magnetic resonance (^{1}H- or ^{13}C-NMR) spectral data of these compounds with those of indole compounds. The spectral data are listed in Table I.

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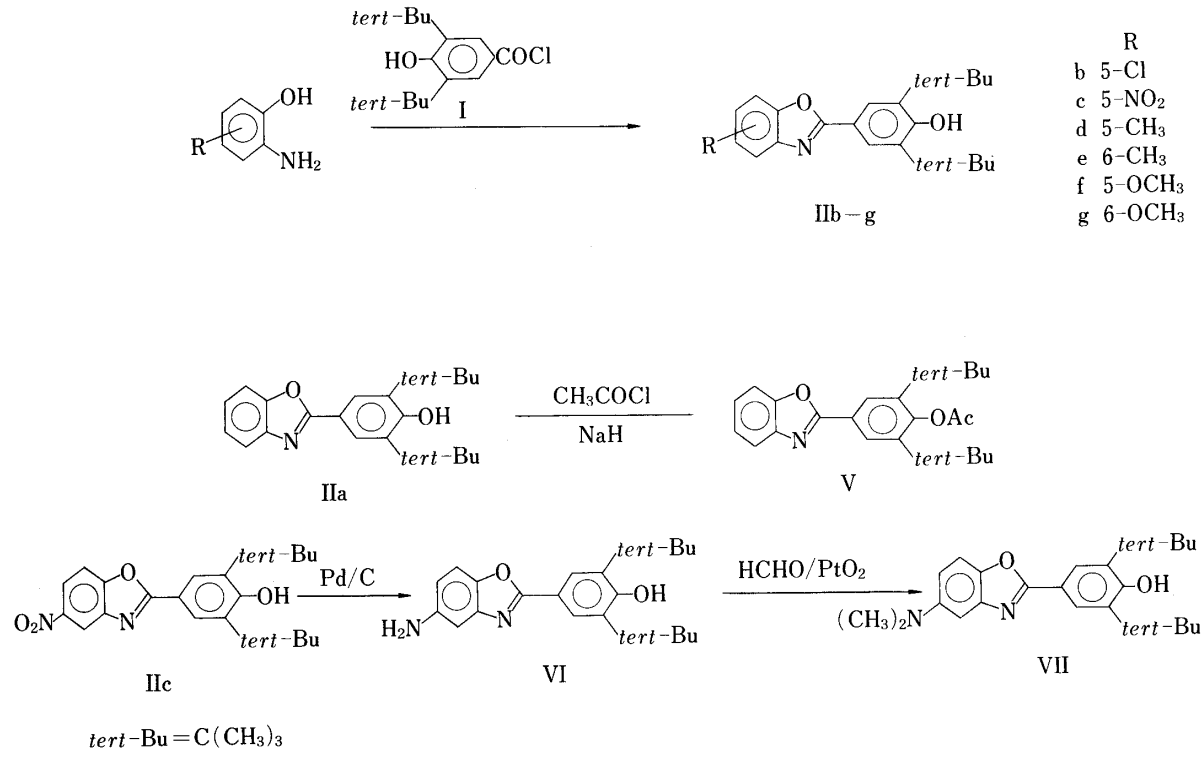

Chart 2

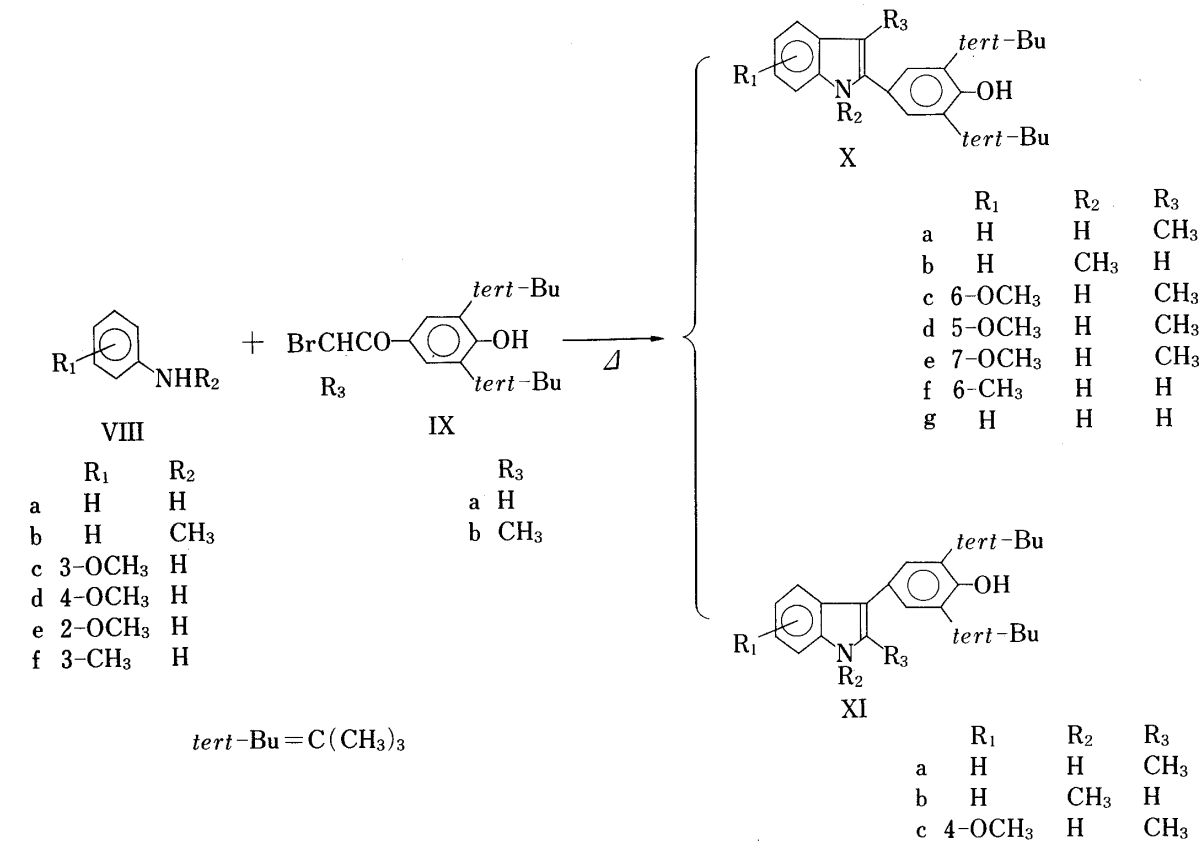

Chart 3

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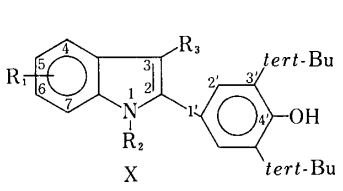
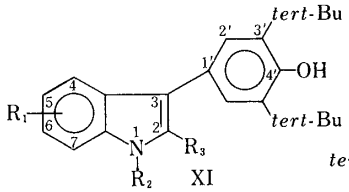
TABLE I. ^{1}H- or ^{13}C-Nuclear Magnetic Resonance Spectral Data ($CDCl_3$)



X



XI

tert-Bu=$C(CH_3)_3$

Compd. No.	R_1	R_2	R_3	^{1}H-NMR chemical shift δ ppm			^{13}C-NMR chemical shift δ ppm	
				C_2-H (CH_3)	C_3-H (CH_3)	Aromatic-H	C_2	C_3
Xa	H	H	CH_3		(2.40)			
b	H	CH_3	H		6.44		142.7	100.7
c	6-OCH_3	H	CH_3		(2.40)	6.76 (J=8 Hz, J=2 Hz), 6.84 (J=2 Hz), 7.40 (J=8 Hz)	136.3	107.0
d	5-OCH_3	H	CH_3		(2.40)	6.78 (J=8 Hz, J=2 Hz), 6.98 (J=2 Hz), 7.20 (J=8 Hz)		
e	7-OCH_3	H	CH_3		(2.40)	6.62 (J=8 Hz, J=2 Hz), 7.00 (J=8 Hz, J=8 Hz), 7.16 (J=8 Hz, J=2 Hz)		
f	6-CH_3	H	H		6.64	6.88 (J=8 Hz, J=2 Hz), 7.04 (J=8 Hz), 7.20 (J=2 Hz)		
g	H	H	H		6.64			
XIa	H	H	CH_3	(2.50)				
b	H	CH_3	H	7.08			126.4	117.7
c	4-OCH_3	H	CH_3	(2.60)		6.44 (J=8 Hz, J=2 Hz), 6.96 (J=8 Hz, J=8 Hz), 6.98 (J=8 Hz, J=2 Hz)		
2-Phenylindole					6.84[a]		137.4[c]	98.5[c]
3-Methyl-2-phenylindole					(2.42)			
3-Methylindole				6.80[b]	(2.30)[b]			
3-Phenylindole				7.03[b]			121.3[c]	117.5[c]
2-Methylindole				6.13[b]	(2.20)[b]			

a) See ref. 7. *b*) See ref. 8. *c*) See ref. 9.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)imidazo[1,2-*a*]pyridine (XII) and -imidazo[1,2-*a*]-pyrimidine (XIIIa, b) were prepared by reacting 2-aminopyridine and 2-aminopyrimidine, respectively, with IXa or IXb under heating.

Compound XIIIa was converted to the 3-methylthio derivative (XIV) on treatment with methanesulfenylchloride. Compound XIV was converted to the corresponding sulfoxide (XV) by oxidation with *m*-chloroperbenzoic acid.

Compounds IIa—VII, Xa—g and XIa—c, and XII—XV thus prepared are listed in Tables II, III, and IV, respectively.

Pharmacology and Discussion

The anti-inflammatory activity of these compounds was examined by using the adjuvant-induced arthritis assay in rats (therapeutic activity) as described by Pearson[13] at a dose of 25 mg/kg (*p.o.*), and the results were compared with that for phenylbutazone (50 mg/kg, *p.o.*) or indomethacin (2 mg/kg, *p.o.*). All the compounds and reference drugs were administered to rats (n=3—6) with established arthritis on days 15 through 27 after injection of the adjuvant.

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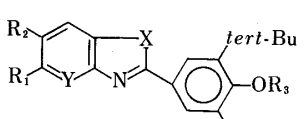
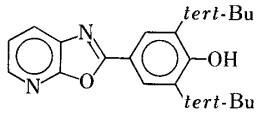
TABLE II



IIa—g IIIa—VIII



IIi

Compd. No.	R_1	R_2	R_3	X	Y	AA[a] (25 mg/kg *p.o.*)	mp (°C)	Recryst. solvent	Yield (%)	Formula	Analysis (%) Calcd (Found)		
											C	H	N
IIa[b]	H	H	H	O	CH	(++)**	169—170	MeOH	83	$C_{21}H_{25}NO_2$	77.99 (77.81	7.79 7.83	4.33 4.39)
IIb[b]	Cl	H	H	O	CH	(−)	197—198	MeOH	22.9	$C_{21}H_{24}NO_2Cl$	70.48 (70.25	6.76 6.67	3.91 3.83)
IIc[b]	NO_2	H	H	O	CH	(NT)	174—175	MeOH	38.8	$C_{21}H_{24}N_2O_4$	68.46 (68.32	6.57 6.51	7.60 7.58)
IId[b]	CH_3	H	H	O	CH	(−)	168—169	MeOH	68.2	$C_{22}H_{27}NO_2$	78.30 (78.42	8.06 8.13	4.15 4.08)
IIe[b]	H	CH_3	H	O	CH	(−)	187—188	MeOH	50.4	$C_{22}H_{27}NO_2$	78.30 (78.23	8.06 8.12	4.15 4.15)
IIf[b]	CH_3O	H	H	O	CH	(−)	177—178	MeOH	42.2	$C_{22}H_{27}NO_3$	74.76 (74.92	7.70 7.79	3.96 3.83)
IIg	H	CH_3O	H	O	CH	(−)	169—170	MeOH	42.8	$C_{22}H_{27}NO_3$	74.76 (74.64	7.70 7.70	3.96 3.96)

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IIh	H	H	H	O	N	(++)**	182—183	MeOH	29.9	$C_{20}H_{24}N_2O_2$	74.05 (73.94	7.46 7.30	8.63 8.54)
IIi						(−)	202—204	Cyclohexane	53.0	$C_{20}H_{24}N_2O_2$	74.05 (74.06	7.46 7.52	8.63 8.59)
IIIa[b]	H	H	H	NH	CH	(−)	300	DMF	9.0	$C_{21}H_{26}N_2O$	78.22 (78.06	8.13 8.05	8.69 8.65)
IIIb[b]	CH_3O	CH_3O	H	NH	CH	(±)*	300	CH_3CN	13.0	$C_{23}H_{30}N_2O_3$	72.22 (72.17	7.91 7.88	7.32 7.32)
IV[b]	H	H	H	S	CH	(−)	103—104	[f]	29.7	$C_{21}H_{25}NOS$	74.30 (74.37	7.42 7.39	4.13 3.91)
V	H	H	CH_3CO	O	CH	(−)	210—211	MeOH	53.1	$C_{23}H_{27}NO_3$	75.59 (75.48	7.45 7.50	3.83 4.03)
VI	NH_2	H	H	O	CH	(−)	202—203	Cyclohexane	77.8	$C_{21}H_{26}N_2O_2$	74.53 (74.45	7.74 7.73	8.28 8.09)
VII	$(CH_3)_2N$	H	H	O	CH	(−)	177—178	MeOH	69.2	$C_{23}H_{30}N_2O_2$	75.38 (75.16	8.25 8.44	7.64 7.50)
IIj[c]	2-(*p*-Hydroxyphenyl)benzoxazole					(±)*							
IIk[d]	2-Phenylbenzoxazole					(−)							
	2,6-Di-*tert*-butylphenol					(−)							
	2,6-Di-*tert*-butyl-4-methylphenol					(−)							
	Phenylbutazone					60—70%[e]							

a) Adjuvant-induced arthritis. ++: Therpeutic effect was larger than or equal to that of phenylbutazone. ±: Therapeutic effect was slight (less than one-third of that of phenylbutazone). −: inactive at 25 mg/kg. **: $p<0.01$ *vs.* arthritis control. *: $p<0.05$ *vs.* arthritis control. NT: not tested.
b) See ref. 10. *c*) See ref. 11. *d*) See ref. 12.
e) Therapeutic effect at 50 mg/kg (*p.o.*). Inhibition (%) of edema formation induced by adjuvant.
f) Purified by silica gel column chromatography.

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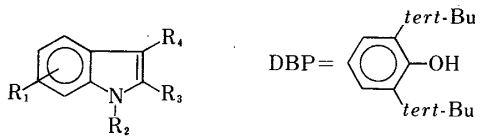
TABLE III



Compd. No.	R_1	R_2	R_3	R_4	AA[a] 25 mg/kg *p.o.*	mp (°C)	Recryst. solvent	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
Xa	H	H	DBP	CH_3	(++)**	130—131	*n*-Hexane	29.9	$C_{23}H_{29}NO$	82.34 (82.44	8.71 8.91	4.18 4.31)
Xb	H	CH_3	DBP	H	(−)	152—153	MeOH–H_2O	2.5	$C_{23}H_{29}NO$	82.34 (82.34	8.71 8.57	4.18 4.30)
Xc	6-OCH_3	H	DBP	CH_3	(−)	207—209	*n*-Hexane	49.3	$C_{24}H_{31}NO_2$	78.87 (78.85	8.55 8.71	3.83 3.90)
Xd	5-OCH_3	H	DBP	CH_3	(−)	124—126	*n*-Hexane	13.7	$C_{24}H_{31}NO_2$	78.87 (79.02	8.55 9.01	3.83 3.85)
Xe	7-OCH_3	H	DBP	CH_3	(−)	143—145	*n*-Hexane	5.5	$C_{24}H_{31}NO_2$	78.87 (78.84	8.55 8.69	3.83 3.71)
Xf	6-CH_3	H	H	DBP	(−)	138—140	*n*-Hexane	30.8	$C_{23}H_{29}NO$	82.34 (82.52	8.71 8.87	4.18 4.32)
Xg	H	H	H	DBP	(++)**	149—151	*n*-Hexane	15.0	$C_{22}H_{27}NO$	82.20 (82.44	8.47 8.53	4.36 4.44)
XIa	H	H	CH_3	DBP	(−)	236—237	*n*-Hexane	9.0	$C_{23}H_{29}NO$	82.34 (82.12	8.71 8.95	4.18 4.26)
XIb	H	CH_3	H	DBP	(+)*	133—134	MeOH–H_2O	11.9	$C_{23}H_{29}NO$	82.34 (82.04	8.71 8.57	4.18 4.30)
XIc	4-OCH_3	H	CH_3	DBP	(NT)	184—186	*n*-Hexane	8.2	$C_{24}H_{31}NO_2$	78.87 (78.70	8.55 8.70	3.83 3.76)
	Phenylbutazone				60—70%[b]							

a) Adjuvant-induced arthritis. ++: Therapeutic effect was larger than or equal to that of phenylbutazone. +: Therapeutic effect was about half that of phenylbutazone. −: inactive at 25 mg/kg. NT: not tested. **: $p<0.01$ *vs.* arthritis control. *: $p<0.05$ *vs.* arthritis control.
b) Therapeutic effect at 50 mg/kg (*p.o.*). Inhibition (%) of edema formation induced by adjuvant.

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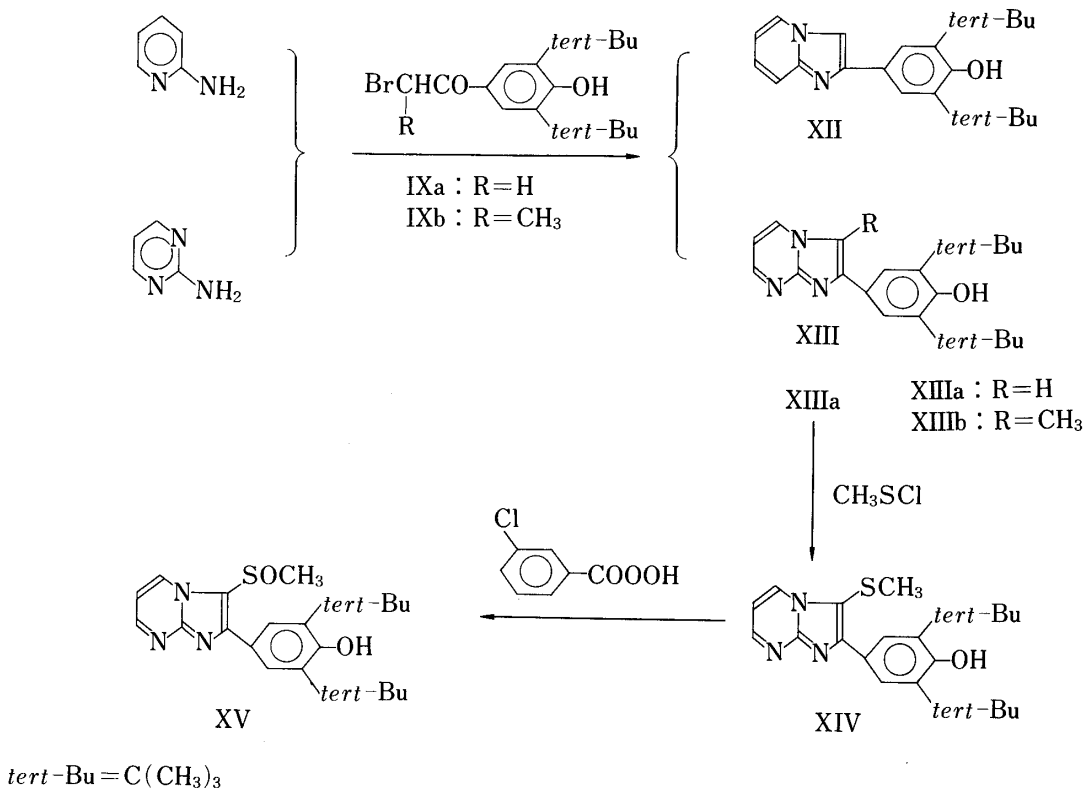
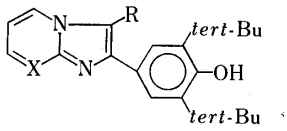


Chart 4

TABLE IV



Compd. No.	X	R	AA[a] 25 mg/kg *p.o.*	mp (°C)	Recryst. solvent	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
XII	CH	H	(+)*	209—211	MeOH–H_2O	68.3	$C_{21}H_{26}N_2O$	78.22 (78.35	8.13 8.31	8.69 8.62)
XIIIa	N	H	(++)**	268—270	$CHCl_3$	42.3	$C_{20}H_{25}N_3O$	74.27 (74.43	7.79 8.01	12.99 12.96)
XIIIb	N	CH_3	(−)	245—265 (dec.)	EtOH	20.8	$C_{21}H_{27}N_3O$	74.74 (74.59	8.06 8.20	12.45 12.36)
XIV	N	SCH_3	(−)	211	EtOH	45.1	$C_{21}H_{27}N_3OS$	68.26 (67.46	7.36 6.80	11.37 11.10)
XV	N	$SOCH_3$	(−)	195	Benzene	63.3	$C_{21}H_{27}N_3O_2S$	65.43 (65.26	7.06 7.24	10.90 10.63)
Indomethacin			70—80%[b]							

a) Adjuvant-induced arthritis. ++: Therapeutic effect was larger than or equal to that of indomethacin. +: Therapeutic effect was about half that of indomethacin. −: inactive at 25 mg/kg. *: $p<0.05$ *vs.* arthritis control. **: $p<0.01$ *vs.* arthritis control.

b) Therapeutic effect at 2 mg/kg (*p.o.*). Inhibition (%) of edema formation induced by adjuvant.

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Table V

Compd. No.	Adjuvant arthritis Therapeutic (25 mg/kg) $\lvert\Delta FT\rvert$ (10^{-2} mm)[a] Test compd./R.D.	MED[b]	CIPE[c] (25 mg/kg, *p.o.*) (%)	Analgesic[d] (50 mg/kg, *p.o.*) (%)
IIa	146±11/225±61 (IM)	5 mg/kg	22 (6.3 mg/kg)	27.0
IIh	311±24/110±41 (PB)		27 (100 mg/kg)	N.T.[e]
Xg	108±41/110±41 (PB)	5 mg/kg	42.2	21.5 (25 mg/kg)
XIIIa	210±60/225±61 (IM)		48.4 (50 mg/kg)	80.6
Indomethacin			29.6 (3 mg/kg)	N.T.
Phenylbutazone			31.7	N.T.
Aminopyrine			N.T.	82.2

a) The change of foot thickness was calculated as the difference between the values on day 15 and day 28, R.D. Reference drug; IM=indomethacin (2 mg/kg, *p.o.*), PB=phenylbutazone (50 mg/kg, *p.o.*).
b) Minimum effective dose ($n=6$).
c) Inhibition (%) of edema formation induced by carrageenin in rats ($n=6$).
d) Inhibition (%) of writhing induced by AcOH in mice ($n=8$—10).
e) N.T.: not tested.

The results are listed in Tables II—IV. Although 2,6-di-*tert*-butylphenol and the 4-methyl derivative did not show any activity, some 2,6-di-*tert*-butylphenols with a heterocyclic group showed potent activity. Among all the compounds tested, IIa and Xg showed very potent activity.

In compounds where benzoxazole of IIa was replaced with other heterocycles (IIh, i, III, IV, Xg, XII, XIIIa), compounds IIh, Xg, XII and XIIIa showed activity. When substituents were introduced into the benzene ring of IIa (compounds IIb—g, VI—VII), none of the derivatives showed activity at the screening dose. Though compound IIj, which lacks the *tert*-butyl groups of IIa, showed very weak activity, compound IIk, in which the 2,6-di-*tert*-butylphenol group of IIa was replaced with a phenyl group, showed no activity. Compound V, which lacks the phenolic hydroxy group of IIa, showed no activity either. These results suggested that the anti-inflammatory activity of 2,6-di-*tert*-butylphenols depends on the heterocyclic group in the 4-position, that bulky *o*-alkyl groups increased activity and that the phenolic hydroxy group was essential for activity. Compounds IIa, IIh, Xg and XIIIa were further examined for anti-inflammatory activity (acute phase) by using the carrageenin-induced rat paw edema assay described by Winter *et al.*[14] and for analgesic activity by using the AcOH-induced writhing assay in mice described by Koster *et al.*[15] The pharmacological results for these compounds, phenylbutazone (25 mg/kg, *p.o.*) and aminopyrine (50 mg/kg, *p.o.*) are listed in Table V. Compounds IIa and Xg showed therapeutic activity at 5 mg/kg (*p.o.*) in adjuvant-induced arthritis in rats and stronger activity than phenylbutazone (25 mg/kg, *p.o.*) in the carrageenin-induced rat paw edema assay, but weaker activity than aminopyrine (50 mg/kg, *p.o.*) in the AcOH-induced writhing assay.

Experimental

All melting points were determined by using a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were obtained with a Hitachi 215 spectrometer. ^{1}H- or ^{13}C-nuclear magnetic resonance (^{1}H- or ^{13}C-NMR) spectra were obtained with a JEOL-MH 100, a JEOL-FX 90 or a JEOL-JNM-FX-100 spectrometer using $(CH_3)_4Si$ as an internal standard.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)benzoxazole (IIa)——3,5-Di-*tert*-butyl-4-hydroxybenzoyl chloride (33 g) was added portionwise to a solution of 13 g of *o*-aminophenol in 120 ml of pyridine, and this mixture was heated at 100 °C for 1 h. The solvent was evaporated off under reduced pressure, and the residue was again heated at 200 °C for

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0.5 h then cooled to room temperature.

To purify the product, the reaction mixture was applied to a column of silica gel and eluted with $CHCl_3$. The product thus obtained was recrystallized from MeOH to give 32 g of IIa; ^{1}H-NMR ($CDCl_3$): 1.52 (18H, s, $-C(CH_3)_3$), 5.64 (1H, s, OH), 7.24—7.32 (2H, m, aromatic H), 7.50—7.60 (1H, m, aromatic H), 7.68—7.76 (1H, m, aromatic H), 8.08 (2H, s, aromatic H). MS *m/z*: 323 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3600 (OH). Compounds IIb—IIi were prepared by the same method.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)benzimidazole (IIIa)——3,5-Di-*tert*-butyl-4-hydroxybenzaldehyde (4.5 g) was added portionwise to a solution of 2.16 g of *o*-phenylenediamine in 25 ml of EtOH at room temperature, and this mixture was stirred for 12 h. The solvent was removed *in vacuo* and the resulting precipitate was collected by filtration, washed with $CHCl_3$ and recrystallized from DMF to give 0.6 g of IIIa. ^{1}H-NMR (DMSO-d_6): 1.44 (18H, s, $-C(CH_3)_3$, 7.0—7.12 (2H, m, aromatic H), 7.30—7.60 (3H, m, OH, aromatic H), 7.90 (2H, s, aromatic H), 12.70 (1H, s, NH). MS *m/z*: 337 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3600 (OH).

Compound IIIb was prepared by the same method.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)benzothiazole (IV)——3,5-Di-*tert*-butyl-4-hydroxybenzoyl chloride (0.67 g) was added portionwise to a mixture of 0.31 g of *o*-aminothiophenol, 0.25 g of AcONa and 5 ml of AcOH at 60 °C under stirring and the reaction temperature was kept at 60 °C for 1 h. After being stirred at room temperature overnight, the reaction mixture was poured into 30 ml of H_2O and then extracted with $CHCl_3$. The extract was dried and concentrated *in vacuo*. The residue was applied to a column of silica gel and eluted with $CHCl_3$ to give 0.25 g of IV. ^{1}H-NMR (DMSO-d_6): 1.48 (18H, s, $-C(CH_3)_3$), 7.30—7.60 (2H, m, aromatic H), 7.68 (1H, s, OH), 7.84 (2H, s, aromatic H), 7.96—8.32 (2H, m, aromatic H). MS *m/z*: 339 (M^+).

2-(4-Acetoxy-3,5-di-*tert*-butylphenyl)benzoxazole (V)——A solution of 2.5 g of IIa in 25 ml of THF was treated with 0.93 g of sodium hydride (60% oil dispersion) at room temperature and the reaction mixture was stirred for 10 min, then cooled below 5 °C. A solution of 1.8 g of acetyl chloride in 5 ml of THF was added dropwise, and the whole was stirred for 0.5 h then concentrated *in vacuo*. The residue was diluted with 50 ml of H_2O and extracted with $CHCl_3$. The extract was dried and concentrated *in vacuo*. The residue was washed with *n*-hexane and recrystallized from MeOH to give 1.5 g of V. ^{1}H-NMR ($CDCl_3$): 1.44 (18H, s, $-C(CH_3)_3$), 2.36 (3H, s, $COCH_3$), 7.20—7.40 (2H, m, aromatic H), 7.46—7.60 (1H, m, aromatic H), 7.64—7.80 (1H, m, aromatic H), 8.20 (2H, s, aromatic H). MS *m/z*: 365 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1740 ($OCOCH_3$).

5-Amino-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)benzoxazole (VI)——A mixture of 3.5 g of IIc and 0.2 g of Pd/C (10%) in 30 ml of AcOEt was stirred in a hydrogen atmosphere. After absorption of the theoretical amount of hydrogen, the catalyst was removed by filtration. The filtrate was concentrated *in vacuo* and the residue was recrystallized from cyclohexane to give 2.5 g of VI. ^{1}H-NMR ($CDCl_3$): 1.50 (18H, s, $-C(CH_3)_3$), 3.20—3.80 (2H, br, NH), 5.56 (1H, s, OH), 6.60 (1H, dd, J=8, 2 Hz, aromatic H), 6.96 (1H, d, J=2 Hz, aromatic H), 7.28 (1H, d, J=8 Hz, aromatic H), 8.0 (2H, s, aromatic H). MS *m/z*: 338 (M^+).

5-Dimethylamino-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)benzoxazole (VII)——A mixture of 2 g of VI, 20 ml of EtOH, 0.3 ml of conc. HCl, 1 ml of HCHO (35%) and 0.05 g of PtO_2 was stirred in a hydrogen atmosphere until the absorption of hydrogen ceased. Then the reaction mixture was filtered to remove the catalyst and the filtrate was evaporated under reduced pressure. The residue was diluted with H_2O and neutralized with aqueous Na_2CO_3 to yield a precipitate. The precipitate was collected by filtration and recrystallized from MeOH to give 1.5 g of VII. ^{1}H-NMR ($CDCl_3$): 1.50 (18H, s, $-C(CH_3)_3$), 2.96 (6H, s, $N(CH_3)_2$), 5.56 (1H, s, OH), 6.74 (1H, dd, J=8, 2 Hz), 7.06 (1H, d, J=2 Hz), 7.36 (1H, d, J=8 Hz), 8.0 (2H, s). MS *m/z*: 366 (M^+).

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-methylindole (Xa) and 3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2-methylindole (XIa)——A mixture of 5 ml of aniline and 3.41 g of 4-(2-bromopropionyl)-2,6-di-*tert*-butylphenol (IXb) was heated at 150 °C for 0.5 h in a nitrogen atmosphere. The reaction mixture was poured into cold dil. HCl and then extracted with $CHCl_3$. The extract was dried and concentrated *in vacuo*. The residue was applied to a column of silica gel and eluted with benzene/*n*-hexane (1 : 1) to give two fractions. The first fraction was concentrated *in vacuo* and the residue was recrystallized from *n*-hexane to give 0.75 g of Xa. ^{1}H-NMR ($CDCl_3$): 1.48 (18H, s, $-C(CH_3)_3$), 2.40 (3H, s, $-CH_3$), 5.26 (1H, s, OH), 7.00—7.60 (6H, m), 7.86 (1H, br, N–H). MS *m/z*: 333 (M^+). The second fraction was treated in a similar manner to give 0.15 g of XIa. ^{1}H-NMR ($CDCl_3$): 1.48 (18H, s, $-C(CH_3)_3$), 2.50 (3H, s, $-CH_3$), 5.12 (1H, s, OH), 7.00—7.68 (6H, m), 7.82 (1H, br, N–H). MS *m/z*: 333 (M^+). Compounds Xb—XIc were prepared by a similar method.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)imidazo[1,2-*a*]pyridine (XII)——A mixture of 3.76 g of 2-aminopyridine, 13.08 g of 4-(2-bromoacetyl)-2,6-di-*tert*-butylphenol and 80 ml of EtOH was refluxed for 2 h and then poured into cold aqueous Na_2CO_3. The resulting precipitate was collected by filtration and recrystallized from aqueous MeOH to give 8.8 g of XII. ^{1}H-NMR ($CDCl_3$): 1.52 (18H, s, $-C(CH_3)_3$), 5.62 (1H, s, OH), 7.20 (1H, t, J=8 Hz), 7.60 (1H, t, J=8 Hz), 7.72 (2H, s), 7.80 (1H, s, C_3-H), 8.34 (1H, d, J=8 Hz), 8.50 (1H, d, J=8 Hz). MS *m/z*: 322 (M^+).

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)imidazo[1,2-*a*]pyrimidine (XIIIa)——A mixture of 1.9 g of 2-aminopyrimidine, 6.5 g of 4-(2-bromoacetyl)-2,6-di-*tert*-butylphenol and 80 ml of methyl ethyl ketone was refluxed for 5 h, then cooled. The solvent was evaporated off under reduced pressure and conc. NH_4OH was added to the residue. The resulting precipitate was collected by filtration and recrystallized from $CHCl_3$ to give 2.2 g of XIIIa. ^{1}H-NMR

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($CDCl_3$): 1.50 (18H, s, $-C(CH_3)_3$), 5.32 (1H, s, OH), 6.76 (1H, dd, J=8, 2 Hz), 7.70 (1H, s, C_3-H), 8.18 (2H, s), 8.38 (1H, dd, J=8, 2 Hz), 8.46 (1H, dd, J=8, 2 Hz). MS m/z: 323 (M^+). Compound XIIIb was prepared by a similar method.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-methylthioimidazo[1,2-*a*]pyrimidine (XIV)——A solution of methanesulfenylchloride (prepared by the reaction of 0.96 g of CH_3SSCH_3 with 1.37 g of thionyl chloride) was added dropwise under cooling to a suspension of 3.3 g of XIIIa in 17 ml of $CHCl_3$. The reaction mixture was stirred for 1 h under cooling and then poured into dil. $NaHCO_3$. The organic layer was separated, dried and concentrated *in vacuo*. The residue was applied to a column of silica gel, eluted with $CHCl_3$ and recrystallized from EtOH to give 1.7 g of XIV. ^{1}H-NMR ($CDCl_3$): 1.28 (3H, s, $S-CH_3$), 1.50 (18H, s, $-C(CH_3)_3$), 5.40 (1H, s, OH), 6.96 (1H, dd, J=8, 8 Hz), 8.18 (2H, s), 8.32 (1H, dd, J=8, 2 Hz), 8.68 (1H, dd, J=8, 2 Hz). MS m/z: 369 (M^+).

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-methylsulfinylimidazo[1,2-*a*]pyrimidine (XV)——*m*-Chloroperbenzoic acid (0.23 g) was added portionwise to a solution of 0.5 g of XIV in 20 ml of $CHCl_3$ at room temperature. The reaction mixture was stirred for 2—3 h and then poured into H_2O. The organic layer was separated, dried and concentrated *in vacuo*. The residue was applied to a column of silica gel and eluted with $CHCl_3$ to afford crude XV, which was recrystallized from benzene to yield 0.33 g of XV. ^{1}H-NMR ($CDCl_3$): 1.50 (18H, s, $-C(CH_3)_3$), 3.12 (3H, s, $SO-CH_3$), 5.46 (1H, s, OH), 6.94 (1H, dd, J=8, 8 Hz), 7.68 (2H, s), 8.64 (1H, dd, J=8, 2 Hz), 9.16 (1H, dd, J=8, 2 Hz). MS m/z: 385 (M^+).

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