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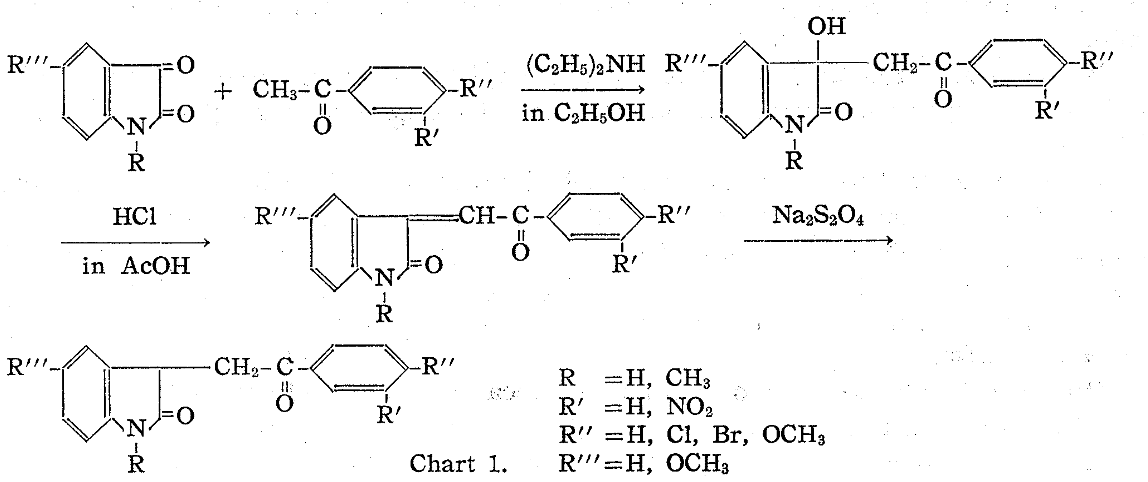
153. Goro Kobayashi and Sunao Furukawa: Studies on Indole Derivatives. I. Synthesis of 3-Phenyl-9*H*-pyridazino[3,4-*b*]indole Derivatives.

(*Pharmaceutical Faculty, University of Nagasaki*[*1])

There are few reports in the literature about pyridazinoindole derivatives: Stiller,1) Topham,2) Suvorov3) described some of 5*H*-pyridazino[4,5-*b*]indoles.

In this paper, we wish to report the synthesis of 3-phenyl-9*H*-pyridazino[3,4-*b*]indoles having new heterocyclic ring system. 3-Phenacyloxindoles, employed as the starting materials, were prepared by the method of Lindwall4) as shown in the Chart 1.



R =H, CH_3
R′ =H, NO_2
R″ =H, Cl, Br, OCH_3
R‴=H, OCH_3

Chart 1.

All 3-hydroxy-3-phenacyloxindoles, 3-phenacylideneoxindoles and 3-phenacyloxindoles which have not been reported in the literature are listed in Table I, Ⅱ and Ⅲ, respectively.

When 3-phenacyloxindole (I) and 2.5 equimolar of hydrazine hydrate in acetic acid were heated on a boiling water bath for 3 hour, the compound (Ⅲ) (3-phenyl-9*H*-pyridazino[3,4-*b*]indole) was obtained in 80% yield.

The structure of this compound (Ⅲ) was assigned from elemental analyses and its infrared spectrum. As shown in Fig. 1, the infrared spectrum of Ⅲ shows no absorption in the carbonyl region, comparing with I which shows an intense band at 1690 cm^{-1} (-NH-CO- and -CO-Ar).

[*1] Showa-machi, Nagasaki (小林五郎, 古川 淳).
1) H. King, E.T. Stiller: J. Chem. Soc., **1937**, 466.
2) R.S. Staunto, S. Topham: J. Chem. Soc., **1953**, 1889.
3) N.N. Suvorov, *et al.*: Zhur. Obshchei Khim., **31**, 2333 (1961); C.A., **56**, 3478 (1962).
4) H.G. Lindwall, J.S. Maclennan: J. Am. Chem. Soc., **54**, 4739 (1932).

The corresponding carbonyl bands of 3-phenacyloxindoles are shown in Table Ⅲ-a. Also, the ultraviolet absorption of Ⅲ has maxima at 270 mμ and 370 mμ, differing from oxindole chromophor (see Table Ⅳ-b).

A number of 3-phenyl-9*H*-pyridazino[3,4-*b*]indoles prepared in the same manner as above are listed in Table Ⅳ-a.

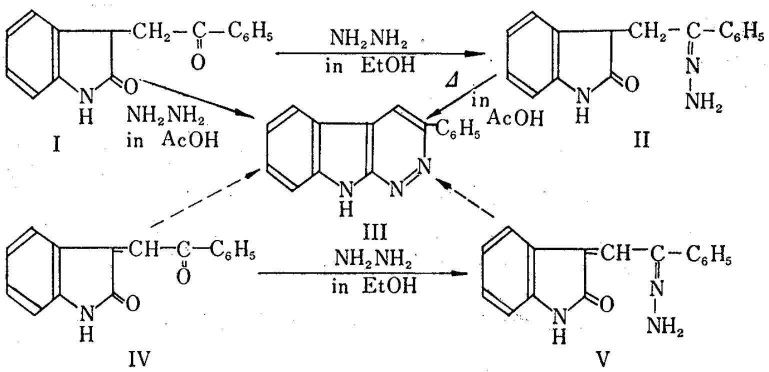


Chart 2.

Further, in order to investigate the path way of this reaction 3-phenacyloxindole hydrazone (Ⅱ) which was prepared in the usual manner, with acetic acid was heated on a boiling water bath for 3 hour. The resulting product was Ⅲ (60%) which was identical with authentic sample by the admixture test and the comparison of the infrared spectrum.

By the same reaction condition, 3-phenacylideneoxindole hydrazone (Ⅴ) with acetic acid gave no cyclization product, but it afforded monoacetyl derivative of Ⅴ, m.p. 230° in 60% yield.

In the case of 3-phenacylideneoxindole (Ⅳ) was treated with 2.5 equimolar of hydrazine hydrate in acetic acid, the resulting products were Ⅲ in only 5% yield and a compound (Ⅵ) in 40% yield, m.p. 251～252°. Analytical values of this compound (Ⅵ) are in good agreement with the formula, $C_{16}H_{13}ON_3$, the hydrazone of Ⅳ, but it was clearly different from Ⅴ, m.p. 203°. Experiments for characterization of the compound (Ⅵ) are now under way.

On the other hand, refluxing the tosylhydrazone of Ⅰ in acetic acid for 6 hours gave Ⅰ in 68% yield, but no cyclization product, and heating that in polyphosphoric acid on a boiling water bath for 3 hours yielded Ⅲ in 58% yield.

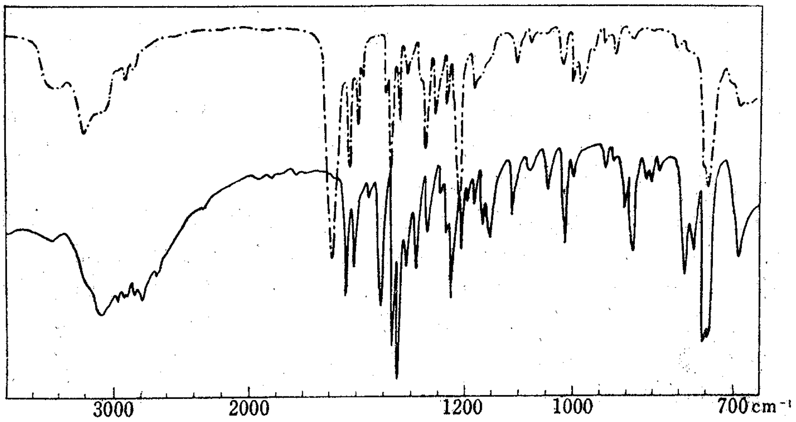
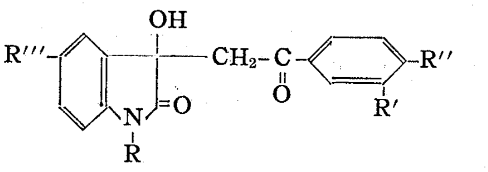


Fig. 1. Infrared Spectra (KBr)

- - - - - 3-phenacyloxindole (Ⅰ)
——— 3-phenyl-9*H*-pyridazino[3,4-*b*]indole (Ⅲ)

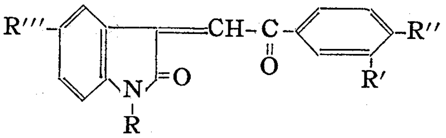
TABLE I.



R	R′	R″	R‴	m.p. (°C)	Yield (%)	Formula	Analysis (%) Calcd.	Analysis (%) Found
CH_3	H	Cl	H	178~179a)	67	$C_{17}H_{14}O_3NCl$	C 67.66 H 4.47 N 4.44	64.22 4.37 4.73
〃	〃	Br	〃	159~162a)	54	$C_{17}H_{14}O_3NBr$	C 56.84 H 3.92 N 3.89	56.38 3.83 3.67
〃	〃	OCH_3	〃	199~197a)	60	$C_{18}H_{17}O_4N$	C 69.44 H 5.50 N 4.50	69.39 5.38 4.71
〃	NO_2	H	〃	139~142a)	75	$C_{17}H_{14}N_2O_5$	C 62.57 H 4.33 N 8.59	62.26 4.13 8.96
H	H	〃	OCH_3	175~177b)	74	$C_{17}H_{15}NO_4$	C 68.67 H 5.08 N 4.71	68.45 5.03 4.83
〃	〃	Cl	〃	177~179b)	62	$C_{17}H_{14}NO_4Cl$	C 61.54 H 4.25 N 4.22	61.37 4.11 4.54
〃	〃	Br	〃	183~184b)	48	$C_{17}H_{14}NO_4Br$	C 54.29 H 3.75 N 3.72	54.35 3.82 3.17
〃	〃	OCH_3	〃	166~168b)	75	$C_{18}H_{17}O_5N \cdot H_2O$	C 64.27 H 5.39 N 4.17	64.35 5.39 4.39
〃	NO_2	H	〃	154~155b)	85	$C_{17}H_{14}O_6N_2$	C 59.65 H 4.12 N 8.18	59.67 4.16 8.18
〃	〃	〃	H	154~157a)	66	$C_{16}H_{12}O_5N_2$	C 61.54 H 3.87 N 8.97	61.48 3.77 8.97

Recrystallized from a) EtOH; b) MeOH.

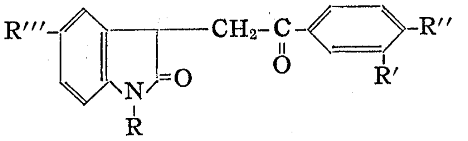
TABLE II.



R	R′	R″	R‴	m.p. (°C)	Yield (%)	Formula	Analysis (%) Calcd.	Analysis (%) Found
CH_3	H	Cl	H	186~173b)	83	$C_{17}H_{12}O_2NCl$	N 4.69	7.87
〃	〃	Br	〃	192~193b)	92	$C_{17}H_{12}O_2NBr$	〃 4.09	4.12
〃	〃	OCH_3	〃	119~123b)	76	$C_{18}H_{15}O_3N$	〃 4.78	5.10
〃	NO_2	H	〃	197~198b)	80	$C_{17}H_{12}O_4N_2$	〃 9.09	9.28
H	H	〃	OCH_3	168~170a,b)	99	$C_{17}H_{13}O_3N$	〃 5.02	5.03
〃	〃	Cl	〃	173~174b)	98	$C_{17}H_{12}O_3NCl$	〃 4.46	4.51
〃	〃	Br	〃	195~197c)	99	$C_{17}H_{12}O_3NBr$	〃 3.91	4.40
〃	〃	OCH_3	〃	174~176d)	95	$C_{18}H_{15}O_4N$	〃 4.53	4.19
〃	NO_2	H	〃	225~227e)	97	$C_{17}H_{12}O_5N_2$	〃 8.64	8.93
〃	〃	〃	H	225b)	77	$C_{16}H_{10}O_4N_2$	〃 9.52	9.58

a) S. Pietra and G. Tacconi [Farmaco (Pavia) Ed. sci., **13**, 893; C. A., **53**, 21875 (1959)] reported m.p. 173°.
Recrystallized from b) EtOH; c) Me_2CO; d) MeOH-benzene; e) AcOH.

TABLE III-a.



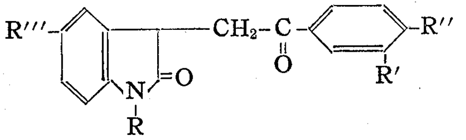
R	R′	R″	R‴	m.p. (°C)	Yield (%)	IR cm^{-1} : $\nu_{C=O}$ (KBr)
H	H	H	H	177[a]		1690
〃	〃	Cl	〃	182～183[a]		1706, 1680
〃	〃	Br	〃	191～192[a]		1698
〃	〃	OCH_3	〃	164～165[a]		1695, 1672
〃	NH_2	H	〃	165[c]	85	1695, 1681
CH_3	H	〃	〃	134～135[a]		1708, 1688
〃	〃	Cl	〃	143～144[c]	60	1703, 1680
〃	〃	Br	〃	152～153[c]	83	1690, 1678
〃	〃	OCH_3	〃	139～141[c]	87	1705, 1677
〃	NH_2	H	〃	147～148[c]	63	1688, 1677
H	H	〃	OCH_3	155～155.5[b,d]	69	1698, 1680
〃	〃	Cl	〃	157.5～158[e]	93	1689
〃	〃	Br	〃	168～169[f]	59	1689
〃	〃	OCH_3	〃	149～150[e]	100	1683

a) These compounds were reported by Lindwall.[4]

b) S. Pietra and G. Tacconi [Farmaco (Pavia) Ed. sci., **13**, 893 (1958); C.A., **53**, 21875 (1959)] reported m.p. 155°.

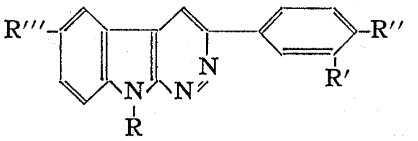
Recrystallized from *c*) EtOH; *d*) benzene; *e*) MeOH; *f*) MeOH-Me_2CO.

TABLE III-b.



R	R′	R″	R‴	Formula	Analysis (%)		
						Calcd.	Found
CH_3	H	Cl	H	$C_{17}H_{14}O_2NCl$	C	68.65	68.25
					H	4.71	4.52
					N	4.68	4.58
〃	〃	Br	〃	$C_{17}H_{14}O_2NBr$	C	59.66	59.38
					H	4.12	3.83
					N	4.09	4.33
〃	〃	OCH_3	〃	$C_{18}H_{17}O_3N$	C	73.20	73.65
					H	5.80	5.80
					N	4.74	4.84
〃	NH_2	H	〃	$C_{17}H_{16}O_2N_2$	C	72.84	72.83
					H	5.75	5.88
					N	9.99	10.16
H	H	〃	OCH_3	$C_{17}H_{15}O_3N$	C	72.58	72.87
					H	5.37	5.25
					N	4.98	5.03
〃	〃	Cl	〃	$C_{17}H_{14}O_3NCl$	C	64.66	64.40
					H	4.47	4.15
					N	4.44	4.73
〃	〃	Br	〃	$C_{17}H_{14}O_3NBr$	C	56.69	56.85
					H	3.91	3.94
					N	3.89	4.46
〃	〃	OCH_3	〃	$C_{18}H_{17}O_4N$	C	69.44	69.18
					H	5.50	5.47
					N	4.50	4.78
〃	NH_2	H	H	$C_{16}H_{14}O_2N_2$	C	72.16	71.68
					H	5.30	5.06
					N	10.52	10.69

TABLE Ⅳ-a.



No.	R	R'	R''	R'''	m.p. (°C)	Yield (%)	Appearance
Ⅳ-1	H	H	H	H	$245^{a)}$	80	pale straw needles
2	〃	〃	Cl	〃	$295^{a)}$	52	pale yellow needles
3	〃	〃	Br	〃	$>300^{c)}$	51	〃
4	〃	〃	OCH_3	〃	$260^{a)}$	50	pale yellow prisms
5	〃	NHAc	H	〃	$280\sim282^{d)}$	47	colorless crystals
6	CH_3	H	〃	〃	$181\sim182^{a)}$	60	pale yellow needles
7	〃	〃	Cl	〃	$229\sim231^{a)}$	40	pale yellow prisms
8	〃	〃	Br	〃	$228\sim230^{a)}$	45	〃
9	〃	〃	OCH_3	〃	$154\sim155^{a)}$	40	pale yellow needles
10	OCH_3	NHAc	H	〃	$225\sim226^{a)}$	47	colorless needles
11	H	H	〃	OCH_3	$240\sim241^{b)}$	41	yellow needles
12	〃	〃	Cl	〃	$265\sim266^{b)}$	31	〃
13	〃	〃	Br	〃	$272^{b)}$	56	〃
14	〃	〃	OCH_3	〃	$217\sim218^{b)}$	29	〃

Recrystallized from *a*) EtOH; *b*) MeOH; *c*) pyridine-H_2O; *d*) EtOH-AcOEt.

TABLE Ⅳ-b.

No.	UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (ε)	Formula		Analysis (%) Calcd.	Analysis (%) Found
Ⅳ-1	270 (46,000) 374 (2,970)	$C_{16}H_{11}N_3$	C H N	78.35 4.52 17.13	78.18 4.55 17.15
2	275.5 (49,400) 376 (2,920)	$C_{16}H_{10}N_3Cl$	C H N	68.70 3.60 15.02	68.69 3.47 14.69
3	277 (51,700) 375 (3,200)	$C_{16}H_{10}N_3Br$	C H N	59.27 3.10 12.99	59.10 3.00 13.23
4	277 (48,900) 380 (3,020)	$C_{17}H_{13}ON_3$	C H N	74.16 4.76 15.26	73.69 4.60 15.43
5	271 (53,400) 376 (3,200)	$C_{18}H_{14}ON_4$	C H N	71.51 4.67 18.53	71.27 4.63 18.71
6	272 (45,600) 384 (2,820)	$C_{17}H_{13}N_3$	C H N	78.74 5.05 16.21	79.05 5.19 16.27
7	277.5 (48,300) 385 (2,900)	$C_{17}H_{12}N_3Cl$	C H N	69.51 4.12 14.32	69.97 4.23 14.32
8	279 (50,000) 385 (2,820)	$C_{17}H_{12}N_3Br$	C H N	60.37 3.58 12.49	60.73 3.67 12.39
9	277.5 (54,000) 390 (3,070)	$C_{18}H_{15}ON_3$	C H N	74.72 5.23 14.40	74.74 5.19 14.40
10	272.5 (49,100) 384 (2,920)	$C_{19}H_{16}ON_4$	C H N	72.13 5.10 18.17	71.74 5.01 18.17
11	280 (37,700) 402 (3,100)	$C_{17}H_{15}ON_3$	C H N	74.16 4.76 15.26	74.17 4.80 15.18
12	284 (41,460) 405 (3,100)	$C_{17}H_{12}ON_3Cl$	C H N	65.91 3.91 13.56	66.01 3.86 13.96

13	285 405	(41, 530) (3, 250)	$C_{17}H_{12}ON_3Br$	C H N	57.64 3.42 11.86	57.81 3.52 12.10
14	280 407	(49, 070) (3, 330)	$C_{18}H_{15}O_2N_3$	C H N	70.80 4.95 13.76	71.13 5.11 13.74

From the results described above, the ring closure to III from VI or V which has a double bond at β-position of oxindole already, was not satisfactory. It would be deduced that the compound (III) was converted from its dihydro compound by air oxidation, but the reaction mechanism has not yet been investigated completely.

Experimental[*2]

1) **Preparation of 3-Phenacyloxindoles**——The procedures were carried out by the methods similar to that described by Lindwall,[4)] and the unknown compounds are listed in Tables I, II, and III, respectively. An attempt to hydrogenate the 3-(3-nitrophenacylidene)oxindole to 3-(3-nitrophenacyl)oxindole by using of $Na_2S_2O_4$ solution was unsuccessful. Therefore, the following procedure was employed. A suspension solution of 6.5 g. of 3-(3-nitrophenacylidene)oxindole in 200 ml. of EtOH was hydrogenated over Pd-C (0.5 g. of charcoal and 15 ml. of 2% $PdCl_2$). The reduction was completed after 4 mol. of H_2 gas had been absorbed. The catalyst was filtered off and the filtrate was concentrated. The residue was dissolved in $CHCl_3$ and the $CHCl_3$ solution was washed with 5% Na_2CO_3 solution, H_2O and dried over anhyd. K_2CO_3. Evaporation of the solvent yielded 5.5 g. of crystals, 3-(3-aminophenacyl)oxindole.

1-methyl-3-(3-aminophenacyl)oxindole was prepared from the corresponding 1-methyl-3-(3-nitrophenacylidene)oxindole by the above procedure.

2) **3-Phenyl-9*H*-pyridazino[3,4-*b*]indole (III)**——After 1.0 g. of 3-phenacyloxindole was dissolved in 6 ml. of AcOH, was added 0.6 ml. of 80% hydrazine hydrate on cooling.

The mixture was heated on a boiling water bath for 2 hr. After evaporation of AcOH *in vacuo*, the brown residue was added with 10 ml. of ice-water. The separated solid was collected, washed with H_2O, and recrystallized from EtOH to give 0.85 g. of crystals, m.p. 240~245°. Further recrystallization for an analytical sample gave slightly straw needles, m.p. 245°.

The other 3-phenyl-9*H*-pyridazino[3,4-*b*]indole derivatives were prepared by cyclization of the corresponding 3-phenacyloxindoles with hydrazine in the same way. Their physical and analytical data are given in Tables IV-a and IV-b.

3) **3-Phenacyloxindole Hydrazone (II)**——A mixture of 1.0 g. of 3-phenacyloxindole, 0.3 g. of 80% hydrazine hydrate and 3 drops of AcOH in 20 ml. of EtOH was refluxed for 2 hr. After evaporation of EtOH, the crude product weighed 0.9 g., m.p. 145~160°.

Recrystallization from EtOH gave 0.5 g. of white crystals, m.p. 170~172°. *Anal.* Calcd. for $C_{16}H_{15}ON_3$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.48; H, 5.72; N, 16.19.

4) **3-Phenacylideneoxindole Hydrazone (V)**——This compound was prepared in the same manner as described above. Recrystallization from MeOH gave colorless crystals, m.p. 203°. *Anal.* Calcd. for $C_6H_{13}ON_3$: C, 72.98; H, 4.98; N, 15.96. Found: C, 72.93; H, 5.06; N, 15.81.

5) **Reaction of 3-Phenacylideneoxindole (IV) with Hydrazine in Acetic Acid**——A solution of 2.5 g. of IV, 1.5 g. of 80% hydrazine hydrate in 20 ml. of AcOH was heated on a boiling water bath for 1 hr., additional in an oil bath (at 140°) for 2 hr. and AcOH was evaporated under reduced pressure. The redbrownish residue was solidified by addition of 80 ml. of H_2O and then on rubbing. An attempt to purify this solid was unsuccessful. The collected solid was dissolved in $CHCl_3$, dried over anhyd. Na_2SO_4 and evaporated. The resulting oily material was again dissolved in benzene and allowed to stand at room temperature overnight.

The separated crystals were collected and extracted with Et_2O repeatedly. The crystals was not dissolved in Et_2O were recrystallized form EtOH to give 0.1 g. of white crystals, m.p. 243~245°. This compound was identical with III obtained previously (by UV and IR spectra) the ethereal layer was condensed to give white crystals. Recrystallization from Et_2O gave 0.6 g. of white prisms, which colored to dark pink when expose on air. m.p. 251~252°, UV λ_{max}^{EtOH} mμ: 252, 280 (shoulder), 310 (shoulder). *Anal.* Found: C, 73.22; H, 4.52; N, 15.81 (The characterization of this material will be reported elsewhere).

6) **Heating of 3-Phenacyloxindole Hydrazone (II) in Acetic Acid**——A solution of 0.5 g. of II in 4 ml. of AcOH was heated on a boiling water bath for 3 hr. After evaporation of AcOH under reduced pressure, the residue was solidified by addition of a small amount of H_2O. The solid was collected by filtration and washed with ice-water.

[*2] All melting points are uncorrected.

Recrystallization from EtOH gave 0.3 g. of white crystals, m.p. 243~245°, which was identified with the authentic sample (m.p. 245°) by IR spectral comparison and by mixed melting point determination.

7) **Heating of 3-Phenacylideneoxindole Hydrazone in Acetic Acid**——A solution of 0.5 g. of 3-phenacylideneoxindole in 5 ml. of AcOH was heated on a boiling water bath for 3.5 hr. The solvent was removed *in vacuo*, and the resulting oily materials was dissolved into $CHCl_3$. The $CHCl_3$ solution was washed with 3% Na_2CO_3 solution, H_2O, and dried. The $CHCl_3$ residue was crystallized by addition of benzene and on standing at room temperature overnight. The crystals was collected by filtration, recrystallized from AcOEt to give 0.32 g. of colorless crystals, m.p. 230°. *Anal.* Calcd. for $C_{18}H_{15}O_2N_3$: C. 70.80; H, 4.95; N, 13.76. Found : C, 70.88; H, 5.05; N, 13.59.

This compound corresponds to 3-phenacylideneoxindole hydrazone monoacetate.

8) **Tosylhydrazone of 3-Phenacyloxindole (VII)**——To a solution of 1.25 g. of I in 20 ml. of EtOH were added 0.9 g. of tosylhydrazine (m.p. 113°) and ca. 10 mg. of tosylchloride as catalyst. The solution was refluxed for 2 hr. The solvent was removed under reduced pressure and resulting solid was filtered and washed with H_2O. Recrystallization from MeOH afforded 1.3 g. (62%) of colorless prisms, m.p. 194° (decomp.). *Anal.* Calcd. for $C_{23}H_{21}O_3N_3S$: C, 65.86; H, 5.05; N, 10.02. Found; C, 66.22; H, 5.20; N, 10.13.

9) **Reaction of VII with Acetic Acid**——A solution of 1.0 g. of VII in 6 ml. of AcOH was refluxed for 6 hr. and then evaporated to dryness. To the residue was added 10 ml. of H_2O and basified with 10% Na_2CO_3. The resulting precipitate was collected by filtration and recrystallized from EtOH to give colorless needles, m.p. 172~174° (0.5 g.), which was identical with an authentic sample (I).

10) **Reaction of VII with Polyphosphoric Acid**——A mixture of 0.5 g. of VII and 5.0 g. of polyphosphoric acid was heated on a boiling water bath for 3 hr. After cooling, the reaction mixture was poured into crushed ice. The resulting precipitate was collected by filtration and washed with H_2O, Et_2O sufficiently. Recrystallization from EtOH yielded 0.2 g. of slightly yellow crystals, m.p. 241~245°. This was identified with authentic sample (III) by admixture, and IR spectral comparison.

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Summary

Several 3-phenyl-9*H*-pyridazino[3,4-*b*]indoles were prepared by heating 3-phenacyloxindoles and hydrazine hydrate in acetic acid solution.

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154. Kunio Nakagawa, Hiroshi Onoue, and Jitsuo Sugita : Oxidation with Nickel Peroxide. IV.[*1] The Preparation of Benzoxazoles from Schiff's Bases.

(*Shionogi Research Laboratory, Shionogi & Co., Ltd.*[*2])

Stephens and Bower reported[1] that the various kinds of Schiff's bases prepared from substituted *o*-aminophenols and benzaldehydes readily underwent dehydrogenation by lead tetraacetate in benzene or acetic acid and caused ring closure to form 2-phenylbenzoxazole derivatives. He proposed that the ring closure of Schiff's bases by lead tetraacetate proceeds by a free radical mechanism described as follow.

[*1] Part I: J. Org. Chem., 27, 1597 (1962); Part II: This Bulletin, 11, 296 (1963); Part III: *Ibid.*, 12, 403 (1964).

[*2] Fukushima-ku, Osaka (中川国夫, 尾上　弘, 杉田実男).

1) F. F. Stephens, J. D. Bower : J. Chem. Soc., **1949**, 2971; **1950**, 1722.