[Chem. Pharm. Bull. 18(9)1822—1830(1970)]

UDC 547.751.04 : 547.821.04 : 547.831.1.04

Studies on Tertiary Amine Oxides. XL.[1] Reactions of Aromatic N-Oxides with Oxindoles in the Presence of Acylating Agents

Masatomo Hamana and Itsumaro Kumadaki[2a]

Faculty of Pharmaceutical Sciences, Kyushu University[2]

(Received February 20, 1970)

1-Methyloxindole (II) reacted as an active methylene compound with acyl–adducts of quinoline 1-oxides (I, IX and VIII), forming 1-methyl-3-(2- or 4-quinolyl)oxindoles (III, XV or XI). The reaction with I in the presence of acetic anhydride or benzoyl chloride further proceeded and gave bis-quinolyl compound (IV) besides mono-quinolyl one (III). The order of effectiveness of acylating agents was acetic anhydride>benzoyl chloride>tosyl chloride. Pyridine 1-oxide (XVII) itself was also able to react with II in hot acetic anhydride to give four kinds of products, 2-pyridyl- (XX), bis-2-pyridyl- (XIX), 4-pyridyl-product (XXI) and acetate of XXI (XVIII).

The reaction of oxindole (XXVI) with I progressed similarly and 3-(2-quinolyl)-oxindole (XXVII) was obtained.

The preceeding paper of this series has revealed that indoles react as aromatic analogs of enamine with quinoline N-oxides in the presence of an acylating agent to produce 3-(2- or 4-quinolyl)indoles, but no reaction occurs with pyridine 1-oxide itself despite a smooth reaction with ethyl nicotinate 1-oxide.[1] Hamana and Yamazaki[3] have previously shown that active methylene compounds of high acidity also react with aromatic N-oxides in the presence of an acylating agent. As an extension of our work on nucleophilic reaction between acyl–adducts of aromatic N-oxides and indole derivatives, we examined reaction with oxindoles, the 3-position of which is known as an active methylene group.[4]

After completion of this study, we got acquainted with the fact that Bruni and Guerra[5] carried out the reactions of quinoline and isoquinoline N-oxides with oxindole and 1-methyloxidole in the presence of benzoyl chloride and obtained the corresponding 3-(2-quinolyl or 1-isoquinolyl)oxindoles. Besides the similar observations to these results, we succeeded in obtaining some more detailed informations as described herein.

At first, the reaction of quinoline 1-oxide (I) with 1-methyloxindole (II) was examined under several conditions. When a solution of I and II in acetic anhydride was warmed at 75°, the reaction mixture gradually colored to dark red. After 8 hours, the mixture of basic products was separated and chromatographed on alumina in chloroform–carbon tetrachloride (1:1) to afford two fractions. The first gave colorless sands (IV) of mp 225—227° after recrystallization from ethanol (above 18% yield). From the second fraction, vermilion red needles (III) of mp 214—215° were obtained upon recrystallization from ethanol (above 37% yield) [No. 1 in Table I].

Since III was too tightly adsorbed on alumina to be completely eluted and the separation of III and IV was not effectively achieved by this procedure, the isolation of each product

---

[1] Part XXXIX: M. Hamana and I. Kumadaki, *Chem. Pharm. Bull.* (Tokyo), **18**, 1742 (1970).

[2] Location: *Katakasu, Fukuoka*; *a*) Present address: *Tokyo College of Pharmacy, Kashiwagi-4-chome, Shinjuku-ku, Tokyo.*

[3] *a*) M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.* (Tokyo), **11**, 411 (1963); *b*) *Idem, ibid.*, **11**, 415 (1963).

[4] P.L. Julian, E.W. Meyer and H.C. Printy, "Heterocyclic Compounds," Vol. 3, ed. by R.C. Elderfield, Wiley, New York, 1952, pp. 126—186.

[5] P. Bruni and G. Guerra, *Ann. Chim.* (Rome), **57**, 688 (1967) [*C.A.*, **67**, 166779y (1967)].

was separately tried in each of two runs using 5 g of I as described in the experimental section, and the yields of III and IV were found to be 60 and 28%, respectively [No. 2 in Table I].

The main product III had an empirical formula $C_{18}H_{14}ON_2$, and its infrared (IR) spectrum showed a strong band at 1630 cm^{-1} attributed to a chelated carbonyl group. Treatment of III with lithium aluminium hydride in ether gave a colorless solution, but red color appeared again during the processing and III was recovered almost quantitatively. Refluxing III with phosphoryl chloride yielded the corresponding unstable chloro-compound (VI) of mp 137°, which was transformed by catalytic reduction over palladium-charcoal to the known 1-methyl-3-(2-quinolyl)indole (VII).[1] These results indicate that III is the expected 1-methyl-3-(2-quinolyl)oxindole[5] and exists predominantly as a chelated form (III', or III'').

The minor product IV had an empirical formula $C_{27}H_{19}ON_3$ in agreement with a bis (quinolyl)-1-methyloxindole, and its IR spectrum exhibited a carbonyl band at 1715 cm^{-1} which suggested that the oxindole ring had no active hydrogen necessary for formation of a chelated structure. In the nuclear magnetic resonance (NMR) spectrum, the ratio of numbers of N-methyl protons to those of aromatic ones was found to be 3:16 and no signal of α-proton of quinoline ring was detected. Upon heating III for 15 hours with one equivalent amount of I in acetic anhydride, IV was formed in 75% yield, and refluxing IV with phosphoryl chloride in a sealed tube resulted in elimination of one quinolyl group as well as substitution with chlorine to give VI. From these observations, the structure of IV was determined as 1-methyl-3,3-bis(2-quinolyl)oxindole.

A similar reaction using benzoyl chloride in chloroform under refluxing condition progressed smoothly and gave III as a predominant product in 63% yield together with a small amount of IV (4%) [No. 3 in Table I]. On the other hand, tosyl chloride was not effective as an acylating agent in this case and carbostyril (V) was formed in 63% yield accompanied with only a very small amount of the bis-quinolyl compound IV (3%) [No. 4 in Table I].

These differences depending upon the nature of acylating agents seem to suggest that the basicity, *i.e.*, the proton-abstracting power, of anions present in the reaction medium may play one of the essential roles for the progressing of the reaction. In order to ascertain this aspect, reactions using tosyl chloride were carried out in the presence of sodium acetate or lithium benzoate [No. 5 and 6 in Table I]. Although the expected increases in yields of III and IV were not observed, there were some analogies noticed between the exper. No. 5 and 2 and also between the exper. No. 6 and 3 with respect to the ratio of III to IV. The low yields of III and IV in these cases may be presumably due to the fact that tosyl chloride-adduct of I would undergo decomposition by the added anions to carbostyril (V) and I.

These results are shown in Chart 1 and Table I.

TABLE I. Reactions of 1-Methyloxindole (II) with Quinoline 1-Oxide (I)

Exper. No.	Acylating agent	Additive	Reaction temp. (°C)	Reaction time (hr)	Product (%)		
					III	IV	V
1	Ac_2O	—	75	8	above 37	above 18	—
2	Ac_2O	—	75—80	10	60	28	—
3	PhCOCl	—	refluxed in $CHCl_3$	5	63	4	—
4	TsCl	—		5	—	3	63
5	TsCl	AcONa		9	3.5	3	25[a]
6	TsCl	PhCOOLi		9	8	below 1	25[a]

a) A considerable amount of I (*ca.* 20%) was recovered.

Subsequently 2-chloroquinoline 1-oxide (VIII) and 4-chloroquinoline 1-oxide (IX) were applied to II. Although VIII and II did not react in the presence of benzoyl chloride, a

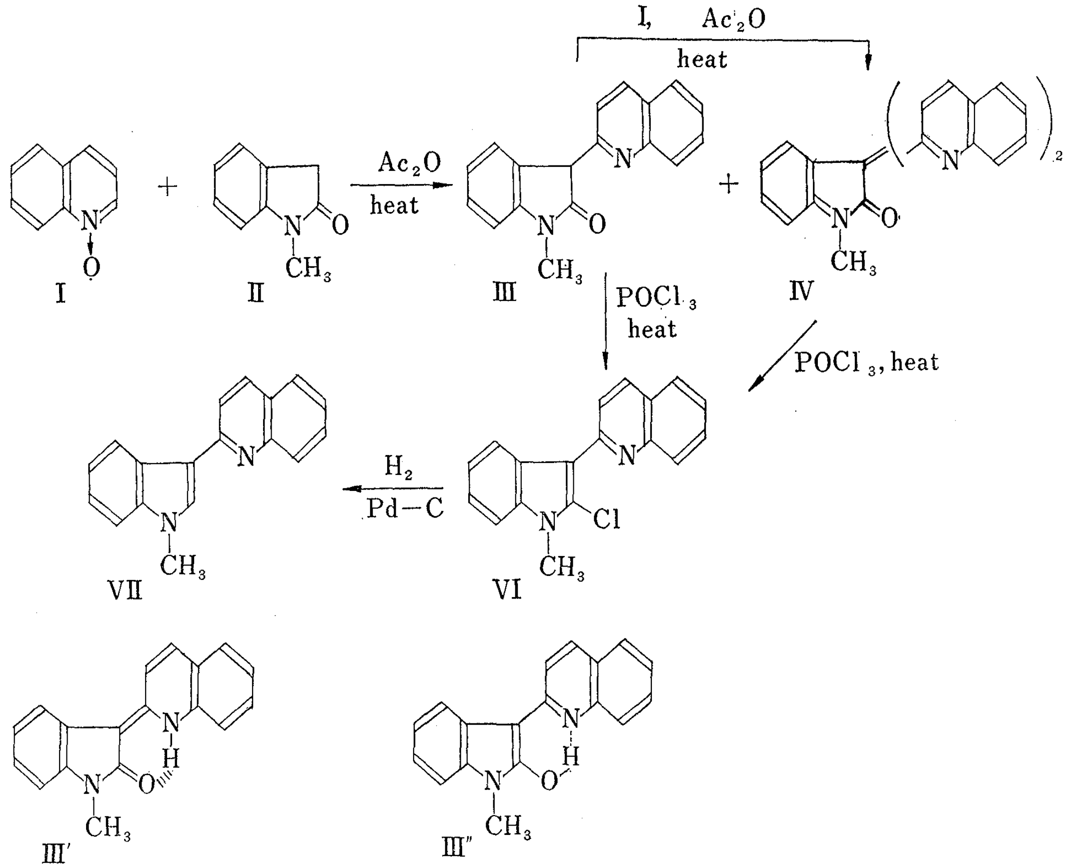

Chart 1

reaction took place when warmed in acetic anhydride, and 1-methyl-3-(2-chloro-4-quinolyl)-oxindole (XI), colorless needles, mp 222—223°, was formed in a small yield of 15% accompanied with carbostyril N-oxide (X), the acetolysis product of VIII.

The structure of XI was confirmed by elemental analysis and IR spectrum ($\nu_{C=O}$ at 1703 cm^{-1}) and further by the following reaction sequence shown in Chart 2. Catalytic reduction of XI over palladium-charcoal gave the corresponding dechlorinated compound (XII), which was converted to the known 1-methyl-3-(4-quinolyl)indole (XIV)[1] through 2-chloroindole derivative (XIII) in the same manner as the structural elucidation of III. The formation of XI, though in a small yield, is significant in view of the fact that reaction of VIII with active methylene compounds such as ethyl cyanoacetate resulted in acetolysis of VIII with formation of X as a sole product.[6]

The reaction of 4-chloroquinoline 1-oxide (IX) with II proceeded readily in the presence of benzoyl chloride to give vermilion red needles of 1-methyl-3-(4-chloro-2quinolyl)oxindole (XV), mp 245—248°, in 65% yield. The structure of XV was unambiguously established from its reductive dechlorination over palladium-charcoal to III and also its transformation to VII[1] through the dichloro-compound (XVI) as shown in Chart 2.

While pyridine 1-oxide itself (XVII) could not react with indole in the presence of an acylating agent,[1] it was found that XVII reacted with 1-methyloxindole (II) when heated in acetic anhydride, although no reaction was observed in the presence of benzoyl chloride or tosyl chloride. A solution of XVII and II in acetic anhydride was heated for 7 hours on an oil-bath (bath temperature, 120—130°), and chromatography of the products on alumina in chloroform afforded four kinds of crystals, *i.e.*, orange needles (XVIII) of mp 233—235° (16%), colorless cubes (XIX) of mp 184—185° (14%), orange yellow needles (XX) of mp 174—174.5° (8.9%) and yellow sands (XXI) of mp 182—183° (5.7%).

---

6) M. Yamazaki, private communication.

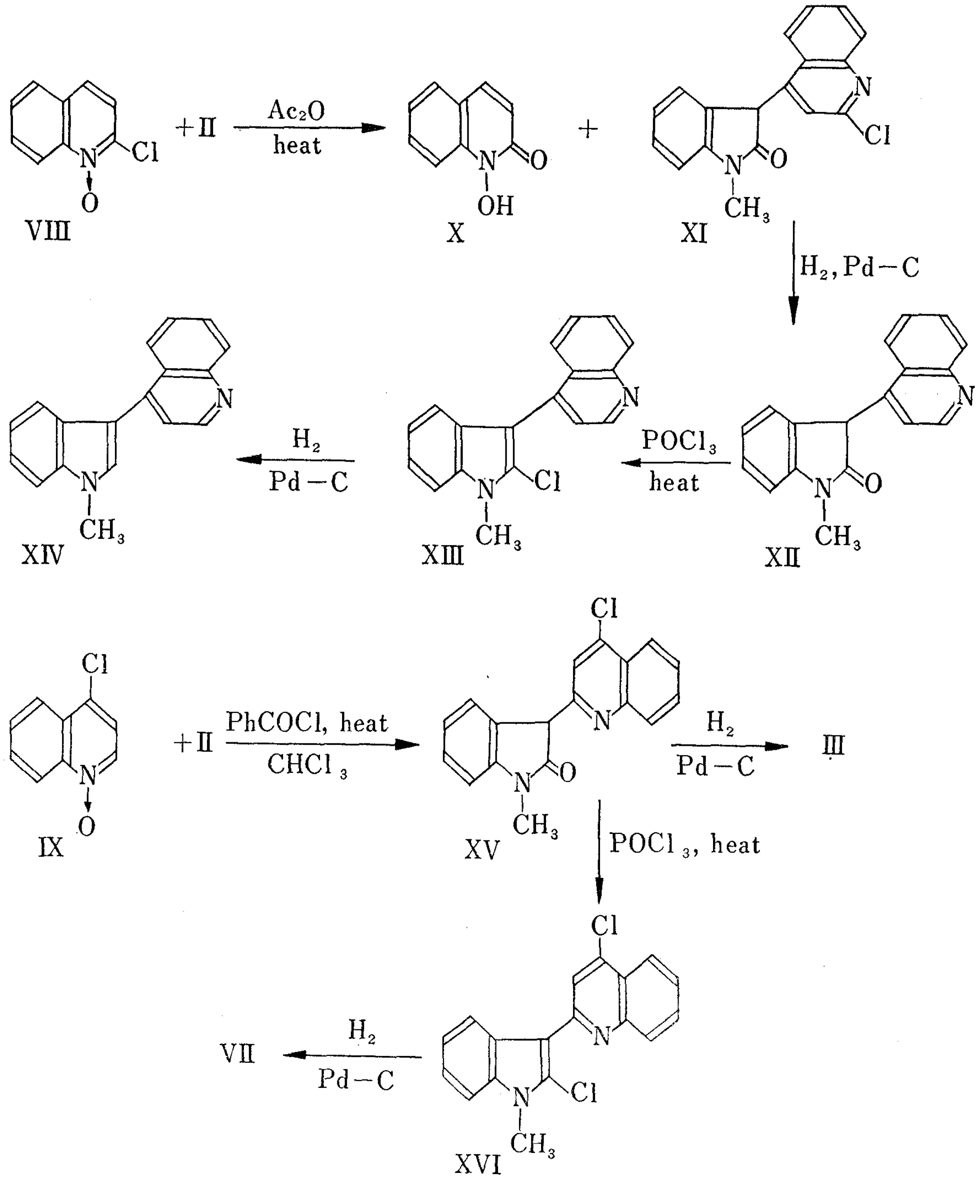

Chart 2

The product XVIII was shown to be an acetate of XXI from elemental analysis, an ester carbonyl band at 1730 cm^{-1} in IR spectrum and its hydrolysis to XXI with 10% sodium hydroxide solution.

The colorless product XIX had an empirical formula $C_{19}H_{15}ON_3$ in agreement with a bis(pyridyl)-1-methyloxindole and its IR spectrum exhibited an absorption band attributable to carbonyl group of oxindole at 1713 cm^{-1}. The NMR spectrum indicated the presence of twelve aromatic protons, two of which appeared as a doublet–quartet centered at τ 1.40 assignable to two α-protons of pyridine ring. Attempted chlorination of XIX with phosphoryl chloride failed. From these observations and also from analogy with the reaction of I and II in acetic anhydride, XIX may be most probably assumed to be 1-methyl-3,3-bis(2-pyridyl)oxindole.

The product XX was apparently a pyridyl-1-methyloxindole from elemental analysis and showed a chelated carbonyl band at 1650 cm^{-1} in IR spectrum, which fact suggested that XX would be 1-methyl-3-(2-pyridyl)oxindole and exist predominantly as an chelated form XX′ or XX″ similarly to III. The NMR spectrum showed the signals due to nine protons in the aromatic region, but a signal assignable to α-proton of pyridine ring was not clearly noticed

(Table II); these observations are in accordance with the chelated structure XX′ or XX″, which would cause the downfield shift of the signal of β-proton of oxindole to aromatic region and also change the nature of the pyridine ring in NMR spectrum.

In order to further confirm the structure of XX, XX was converted by heating with phosphoryl chloride in a sealed tube into a chlorinated compound (XXII) (colorless needles,

Table II. NMR Spectra of XIX–XXV[a]

Compound	Numbers of protons in aromatic region	α-Proton of pyridine ring chemical shift (τ)	Numbers
XIX	12	1.40 (d–q)[b]	2
XX	9	—	—
XXI	9	1.51 (d-broad)	2
XXII	8	1.25 (d–q)[b]	1
XXIII	9	1.15 (d–t)[b]	1
XXIV	8	1.35 (d–d)[b]	2
XXV	9	1.30 (braod)	2

a) Spectra were determined on solution in $CDCl_3$, using TMS as internal reference by JNM-3H-60 spectrometers operated at 60 Mc.

b) d: doublet, t: triplet, q: quartet

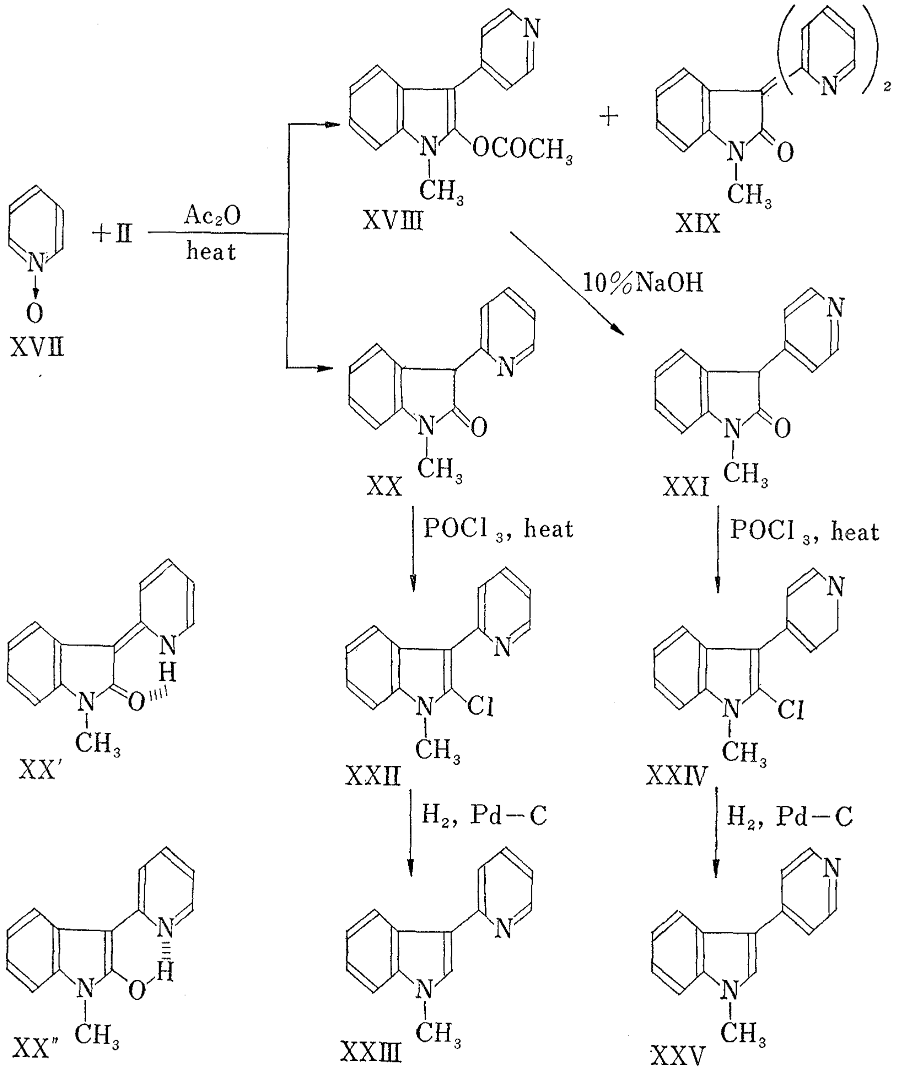

Chart 3

mp 89—91°), which was subsequently dechlorinated by catalytic reduction to XXIII (colorless sands, mp 83—84°). The IR spectra indicated that both XXII and XXIII had indole nucleus, and the NMR spectra showed a signal attributed to one α-proton of pyridine ring in each compound as shown in Table II. Further the ultraviolet (UV) spectrum of XXIII was closely similar to that of 3-(2-pyridyl)indole.7) Thus, the structures of XX, XXII and XXIII were determined as shown in Chart 3.

From the analytical values XXI is apparently an isomer of XX. The IR spectrum displayed a carbonyl band at 1645 cm^{-1} as well as O-H bands at 3100—2400 cm^{-1}, indicating that XXI could partly enolize but did not exist as a chelated form. The NMR spectrum showed the presence of two α-protons of pyridine ring (Table II). These observations indicated that XXI was 1-methyl-3-(4-pyridyl)oxindole. This was confirmed by conversion of XXI with phosphoryl chloride to XXIV which was dechlorinated to XXV, and by the IR, NMR and UV7) spectral examinations of XXIV and XXV in the same manner as the case of the structural elucidation of XX.

Consequently XVIII was determined as 1-methyl-2-acetoxy-3-(4-pyridyl)indole.

Finally, the reaction of oxindole itself (XXVI) was examined. The reaction of XXVI with I in the presence of benzoyl chloride proceeded smoothly under refluxing condition in chloroform, and 3-(2-quinolyl)oxindole (XXVII)5) was obtained as red neenles of mp 275—280° in 60% yield. The IR spectrum exhibited a chelated carbonyl band at 1630 cm^{-1} and broad bands at 3150—2500 cm^{-1} ($\nu_{N-H,O-H}$). Attempted reduction of XXVII to 3-(2-quinolyl)-indole (XXIX)1) with lithium aluminium hydride failed, XXVII being recovered; however, refluxing with phosphoryl chloride gave the corresponding chloro-compound (XXVIII) (colorless sands, mp 196—200°), which was successfully transformed by catalytic reduction to XXIX1) (Chart 4).

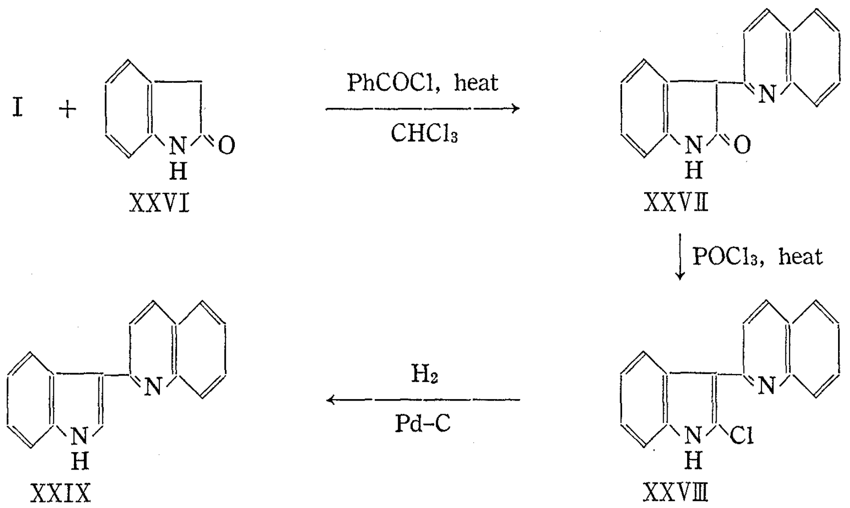

Chart 4

Since this result apparently shows that there is no essential difference between the reactivity of 1-methyloxindole (II) and that of oxindole (XXVI), we did not further study the reaction of XXVI.

From the results described above it is now shown that both 1-methyloxindole and oxindole are capable of reacting as active methylene compounds with aromatic N-oxides in the presence of an acylating agent. The order of effectiveness of acylating agents is the same as that observed in the previously reported reactions of the usual active methylene compounds,3) and contrary to those in the reactions of indoles1) and cyclohexanone enamines;8)

---

7) J.C. Powers, *J. Org. Chem.*, **30**, 2534 (1965).
8) M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), **13**, 912 (1965).

that is, acetic anhydride>benzoyl chloride>tosyl chloride. Moreover, the reactivities of oxindoles are apparently higher than those of the usual active methylene compounds, and it is particularly interesting that the bis-quinolyl- and bis-pyridyl-oxindoles are formed in the presence of acetic anhydride.

Bruni and Guerra[5] have described that there are some correlation between the reactivities of oxindoles and their abilities of enolization. In any event, further work should be done in order to elucidate the essential feature of these reactions.[9]

Experimental[10]

Reaction of Quinoline 1-Oxide (I) with 1-Methyloxindol (II)——1) A solution of quinoline 1-oxide (I) (0.8 g) and 1-methyloxindole (II) (0.85 g) in Ac_2O (4 ml) was heated around 75° for 8 hr to give a dark red solution. After evaporating Ac_2O *in vacuo*, the residue was made alkaline with 10% Na_2CO_3 and extracted with $CHCl_3$. The extracted substances were chromatographed on alumina in $CHCl_3$–CCl_4 (1:1). The first effluent was recrystallized from EtOH to give 0.2 g of 1-methyl-3,3-bis(2-quinolyl)oxindole (IV), colorless sands, mp 225—227°. IR cm^{-1}: $\nu_{C=O}$ 1715 (Nujol). *Anal.* Calcd. for $C_{27}H_{19}ON_3$: C, 80.77; H, 4.77; N, 10.47. Found: C, 80.56; H, 4.98; N, 10.07.

The second fraction afforded 0.55 g of 1-methyl-3-(2-quinolyl)oxindole (III), vermilion red needles, mp 214—215°, on recrystallization from EtOH. IR cm^{-1}: $\nu_{C=O}$ 1630 (Nujol). *Anal.* Calcd. for $C_{18}H_{14}ON_2$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.56; H, 4.87; N, 10.43.

This procedure is not suitable for the complete separation of III and IV, because of the strong adsorbing power of III on alumina. To obtain the correct yield of each compound, two separate experiments were carried out as described below.

2) A solution of I (4 g) and II (4 g) in Ac_2O (12 ml) was heated at 75—80° for 10 hr, and the products were extracted with $CHCl_3$ as mentioned above.

The $CHCl_3$ extract was concentrated to 10 ml and MeOH (20 ml) was added to precipitate III. The yield of III was 60% (5.1 g).

The $CHCl_3$ extract from another run was chromatographed on alumina in $CHCl_3$–CCl_4 (1:2), and the effluent was recrystallized from MeOH to give 1.42 g of IV (28%). Successive elution with $CHCl_3$ gave 2.5 g of III, but the column was strongly colored and the complete elution of III was not effected.

3) To an ice-cooled solution of I (0.8 g) in $CHCl_3$ (10 ml), PhCOCl (0.8 g)–$CHCl_3$ (10 ml) and II (0.83 g)–$CHCl_3$ (10 ml) were successively added with stirring, and stirring was continued for 20 min, no coloration being observed. After refluxing for 5 hr, the resulted dark red solution was shaked with 10% Na_2CO_3 (10 ml) for 30 min and extracted with $CHCl_3$. The extract was evaporated and the residue was recrystallized from EtOH to yield 0.81 g of III. The mother liquor was evaporated and the residue was chromatographed on alumina in $CHCl_3$–CCl_4 (1:2) to give two fractions. Upon recrystallization from EtOH, the first fraction gave 0.04 g of IV and the second yielded an additional 0.9 g of III.

4) To an ice-cooled solution of I (0.8 g) in $CHCl_3$ (10 ml), TsCl (1.2 g)–$CHCl_3$ (8 ml) and II (0.83 g)–$CHCl_3$ (10 ml) were successively added with stirring, and the whole was refluxed for 5 hr. The reaction mixture was shaken with 10% Na_2CO_3 (12 ml) for 30 min and extracted with $CHCl_3$. The extracted substances were chromatographed on alumina with CCl_4, $CHCl_3$ and EtOH. The first fraction eluted with CCl_4–$CHCl_3$ (2:1) was recrystallized from MeOH to give 0.03 g of IV, mp 223—225°. From the second fraction, 0.44 g of II was recovered after recrystallization from MeOH–H_2O. The third fraction eluted with $CHCl_3$–EtOH (100:1) afforded 0.5 g of carbostyril (V), mp 195—198° (MeOH–H_2O).

5) To a solution of I, II and TsCl in $CHCl_3$ prepared in the same way as in 4) was added AcONa (0.5 g), and the whole was refluxed for 9 hr. Similar processing as above gave 0.05 g of III, 0.03 g of IV and 0.2 g of V. A considerable amount of I (*ca.* 20%) was recovered as its picrate, mp 143—144°, from the mother liquor from recrystallization of III and IV.

6) A similar reaction using PhCOOLi (0.7 g) in place of AcONa afforded a trace of IV, 0.12 g of III and 0.22 g of V; a considerable amount of I was recovered as its picrate.

1-Methyl-2-chloro-3-(2-quinolyl)indole (VI)——1) A mixture of 1-methyl-3-(2-quinolyl)oxindole (III) (0.64 g) and $POCl_3$ (10 ml) was refluxed for 1 hr. The reaction mixture was concentrated *in vacuo*, treated with ice-water, made alkaline with 10% Na_2CO_3 and extracted with $CHCl_3$. The extract was evaporated and the residue was recrystallized from $CHCl_3$–MeOH to give 0.65 g of VI, faintly pink crystals, mp 137°. IR cm^{-1}: $\nu_{C=C(\text{indole})}$ 1600 (Nujol). *Anal.* Calcd. for $C_{18}H_{13}N_2Cl$: C, 73.78; H, 4.47; N, 9.56. Found: C, 73.11; H, 4.37; N, 8.86.[11]

---

9) The tautomerism of products obtained in this work, especially that of 3-(2-pyridyl or 2-quinolyl)-oxindoles, is an interesting subject, but remains to be elucidated.

10) All melting points are uncorrected.

11) Since VI was markedly unstable, the correct analytical data were obtained with difficulty.

2) A mixture of 1-methyl-3,3-bis(2-quinolyl)oxindole (IV) (0.3 g) and $POCl_3$ (10 ml) was heated in a sealed tube at 130—150° for 6 hr. The reaction mixture was concentrated *in vacuo*, treated with ice–water, made alkaline with 10% Na_2CO_3 and extracted with $CHCl_3$. The extract was passed through an alumina column and the effluent was recrystallized from MeOH to give 0.14 g of colorless needles, mp 129—130°, which was proved identical with VI obtained from III.

1-Methyl-3-(2-quinolyl)indole (VII)——A solution of VI (0.13 g) in EtOH (50 ml) was hydrogenated over 20% Pd–C (0.25 g) for 3 hr. The catalyst was filtered and washed with 50% EtOH containing AcONa (0.1 g). The combined filtrate and washings were evaporated *in vacuo*, and the residue was recrystallized from EtOH to give 0.09 g of 1-methyl-3-(2-quinolyl)indole (VII),[1] pale yellow needles, mp 181—183°.

Reaction of 2-Chloroquinoline 1-Oxide (VIII) with II——A solution of VIII (0.8 g) and II (0.7 g) in Ac_2O (4 ml) was warmed at 50—55° for 48 hr. The reaction mixture was concentrated *in vacuo*, treated with conc. $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was evaporated and the residue was recrystallized from EtOH to give 0.08 g of carbostyril N-oxide (X), colorless needles, mp 182—185°.

The residue from the mother liquor was dissolved in $CHCl_3$, passed through an alumina column and recrystallized from acetone–EtOH to yield 0.21 g of 1-methyl-3-(2-chloro-4-quinolyl)oxindole (XI), colorless needles, mp 222—223°. IR cm^{-1}: $\nu_{C=O}$ 1703 (Nujol). *Anal.* Calcd. for $C_{18}H_{13}ON_2Cl$: C, 69.68; H, 4.24; N, 9.07. Found: C, 69.83; H, 4.25; N, 8.83.

Conversion of 1-Methyl-3-(2-chloro-4-quinolyl)oxindole (XI) to 1-Methyl-3-(4-quinolyl)indole (XIV)—— A solution of XI (0.37 g) in MeOH (40 ml) was hydrogenated over 20% Pd–C (0.25 g) at *ca.* 50°. After 2 hr, the catalyst was filtered and washed with Na_2CO_3 (1 ml) and then with acetone. The combined filtrate and washings were concentrated *in vacuo* and extracted with $CHCl_3$. The extract was passed through an alumina column. From the first eluate was recovered 0.1 g of XI. The second effluent was recrystallized from EtOH to give 0.16 g of 1-methyl-3-(4-quinolyl)oxindole (XII), colorless needles, mp 136—137° (turned to red at 100°). IR cm^{-1}: $\nu_{O-H(H_2O)}$ 3400—3200; $\nu_{C=O}$ 1700 (Nujol). *Anal.* Calcd. for $C_{18}H_{14}ON_2 \cdot 2H_2O$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.45; H, 5.91; N, 8.83.

A mixture of XII (0.12 g) and $POCl_3$ (5 ml) was heated in a sealed tube at 120—130° for 3 hr. The product was purified by chromatography on alumina in $CHCl_3$ and recrystallized from petr. ether to give 0.06 g of 1-methyl-2-chloro-3-(4-quinolyl)indole (XIII), colorless needles, mp 134—136°. IR cm^{-1}: $\nu_{C=C(indole)}$ 1590 (Nujol).

A solution of XIII (0.05 g) in MeOH (30 ml) was hydrogenated over 15% Pd–C (0.1 g) at 50°. The catalyst was filtered and washed with $NaHCO_3$ solution. The combined filtrate and washings were concentrated *in vacuo* and extracted with $CHCl_3$. The extract was passed through an alumina column to give 0.02 g of 1-methyl-3-(4-quinolyl)indole[1] (XIV), faint yellow needles, mp 140—144°.

Reaction of 4-Chloroquinoline 1-Oxide (IX) with II——To an ice-cooled solution of IX (1 g) in $CHCl_3$ (10 ml), PhCOCl (0.8 g) –$CHCl_3$ (8 ml) and II (0.85 g)–$CHCl_3$ (10 ml) were added with stirring, and the whole was refluxed for 10 hr. After cooling, the reaction mixture was shaken with 10% Na_2CO_3 (10 ml) and extracted with $CHCl_3$. The extracted substance was recrystallized from $CHCl_3$–EtOH to give 1.12 g of 1-methyl-3-(4-chloro-2-quinolyl)oxindole (XV), red needles, mp 245—248°. IR cm^{-1}: $\nu_{C=O}$ 1625 (Nujol). *Anal.* Calcd. for $C_{18}H_{13}ON_2Cl$: C, 69.62; H, 4.24; N, 9.08. Found: C, 69.62; H, 4.23; N, 9.16.

Reaction of 1-Methyl-3-(4-chloro-2-quinolyl)oxindole (XV)——1) Conversion to III: A solution of XV (0.2 g) in EtOH (80 ml) was hydrogenated over 20% Pd–C at 30—40°, and usual processing furnished 0.09 g of III, red needles, mp 209—215° (EtOH).

2) Conversion to VII: A mixture of XV (0.2 g) and $POCl_3$ (5 ml) was refluxed for 1 hr, concentrated *in vacuo*, treated with ice–water, made alkaline with 10% Na_2CO_3 and extracted with $CHCl_3$. Recrystallization of the extracted substances from $CHCl_3$–EtOH gave 0.2 g of 1-methyl-2-chloro-3-(4-chloro-2-quinolyl)-indole (XVI), pink prism, mp 154—155°. *Anal.* Calcd. for $C_{18}H_{12}N_2Cl$: C, 66.09; H, 3.70; N, 8.57. Found: C, 66.01; H, 3.61; N, 8.67.

A solution of XVI (0.1 g) in MeOH was hydrogenated over 20% Pd–C (0.12 g). After addition of NaOAc (0.1 g)–H_2O (5 ml), the catalyst was filtered and washed with acetone. The combined filtrate and washings were evaporated *in vacuo* and extracted with $CHCl_3$. Recrystallization of the extracted substance from EtOH yielded 0.07 g of VII, colorless sands, mp 182—183°.

Reaction of Pyridine 1-Oxide (XVII) with II——Pyridine 1-oxide (XVII) (0.15 g) was azeotropically dehydrated with $CHCl_3$, and dissolved in Ac_2O (10 ml). To this solution was added II (2.3 g), and the whole was heated at 120—130° for 7 hr. The reaction mixture was concentrated *in vacuo*, neutralized with 10% Na_2CO_3 and extracted with a large amount of $CHCl_3$. The extract was concentrated to 30 ml to deposite precipitates, which were filtered and recrystallized from $CHCl_3$ to give 0.67 g of 1-methyl-2-acetoxy-3-(4-pyridyl)indole (XVIII), orange yelolw prisms, mp 233—235°. IR cm^{-1}: $\nu_{C=O}$ 1730 (Nujol). *Anal.* Calcd. for $C_{16}H_{14}O_2N_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.10; H, 5.48; N, 10.39.

The $CHCl_3$ filtrate and the mother liquor from recrystallization of XVIII were combined, passed through an alumina column and eluted with $CHCl_3$ to separate three fractions.

The first fraction was recrystallized from MeOH to give 0.35 g of 1-methyl-3,3-bis (2-pyridyl)oxindole (XIX), colorless cubes, mp 184—185°. IR cm^{-1}: $\nu_{C=O}$ 1713 (Nujol). *Anal.* Calcd. for $C_{19}H_{15}ON_3$: C, 75.73; H, 5.02; N, 13.95. Found: C, 75.67; H, 5.16; N, 13.67.

The second was recrystallized from benzene to yield 0.25 g of 1-methyl-3-(2-pyridyl)oxindole (XX), orange yellow needles, mp 174—174.5°. IR cm^{-1}: $\nu_{C=O}$ 1650 (Nujol). *Anal.* Calcd. for $C_{14}H_{12}ON_2$: C, 74.99; H, 5.38; N, 12.49. Found: C, 74.90; H, 5.62; N, 12.55.

The third fraction was recrystallized from benzene to give 0.2 g of 1-methyl-3-(4-pyridyl)oxindole (XXI), yellow sands, mp 182—183°. IR cm^{-1}: ν_{O-H} 3100—2400 (weak and broad); $\nu_{C=O}$ 1645 (Nujol). *Anal.* Calcd. for $C_{14}H_{12}ON_2$: C, 74.99; H, 5.38; N, 12.49. Found: C, 74.65; H, 5.68; N, 12.16.

Hydrolysis of 1-Methyl-2-acetoxy-3-(4-pyridyl)indole (XVIII)——A suspension of XVIII (0.6 g) in 10% NaOH (30 ml) was heated on a water-bath for 1.5 hr. The cooled solution was bubbled with CO_2 gas to separate out precipitates, which were taken up in $CHCl_3$ followed by recrystallization from EtOH–benzene to give XXI, yellow sands, mp 182—185°.

Conversion of 1-Methyl-3-(2-pyridyl)oxindole (XX) to 1-Methyl-3-(2-pyridyl)indole (XXIII)——A mixture of XX (0.42 g) and $POCl_3$ (20 ml) was heated in a sealed tube at 150° for 5 hr. The reaction mixture was concentrated *in vacuo*, poured on ice–water, neutralized with Na_2CO_3 and extracted with $CHCl_3$. The extract was passed through an alumina column and eluted with $CHCl_3$–CCl_4 (1:1). Recrystallization of the effluent from benzene–petr. ether gave 0.3 g of 1-methyl-2-chloro-3-(2-pyridyl)indole (XXII), unstable colorless needles, mp 89—91°. IR cm^{-1}: $\nu_{C=C(indole)}$ 1589 (Nujol). *Anal.* Calcd. for $C_{14}H_{11}N_2Cl$: C, 69.28; H, 4.57; N, 11.54. Found: C, 69.50; H, 5.29; N, 11.07.

A solution of XXII (0.13 g) in MeOH (20 ml) was hydrogenated over 20% Pd–C (0.25 g). The reaction mixture was processed in usual way and the product was recrystallized from benzene–petr. benzine to give 0.05 g of 1-methyl-3-(2-pyridyl)indole (XXIII), colorless sands, mp 83—84°. IR cm^{-1}: $\nu_{C=C(indole)}$ 1590 (Nujol). UV, λ_{max}^{EtOH} (log ε): 224 (4.45), 268 (4.10), 316 (4.18).[12] *Anal.* Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.28; H, 5.78; N, 13.07.

Conversion of 1-Methyl-3-(4-pyridyl)oxindole (XXI) to 1-Methyl-3-(4-pyridyl)indole (XXV)——A mixture of XXI (0.3 g) and $POCl_3$ (20 ml) was refluxed for 1.5 hr. The reaction mixture was processed in usual way and the product was recrystallized from benzene–MeOH to give 0.25 g of 1-methyl-2-chloro-3-(4-pyridyl)-indole (XXIV), colorless sands, mp 157—159°. *Anal.* Calcd. for $C_{14}H_{11}N_2Cl$: C, 69.28; H, 4.57; N, 11.54. Found: C, 69.49; H, 4.81; N, 11.53.

A solution of XXIV (0.19 g) in MeOH (20 ml) was hydrogenated over 20% Pd–C (0.25 g). Usual processing afforded 0.08 g of 1-methyl-3-(4-pyridyl)indole (XXV), colorless sands, mp 82—83°. IR cm^{-1}: $\nu_{C=C(indole)}$ 1593 (Nujol). UV λ_{max}^{EtOH} mμ (log ε): 223 (4.49), 275 (3.98), 320 (4.18).[13] *Anal.* Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.65; H, 5.90; N, 13.16.

Reaction of Quinoline 1-Oxide (I) with Oxindole (XXVI)——To an ice-cooled solution of I (1.76 g) in $CHCl_3$ (15 ml), PhCOCl (2.2 g)–$CHCl_3$ (10 ml) and then XXVI (2 g)–$CHCl_3$ (10 ml) were added dropewise under stirring to give a faintly colorlerd solution. This solution was refluxed for 5 hr, shaken with 10% Na_2CO_3 (20 ml) for 30 min and extracted with $CHCl_3$ (*ca.* 1 liter). The extract was dried over Na_2SO_4 and concentrated to *ca.* 50 ml and cooled to give 2.3 g of 3-(2-quinolyl)oxindole (XXVII), red needles, mp 275—280°. IR cm^{-1}: ν_{N-H} 3150—2500; $\nu_{C=O}$ 1630 (Nujol). *Anal.* Calcd. for $C_{17}H_{12}ON_2$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.13; H, 4.61; N, 11.05.

Conversion of 3-(2-Quinolyl)oxindole (XXVII) to 3-(2-Quinolyl)indole (XXIX)——A mixture of XXVII (0.4 g) and $POCl_3$ (12 ml) was refluxed for 3.5 hr, concentrated *in vacuo*, poured on ice–water, neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated to *ca.* 10 ml to precipitate a small amount of resinous substance, from which the supernatant was separated and evaporated. The residue was recrystallized from MeOH to give 0.07 g of 2-chloro-3-(2-quinolyl)indole (XXVIII), colorless sands, mp 196—200°. IR cm^{-1}: ν_{N-H} 3150; $\nu_{C=C}$ 1600 (Nujol). *Anal.* Calcd. for $C_{17}H_{11}N_2Cl$: C, 73.36; H, 3.97; N, 10.05. Found: C, 73.19; H, 3.97; N, 10.39.

A solution of XXVIII (0.05 g) in MeOH (20 ml) was hydrogenated over 20% Pd–C (0.25 g). The catalyst was filtered and NaOAc (0.1 g) was added to the filtrate which was evaporated *in vacuo*. The residue was extracted with $CHCl_3$, and the extracted product was recrystallized from benzene–petr. ether to give 0.02 g of 3-(2-quinolyl)indole (XXIX),[1] yellow leaflets, mp 190—191°.

Acknowledgement A part of expenses for this work was defrayed by the Grant-in-Aid for Scientific Research from the Ministry of Education, which is gratefully acknowledged. Thanks are also due to Messrs. K. Ishimura and Y. Inoue for elemental analysis, to Mr. H. Matsui and Miss K. Soeda for the measurement of IR and UV spectra and to Mr. S. Takeo for the measurement of NMR spectra.

---

[12] UV of 3-(2-pyridyl)indole, λ_{max}^{EtOH} mμ (log ε): 223 (4.44), 267 (4.06), 311 (4.09) (Lit. 8).

[13] UV of 3-(4-pyridyl)indole, λ_{max}^{EtOH} mμ (log ε): 220 (4.40), 275 (3.89), 312 (4.02) (Lit. 8).