Studies on the Syntheses of Azole Derivatives. Part I. Formation of 1-Substituted-3-hydroxy-1*H*-indazole and 1-Substituted benzimidazolin-2-one Derivatives by Thermal Reaction of *N*-Substituted-*N*-arylcarbamoyl Azides. (1)

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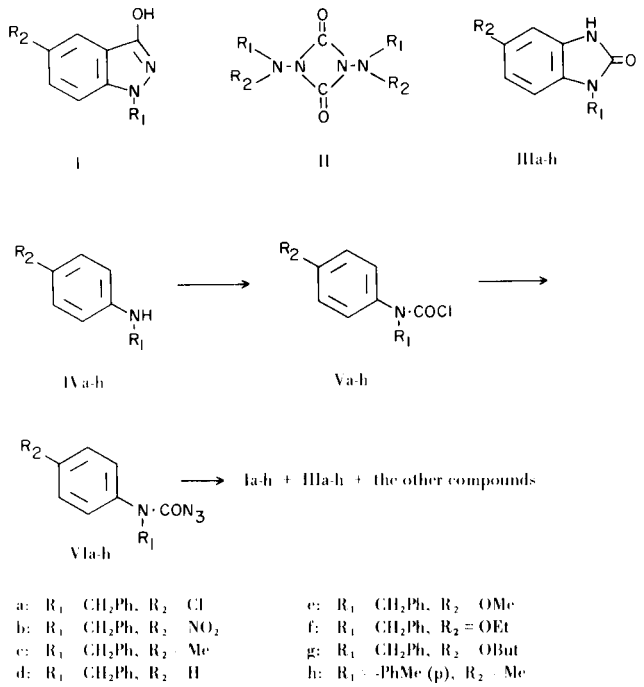
The formation of 1-substituted-3-hydroxy-1*H*-indazole and 1-substituted-benzimidazolin-2-one derivatives by thermal reaction of *N*-substituted-*N*-arylcarbamoyl azides was examined.

Since few studies on indazole derivatives possessing sedative (3) and antiinflammatory (4) activity have been published, we synthesized 1-substituted-3-hydroxy-1*H*-indazoles (I) from *N*-substituted-*N*-arylcarbamoylazides (VI) *via* the Curtius rearrangement in order to investigate the correlation between the above activities and the structure of indazole derivatives *in vivo*. Stollé (5) has reported the formation of I with compound II as a by-product on heating VI in xylene while Baiocchi (6) obtained 1-substituted-benzimidazolin-2-one (III) together with I by heating VI in tetralin. Little has been reported (7) on this reaction of carbamoyl azide. Our interest in the synthesis of I and the by-products formed, therefore, led to a re-examination of this reaction.

SCHEME 1



a: R_1 CH_2Ph, R_2 Cl
b: R_1 CH_2Ph, R_2 NO_2
c: R_1 CH_2Ph, R_2 Me
d: R_1 CH_2Ph, R_2 H
e: R_1 CH_2Ph, R_2 OMe
f: R_1 CH_2Ph, R_2 = OEt
g: R_1 CH_2Ph, R_2 OBut
h: R_1 = PhMe (p), R_2 = Me

The Curtius rearrangement has been applied to a number of azides (VIa-h), which were prepared from the *N*-substituted-*N*-arylcarbamoyl chloride (Va-h). The products obtained were separated by column chromatography. The compounds (VIa-h) gave the products I and III in a ratio (III/I) in proportion to the electron-donating character of the group on the benzene ring as shown in Table I. In the case of the alkoxy group, VIe-g gave III in comparatively good yield and the ratio (III/I) was high. Compounds I and III are characterized in Table II.

When compounds VIa, VIc, and VId were used as starting materials, 3-[α-benzyl-α-(4-chlorophenyl)hydrazinocarbonyl]-5-chloro-(VIIa), 3-[α-benzyl-α-(4-methylphenyl)hydrazinocarbonyl]-5-methyl-(VIIb) and 3-[(α-benzyl-α-phenylhydrazinocarbonyl)]-1-benzylbenzimidazolin-3-one (VIIc) were obtained, respectively, in addition to I and III. Microanalyses and molecular weight determination established the empirical formulae of $C_{28}H_{22}ClN_4O_2$, $C_{30}H_{28}N_4O_4$ and $C_{28}H_{24}N_4O_2$ for VIIa, VIIb and VIIc, respectively. Their spectra were quite similar. The ir spectrum (chloroform) of VIIa exhibited ν NH at 3320 and ν C=O at 1743 and 1709 cm^{-1} and the nmr spectrum (δ in deuteriochloroform) showed two singlets due to two methylene groups at 4.72 and 4.91, respectively. In addition, a one proton signal due to the C_4–H at 8.16 as a doublet (J = 3.0 cps) was observed at a lower field than the other aromatic protons because of the deshielding effect of the carbonyl group at the C-3 position. Furthermore, a one proton signal was observed at 10.42 which indicated the presence of the proton exchangeable with deuterium oxide. The formation of 1-benzyl-5-substituted-benzimidazolin-2-one (IIIa) on heating VIIa with sodium ethoxide in a sealed tube also supported the structure of VIIa. In the mass spectrum of VIIa an extremely weak parent peak was shown at m/e 517. The mass spectrum of VIIb exhibited a fragmentation pattern similar to VIIa. Solutions of the benzimida-

TABLE I

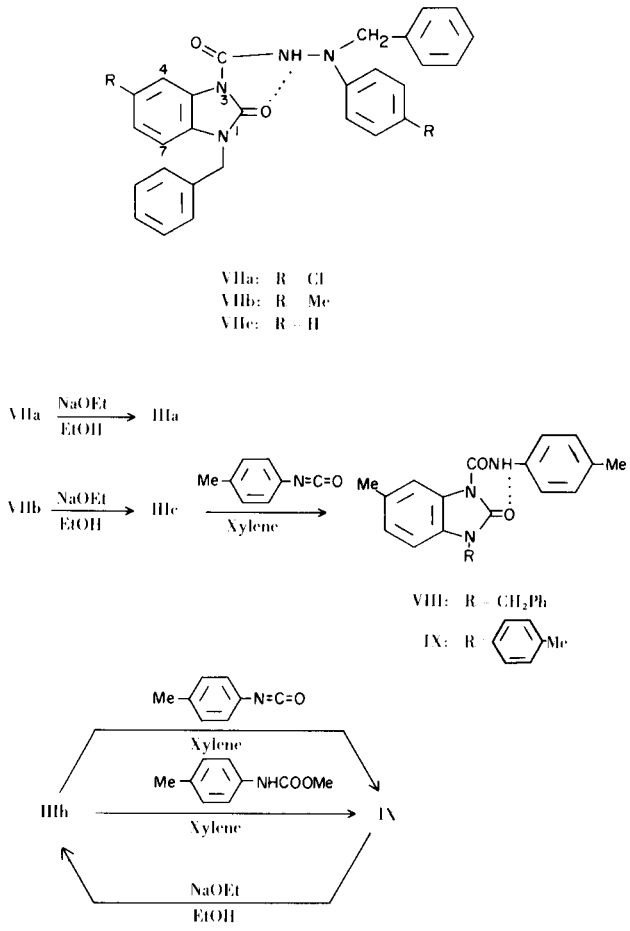
Yields of 1,5-Disubstituted-3-hydroxy-1*H*-indazole (I) and 1,5-Disubstituted-benzimidazolin-2-one (III) on Thermal Reaction of Various Carbamoyl Azides

	Ia-h		IIIa-h		
	M.p. (°C)	Yield (%)	M.p. (°C)	Yield (%)	Yield Ratio (III/I)
a	206-207 [lit. (4), 213]	46.4	179-180 [lit. (4), 176]	5.3	0.11
b	249-250 [lit. (4), 250]	37.0	233-234 [lit. (4), 234]	1.6	0.04
c	(a)	63.1	(a)	9.5	0.15
d	167 [lit. (3b), 167]	66.9	(a)	6.7	0.10
e	189-190 [lit. (4), 187]	15.2	178-179 [lit. (4), 189]	35.6	2.34
f	(a)	12.3	(a)	43.1	3.50
g	(a)	7.5	(a)	48.3	6.44
h	201-202 [lit. (3b), 202]	51.0	(a)	5.1	0.10

(a) The physical data for the above compounds are shown in Table II.

zolin-2-ones (IIIc and IIIh) and *p*-tolyl isocyanate in xylene upon extensive heating gave 1-benzyl-5-methyl-3-[*N*-(4-methylphenyl)carbamoyl]benzimidazolin-2-one (VIII), 5-methyl-1-(4-methylphenyl)-3-[*N*-(4-methylphenyl)carbamoyl]benzimidazolin-2-one (IX), and a small amount of di-*p*-tolylurea. The heating of IIIh with methyl-*p*-tolylcarbamate under similar conditions also afforded IX.

SCHEME 2



Compounds VIIa, VIIb, VIIc, VIII and IX showed an extremely weak amide NH band in their ir spectra when recorded in nujol mull; however, when recorded in chloroform at higher concentration, the amide NH band was observed in all the compounds. These facts indicate that intramolecular hydrogen bonding occurs between the NH and C=O group at the C-2 position.

Finally, a novel compound (A) having the molecular formula of $C_{28}H_{20}Cl_2N_4O_2$, m.p. 176.5-177.5°, was also obtained from *N*-benzyl-*N*-(4-chlorophenyl)carbamoyl azide (VIa) as a third product and similar compounds (B and C) having the molecular formula of $C_{28}H_{20}N_6O_6$, m.p. 189.5-190.5° and $C_{28}H_{22}N_4O_2$, m.p. 122-123°, were obtained from *N*-benzyl-*N*-(4-nitrophenyl)carbamoyl azide (VIb) and *N*-benzyl-*N*-phenylcarbamoyl azide (VId), respectively. These compounds appear different from the compound II reported by Stollé since heating of these compounds gave no indazole derivatives (Ia,b,d). Also their structures are different from that of VII as evidenced by their spectra which did not show the presence of hydroxyl and amino groups nor the two types of carbonyl groups, which the spectra of VII revealed. The nmr spectrum of compound A (δ in DMSO-d_6) showed two methylene groups. One of them resonanced at 4.83 as a singlet and the other appeared as a typical AB type of doublet with J = 15 cps at 4.40 and 4.80, which signal collapsed to a singlet at 80°. The latter signal indicated that this methylene group is a part of a ring system. Compounds B and C also showed the same behavior as A in its nmr spectra. Therefore, these compounds (A, B and C) were tentatively

TABLE II

Ic, f, g and IIIc, d, f, g, h

	M.p. (°C) Appearance	Formula	Calcd. (Found) C	H	N	$FeCl_3$ Test	IR (Nujol) cm^{-1} ν OH	ν C=N (a)	NH	ν C=O
Ic	180-181 (EtOH) colorless needles	$C_{15}H_{14}N_2O$	75.60 (75.74	5.92 5.98	11.76 12.03)	+	2750 (broad)	1553		
If	196-197 (EtOH) colorless needles	$C_{16}H_{16}N_2O_2$	71.62 (71.56	6.01 6.23	10.44 10.47)	+	2700 (broad)	1550		
Ig	148-149 (EtOH) colorless needles	$C_{18}H_{20}N_2O_2$	72.95 (72.64	6.80 6.85	9.45 9.46)	-	2650 (broad)	1550		
IIIc	185-186 (EtOH) colorless needles	$C_{15}H_{14}N_2O$	75.60 (75.90	5.92 5.99	11.76 11.75)	-			3200-2700	1703
IIId	197-198 (EtOH) colorless needles	$C_{14}H_{12}N_2O$	74.99 (74.58	5.38 5.46	12.49 12.29)	-			3200-2700	1700
IIIf	178-179 (EtOH) colorless needles	$C_{16}H_{16}N_2O_2$	71.62 (71.99	6.01 5.86	10.44 10.83)	-			3200-2700	1705
IIIg	142-143 (EtOH) colorless needles	$C_{18}H_{20}N_2O_2$	72.95 (72.88	6.80 6.79	9.45 9.44)	-			3150-2700	1700
IIIh	223-224 (EtOH) colorless needles	$C_{15}H_{14}N_2O$	75.60 (75.16	5.92 5.77	11.76 11.77)	-			3230-2700	1710

(a) This lower field shift is similar to the data of the literature (8).

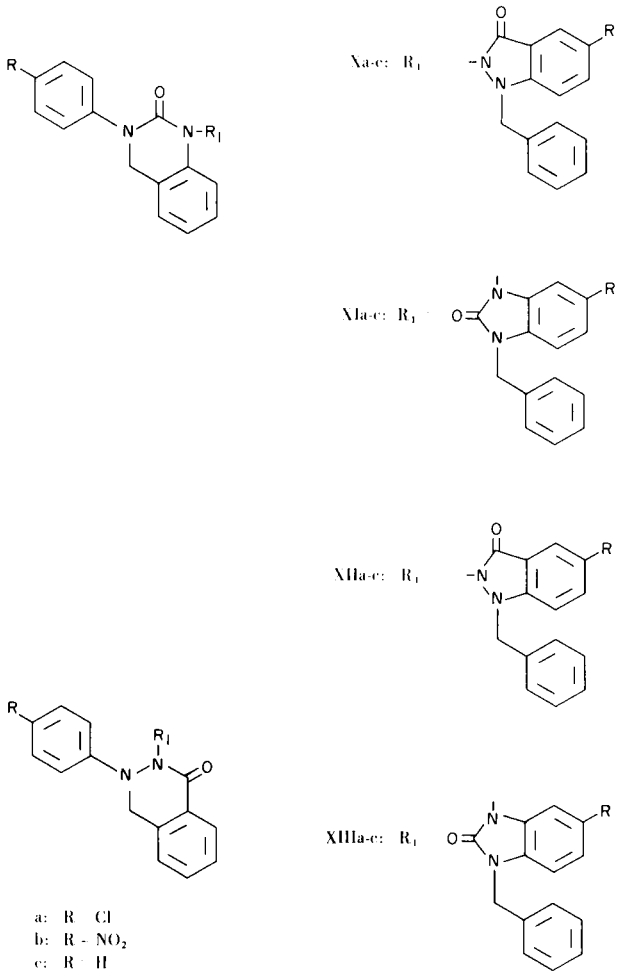
TABLE III

N-Benzyl-*N*-(4-substituted-phenyl)carbamoyl Chloride (V) (a)

	B.p. °C (mmHg)	Yield (%)	Formula	Analyses Calcd. C	H	N	Found C	H	N	IR ν max (liquid), cm^{-1} (C=O
Vd	145 (0.15	81.6	$C_{15}H_{14}ClNO$	69.36	5.43	5.39	69.53	5.71	5.60	1730
Vf	167 (0.20)	84.3	$C_{16}H_{16}ClNO_2$	66.32	5.57	4.83	66.49	5.55	4.86	1735
Vg	189 (0.40)	82.1	$C_{18}H_{20}ClNO_2$	68.05	6.35	4.41	68.27	6.45	4.22	1733

(a) The compounds (Va, Vb, Vc and Ve) have been already known.

SCHEME 3



assigned the structures Xa-c, XIa-c, XIIa-c or XIIIa-c, respectively. However, the correct structures of these compounds remain to be confirmed.

Baiocchi's report (6) was found to be correct concerning the by-product (III) obtained in the formation of I, but, the formation of II, which was reported by Stollé, was not observed. On the other hand, the novel compounds A, B and C which were not found by Baiocchi, were obtained by us.

Finally, the effects of the indazole derivatives (I) on plantar edema induced by carrageenin in the rat were examined (1) as shown in Table IV. No effective compounds were found.

EXPERIMENTAL (9)

N-Benzyl-*N*-(4-substituted-phenyl)carbamoyl Chloride (V).

A cooled mixture of *N*-benzyl-4-substituted-aniline (IV), dry pyridine (1.5 moles), a 30% toluene solution of phosgene (5 moles), and benzene was stirred for 1 hour and then heated gently to remove excess phosgene. The organic layer was washed with water, dried, evaporated, and distilled *in vacuo* to give Vc, Vf and Vg (*cf.* Table III).

N-Benzyl-*N*-(4-substituted-phenyl)carbamoyl Azide (VI).

A mixture of the carbamoyl chloride, an equivalent molar amount of sodium azide, and a fifteen fold excess of methanol was refluxed for 24 hours. Excess sodium azide was removed by filtration and the solvent was evaporated. The remaining residue was extracted with ether. The ethereal extract was washed with water, dried, and evaporated to give an oil, which was used in the following reaction without purification because of instability.

The Thermal Reaction of *N*-Benzyl-*N*-(4-chlorophenyl)carbamoyl Azide (VIa).

A solution of 12.6 g. of VIa in 126 ml. of dry xylene was refluxed for 9 hours and 4.9 g. of 1-benzyl-5-chloro-3-hydroxy-

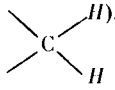
TABLE IV

The Effect of 1,5-Disubstituted-3-hydroxy-1*H*-indazole (I) on Carrageenin-Induced Edema in Rats

R_1	R_2	Rats	Dose (mg./kg)	Inhibition (%) (Hours) 2	3	4	5
H	$-CH_2Ph$	6	30	14.4	2.9	1.2	
CH_3	$-C_6H_4CH_3$ (*p*)	6	30		7.0	-5.2	
CH_3	$-CH_2Ph$	6	30	11.2	14.3	28.6	
Cl	$-CH_2Ph$	6	30	15.4	21.0	25.9	
C_2H_5O	$-CH_2Ph$	6	30		24.4		24.5

1*H*-indazole (Ia) which precipitated as colorless silk-like crystals was collected by filtration. This product showed one spot on silica gel thin layer chromatography using chloroform as an eluant and gave a positive ferric chloride test. The xylene filtrate was evaporated and a solution of 6.5 g. of the resulting residue in 100 ml. of ether was extracted twice with 20 ml. of 2% sodium hydroxide solution. The combined aqueous layer was acidified with hydrochloric acid. The crude crystals obtained were chromatographed on silica gel using benzene-chloroform (9:1) as an eluant. The first eluate afforded 0.3 g. of Ia and the successive fraction gave 0.20 g. of 1-benzyl-5-chlorobenzimidazolin-2-one (IIIa) (see Table I). The above ethereal layer was evaporated and the remaining residue was chromatographed on silica gel to give four fractions. The first fraction with benzene as an eluant afforded 0.6 g. of colorless crystals, m.p. 196-197°, whose recrystallization from ethanol-chloroform (4:1) afforded 1-benzyl-3-[α-benzyl-α-(4-chlorophenyl)hydrazinocarbonyl]-5-chlorobenzimidazolin-2-one (VIIa) as colorless silk-like crystals, m.p. 197-198°; ir ν max (nujol), cm^{-1} 3274 (weak) (NH), 1735, 1710 (C=O); ν max (chloroform), 3320 (NH), 1743, 1708 (C=O); nmr (ppm in deuteriochloroform), 4.72, 4.91 (2H, each, two singlets, 2 x $-CH_2-$), 8.16 (1H, doublet, J = 3.0 cps, C_4–H), 6.52-7.37 (16H, multiplet, C_6–H, C_7–H, N-C_6H_4–Cl, 2 x C_6H_5), 10.42 (1H, broad, NH); mass spectrum m/e 517 (M^+), 260 (M^+-257), 258 (M^+-259).

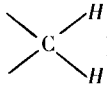
Anal. Calcd. for $C_{28}H_{22}Cl_2N_4O_2$: C, 65.00; H, 4.29; N, 10.83; Mol. Wt. 517.4. Found: C, 64.86; H, 4.32; N, 10.93; Mol. Wt. 516.5.

The second benzene eluate gave 0.46 g. of colorless needles, m.p. 176.5-177.5° (from ethanol); ir ν max (nujol), cm^{-1} 1790, 1743 (C=O); nmr (ppm in DMSO-d_6) 4.83 (2H, singlet, $-CH_2-$), 4.40, 4.80 [(1H each, doublet, J = 15.0 cps, ), whose signals were observed at 4.57 (2H) as a singlet at 80°], 7.33 (5H, singlet, $-C_6H_5$), 6.43 (2H, doublet, J = 9.0 cps, aromatic protons), 6.90-7.65 (9H, multiplet, aromatic protons).

Anal. Calcd. for $C_{28}H_{20}Cl_2N_4O_2$: C, 65.25; H, 3.91; N, 10.87; Mol. Wt. 515.4. Found: C, 64.84; H, 4.32; N, 11.10; Mol. Wt. 510.9.

The third fraction (chloroform-benzene, 1:2) and the fourth fraction (chloroform-benzene, 9:1) gave 3.6 g. of an oil and 0.40 g. of IIIa, respectively (see Table I).

The Thermal Reaction of *N*-Benzyl-*N*-(4-nitrophenyl)carbamoyl Azide (VIb).

A solution of 15.0 g. of VIb in 150 ml. of dry xylene was treated under the same conditions as above and 4.8 g. of 1-benzyl-3-hydroxy-5-nitro-1*H*-indazole (Ib) precipitated as colorless silk-like crystals on cooling. The crystals, collected by filtration showed one spot on silica gel thin layer chromatography using chloroform as an eluant and gave a positive ferric chloride test. The xylene filtrate was condensed to half of its volume. Refrigeration produced 4.4 g. of yellow prisms of VIb, m.p. 189.5-190.5° (from benzene); ir ν max (nujol), cm^{-1} 1753, 1645 (C=O); nmr (ppm in DMSO-d_6) 5.41 (2H, singlet, $-CH_2-$), 4.95, 5.26 [(1H, each, doublet, J = 15.0 cps, ), whose signals were observed at 5.10 (2H) as singlet at 100°], 7.45 (5H, singlet, $-C_6H_5$), 7.09 (2H, doublet, J = 9.0 cps, aromatic protons), 7.20-7.66 (9H, multiplet, aromatic protons), 7.20-7.66 (9H, multiplet, aromatic protons), 8.08-8.57 (5H, multiplet, aromatic protons).

Anal. Calcd. for $C_{28}H_{20}N_6O_6$: C, 62.68; H, 3.76; N, 15.67; Mol. Wt. 536.5. Found: C, 62.86; H, 4.18; N, 15.52; Mol. Wt. 539.3.

The xylene filtrate was further evaporated and a solution of the resulting residue in 80 ml. of ether was extracted with 2% sodium hydroxide solution. The aqueous layer was acidified with hydrochloric acid and the precipitate of Ib was collected by filtration, washed with water, dried, and recrystallized from ethanol to give 0.15 g. of Ib. The ethanolic mother liquor was chromatographed on silica gel using ethyl acetate as an eluant to give 0.21 g. of 1-benzyl-5-nitrobenzimidazolin-2-one (IIIb).

After evaporation of the ethereal layer described above, followed by silica gel chromatography of the resulting residue, the benzene eluate gave 0.4 g. of yellow prisms, m.p. 189.5-190.5°, whose spectroscopic data was identical with those of yellow prisms initially obtained.

The Thermal Reaction of *N*-Benzyl-*N*-(4-methylphenyl)carbamoyl Azide (VIc).

A solution of 10.4 g. of VIc in 104 ml. of xylene was refluxed for 9 hours and 5.6 g. of the crude precipitate, which was collected by filtration as colorless needles, gave a positive ferric chloride test and showed two spots on silica gel thin layer chromatography (chloroform-ethanol, 9:1). The crystals obtained were extracted twice with 50 ml. of 20% sodium hydroxide solution and the alkaline extract was acidified with hydrochloric acid. The precipitate was collected by filtration, washed with water, and dried to give 5.1 g. of 1-benzyl-3-hydroxy-5-methyl-1*H*-indazole (Ic) (see Table II).

The substance (0.55 g.) which was insoluble in 20% sodium hydroxide solution was chromatographed on silica gel. The first chloroform eluate gave 0.53 g. of 1-benzyl-5-methylbenzimidazolin-2-one and the second one with chloroform afforded 0.02 g. of Ic.

Evaporation of the xylene filtrate above gave 3.8 g. of an oil whose solution in 60 ml. of ether was extracted with 30 ml. of 2% sodium hydroxide solution. The aqueous layer was acidified with hydrochloric acid to afford 0.7 g. of Ic. The ethereal layer was evaporated and the resulting residue was chromatographed on silica gel to give four components.

The initial fraction with benzene as eluant gave 0.35 g. of colorless crystals, m.p. 183-185°, whose recrystallization from ethanol-chloroform (4:1) afforded 1-benzyl-3-[α-benzyl-α-(4-methylphenyl)-hydrazinocarbonyl]-5-methylbenzimidazol-2-one (VIIb) as colorless silk-like crystals, m.p. 184-185°; ir ν max (nujol), cm^{-1} 3275 (weak) (NH), 1737, 1718 (C=O), ν max (chloroform), 3320 (NH), 1748 1702 (C=O); nmr (ppm in deuteriochloroform), 2.19, 2.28 (3H each, two singlets, 2 x CH_3), 4.74, 4.89 (4H, two singlets, 2 x $-CH_2-$), 7.98 (1H, quartet, J = 3.0, 1.0 cps, C_4–H), 6.70-7.4 (16H, multiplet, C_6–H, C_7–H, 2 x C_6H_5, N–C_6H_4–Cl), 10.46 (1H, broad, NH); mass spectrum m/e 239 (M^+-237), 238 (M^+-238).

Anal. Calcd. for $C_{30}H_{28}N_4O_2$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.35; H, 5.94; N, 11.60.

The second benzene eluate gave 2.1 g. of an oil of unknown structure. The third chloroform eluate gave 0.35 g. of IIIc and the fourth chloroform fraction afforded 0.05 g. of Ic.

The Thermal Reaction of *N*-Benzyl-*N*-phenylcarbamoyl Azide (VId).

A solution of 14.1 g. of VId in 141 ml. of xylene was refluxed for 9 hours and the mixture was treated by a method similar to that above to give 8.3 g. of 1-benzyl-3-hydroxy-1*H*-indazole (Id) as colorless needles, m.p. 167° (from benzene), 835 mg. of 1-

benzylbenzimidazolin-2-one (IIId) as colorless needles, m.p. 197-198° (from ethanol). In addition, 650 mg. of 1-benzyl-3-(α-benzyl-α-phenylhydrazinocarbonyl)benzimidazolin-2-one was obtained as the third product, m.p. 147-148° (from ethanol-chloroform) as colorless silk-like crystals; ir ν max (nujol), cm^{-1} 3260 (weak) (NH), 1733, 1704 (C=O); ν max (chloroform), 3300 (NH), 1740, 1700 (C=O); nmr (ppm in deuteriochloroform), 4.87, 5.05 (2H each, two singlets, 2 x $-CH_2-$), 8.25 (1H, quartet, J = 9.0, 2.5 cps, C_4H), 6.9-7.5 (18H, multiplet, C_5-H, C_6H, C_7-H, 3 x C_6H_5), 10.48 (1H, broad, NH).

Anal. Calcd. for $C_{28}H_{24}N_4O_2$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.98; H, 5.58; N, 12.35.

Finally, 290 mg. of compound C which would be one of Xc, XIc, XIIc, and XIIIc (see Scheme 3) was obtained as colorless needles, m.p. 122-123° (from ethanol); ir ν max (nujol), cm^{-1} 1790, 1733 (C=O); nmr (ppm in deuteriochloroform), 4.79 (2H, singlet, $-CH_2-$), 4.28, 4.78 [(2H each, two doublets, J = 15 cps, ), whose signals were observed at 4.53 (2H) as a singlet at 65°], 6.45-6.65 (2H, multiplet, aromatic protons), 6.80-7.55 (16H, multiplet, aromatic protons).

Anal. Calcd. for $C_{28}H_{22}N_4O_2$: C, 75.32; H, 4.97; N, 12.55. Found: C, 75.51; H, 5.18; N, 12.44.

The Thermal Reaction of *N*-Benzyl-*N*-(4-ethoxyphenyl)carbamoyl Azide (VIf).

A solution of 12.0 g. of VIf in 120 ml. of xylene was refluxed for 9 hours. After cooling, 4.97 g. of colorless needles precipitated. The crystals, which were collected by filtration, showed two spots on silica gel thin layer chromatography using chloroform-ethanol (9:1) as an eluant and gave a slightly positive ferric chloride test. The crystals were shaken with 15 ml. of 2% sodium hydroxide solution. The substance which was insoluble in 2% sodium hydroxide was recrystallized from ethanol to give 4.26 g. of 1-benzyl-5-ethoxybenzimidazolin-2-one (IIIf). The above 2% sodium hydroxide solution was acidified with hydrochloric acid and the crystals (0.31 g.) obtained were combined with the above ethanolic filtrate of IIIf. The first fraction on silica gel chromatography using chloroform-benzene (9:1) as an eluant afforded 0.25 g. of 1-benzyl-5-ethoxy-3-hydroxy-1*H*-indazole (If). The last eluate gave 0.44 g. of IIIf.

Finally, the xylene filtrate was condensed to one-third of its volume. After cooling, 0.98 g. of If was precipitated and collected by filtration. The removal of the filtrate gave 4.8 g. of a residue, which was chromatographed on silica gel using benzene-chloroform (3:1) as an eluant. The first eluate gave 4.6 g. of an oil, whose structure was not confirmed and the second eluate afforded 0.12 g. of If.

The thermal decomposition of VIc, VIg, and VIh was also examined by similar procedures to those above and the results are summarized in Tables I and II.

1-Benzyl-5-methyl-3-[*N*-(4-methylphenyl)carbamoyl]benzimidazolin-2-one (VIII).

A mixture of 65 mg. of 1-benzyl-5-methylbenzimidazolin-2-one (IIIc), 100 mg. of *p*-tolyl isocyanate in 20 ml. of dry xylene in a sealed tube was heated at 220-230° for 15 hours. The precipitate of di-*p*-tolylurea was removed by filtration to give colorless plates, m.p. 265-266° (from ethanol) [lit. (10), m.p. 265-266°]. The xylene filtrate was evaporated to give VIII, whose recrystallization from ethanol afforded 75 mg. of colorless silk-like crystals, m.p. 135-136°; ir ν max (nujol), cm^{-1} 3170-3050 (NH), 1730, 1695 (C=O); ν max (chloroform), 3225 (NH), 1732, 1693 (C=O); nmr (ppm in deuteriochloroform), 2.29, 2.35 (3H, two singlets, 2 x CH_3), 5.02 (2H, singlet, $-CH_2-$), 8.21 (1H, quartet, J = 3.0, 1.0 cps, C_4-H), 6.85-7.63 (11H, multiplet, C_6-H, C_7-H, $N-C_6H_4-CH_3$, C_6H_5), 11.20 (1H, broad, NH).

Anal. Calcd. for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31. Found: C, 74.36; H, 5.72; N, 11.18.

1-(4-Methylphenyl)-5-methyl-3-[*N*-(4-methylphenyl)carbamoyl]-benzimidazolin-2-one (IX).

(a) A mixture of 30 mg. of 1-(4-methylphenyl)-5-methylbenzimidazolin-2-one (IIIh), 100 mg. of methyl *p*-tolylcarbamate, and 15 ml. of dry xylene was heated at 210-220° in a sealed tube for 15 hours and the usual work-up gave 26 mg. of IX as colorless silk-like crystals, m.p. 161-162° (from ethanol); ir ν max (nujol), cm^{-1} 3220-3100 (NH), 1745, 1695 (C=O); ir ν max (chloroform), 3250 (NH), 1735, 1695 (C=O); nmr (ppm in deuteriochloroform), 2.28, 2.39 (6H, two singlets, 2 x CH_3), 8.17 (1H, quartet, J = 3.0 and 1.0 cps, C_4-H), 6.85-7.53 (10H, multiplet, C_6-H, C_7-H, 2 x C_6H_4), 11.07 (1H, broad, NH); mass spectrum m/e 238 (M^+-133), 134 (M^+-237).

Anal. Calcd. for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31. Found: C, 74.46; H, 5.69; N, 11.28.

(b) A mixture of 30 mg. of IIIh, 50 mg. of *p*-tolyl isocyanate, and 20 ml. of dry xylene was heated at 220-230° in a sealed tube for 15 hours. The usual work-up gave 20 mg. of IX as colorless silk-like crystals, which were identical to IX obtained above by comparison of the spectroscopic data.

The Thermal Decomposition of 1-Benzyl-3-[α-benzyl-α-(4-chlorophenyl)hydrazinocarbonyl]-5-chlorobenzimidazolin-2-one (VIIa).

A solution of 75 mg. of VIIa in ethanolic sodium ethoxide (prepared from 50 ml. of ethanol and 1 g. of metallic sodium) was heated at 230-240° in a sealed tube for 10 hours. After the reaction, the solvent was evaporated to give a residue, whose aqueous solution was acidified with hydrochloric acid and extracted with ether. The extract was washed with water, dried and evaporated to give an oil, whose ethanolic solution was allowed to stand at room temperature to give 34 mg. of 1-benzyl-5-chlorobenzimidazol-2-one (IIIa) as colorless needles, m.p. 179-180° (from ethanol), identical with an authentic sample by comparison of their spectroscopic data and mixed melting point test.

Decomposition of 1-Benzyl-3-[α-benzyl-α-(4-methylphenyl)hydrazinocarbonyl]-5-methylbenzimidazolin-2-one (VIIb).

A solution of 100 mg. of VIIb in ethanolic sodium ethoxide solution (prepared from 50 ml. of ethanol and 1 g. of metallic sodium) was treated by the same method as above and 35 mg. of 1-benzyl-5-methylbenzimidazolin-2-one (IIIc) was obtained as colorless needles, m.p. 185-186° (from ethanol), identical with authentic sample.

Decomposition of 5-Methyl-1-(4-methylphenyl)-3-[*N*-(4-methylphenyl)carbamoyl]benzimidazolin-2-one (IX).

The same treatment as above of a solution of 150 mg. of IX in ethanolic sodium ethoxide solution (prepared from 50 ml. of ethanol and 1 g. of metallic sodium) afforded 60 mg. of 1-benzyl-5-methylbenzimidazolin-2-one (IIIh) as colorless prisms, m.p. 223-224° (from ethanol). Furthermore, silica gel chromatography of the mother liquor obtained from the recrystallization of IIIh, gave *p*-tolylurethane as colorless needles, m.p. 51-52° (from ligroin), whose ir spectrum was identical with that of an authentic sample.

Investigation of the Effects of I on Planter Edema Induced by Carrageenin in the Rats.

Screening tests on the antidropical activity of the right foot pad of rats with the use of carrageenin (11) was carried out as follows. Six Wistar male rats were used for one group after fasting for 24 hours. A suspension of the compounds listed in Table IV in 5% gum-arabic was given orally per 30 mg./kg one hour before giving the carrageenin by injection. A 0.1% suspension of carrageenin in physiological saline solution was sterilized for 30 minutes at 120° in an autoclave and 0.1 ml. of the above suspension was then injected to the right foot pad under the skin. Their volumes were compared with those of the relative group (12). These results are summarized in Table IV.

Acknowledgment.

We are grateful to Vice President S. Uehara and Director Dr. S. Ikawa, Taisho Pharmaceutical Co., Ltd., for their encouragement. We also thank Dr. I. Tanaka and Dr. T. Seki, Taisho Pharmaceutical Co., Ltd., Dr. K. Fukumoto and Dr. S. Shibuya, Pharmaceutical Institute, Tohoku University, for their kind discussion. Further we also thank Mr. S. Hirata for mass spectral measurement.

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Received February 24, 1970 Aobayama, Sendai, Japan