[Chem. Pharm. Bull. 18(9)1742—1750(1970)]

UDC 547.751.04 : 547.831.1.04 : 547.826.1.04

Studies on Tertiary Amine Oxides. XXXIX.[1] Reactions of Aromatic N-Oxides with Indoles in the Presence of Acylating Agents[2]

MASATOMO HAMANA[3] and ITSUMARO KUMADAKI[3a]

Faculty of Pharmaceutical Sciences, Kyushu University[3]

(Received January 21, 1970)

Indole (II) was found to react as an aromatic analog of enamine with acyl–adducts of quinoline 1-oxide (I) and ethyl nicotinate 1-oxide (VI) under refluxing condition in chloroform, and 3-(2-quinolyl)indole (III) and ethyl 6-(3-indolyl)nicotinate (VII) were obtained, respectively, but no reaction occured with pyridine 1-oxide. Benzoyl chloride was most effective as an acylating agent.

1-Methylindole (VIII) underwent similar reactions. The reaction with I gave 1-methyl derivative of III (IX) as well as 4-quinolyl compound (X). From the reaction with 2-chloroquinoline 1-oxide (XI), 1-methyl-3-(2-chloro-4-quinolyl)indole (XIII) and 1-benzoyloxy-2-hydroxy-4-(1-methyl-3-indolyl)-1,4-dihydroquinoline (XIV) were produced, the isolation of XIV being significant from the mechanistic view point. 4-Chloroquinoline 1-oxide and VIII afforded 2-quinolyl compound (XVI).

Further 2-phenylindole was shown to react with I under similar conditions, but skatole resisted the reaction.

Previous papers of this series have shown that treatment of acyl–adducts of pyridine or benzopyridine N-oxides with enamnies of cyclohexanone leads to introduction of α-cyclohexanonyl group into the pyridine ring in good yields.[4] Further, quinoline 1-oxide (I) was found to react with antipyrine, which can be regarded as an aromatic analog of enamine, in the presence of benzoyl chloride to afford 4-(2-quinolyl)antipyrine as a major product.[5]

In an attempt to widen the scope of this type of reaction and also to introduce pyridyl or quinolyl group into indole nucleus, we carried out the reaction of aromatic N-oxides with

TABLE I. Reaction of Indoles with Aromatic N-Oxides in the Presence of an Acylating Agent

Indole	Aromatic N-oxide	Acylating agent	Solvent	Reflux period (hr)	Product yield (%)
Indole	quinoline	PhCOCl	$CHCl_3$	2	III (67)
		TsCl	$CHCl_3$	0.66	III (57), IV (a little)
		Ac_2O	——	10	V (10)
	ethyl nicotinate	PhCOCl	$CHCl_3$	2.5	VII (30)
		TsCl	$CHCl_3$	5	VII (5), IV (17)
1-Methylindole	quinoline	PhCOCl	$CHCl_3$	7	IX (56), X (10)
		TsCl	$CHCl_3$	7	IX (12), carbostyril (54)
	2-chloroquinoline	PhCOCl	$CHCl_3$	10	XIII (65), XIV (16)
	4-chloroquinoline	PhCOCl	$CHCl_3$	3	XVI (57)
2-Phenylindole	quinoline	PhCOCl	$CHCl_3$	5	XVII (40)

---

[1] Part XXXVIII: M. Yamazaki, K. Noda and M. Hamana, *Chem. Pharm. Bull.* (Tokyo), **18**, 901 (1970).

[2] A part of the work has been preliminarily reported in *Chem. Pharm. Bull.* (Tokyo), **15**, 363 (1967).

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

[4] *a*) M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), 13, 912 (1965); *b*) *Idem, ibid.*, **14**, 762 (1966); *c*) *Idem, ibid.*, **15**, 474 (1967).

[5] M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), **15**, 1380 (1967).

some indoles in the presence of an acylating agent. The results obtained are summarized in Table I.

A solution of quinoline 1-oxide (I), indole (II) (1 eq.) and benzoyl chloride in chloroform was refluxed for two hours on a water–bath. The dark brownish red solution was cooled and treated with potassium carbonate solution, and the basic portion was purified by chromatography on alumina in chloroform, followed by recrystallization from benzene to give pale yellow leaflets (III) of mp 190—191°. This compound (III) had an empirical formula, $C_{17}H_{12}N_2$, in agreement with that of a quinolylindole, and was proved not identical with 2-(2-quinolyl)indole⁶⁾ prepared from 2-acetylquinoline by the Fischer's method. Therefore, III was probably assumed to be 3-(2-quinolyl)indole; its yield was 67%.

In order to obtain III by another route, the Pfitzinger reaction⁷⁾ of 3-acetylindole and the preparation of 2-quinolylacetaldehyde requisite for the starting material in the Fischer's reaction were tried, but all attempts failed. Recently, Powers⁸⁾ has demonstrated that the reaction of indole magnesium bromide with 2-chloropyridine gives 3-(2-pyridyl)indole, which fact is in accordance with the generally accepted reactivity of indole Grignard reagent⁹⁾. Accordingly, the reaction of indole magnesium bromide with 2-chloroquinoline was carried out, and III was successfully isolated although in a very poor yield of below 1%. Thus, the structure of III was determined as 3-(2-quinolyl)indole.

Colonna and Bruni¹⁰⁾ have also shown that III is produced in 57% yield from I and II under essentially the same condition, and Dobeneck and Goltzsche¹¹⁾ obtained III by pyrolytic degradation of a product formed from 1-methylquinolinium iodide and II, but both groups did not determine its structure chemically.

A similar reaction proceeded in the presence of tosyl chloride as an acylating agent, and gave III in 57% yield accompanied with a small amount of 1-tosyl-2-(3-indolyl)indoline (IV), colorless needles, mp 188—190°. The structure of IV was confirmed by direct comparison with an authentic sample prepared by tosylating 2-(3-indolyl)indoline¹²⁾ obtained from II and hydrogen chroride in benzene. The formation of IV is apparently due to dimerization of indole by means of hydrogen chloride or/and *p*-toluenesulfonic acid produced in the course of reaction followed by tosylation of indoline N–H of the indole dimer.

When a solution of I and II in acetic anhydride was refluxed for ten hours, 1-acetyl-3-(2-quinolyl)indole (V) was isolated as colorless needles of mp 194—194.5° in a low yield of 10%. The structure of V was affirmed by elemental analysis and infrared (IR) spectrum examination.

Attempted reactions of II with pyridine 1-oxide under various conditions failed, no formation of pyridylindole being noticed. This result shows apparently that pyridine 1-oxide is not reactive enough to enter into reaction with indole, an aromatic analog of enamine, quite similarly to the reaction with antipyrine.⁵⁾ In enhancing the reactivity of α-position of pyridine nucleus towards nucleophilic attack, ethyl nicotinate 1-oxide (VI) was applied to indole in the presence of benzoyl chloride and pale yellow crystals (VII) of mp 169—170° were obtained in 43% yield. The empirical formula of VII, $C_{16}H_{14}O_2N_2$, agreeded with that of an expected ethyl indolynicotinate. Oxidation of VII with potassium permanganate followed by methylation with diazomethane afforded dimethyl pyridine–2,5-dicarboxylate,

---

6) H.F. Sasse, *J. Chem. Soc.*, **1960**, 530.

7) *a*) W. Pfitzinger, *J. Prakt. Chem.*, 33, 100 (1886); *b*) R.C. Elderfield, "Heterocyclic Compounds," Vol. 4, ed. by R.C. Elderfield, Wiley, New York, 1952.

8) J.C. Powers, *J. Org. Chem.*, **30**, 2534 (1965).

9) R.A. Heacock and S. Kasparek, "Advances in Heterocyclic Chemistry," Vol. 10, ed. by A.R. Katritzky and A.J. Boulton, Academic Press, New York and London, 1969.

10) M. Colonna and P. Bruni, *Boll. Sci. Fac. Chim. Ind. Bologna*, **23**, 401 (1965) [*C.A.*, **64**, 17536 (1966)].

11) H. von Dobeneck and W. Goltzsche, *Chem. Ber.*, **95**, 1848 (1962).

12) H.F. Hodson and F. Smith, *J. Chem. Soc.*, **1957**, 3544.

which was proved identical with an authentic sample similarly prepared from aldehyde collidine. Thus, VII was determined to be ethyl 6-(3-indolyl)nicotinate.

Tosyl chloride could be used as an acylating agent also in this case, but the yield of VII was much lower (5%) and IV was formed in 17% yield.

These results are shown in Chart 1.

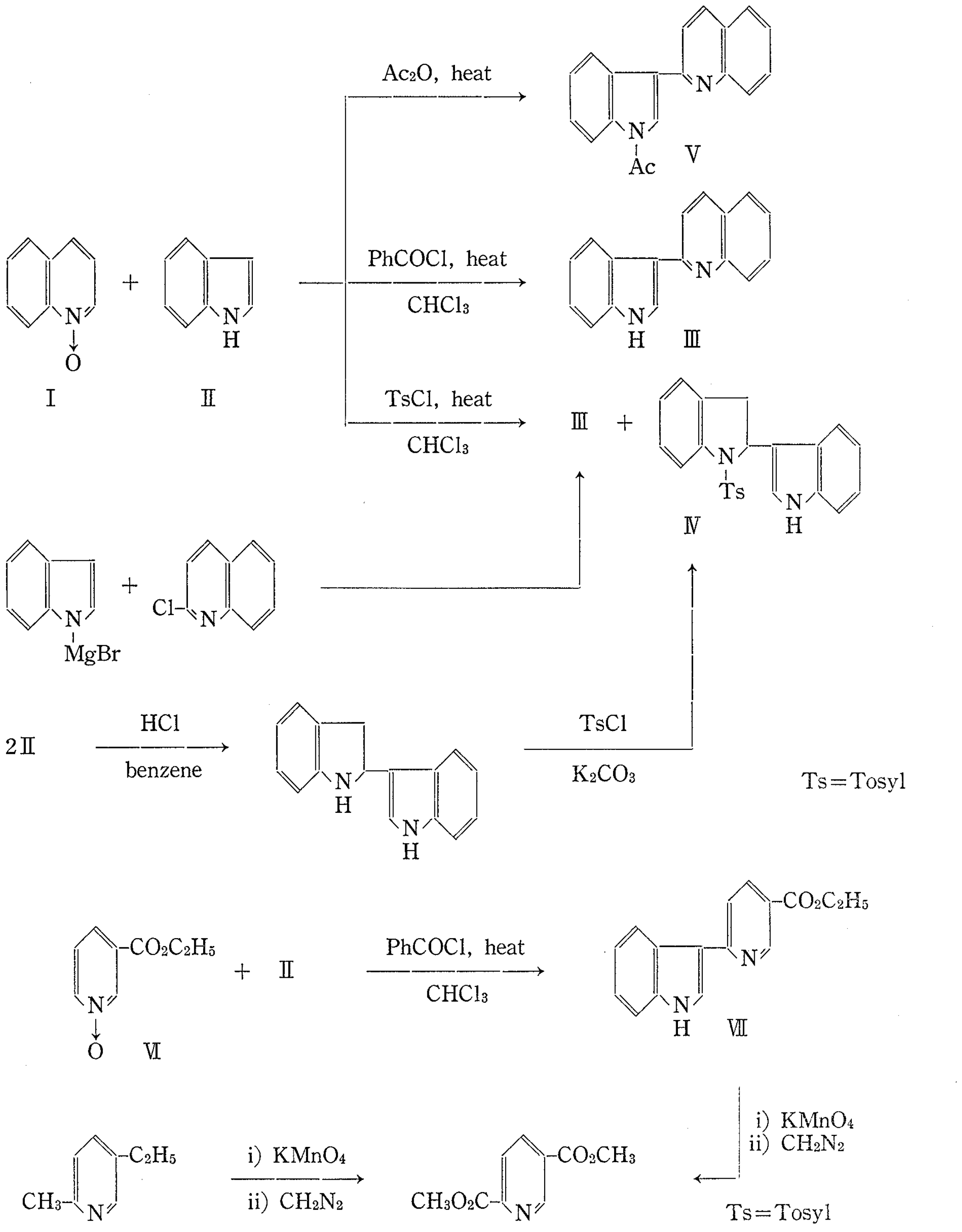


Chart 1

Subsequently, similar reactions of 1-methylindole (VIII) were examined in some detail. When a solution of I, VIII and benzoyl chroride in chloroform was refluxed for seven hours, 1-methyl-3-(2-quinolyl)indole (IX) (pale yellow needles, mp 182—183°) and 1-methyl-3-(4-quinolyl)indole (X) (pale yellow needles, mp 147—148°) were isolated in 56 and 10% yields, respectively. Both products had the same and correct composition, $C_{18}H_{14}N_2$, for quinolyl-1-methylindole. Confirmation of the structure of IX was obtained from elemental analysis, IR spectrum and especially from the close similarity of the ultraviolet (UV) spectra of IX and 3-(2-

quinolyl) indole (III) as shown in Fig. 1. Proof of the proposed structure for X was provided by the fact that X was formed by reductive dechlorination of the product obtained from a similar reaction of VIII with 2-chloroquinoline 1-oxide (XI) as mentioned below, and also by the analogy of the reaction mode between I and enamines of cyclohexanone[4]. For a further confirmation of the structure of X, synthesis of 1-methyl-2-(2-quinolyl) indole, an alternatively conceivable product, was effected by the Fischer's reaction of α-methylphenylhydrazone of 2-acetylquinoline, and it was made clear that both compounds were not identical.

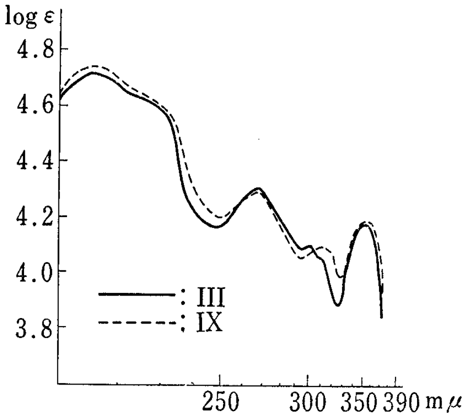


Fig. 1

The use of tosyl chloride in place of benzoyl chloride resulted in decrease of the yield of IX to 12% and gave a considerable amount of carbostyril (54%). Acetic anhydride was found to be ineffective as an acylating agent in this case, the starting materials being recovered.

Then we examined the reactions of VIII in the presence of benzoyl chloride with 2-chloroquinoline 1-oxide (XI) and 4-chloroquinoline 1-oxide (XII), which had been shown to be attacked by cyclohexanone enamines on the 4- and the 2-position, respectively.[4c)]

Upon refluxing a solution of VIII, XI and benzoyl chloride in chloroform for ten hours, pale yellow needles of 1-methyl-3-(2-chloro-4-quinolyl)indole (XIII), mp 140—140.5° was obtained in 65% yield accompanied with colorless powders (XIV) (16%). As described before, XIII was readily reduced to 1-methyl-3-(4-quinolyl)indole (X) with hydrogen over palladium–charcoal in ethanol at 50°. The latter product (XIV) was sparingly soluble in common organic solvents, but could be recrystallized from pyridine–water and melted at 293—293.5°. Although its empirical formula $C_{25}H_{20}O_3N_2$ was in agreement with the sum of those of benzoic acid ($C_7H_6O_2$) and 1-methyl-3-(2-hydroxy-4-quinolyl)indole (XV) ($C_{18}H_{14}ON_2$) which corresponded to the hydrolysis product of XIII, XIV was apparently not a simple salt of these two compounds because it did not change with sodium carbonate solution. Treatment of XIV with 10% ethanolic potassium hydroxide under reflux resulted in elimination of benzoic acid to give 1-methyl-3-(2-hydroxy-4-quinolyl)indole (XV) which was successively converted into XIII by refluxing with phosphoryl chloride; conversely, XIII could be transformed into XV on heating with concentrated hydrochloric acid at 150—160°. These results demonstrated that XIV was 1-benzoyloxy-2-hydroxy-4-(1-methyl-3-indolyl)-1,4-dihydroquinoline. Since its IR spectrum displays two strong carbonyl bands at 1723 and 1690 cm^{-1} as well as O–H bands at 3200 and 3100 cm^{-1}, it may be a tautomeric mixture of the hydroxy structure (XIV) and the oxo form (XIV').

The reaction of 4-chloroquinoline 1-oxide (XII) with VIII in the presence of benzoyl chloride progressed smoothly to give 1-methyl-3-(4-chloro-2-quinolyl)indole (XVI), yellow needles, mp 157.8—158°, as the sole product in 57% yield. Catalytic reduction of XVI yielded IX.

These reactions of 1-methylindole are shown in Chart 2.

In all the reactions mentioned above, quinolyl and pyridyl groups were introduced always into β-position of indole nucleus, no α-substituted indole being produced in spite of the fact that both α- and β-positions of indole were not substituted. In exploring the possibility of substitution on α-position of indole nucleus, skatole was chosen as a β-substituted indole and the similar reactions with I were examined under various conditions, but no reaction was observed in all cases as noticed by Colonna and Bruni.[10)]

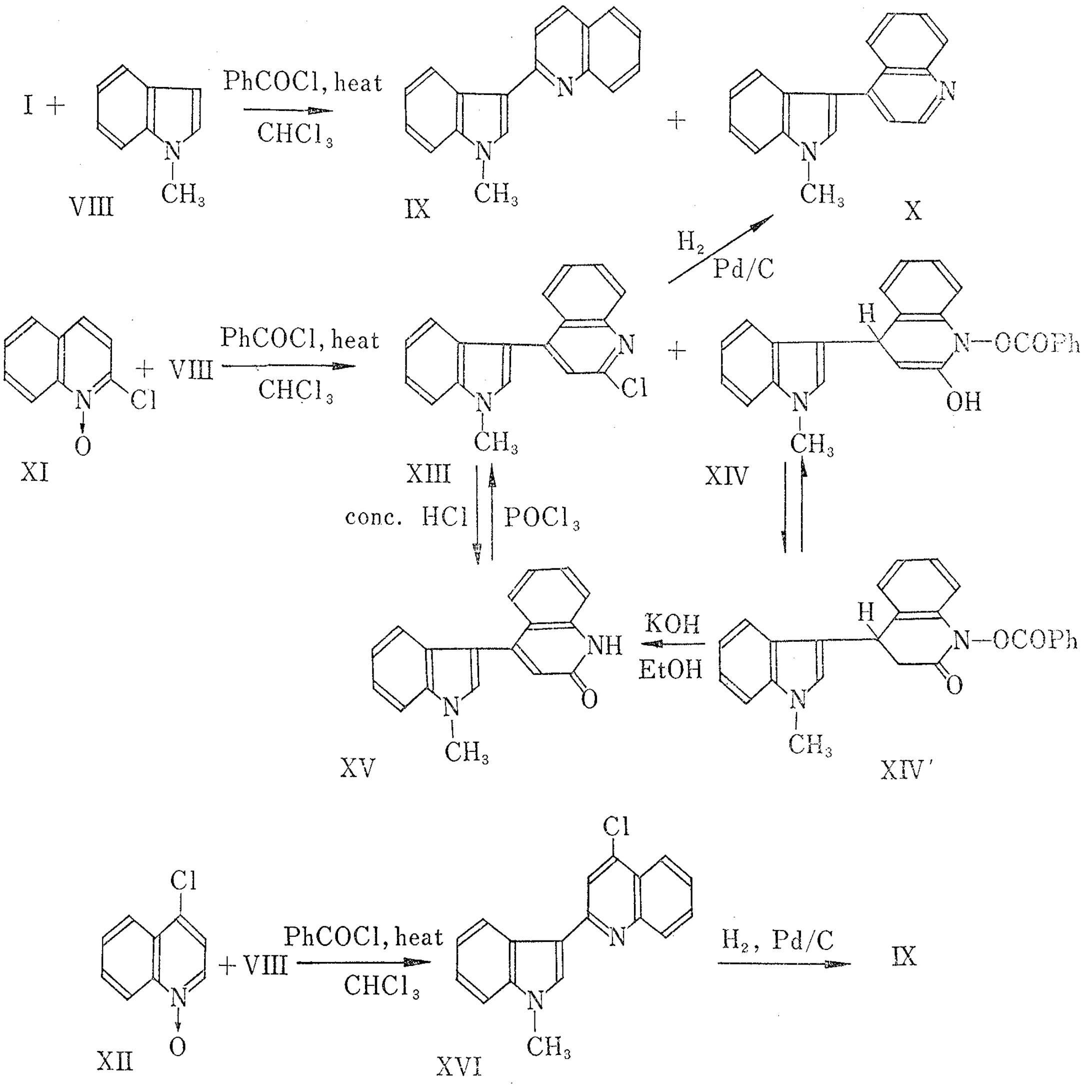


Chart 2

On the other hand, 2-phenylindole reacted in the presence of benzoyl chloride with quinoline 1-oxide (I) in chloroform under refluxing condition to give 2-phenyl-3-(2-quinolyl)indole (XVII) as pale yellow leaflets of mp 273—274° in 40% yield.[10] The structure of XVII was confirmed by direct comparison with an authentic sample obtained from ω-benzoylquinaldine α-methylphenylhydrazone (Chart 3).

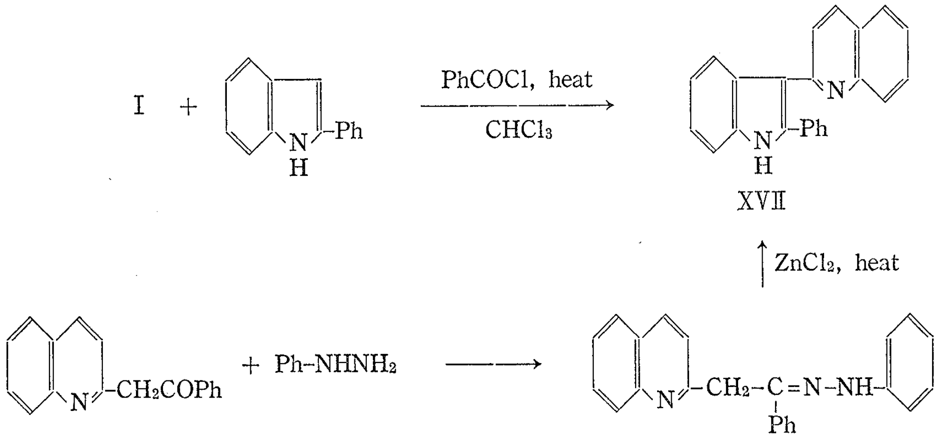
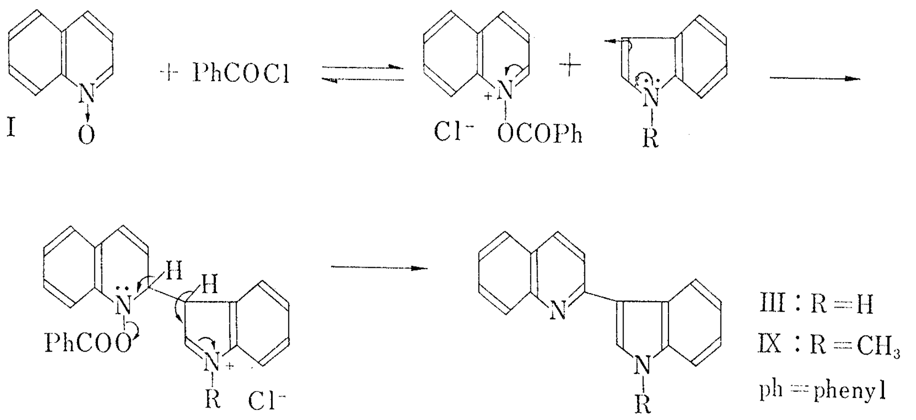


Chart 3

These results are in accord with the observations by Colonna and Bruni,[10] and apparently demonstrate that nucleophilic activity of α-position of indole ring does not appear in the reactions with acyl–adducts of aromatic N-oxides, and also that a considerably bulky group at α-position does not sterically hinder substitution on active β-position of indole nucleus.

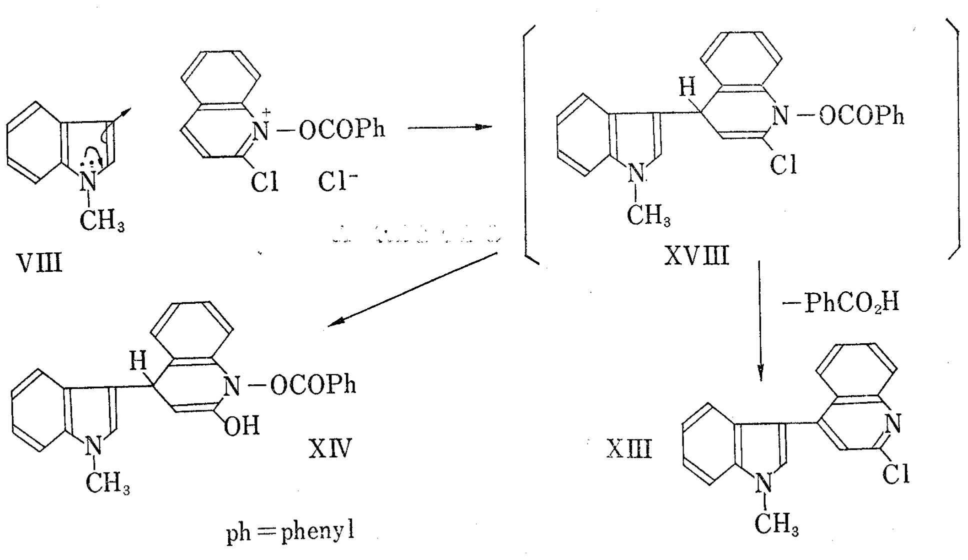
As a consequence of the experiments described above, the following conclusions may be drawn: (i) indoles having no substituent at β-position react as an aromatic analog of enamine with acyl–adducts of aromatic N-oxides under refluxing conditions in chloroform to give β-substituted indoles in generally good yields, no formation of α-substituted product being noticed; (ii) As for aromatic N-oxide, quinoline N-oxides are enough reactive and both the 2- and 4-positions undergo nucleophilic attack by indoles, the reactivity of the former being predominant, whereas pyridine N-oxides are much less reactive; (iii) the order of effectiveness of acylating agents is as follows: benzoyl chloride>tosyl chloride>acetic anhydride.

The essential course of the reaction may be well assumed to be quite similar to those of the reaction of enamines[4] and antipyrine[5] with acyl–adducts of aromatic N-oxides as exemplified below.



III : R=H
IX : R=CH3
ph=phenyl

In connection with the reaction mechanism, it is particularly significant that 1-benzoyloxy-2-hydroxy-4-(1-methyl-3-indolyl)-1,4-dihydroquinoline (XIV) was isolated from the reaction of VIII and XI. The formation of XIV might be rationalized by hydrolysis of the corresponding 2-chloroquinoline derivative (XVIII) which could be reasonably formed as a reaction intermediate leading to the main product XIII. There is no precedent for the isolation of such an 1,4-dihydroquinoline type intermediate in the reactions of aromatic N-oxides



VIII

XVIII

XIV

XIII

ph=phenyl

in the presence of an acylating agent, whereas 1,2-dihydroquinoline type adducts were previously obtained by Hamana and Funakoshi[13] and also by Yoshikawa.[14]

Experimental[15]

Reaction of Quinoline 1-Oxide (I) with Indole (II)——1) To an ice-cooled solution of quinoline 1-oxide (I) (0.8 g) and indole (II) (0.7 g) in $CHCl_3$ (10 ml), PhCOCl (0.8 g) was added dropwise with stirring. The whole was stirred at room temperature further 1 hr and then refluxed for 2 hr. The cooled reaction mixture was shaken with 10% K_2CO_3 for 3 hr and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and passed through an alumina column, and the effluent was recrystallized from benzene to give 0.9 g of 3-(2-quinolyl)indole (III), pale yellow leaflets, mp 190—191°. IR cm^{-1}: $\nu^{\text{Nujol}}_{\text{N-H}}$ 3300; $\nu^{\text{Nujol}}_{\text{C=C(indole)}}$ 1603. *Anal.* Calcd. for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.84; H, 4.81; N, 11.51.

2) The similar reaction using TsCl (1.2 g) in place of PhCOCl was carried out under reflux for 40 min, and the reaction mixture was treated in the same manner. Chromatography of the products in $CHCl_3$ on alumina afforded two fractions. The first was recrystallized from benzene–ether to give 0.02 g of 1-tosyl-2-(3-indolyl)-indoline (IV), colorless prisms, mp 188—190°, which was proved to be identical with an authentic sample prepared as described below by admixture and IR spectrum examination. *Anal.* Calcd. for $C_{23}H_{20}O_2N_2S$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.10; H, 5.36; N, 7.27. Recrystallization of the second fraction from benzene yielded 0.77 g of III.

3) A mixture of I (0.8 g) and II (0.7 g) in Ac_2O (2.2 ml) was refluxed for 10 hr, poured into water, basified with Na_2CO_3 and extracted with $CHCl_3$. The extract was passed through an alumina column, and the effluent was recrystallized from $CHCl_3$–EtOH to give 0.15 g of 1-acetyl-3-(2-quinolyl)indole (V), colorless prisms, mp 194—194.5°. IR cm^{-1}: $\nu^{\text{Nujol}}_{\text{C=O}}$ 1705. *Anal.* Calcd. for $C_{19}H_{14}ON_2$: C, 79.70; H, 4.93; N, 9.78. Found: C, 79.92; H, 4.91; N, 9.97. From the mother liquor 0.43 g of II was recovered.

3-(2-Quinolyl)indole (III)——To a solution of EtMgBr in ether prepared from 1.5 g of Mg, 5 g of EtBr and 50 ml of ether, II (5 g) in ether (20 ml) was added and refluxed for 40 min. To this solution, 2-chloroquinoline (6.7 g) in ether (10 ml) was added with ice-cooling and stirring. After stirring for 15 min, the solution was refluxed for 3 hr. The cooled reaction mixture was treated with conc. NH_4Cl solution and extracted with ether. The extracted substances were submitted to steam distillation to remove unchanged II and 2-chloroquinoline and the residue was extracted with $CHCl_3$, purified three times by chromatography on alumina and once by thin-layer chromatography (TLC) [silica gel: benzene–ether (3:1)]. The fluorescent zone corresponding to III under UV lamp was collected and extracted with $CHCl_3$. Evaporation of $CHCl_3$ gave 0.015 g of yellow crystals, mp 176—180°. This was shown to be identical with III by admixture and comparison of IR spectra.

1-Tosyl-2-(3-indolyl)indoline (IV)——An ice-cooled solution of II (3 g) in dry benzene (70 ml) was saturated with anhydrous HCl to deposite white precipitates, which were filtered and treated successively with conc. NH_4OH and $CHCl_3$. The $CHCl_3$ layer was separated and shaked with 10% K_2CO_3 (30 ml) and TsCl (2.5 g). The $CHCl_3$ layer was separated, dried over Na_2SO_4 and evaporated. Recrystallization of the residue from benzene gave 2 g of colorless prisms, mp 188—190°, which was identical with IV.

Reaction of Ethyl Nicotinate 1-Oxide (VI) with II——1) To an ice-cooled solution of VI (1.1 g) and II (0.8 g) in $CHCl_3$, PhCOCl (1.1 g) in $CHCl_3$ (10 ml) was added dropwise with stirring and the whole was refluxed for 2.5 hr. The cooled reaction mixture was shaken with 10% K_2CO_3 (10 ml) and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and passed through an alumina column. The effluent was recrystallized from MeOH to give 0.7 g of ethyl 6-(3-indolyl)nicotinate (VIII), pale yellow sands, mp 169—170°. IR cm^{-1}: $\nu^{\text{Nujol}}_{\text{C=O}}$ 1690; $\nu^{\text{Nujol}}_{\text{N-H}}$ 3250. *Anal.* Calcd. for $C_{16}H_{14}O_2N_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72. 28; H, 5.73; N, 10.30.

2) To an ice-cooled solution of VI (1 g) and TsCl (1.2 g) in $CHCl_3$ (10 ml) was added II (0.7 g) in $CHCl_3$ (7 ml), and the solution was refluxed for 5 hr. On working up in the same manner, 0.09 g of VII and 0.19 g of IV were obtained.

Dimethyl Pyridine-2,5-dicarboxylate from Ethyl 6-(3-Indolyl)nicotinate (VII)——A mixture of VII (0.5 g) and $KMnO_4$ (5 g) in H_2O (100 ml) was refluxed for 2 hr. After decomposition of excess of $KMnO_4$ with EtOH, deposited MnO_2 was filtered and washed with water. The filtrate and washings were combined, acidified with 10% HCl and evaporated to dryness *in vacuo*. The residue was suspended in dioxane (20 ml) and treated with a solution of CH_2N_2 in ether for 30 min at room temperature. Acetic acid was added dropwise until evolution of N_2 had ceased, and the organic layer was shaken with 10% Na_2CO_3 and evaporated. The residue was recrystallized from MeOH to afford 0.1 g of dimethyl pyridine-2,5-dicarboxylate, colorless needles, mp 163—164°. IR cm^{-1}: $\nu^{\text{Nujol}}_{\text{C=O}}$ 1715. *Anal.* Calcd. for $C_9H_9O_4N_2$: C, 55.38; H, 4.65;

---

[13] M. Hamana and K. Funakoshi, *Yakugaku Zasshi*, **80**, 1031 (1960).

[14] T. Yoshikawa, *Yakugaku Zasshi*, **81**, 1061 (1961).

[15] All melting and boiling points are uncorrected.

N, 7.18. Found: C, 55.17; H, 4.42; N, 7.07. This was proved identical with an authentic sample prepared in the same manner from aldehyde collidine by admixture and comparison of IR spectra.

Reaction of I with 1-Methylindole (VIII)——1) To an ice-colled solution of I (0.8 g) in $CHCl_3$ (10 ml), PhCOCl (0.8 g) in $CHCl_3$ (10 ml) and VIII (0.8 g) in $CHCl_3$ (10 ml) were successively added with stirring. The whole was refluxed for 7 hr, cooled to room temperature, shaken with 10% Na_2CO_3 (10 ml) and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and passed through an alumina column. The first eluate afforded a trace of VIII. The second fraction was recrystallized from $CHCl_3$–MeOH to give 0.8 g of 1-methyl-3-(2-quinolyl)indole (IX), pale yellow needles, mp 182—183°. *Anal.* Calcd. for $C_{18}H_{14}N_2$: C, 83.69; H, 5.46; N, 10.85. Found: C, 83.53; H, 5.12; N, 10.68. The third fraction was recrystalilzed from MeOH to yield 0.14 g of 1-methyl-3-(4-quinolyl)indole (X), pale yellow needles, mp 147—148°. *Anal.* Calcd. for $C_{18}H_{14}N_2$: C, 83.69; H, 5.46; N, 10.58. Found: C, 83.43; H, 5.46; N, 10.50.

2) The reaction using TsCl (1.2 g) in place of PhCOCl and working up in the same manner gave 0.15 g of IX and 0.43 g of carbostyril, colorless needles, mp 186—190°.

1-Methyl-2-(2-quinolyl)indole——A solution of 2-acetylquinoline[16] (0.26 g), α-methylphenylhydrazine (0.2 g) and AcOH (1 drop) in EtOH (20 ml) was refluxed for 15 min. The residue from removal of EtOH was treated with $NaHCO_3$ solution and extracted with ether. The extracted substance was distilled under reduced pressure to give 0.2 g of an oil, bp 160—180° (0.035 mmHg) (bath temp.). A mixture of this oil and P_2O_5–conc. H_3PO_4 (1:1) (2 g) was heated at 210° for 15 min, poured on crushed ice, basified with NH_4OH and extracted with ether. Ether was evaporated and the residue was purified by chromatography on alumina in petr. ether–ether (1:1), followed by recrystallizing twice from EtOH to give 0.01 g of 1-methyl-2-(2-quinolyl)indole,[17] pale yellow needles, mp 174—175°.

Reaction of 2-Chloroquinoline 1-Oxide (XI) with VIII——2-Chloroquinoline 1-oxide (XI) (2.7 g) was azeotropically dehydrated with $CHCl_3$ and dissolved in $CHCl_3$ (10 ml). To this solution were added VIII (2 g) and then PhCOCl (2.1 g) in $CHCl_3$ (5 ml) with ice-cooling and stirring, and the whole was refluxed for 10 hr to deposite gradually colorless crystals. After cooling, the reaction mixture was shaken with 10% Na_2CO_3 (20 ml) for 30 min and the precipitates were filtered and washed successively with water and $CHCl_3$. The filtrate was extracted with $CHCl_3$. The extract was concentrated and chromatographed over alumina with $CHCl_3$ and MeOH. The first fraction eluted with $CHCl_3$ was recrystallized from acetone–MeOH to give 2.9 g of 1-methyl-3-(2-chloro-4-quinolyl)indole (XIII), pale yellow needles, mp 140—140.5°. IR cm⁻¹: $\nu_{\mathrm{C=C(indole)}}^{\mathrm{Nujol}}$ 1580. *Anal.* Calcd. for $C_{18}H_{13}N_2Cl$: C, 73.83; H, 4.47; N, 9.56. Found: C, 73.50; H, 4.54; N, 9.14. The fraction eluted with $CHCl_3$–MeOH (100:3) and the above-mentioned precipitates were combined and recrystallized from pyridine–H_2O to afford 0.54 g of 1-benzoyloxy-2-hydroxy-4-(1-methyl-3-indolyl)-1,4-dihydroquinoline (XIV), colorless powder, mp 293—293.5°. IR cm⁻¹: $\nu_{\mathrm{O-H}}^{\mathrm{Nujol}}$ 3200, 3100; $\nu_{\mathrm{C=O}}^{\mathrm{Nujol}}$ 1723, 1690. *Anal.* Calcd. for $C_{25}H_{20}O_3N_2$: C, 75.74; H, 5.09; N, 7.07. Found: C, 76.09; H, 5.09; N, 7.49.

Reaction of 1-Methyl-3-(2-chloro-4-quinolyl)indole (XIII)——1) Reduction to X: A solution of XIII (0.8 g) in EtOH (50 ml) was hydrogenated at 50° over 20% palladium–charcoal. After 3 hr the catalyst was filtered and washed successively with 3% AcONa (10 ml) and $CHCl_3$. The filtrate and washings were combined and evaporated *in vacuo*. The residue was treated with water and extracted with $CHCl_3$. The extracted substances were recrystallized from MeOH to afford 0.2 g of unchanged XIII. The mother liquor was evaporated, and the residue was purified by chromatography on alumina in $CHCl_3$ to give two fractions. The first gave an additional 0.5 g of XIII. The second fraction was recrystallized from MeOH to yield 0.01 g of X, yellow needles, mp 147—148°.

2) Conversion to 1-methyl-3-(2-hydroxy-4-quinolyl)indole (XV): A mixture of XIII (0.1 g) and conc. HCl (10 ml) was heated in a sealed tube at 150—160° for 6 hr. The reaction mixture was diluted with H_2O, basified with $NaHCO_3$ and extracted with $CHCl_3$. The extracted substances were recrystallized from $CHCl_3$–MeOH to yield 0.06 g of XV, colorless sands, mp 290—290.5°. IR cm⁻¹: $\nu_{\mathrm{N-H}}^{\mathrm{Nujol}}$ 3100—2200, $\nu_{\mathrm{C=O}}^{\mathrm{Nujol}}$ 1650. *Anal.* Calcd. for $C_{18}H_{14}ON_2$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.76; H, 5.28; N, 10.54. The reaction did not proceed at 110—130° for 3 hr, XIII being recovered almost quantitatively.

Reaction of 1-Benzoyloxy-2-hydroxy-4-(1-methyl-3-indolyl)-1,4-dihydroquinoline (XIV)——1) Conversion to XV: A suspension of XIV (0.35 g) in 10% alcoholic KOH (20 ml) was refluxed for 3 hr, and then concentrated *in vacuo*. The residue was dissolved in water and bubbled with CO_2 gas, and the resultant precipitates were filtered and recrystallized from $CHCl_3$–MeOH to afford 0.15 g of XV, colorless sands, mp 290—290.5°. The filtrate was acidified with dil. HCl and extracted with $CHCl_3$ to give 0.06 g of benzoic acid (mp 119—122°).

2) Conversion of XV to XIII: A mixture of XV (0.19 g) and $POCl_3$ (5 ml) was refluxed for 2 hr. The reaction mixture was concentrated *in vacuo*, poured on crushed ice, basified with 10% Na_2CO_3 and extracted with $CHCl_3$. The extracted substances were recrystallized from $CHCl_3$–MeOH to give 0.12 g of XIII, pale yellow crystals, mp 140.5°.

---

[16] T. Nakashima, *Yakugaku Zasshi*, 77, 1298 (1957).

[17] D.A. Shirley and P.A. Loussel, *J. Am. Chem. Soc.*, **75**, 375 (1953).

Reaction of 4-Chloroquinoline 1-Oxide (XII) with VIII——To an ice-cooled solution of XII (0.31 g) in $CHCl_3$ (10 ml), PhCOCl (0.25 g) and VIII (0.22 g) in $CHCl_3$ (10 ml) were successively added with stirring. The reaction mixture was refluxed for 3 hr, cooled to room temperature, shaken with 10% Na_2CO_3 (5 ml) for 1 hr and extracted with $CHCl_3$. The extracted substances were recrystallized from $CHCl_3$–MeOH to give 0.27 g of 1-methyl-3-(4-chloro-2-quinolyl)indole (XVI), pale yellow needles, mp 157.8—158°. *Anal.* Calcd. for $C_{18}H_{13}N_2Cl$: C, 73.83; H, 4.47; N, 9.56. Found: C, 73.57; H, 4.58; N, 9.10.

Reduction of 1-Methyl-3-(4-chloro-2-quinolyl)indole (XVI) to IX——A solution of XVI (0.1 g) in EtOH (50 ml) was hydrogenated at ordinary temperature and pressure over 20% palladium-charcoal (0.1 g). After addition of AcONa (0.1 g), the catalyst was filtered and washed successively with water and EtOH. The filtrate and washings were combined and evaporated *in vacuo*. The residue was extracted with $CHCl_3$ and recrystallized from EtOH to afford 0.07 g of IX, pale yellow crystals, mp 182—183°.

Reaction of I with 2-Phenylindole——To an ice-cooled solution of I (0.8 g) in $CHCl_3$ (10 ml), PhCOCl (0.8 g) in $CHCl_3$ (5 ml) and 2-phenylindole (1.1 g) in $CHCl_3$ (10 ml) were successively added with stirring. The whole was refluxed for 5 hr, cooled to room temperature, shaken with 10% Na_2CO_3 (10 ml) for 1 hr and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and passed through an alumina column. The effluent was recrystallized from $CHCl_3$–EtOH to give 0.72 g of 2-phenyl-3-(2-quinolyl)indole (XVII), pale yellow leaflets, mp 272—274°. IR cm^{-1}: $\nu_{\text{N-H}}^{\text{Nujol}}$ 3125, $\nu_{\text{C=C(indole)}}^{\text{Nujol}}$ 1600. *Anal.* Calcd. for $C_{23}H_{16}N_2$: C, 86.22; H, 5.03; N, 8.74. Found: C, 85.88; H, 4.78; N, 8.78.

2-Phenyl-3-(2-quinolyl)indole (XVII)——A solution of ω-benzoylquinaldine (1 g), $PhNHNH_2$ (0.7 g) and AcOH (2 drops) in EtOH (10 ml) was refluxed for 0.5 hr. After cooling the precipitated phenylhydrazone was collected and recrystallized from EtOH to give colorless crystals (mp 122—123°), which was heated with $ZnCl_2$ (6 g) at 170—190° for 0.5 hr. The reaction mixture was poured on 5% HCl and extracted with $CHCl_3$. The extract was shaken with 5% NaOH, dried over Na_2SO_4 and evaporated. The residue was recrystallized from $CHCl_3$–MeOH to afford 0.3 g of pale yellow leaflets of mp 273—274°, which was identical with XVII obtained from the foregoing experiment.

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 S. Takeo for the measurement of NMR spectrum.