present results show an additional difference between the alkaline phosphatase of human placenta and intestine in the inhibition by inorganic phosphate, which fact further emphasizes their distinctiveness and suggests that this property can be used to distinguish the original tissue of the alkaline phosphatases in serum in combination with L-phenylalanine inhibition, without the use of heat stability method.

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Bromination of 3-*tert*-Butylindoles with N-Bromosuccinimide

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Reaction of 3-*tert*-butylindole (**1a**) with NBS in acetic acid gave 3-*tert*-butyloxindole (**2a**) and 6-bromo-3-*tert*-butylindole (**3a**) instead of 2-bromo derivative (**5a**). Reactions of 1-acetyl-(**1b**) and 1-*tert*-butyl-(**1c**) derivatives under similar conditions gave 3-bromo-oxindole (**6b**) and the brominated indole (**7**) respectively. On the other hand reaction of **1a** with NBS in boiling carbon tetrachloride in the presence of benzoyl peroxide gave unstable **5a** as a main product. Reaction of **1b** under similar condition did not proceed, but **1c** gave **7** as a main product.

Keywords——bromination; 3-substituted indoles; N-bromosuccinimide; solvent effect; 6-bromoindoles; 2-bromoindoles; 3-substituted oxindoles

We have previously reported the bromination of 3-phenylindoles[2] and 3-methylindoles[3] with N-bromosuccinimide (NBS) in acetic acid or in carbon tetrachloride. This paper describes the reaction of 3-*tert*-butylindoles (**1**) having a bulky substituent at 3-position with NBS in acetic acid or carbon tetrachloride.

The reaction of 3-*tert*-butylindole (**1a**) with NBS in acetic acid at 20° gave 3-*tert*-butyloxindole (**2a**, 24%), mp 161—162°, 6-bromo-3-*tert*-butylindole (**3a**, 22%), mp 89.5—91.0°, and brominated 3-*tert*-butyloxindole (**4a**, 0.8%) along with the recovered starting material (47%). The corresponding 2-bromo derivative (**5a**) was not isolated in contrast with the bromination of 3-phenyl- and 3-methylindoles,[2,3] but the 6-brominated derivative (**3a**) without affecting at 2-position was isolated for the first time. The position of bromine atom in **3a** was confirmed by the nuclear magnetic resonance (NMR) spectrum of its 1-acetyl derivative (**3b**) which showed a down field fine doublet for 7-H.

The reaction of 1-acetyl-3-*tert*-butylindole (**1b**) under the same condition gave 1-acetyl-3-bromo-3-*tert*-butyloxindole (**6b**, 28%), mp 82.5—83.5°, and the 6-bromoindole (**3b**, 4%) besides the recovered **1b** (58%). 3-Bromo-oxindole derivatives have been obtained by the bromination of 1-acetyl-3-phenyl- and 3-methylindoles.[2,3]

The reaction of 1,3-di-*tert*-butylindole (**1c**) which was obtained as a by-product in the preparation of 3-*tert*-butylindole, with NBS under the same condition gave the brominated 1,3-di-*tert*-butylindole (**7**, 30%), the oxindole (**2c**, 5%), and 3-bromo-oxindole (**6c**, 5.5%) along with

1) Location: *Yayoi-cho, Chiba-shi, 280, Japan.*
2) T. Hino, M. Tonozuka, and M. Nakagawa, *Tetrahedron*, **30**, 2123 (1974). Earlier references are cited herein.
3) T. Hino, T. Nakamura, and M. Nakagawa, *Chem. Pharm. Bull.* (Tokyo), **23**, 2990 (1975).

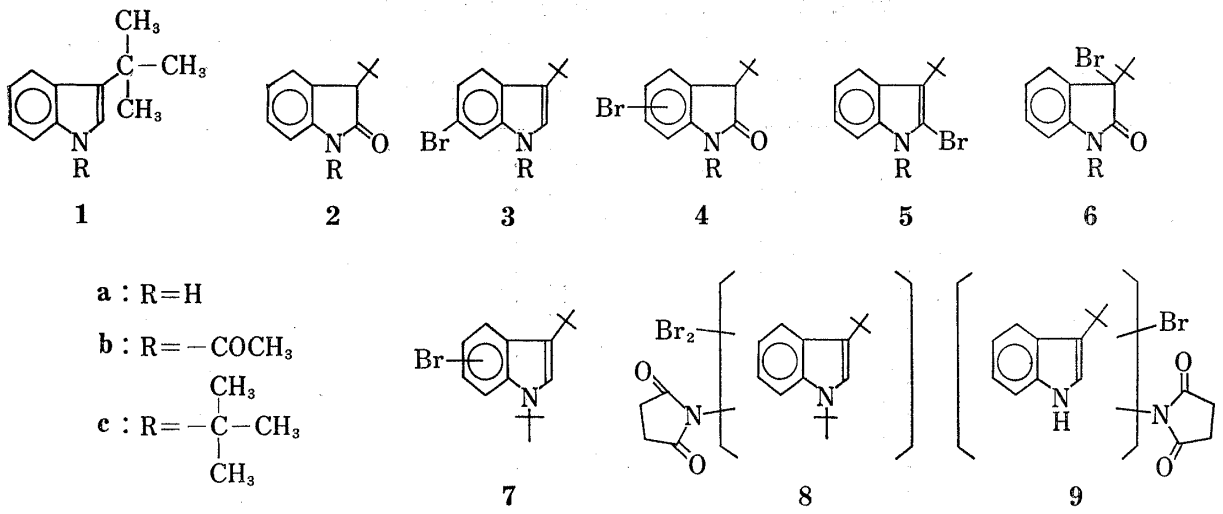

Chart 1

the recovered **1c** (26%). The compound (**7**) showed a sharp melting point at 98.5—100°, but its NMR spectrum clearly showed the presence of two isomers. Although these separation failed, the presence of 2-proton (6.81 and 6.84 ppm) in its NMR spectrum indicates that the compound is probably a mixture of 5- and 6-bromo-1,3-di-*tert*-butylindoles.

On the other hand the bromination of **1a** with NBS in boiling carbon tetrachloride in the presence of benzoyl peroxide (BPO) gave 2-bromo-3-*tert*-butylindole (**5a**, 66%) and the oxindole (**2a**, 24%). The 2-bromo derivative (**5a**) was isolated as a colorless oil after silica gel column separation of the reaction mixture and showed a single spot on thin-layer chromatography (TLC). Although it is not so stable to be purified its structure was supported by spectral data. Furthermore, hydrolysis of **5a** with ethanolic hydrochloric acid gave the oxindole (**2a**, 22%) and the 6-bromoindole (**3a**, 18%) besides trace amounts of **4a** and **1a**. Although mechanism of the bromine migration is not clear, the similar instability of 2-bromoindole was also observed in 1-acetyl-2-bromo-3-methylindole.[3] These results suggest that **2a**, **3a**, and **4a** obtained in the reaction of **1a** with NBS in acetic acid described above may be derived from 2-bromo derivative (**5a**) in the reaction condition.

On the other hand the reaction of 1-acetyl derivative (**1b**) with NBS in boiling carbon tetrachloride for 5 hours in the presence of benzoyl peroxide did not proceed as reported previously in the case of 1-acetyl-3-phenylindole.[2] However, the reaction of **1c** under the same condition gave **7** (30%), **2c** (1%), **8** (6%), and **9** (5%) besides recovered **1c** (48%). The structures of **8**

Table I. Analytical Data of 3-*tert*-Butylindoles

Compd. No.	mp (°C)	Recryst.[a] solvent	Formula	Calcd.				Found			
				C	H	N	Br	C	H	N	Br
1b	114.5—115.5	B–H	$C_{14}H_{17}ON$	78.10	7.96	6.51		78.16	8.08	6.27	
1c	67—68	MeOH	$C_{16}H_{23}N$	83.78	10.11	6.11		83.70	10.15	5.97	
2a	161—162	B–H	$C_{12}H_{15}ON$	76.19	7.94	7.41		76.12	8.00	7.29	
3a	89.5—91	B–H	$C_{12}H_{14}NBr$	57.14	5.56	5.56	31.75	57.16	5.66	5.83	31.41
3b	179.5—181	B–H	$C_{14}H_{16}ONBr$	57.16	5.48	4.76	27.16	57.19	5.48	4.85	27.10
6b	82.5—83.5	H	$C_{14}H_{16}O_2NBr$	54.21	5.20	4.54	25.76	54.24	5.21	4.61	25.90
8	250—253	B–H	$C_{20}H_{24}O_2N_2Br$	49.61	5.00	5.79	33.00	49.87	5.07	5.74	33.20
9	227—230	B	$C_{16}H_{17}O_2N_2Br$	55.03	4.91	8.02	22.88	54.57	4.77	8.04	23.13

a) B-H: benzene–hexane, B: benzene, H: hexane.

Table II. The UV and IR Data of 3-*tert*-Butylindoles

Compd. No.	λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$)		λ_{min}^{EtOH} nm ($\varepsilon \times 10^{-3}$)		IR (KBr) cm^{-1} ($\nu_{C=O}$)
1b	241(19.0)	262(8.5)sh	220(6.7)	280(4.4)	1713
	271(7.2)	292(7.0)	296(6.1)		
	300(7.6)				
1c	229(36.2)	291(5.9)	250(1.3)		
2a	253(8.2)	280(2.0)sh	227(2.2)		1710
3a	229(39.2)	288(6.1)	254(1.3)		
3b	244(19.8)	272(10.8)	223(8.0)	261(9.1)	1720
	294(5.7)	304(5.1)	290(5.2)	300(4.4)	
6b	233(14.6)		216(8.3)		1753, 1725
8	236(50.1)	293(6.1)	217(16.0)	268(4.2)	1732
	300(6.6)	308(5.9)			
9	226(42.0)	283(6.5)	255(3.3)		1720
	291(6.3)				

Table III. The NMR and Mass Data of 3-*tert*-Butylindoles

Compd. No.	NMR (in $CDCl_3$, ppm)							Mass	
	3-H	3-*tert*-Butyl	1-*tert*-Butyl	Acetyl	2-H	7-H	NH	M^+ (%)	Base peak
1b	—	1.45(s)	—	2.53(s)	7.01	8.38(dd)[a]	—	215(18)	158 ($M-C_4H_9$)
1c	—	1.44(s)	1.70(s)	—	6.96(s)	—	—	229(32)	158 ($M-C_5H_{11}$)
2a	3.12	1.10	—	—	—	—	8.80	189(12)	133 ($M-C_4H_8$)
3a	—	1.42	—	—	6.86(d)	—	7.80[b]	253(10)	157 (M−Br−Me)
								251(10)	
3b	—	1.43	—	2.60	7.09	8.71(d)	—[c]	295(42)	238, 236
						(J=2 Hz)		293(42)	($M-C_4H_9$)
6b	—	1.24	—	2.70	—	8.18	—	311(6)	158, 144
								309(6)	
8	—	1.37	1.68	—	—	—	—[d]	486(5)	415, 413, 411
								484(10)	($M-C_4H_8-CH_3$)
								482(5)	
9	—	1.40	—	—	—	—	8.16[e]	350(35)	335, 333
								348(35)	($M-CH_3$)

a) J=2 and 7 Hz
b) arom H: 7.15 (d-d, J=2 and 8 Hz), 7.47 (d, J=2 Hz), 7.65 (d, J=8 Hz)
c) atom H: 7.38 (d-d, J=2 and 8 Hz), 7.61 (d, J=8 Hz)
d) arom H: 7.95 (s), 8.12 (s); other signal; 2.84 (s, 4H, $COCH_2CH_2CO$)
e) arom H: 6.74 (d, J=2 Hz), 7.1 (d-d, J=2 and 8 Hz), 7.92 (d, J=2 Hz); other signal; 2.75 (s, 4H, $COCH_2CH_2CO$)

and **9** were tentatively assigned as indicated by their spectral data as well as elemental analysis, but the position of the substituents are uncertain.

These results may be rationalized by the mechanism proposed in the previous papers[2,3]: The initial step of the reaction is the attack of bromonium ion at 3-position of the indole in acetic acid, while the attack of bromine radical at 2-position in carbon tetrachloride. The *tert*-butyl group at 3-position appears to inhibit the approach of bromonium ion to 3-position,[4] but does not hinder the attack of bromine radical at 2-position. In the bromination of **1c**, two *tert*-butyl groups prevent both bromine radical and bromonium ion to attack at 2 or 3-position, and

4) Protonation of **1a** is known to occur easier than that of 3-methylindole due to the releaf of steric hindrance between *tert*-butyl group and 4-H.[5] This is further supported by the fact that a mixed dimer of **1a** and 2-methylindole is produced by the acid catalyzed reaction, though the acid catalyzed dimerization of **1a** itself does not occur.[6]
5) R.L. Hinman and J. Lang, *J. Am. Chem. Soc.*, **86**, 3796 (1964).
6) W.E. Noland and C.F. Hammer, *J. Org. Chem.*, **25**, 1525 (1960).

the bromination of the benzene ring has occurred instead. In the case of **1b**, 1-acetyl group prevent not only the attack of bromine radical at 2-position (steric hindrance), but also bromination of benzene ring (electronic effect).

The analytical and spectral data of pure compounds are summarized in Table I, II, and III.

Experimental[7]

3-*tert*-Butylindoles——3-*tert*-Butylindole (**1a**) was prepared by the alkylation of indole Grignard reagent with *tert*-butyl bromide following the procedure given by Smith.[8] Changing the solvent from ether to toluene after making the indole Grignard reagent raised the yield of **1a** to 30%. 1,3-Di-*tert*-butylindole (**1b**) was obtained as a by-product. 1-Acetyl-3-*tert*-butylindole (**1b**) was obtained by refluxing **1a** with Ac_2O–AcONa or AcCl. The yield of **1b** was 55% in the former method and 80% in the latter method.

Bromination of 1a with NBS in Acetic Acid——To a solution of **1a** (865 mg, 5 mmol) in AcOH (10 ml) was added NBS (890 mg, 5 mmol) in AcOH (40 ml) at 20° during 30 min under N_2 stream. The mixture was stirred at 20° for 4 hr and poured into a solution of NaOH (40 g) in H_2O (150 ml) under cooling. The mixture was adjusted its pH to 10—11 by the addition of 10% NaOH and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried and evaporated to leave a brown residue (1.17 g). The separation by silica gel column and preparative TLC gave **3a** (274 mg, 22%), **1a** (405 mg, 47%), **4a** (11 mg, 0.8%), and **2a** (230 mg, 24%). The structure of **4a** was assigned by the following spectral data. **4a**, mp 245—248°. λ_{max}^{EtOH} 256, 290, 298^{sh} nm; λ_{min} 238, 280 nm. ν_{max}^{KBr} 3170 (NH), 1700 cm^{-1} (C=O). Mass Spectrum *m/e* (rel. intens.); 269 (10), 267 (10, M^+), 213, 211 (100, $M-C_4H_8$).

A solution of **3a** (840 mg) in AcCl (20 ml) was refluxed for 18 hr to give **3b** (600 mg, 61.3%).

Bromination of 1-Acetyl-3-*tert*-butylindole (1b) with NBS in AcOH——To a solution of **1b** (2.15 g, 10 mmol) in AcOH (30 ml) was added NBS (1.78 g, 10 mmol) in AcOH (80 ml) at 20° under N_2 stream. The mixture was stirred for 5 hr at 20° and evaporated *in vacuo* (under 40°). The residue was diluted with H_2O and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried and evaporated to leave a residue (2.62 g) which was recrystallized from benzene–hexane to give **1b** (330 mg). The mother liquor was chromatographed over silica gel column. Elution with benzene–hexane (1: 4) gave **6b** (884 mg, 29%). Elution with benzene–hexane (3: 7—1: 1) gave a mixture of **1b** and **3b** (750 mg). Elution with benzene–hexane (1: 1) gave **1b** (312 mg). The second fraction (750 mg) was hydrolyzed with EtOH (20 ml)–10% NaOH (2 ml) at room temperature to give a mixture (600 mg) of **1a** and **3a** which was separated by silica gel column to give **3a** (96 mg) and **1a** (476 mg).

Bromination of 1,3-Di-*tert*-Butylindole (1c) with NBS in AcOH——To a solution of **1c** (1.14 g, 5 mmol) in AcOH (15 ml) was added NBS (890 mg, 5 mmol) in AcOH (50 ml) at 20° under N_2 stream. The mixture was stirred at 20° for 2 hr and evaporated *in vacuo*. The residue was extracted with CCl_4. The CCl_4 soluble fraction gave an oil (1.55 g) which was chromatographed over silica gel. Elution with hexane gave **7** (450 mg, 30%) and **1c** (295 mg, 26%). The crude **7** was recrystallized from MeOH to give colorless prisms, mp 98.5—100°. *Anal.* Calcd. for $C_{16}H_{22}NBr$: C, 62.34; H, 7.19; N, 4.54; Br, 25.92. Found: C, 62.43; H, 7.21; N, 4.74; Br, 25.85. λ_{max}^{EtOH} nm (ε); 234 (37400), 292 (5100), 300 (5200); λ_{min} 213 (14500), 260 (1700), 296 (5000). Mass Spectrum *m/e* (rel. intens.); 309, 307 (30, M^+), 294, 292 (26, M—Me), 238, 236 (100, $M-(Me+C_4H_8)$), 157 (32, $M-(Br+C_4H_8)$). The NMR spectrum (CCl_4) showed a singlet (9H) for 3-*tert*-butyl at 1.40 ppm, two close singlets (total 9H) for 1-*tert*-butyl at 1.68 and 1.72 ppm, two close singlets for 2-H at 6.81 and 6.84 ppm, and multiplets for aromatic protons between 6.9—7.8 ppm, indicating a mixture of two isomers. Hydrolysis of **7** with boiling EtOH–HCl recovered the starting material. These data suggested that **7** was a mixture of 5- and 6-bromo-1,3-di-*tret*-butylindoles.

Elution with CH_2Cl_2–hexane (1: 1) gave **6c** (90 mg, 5.5%) as an oil. λ_{max}^{EtOH} 220 nm. IR (neat); 1720 cm^{-1} (C=O). Mass Spectrum *m/e* (rel. intens.); 325 (13), 323 (13, M^+), 245 (14, M—Br), 269, 267 (18, $M-C_4H_8$), 213, 211 (100, $M-2\times C_4H_8$). NMR ($CDCl_3$) δ 1.20 (s), 1.71 (s, 6.9—7.55 (m). Elution with CH_2Cl_2 gave **2c** (63 mg, 5%), as an oil. λ_{max}^{EtOH} 258, 285 nm. IR (neat); 1700 cm^{-1} (C=O). Mass Spectrum *m/e* (rel. intens.); 245 (10, M^+), 189 (20, $M-C_4H_8$), 133 (100, $M-2\times C_4H_8$). NMR ($CDCl_3$) δ 1.08 (s, 3-*t*-Bu), 1.70 (s, N-*t*-Bu), 2.91 (s, 3-H), 6.9—7.3 (m, arom., H).

Bromination of 1a with NBS in CCl_4–BPO——A mixture of **1a** (520 mg, 3 mmol), NBS (535 mg, 3 mmol) and BPO (2 mg) in CCl_4 (15 ml) was refluxed for 3.5 hr under N_2 stream. After cooling insoluble succinimide (285 mg) was removed by filtration and the filtrate was evaporated to leave a brown oil (870 mg) which was chromatographed over silica gel. Elution with benzene–hexane (1: 1) gave **5a** (505 mg, 66%) which showed a

7) All melting points are not corrected. The ultraviolet (UV) spectra were taken with a Hitachi EPS-3T spectrophotometer. The NMR spectra were measured with a JEOL 4H-100 spectrometer. The mass spectra were determined with a Hitachi RMU-6E spectrometer.

8) G.F. Smith and A.E. Waters, *J. Chem. Soc.*, **1961**, 940.

single spot on TLC, but decomposed on standing. λ_{max}^{EtOH} 224, 284, 292 nm, λ_{min} 246, 290 nm. IR (CCl_4); 3470 cm^{-1} (NH). Mass Spectrum *m/e* (rel. intens); 253, 251 (33, M^+), 238, 236 (100, M−Me). NMR (CCl_4) δ 1.57 (s, 3-*t*-Bu), 6.8—7.8 (m, arom H and NH). Elution with CH_2Cl_2 gave **2a** (137 mg, 24%) which was identical with the sample obtained above.

5a (490 mg) was refluxed with EtOH (10 ml)–10% HCl (5 ml) for 3 hr. The usual work-up gave a brown oil (390 mg) which was separated by silica gel column and preparative TLC to give **3a** (129 mg), **1a** (24 mg), **4a** (27 mg) and **2a** (123 mg). These were identical with the samples obtained above (IR).

The bromination of **1b** (540 mg) under the same condition for 5 hr recovered 1b and NBS quantitatively.

Bromination of 1c with NBS in CCl_4–BPO——A mixture of **1c** (1.37 g, 6 mmol), NBS (1.07 g, 6 mmol), and BPO (5 mg) in CCl_4 (30 ml) was refluxed for 3 hr under N_2 stream. After cooling insoluble succinimide (526 mg) was removed by filtration and the filtrate was evaporated to leave an oil (1.87 g) which was separated by silica gel column. The first fraction eluted with hexane gave **7** (574 mg, 31%) which was identical with the above sample (IR and mmp). The second fraction eluted the same solvent gave **1c** (651 mg 48%). Elution with CH_2Cl_2 gave **8** (146 mg). The next fraction eluted with the same solvent gave **9** (119 mg).

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Acidic Properties of Benzimidazoles and Substituent Effects. II.[1] The Substituent Effect on the Imidazole Formation from *p*-Substituted-*o*-phenylenediamines and on the Acid Dissociation of the Benzimidazoles

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2-(2-Pyridyl)benzimidazole and 5(or 6)-substituted derivatives were synthesized by the condensation of *p*-substituted-*o*-phenylene diamines with α-picoline in the presence of sulfur or with picolinic acid. These acid dissociation constants were measured in aqueous buffers at 20° by spectrophotometry and fitted the Hammett equation with the use of σ_{para} (ρ=1.3).

On the other hand, 2-(2-pyridyl)benzimidazole was nitrated to give its mono-nitro compound which was identical with 5(or 6)-nitro-2-(2-pyridyl)benzimidazole obtained from *p*-nitro-*o*-phenylene diamine. The correlation of the position of substituent groups with their effects for the acidity of 2-(2-pyridyl)benzimidazoles was discussed.

Keywords——benzimidazole cyclization between *p*-substituted-*o*-phenylenediamines and α-picoline in the presence of sulfur; benzimidazole cyclization between *p*-substituted-*o*-phenylenediamines and picolinic acid; nitration of 2-(2-pyridyl)benzimidazole; measurement of acid dissocn. constants of 2-(2-pyridyl)-5-substituted-benzimidazoles; correlation of substituent constants and acidities of 2-(2-pyridyl)-5-substituted-benzimidazoles

Earlier, we have reported the synthesis of 2-(2-pyridyl)benzimidazole derivatives with a substituent in 1-position,[3] and the relationship between acid dissociation constants and hydrogen bond equilibrium constants of 2-substituted-benzimidazoles has been studied in rela-

1) Part I: T. Hisano and M. Ichikawa, *Chem. Pharm. Bull.* (Tokyo), **22**, 1923 (1974).
2) Location: *Oe-honmachi, Kumamoto, 862, Japan.*
3) T. Hisano and M. Ichikawa, *Yakugaku Zasshi*, **91**, 1136 (1971).