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

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1-Methyl-2-ethoxy-, 2-ethoxy- and 3-methoxy-indoles (I, II, and III) were applied to some N-oxides of pyridine series in the presence of an acylating agent. The reaction of I with quinoline 1-oxide (IV) in the presence of tosyl chloride or benzoyl chloride progressed in the cold, and 1-methyl-2-ethoxy-3-(2-quinolyl)indole (V) was obtained in good yields. The reaction under heating was prone to afford the oxindole derivative (VI), the total yield being decreased. Not only 2-chloro- and 4-chloroquinoline 1-oxides (X and XIII) but also pyridine and 4-chloropyridine 1-oxides (XXII and XXVII) were shown to react similarly with I in the presence of tosyl chloride to give the corresponding 3-substituted indoles, XI, XIV, XXIII, and XXVIII, respectively.

Similar reaction of II with IV yielded 2-ethoxy-3-(2-quinolyl)indole (XXX).

The reaction of III with IV or ethyl nicotinate 1-oxide (XLIII) led to the formation of 2-substituted-3-methoxy-indoles (XXXIII and XLIV), although the yield of XLIV was very poor.

The mechanism of the reductive de-ethoxylation of 2-ethoxy-3-(2-quinolyl or 2-pyridyl)indoles (V, XIV, XXX, and XXIII) by lithium aluminium hydride was discussed.

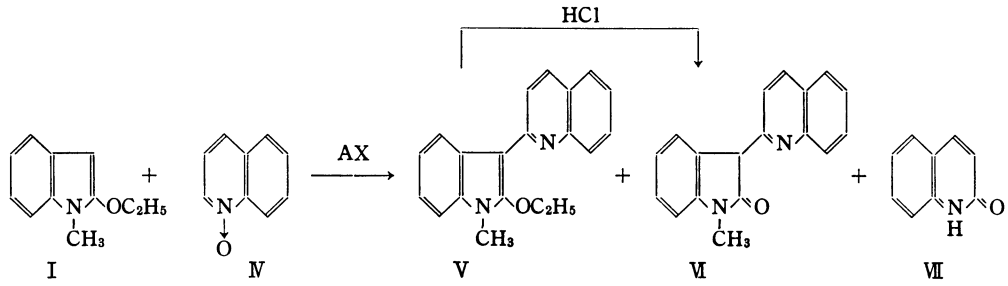
Recent papers of this series have described the nucleophilic reaction of aromatic N-oxides with indoles[3] and oxindoles[4] in the presence of an acylating agent, and it has been shown that indoles enter into reaction as aromatic enamines[3,5] and the reaction with oxindoles bears some resemblances to that with active methylene compounds.[4,6] Furthermore, enol ethers[7] have been previously shown to react also with quinoline N-oxides under similar conditions although their reactivities are rather lower than those of enamines.[8]

As further extension of our study on nucleophilic reaction between acyl-adducts of aromatic N-oxides and indole derivatives, we examined the reactions with 1-methyl-2-ethoxyindole(I), 2-ethoxyindole (II) and 3-methoxyindole (III). The reactivities of both I and II may be reasonably expected to be much enhanced, however it is particularly interesting to elucidate whether III could enter into reaction with aromatic N-oxides to afford 2-substituted-3-methoxyindoles or not.

At first, the reaction of 1-methyl-2-ethoxyindole (I)[9] with quinoline 1-oxide (IV) was carried out under various conditions, and the results shown in Chart 1 were obtained.

Treatment of I with IV and tosyl chloride in chloroform at low temperatures for 3 hours gave the expected 1-methyl-2-ethoxy-3-(2-quinolyl)indole (V), pale yellow sands of mp 104.5—

1) Part XLII: M. Hamana and T. Matsumoto, *Yakugaku Zasshi*, **91**, 269 (1971).
2) Location: *Katakasu, Fukuoka*; *a*) Present address: *Tokyo College of Pharmacy, Kashiwagi-4-chome, Shinjuku-ku, Tokyo.*
3) M. Hamana and I. Kumadaki, *Chem. Pharm. Bull.* (Tokyo), **18**, 1742 (1970)
4) M. Hamana and I. Kumadaki, *Chem. Pharm. Bull.* (Tokyo), **18**, 1822 (1970)
5) M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), **15**, 1380 (1967).
6) M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.* (Tokyo), **11**, 415 (1963)
7) M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), **18**, 26 (1970).
8) *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); *d*) *Idem, Yakugaku Zasshi*, **89**, 641 (1969).
9) J. Harley-Mason and T.J. Leeney, *Proc. Chem. Soc.* (London), **1964**, 368.



AX:					
$TsCl-CHCl_3$	0—20°, 3 hr	66%	trace	6%
$TsCl-CHCl_3$	reflux, 3 hr	8%	17.4%	2%
$C_6H_5COCl-CHCl_3$	0°, 8 hr	53.6%	—	—
$C_6H_5COCl-CHCl_3$	reflux, 5 hr	trace	46%	—
Ac_2O	0°, 36 hr	—	—	—
Ac_2O	reflux, 6 hr	—	30%	—

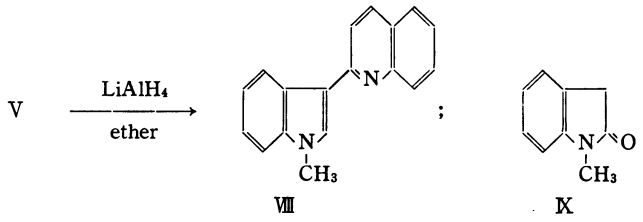


Chart 1

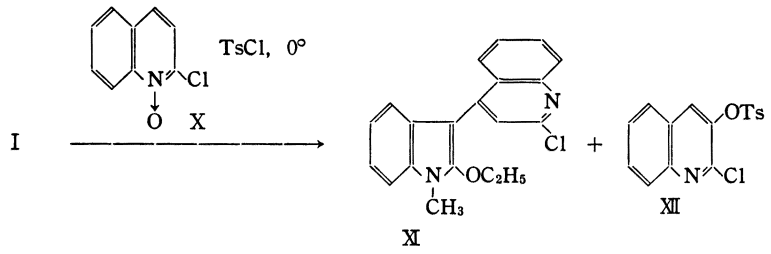
106°, as the predominant product in 66% yield, accompanied with a very small amount of carbostyril (VII) and a trace of 1-methyl-3-(2-quinolyl)oxindole (VI).[4] The product V has the correct empirical formula, and underwent easily acid hydrolysis to VI.[4] Treatment of V with lithium aluminium hydride resulted in reductive elimination of 2-ethoxy group to afford 1-methyl-3-(2-quinolyl)indole (VIII[3]). When the reaction was carried out under reflux, the total yield of products much decreased and VI was formed as a major product, V being a minor one.

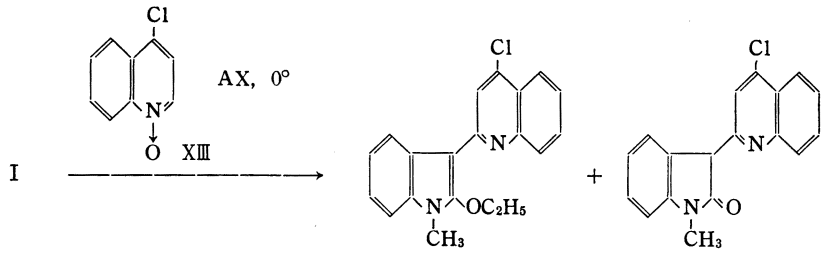
The fairly similar results were obtained from the reaction in the presence of bezoyl chloride, but no reaction occured in the cold by means of acetic anhydride and only VI was formed in 30% yield under refluxing condition.

As for the formation of VI under heating, two courses may be conceivable; *i. e.*, the first is the decomposition of V initially formed, and the second is the preceding decomposition of I to 1-methyloxindole (IX) followed by reaction with IV. The reaction in hot acetic anhydride may be assumed to follow the second path, because of no formation of V even in prolonged reaction at 0°. Conversely it seems very likely that the reaction in the presence of tosyl chloride proceeds by the first course, since IX was shown to react with IV only with difficulty in the presence of tosyl chloride[4]; the decrease in yields may be probably due to the decomposition of I under such condition. The reaction in the presence of benzoyl chloride seems to be similar to that using tosyl chloride, but there is a possibility that both paths are concurrent.

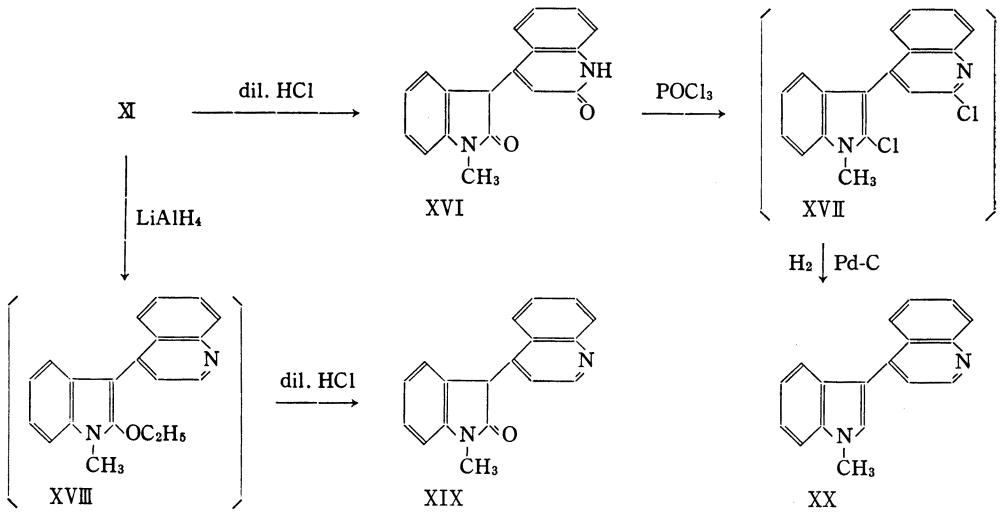
Similarly 2-chloroquinoline 1-oxide (X) reacted with I in the presence of tosyl chloride under ice-cooling, and 1-methyl-2-ethoxy-3-(2-chloro-4-quinolyl)indole (XI), faint yellow sands of mp 132—133°, and 2-chloro-3-tosyloxyquinoline (XII),[10] colorless needles of mp 108—109°, were obtained in 37 and 10% yields, respectively.

10) The structure of XII was confirmed by elemental analysis, comparison of infrared (IR) spectra and admixture with an authentic sample kindly supplied by Prof. M. Yamazaki (Fukuoka University).





AX:	TsCl	C6H5COCl
XIV	67%	17%
XV	1%	0.5%



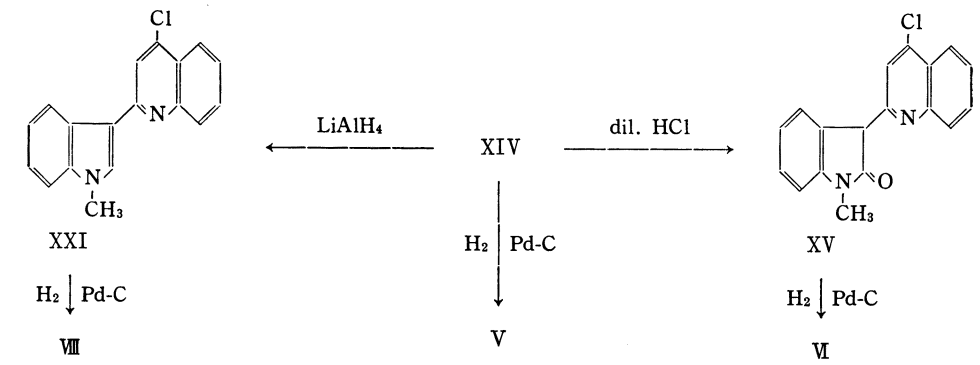


Chart 2

The reaction of 4-chloroquinoline 1-oxide (XIII) progressed more readily under the same condition, and afforded 1-methyl-2-ethoxy-3-(4-chloro-2-quinolyl)indole (XIV), faint yellow leaflets of mp 127.5—128°, in 67% yield accompanied with a samll amount of 1-methyl-3-(4-chloro-2-quinolyl)oxindole (XV)[4] (1%). The use of benzoyl chloride in place of tosyl chloride caused the decrease of the reaction yield in this case.

The structures of XI and XIV were determined by the reaction sequences shown in Chart 2.

Treatment of XI with diluted hydrochloric acid in methanol resulted in the hydrolysis of both ethoxy and chloro groups with the formation of 1-methyl-3-(2-hydroxy-4-quinolyl)oxindole (XVI), which was subsequently converted to 1-methyl-3-(4-quinolyl)indole (XX)[3] through a dichloro compound XVII. Reduction of XI with lithium aluminium hydride followed by treatment with diluted hydrochloric acid yielded 1-methyl-3-(4-quinolyl)oxindole (XIX)[4]; hence, XI underwent only the reductive dechlorination upon treatment with lithium aluminium hydride contrary to V.

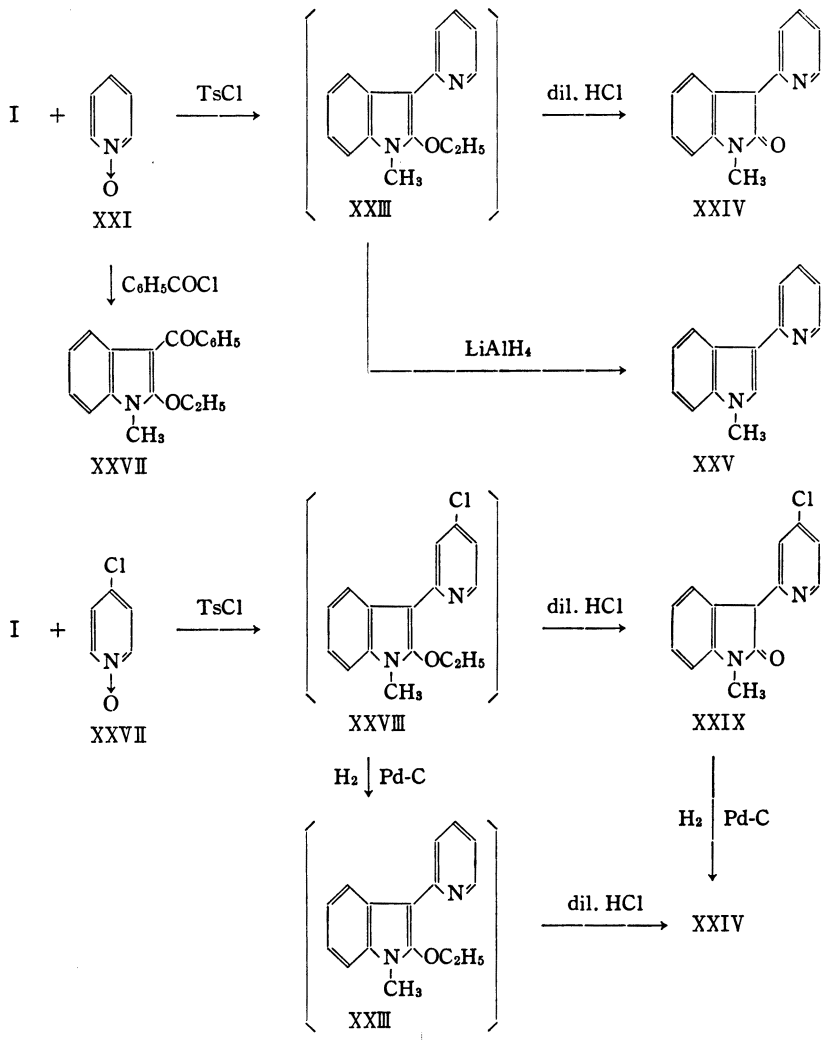


Chart 3

Differently from the behavior of XI, acid hydrolyss of XIV gave 1-methyl-3-(4-chloro-2-quinolyl)oxindole (XV), the chloro group of quinoline ring being not attacked. Treatment

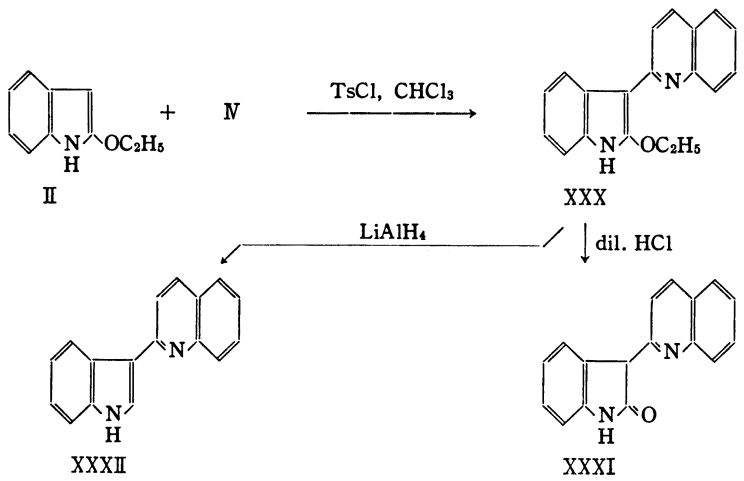
with lithium aluminium hydride led to the formation of the de-ethoxylated XXI quite similarly to the case of V. Reductive dechlorination of XIV, XV and XXI with hydrogen in the presence of palladium charcoal were normally effected to give V, VI and VIII, respectively.

Subsequently the reactions of I with N-oxides of pyridine and 4-chloropyridine were tried. When I was treated at room temperatures with pyridine 1-oxide (XXII) and tosyl chloride in chloroform, the reaction took place and an oily product (XXIII) was obtained after purification by chromatography on an alumina column. This product XXIII gave a picrate, $C_{10}H_{16}ON_3 \cdot C_6H_3O_7N_3$, of mp 179—180°. Since it was difficult to separate XXIII from I by distillation under reduced pressure, XXIII was subjected to acid hydrolysis to give the known 1-methyl-3-(2-pyridyl)oxindole (XXIV).[4] The overall yield of XXIV from XXII was only 20%. Similarly to 2-quinolyl analogue V, XXIII was reduced to 1-methyl-3-(2-pyridyl)-indole (XXV)[4] with lithium aluminium hydride. When benzoyl chloride was employed as an acylating agent, no formation of XXIII was detected and only a product conceivable to be 1-methyl-2-ethoxy-3-benzoylindole (XXVI) from its elemental analysis and infrared (IR) spectrum was formed.

The reaction of 4-chloropyridine 1-oxide (XXVII) with I in the presence of tosyl chloride progressed similarly to give 1-methyl-2-ethoxy-3-(4-chloro-2-pyridyl)indole (XXVIII), yellow-orange sands of mp 213—215°, which was hydrolyzed to an oxindole derivative (XXIX) followed by catalytic reduction in the presence of palladium charcoal to give XXIV.[4] Reversely, the catalytic reduction of XXVIII and succesive hydrolysis of the product also afforded XXIV.

These results are shown in Chart 3.

Next, 2-ethoxyindole (II) was applied to quinoline 1-oxide (IV). In the presence of tosyl chloride the reaction progressed in the cold and 2-ethoxy-3-(2-quinolyl)indole (XXX) was formed as yellow needles of mp 179—180° in 28.3% yield; its empirical formula was found to be $C_{19}H_{16}ON_2 \cdot \frac{1}{2}C_2H_5OH \cdot \frac{1}{2}H_2O$ from elemental analysis. Acid hydrolysis of XXX gave the known oxindole derivative XXXI,[4] and the reaction with lithium aluminium hydride apparently caused de-ethoxylation to give 3-(2-quinolyl)indole (XXXII)[3] although in a poor yield with 50% recovery of XXX. The poor yield of XXXII may be due to the presence of N-H group or the crystalline ethanol and water.



Further reaction of II was not carried out with other aromatic N-oxides.

The results mentioned above demonstrate that the nucleophilic reactivities of I and II towards acyl-adducts of aromatic N-oxides are apparently higher than those of indoles and oxindoles, and it was shown that the reactions proceeded not only in the cold but gave appre-

ciably better results as compared with those under heating, and tosyl chloride is the most efficient as an acylating agent. Such enhanced reactivities of I and II can be ascribed to the fact that their 3-position is doubly activated by both of aromatic enamine's and enol ether's structures. Although the yields were not always satisfactory probably due to the instabilities of I and II, further examinations under a variety of conditions might be expected to improve this aspect.

Then we examined the reaction of 3-methoxyindole (III)[11] and quinoline 1-oxide (IV) in the presence of an acylating agent and succeeded in the introduction of 2-quinolyl group into the 2-position of indole nucleus as shown in Chart 4.

When IV was treated at 0° for 7 hours with III and benzoyl chloride (1 eq) in chloroform, 2-(2-quinolyl)-3-methoxy-indole (XXXIII) was obtained in 30% yield. Recrystallization of XXXIII from ethanol afforded yellow needles of mp 138—139° or yellow powder of mp 139—140° depending on slight differences of the conditions. No depression of the melting point was observed when they were mixed, but the N-H streching band in the IR spectrum of the former appears as a broad one around 3200 cm^{-1} and that of the latter shows up as a sharp one at 3400 cm^{-1}, and the absorption bands in other region are also not completely superimposable. Accordingly they seem to be dimorphic forms.

Oxidation of XXXIII with potassium permanganate gave methyl N-quinaldylanthranilate (XXXV) which was converted by alkaline hydrolysis to the corresponding acid (XXXVI),[12] which was proved identical with an authentic sample prepared from quinaldyl chloride and anthranilic acid; conversely XXXVI was transformed by methylation to XXXV. Transformation of XXXIII to 2-(2-quinolyl)indole (XXXIX)[3] was accomplished through the 3-hydroxy- (XXXVII) and the 3-chloro-indole (XXXVIII) by successive treatment with pyridine hydrochloride[13] and phosphoryl chloride and then by catalytic reduction of XXXVIII: the overall yield was below 10%. Contrary to V and XIV, XXXIII did not react with lithium aluminium hydride.

The reaction in the presence of tosyl chloride gave 3-methoxy-1,2-bis(2-quinolyl)indole (XXXIV) as pale yellow needles of mp 116—117.5° besides XXXIII in respective small yields of 3 and 2%. The reaction in warm acetic anhydirde resulted in the formation of only XXXIV in 43% yield.

The structure of XXXIV was deduced by its conversion through XL to methyl N-(2-quinolyl)anthranilate (XLI), which was proved identical with an authentic specimen obtainable together with 12-H-quinolino[2,1-*b*]quinazolone-12[14] from the reaction of methyl anthranilate and 2-chloroquinoline at 160°.

These results are shown in Chart 4.

Whereas all attempted reactions of III with pyridine 1-oxide (XXII) were unsuccessful, ethyl nicotinate 1-oxide (XLIII) was found to react with III in the presence of benzoyl chloride (1 eq) to give yellow needles (XLIV) of mp 151—153°, although in a very small yield of 3.8%. The IR spectrum of XLIV exhibited an ester–carbonyl band at 1703 cm^{-1}, which suggests that the ester group conjugates with an electron-donating group. The nuclear magnetic resonance (NMR) spectrum of XLIV shows one α-proton of pyridine ring at 0.91 τ, which is faintly splitted into a triplet probably due to a long range coupling. From these observations and also by anlogy with the reaction of III with IV and with that of indole with XLIII,[3] XLIV may well be assumed to be 2-(5-methoxycarbonyl-2-pyridyl)-3-methoxy-indole.

No reaction was observed in the presence of tosyl chloride and the reaction in acetic anhydride afforded only 1-acetyl-3-methoxyindole (XLV) in 30% yield.

11) A. Etienne, *Bull. Soc. Chim. France*, **1948**, 651 [*C. A.*, **42**, 7289 (1948)].
12) K. Ueda, *Yakugaku Zasshi*, **57**, 817 (1937).
13) P.N. Rao and L.S. Axelrod, *J. Chem. Soc.*, **1961**, 4769.
14) P.K. Bosen and D.C. Sen, *J. Chem. Soc.*, **1931**, 2841.

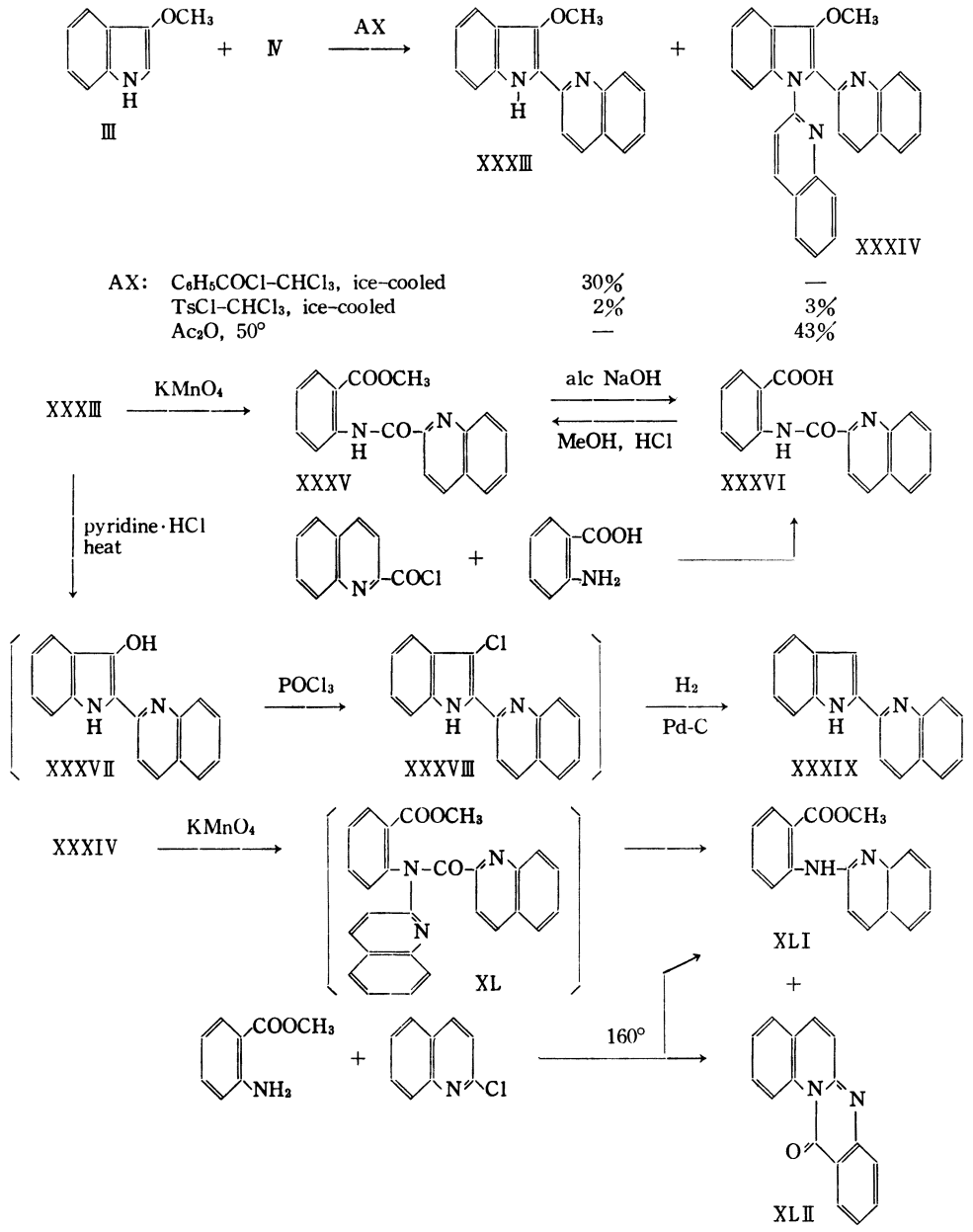
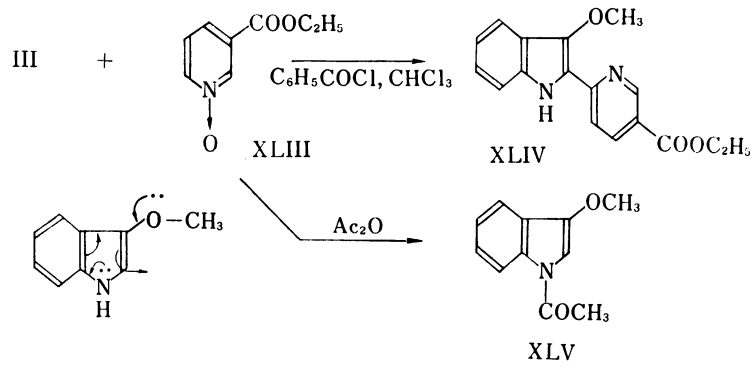


Chart 4

From these results the nucleophilic reactivity of III towards acyl-adducts of aromatic N-oxides is apparently higher than those of aromatic enol ethers such as anisole.[7] This enhanced reactivity of the 2-position of III may be probably ascribed to the combined activation by both of the enol ether's structure and the inherent polarization of indole nucleus as shown above. In view of the unsuccessful reaction[3] of skatol with quinoline 1-oxide, this line of approach to 2-substituted indoles might be expected as promising, although only few experiments were carried out yet.

As described above, 2-ethoxy-3-(2-quinolyl- or 2-pyridyl) indoles, V, XIV, XXX and XXIII underwent reductive de-ethoxylation on treatment with lithium aluminium hydride.



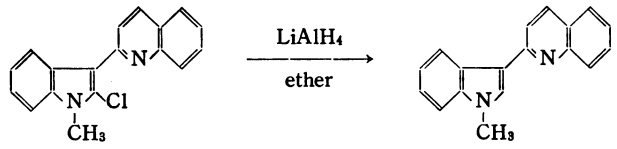
Finally, we carried out some examinations on this interestng reduction in order to explore its essential features. The results are shown in Table I together with the above-mentioned ones.

TABLE I. Reaction with Lithium Aluminium Hydride

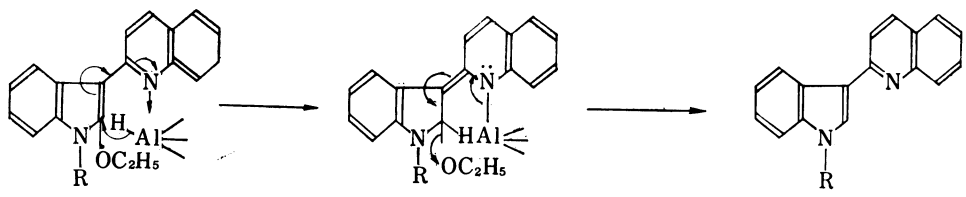
Substrate	Reductive elimination	Product
I	—	—
2-Ethoxyquinoline	—	—
V	de-ethoxylation	VIII
XIV	de-ethoxylation	XXI
XXIII	de-ethoxylation	XXV
XXX	de-ethoxylation	XXXIII[a]
1-Methyl-2-chloro-3-(2-quinolyl)indole (XLVI)[b]	dechlorination[b]	VIII
VI	—	—
XVIII	—	—
XXXIII	—	—

a) a small amount

b)



This reductive de-ethoxylation is not essential to α-ethoxy group of indole, and the electron-attracting property of the nitrogen atom of pyridine ring alone is not efficient for the initiation of the reaction. The compounds able to be reduced have two common structural chracteristics; the first is the ethoxy group on α-position of indole ring and the second is the connection between 2-quinolyl or 2-pyridyl group and 3-indolyl moiety. From this point of view, we wish to propose here the following cyclic course which involves both electronic and spacial requirements.



This is supported by the reductive dechlorination of 1-methyl-2-chloro-3-(2-quinolyl) indole (XLVI),[4] and the resistance of XXXIII to such reduction, in spite of the spacial similarity, may be due to the electron-donating effect of a lone pair of nitrogen of indole ring; it might compensate the electron-defficiency at β-position of indole.

Experimental[15]

Reaction of Quinoline 1-Oxide (IV) with 1-Methyl-2-ethoxyindole (I)——1) To a solution of IV (0.8 g) in $CHCl_3$ (5 ml), a solution of TsCl (1.2 g) in $CHCl_3$ (10 ml) and that of I (1.05 g) in $CHCl_3$ (10 ml) were successively added under ice-cooling and stirring. After 3 hr's stirring, the reaction mixture was shaken with 10% Na_2CO_3 for 1 hr, $CHCl_3$ layer was separated and H_2O layer was extracted with $CHCl_3$. The combined $CHCl_3$ solution was dried over Na_2SO_4 and concentrated, and the residue was chromatographed on alumina in $CHCl_3$–CCl_4. The first fraction eluted with $CHCl_3$–CCl_4 (2:3) was recrystallized from EtOH to give 1.1 g of 1-methyl-2-ethoxy-3-(2-quinolyl)indole (V), pale yellow sands, mp 104—105°. IR cm^{-1}: $\nu_{c=c}$ 1600 (Nujol). *Anal.* Calcd. for $C_{20}H_{18}ON_2$: C, 79.44; H, 6.00; N, 9.27. Found: C, 79.45; H, 6.03; N, 9.45. The second fraction eluted with $CHCl_3$–CCl_4 (1:1) was recrystallized from EtOH to give a few mg of 1-methyl-3-(2-quinolyl)oxindole (VI).[4] The column was further eluted with $CHCl_3$–CCl_4 (1:1) containing 3% EtOH to give 0.065 g of carbostyril (VII), mp 195—196° (H_2O).

2) The same reaction mixture was refluxed for 3 hr and processed in the same way to afford 0.13 g of V, 0.26 g of VI and 0.02 g of VII.

3) A reaction mixture using C_6H_5COCl (0.9 g) in place of TsCl was stirred for 8 hr under ice-cooling to yield 0.9 g of V as a sole product.

4) A solution of IV (0.8 g), I (0.9 g) and C_6H_5COCl (0.9 g) in $CHCl_3$ (25 ml) was refluxed for 5 hr to give 0.7 g of VI and a trace of V.

5) A mixture of IV (0.8 g), Ac_2O (1 ml) and I (1.05 g) in $CHCl_3$ (10 ml) was kept at 0° in a refrigerator for 36 hr. No product was detected, and 0.7 g of I and a small amount of IV (0.7 g as picrate, mp 143—146°) were recovered.

6) A solution of IV (0.8 g) and I (1.05 g) in Ac_2O (4 ml) was refluxed for 6 hr, concentrated *in vacuo*, treated with Na_2CO_3 solution and worked up similarly to give 0.45 g of VI.

Reaction of 1-Methyl-2-ethoxy-3-(2-quinolyl)indole (V)——1) A solution of V (0.1 g) in EtOH (5 ml) containing conc. HCl (2 ml) was refluxed for 5 hr, concentrated *in vacuo*, treated with 10% Na_2CO_3 and extracted with $CHCl_3$. The extracted substance was recrystallized from EtOH to give 0.05 g of 1-methyl-3-(2-quinolyl)oxindole (VI),[4] red needles, mp 213—215°.

2) To a solution of $LiAlH_4$ (0.1 g) in ether (20 ml), V (0.3 g)–ether (30 ml) was added dropwise, and the whole was refluxed for 10 hr. To the reaction mixture was added H_2O (5 ml) to give precipitates, which was filtered and washed with ether. The filtrate and washings were combined, dried over Na_2SO_4 and evaporated. The residue was recrystallized from benzene to give 0.14 g of 1-methyl-3-(2-quinolyl)indole (VIII),[3] yellow leaflets, mp 182—183°.

Reaction of 2-Chloroquinoline 1-Oxide (X) with I——The N-oxide (X) (1 g) was dehydrated azeotropically with $CHCl_3$ and dissolved in $CHCl_3$ (10 ml). To this solution, TsCl (0.9 g) in $CHCl_3$ (10 ml) and I (1 g) in $CHCl_3$ (10 ml) were added under ice-cooling and stirring. After 6 hr's stirring at room temperatures, the reaction mixture was shaken with 10% Na_2CO_3 for 5 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 MeOH to give 0.7 g of 1-methyl-2-ethoxy-3-(2-chloro-4-quinolyl)indole (XI), faint yellow sands, mp 132—133°. IR cm^{-1}: $\nu_{c=c}$ (indole) 1589 (Nujol). *Anal.* Calcd. for $C_{20}H_{17}ON_2Cl$: C, 71.45; H, 5.01; N, 8.32. Found: C, 71.11; H, 4.99; N, 8.32.

Concentration and cooling of the mother liquor afforded 0.16 g of 2-chloro-3-tosyloxyquinoline (XII),[10] colorless needles, mp 108—109°. IR cm^{-1}: ν_{SO_2} 1368, 1195 (Nujol). *Anal.* Calcd. for $C_{16}H_{12}O_3NSCl$; C, 57.53; H, 3.62; N, 4.19. Found: C, 57.04; H, 3.51; N, 4.30.

Reaction of 4-Chloroquinoline 1-Oxide (XIII) with I——1) To a solution of XIII (1 g) in $CHCl_3$ (5 ml), TsCl (1.1 g)–$CHCl_3$ (12 ml) and I (1 g)–$CHCl_3$ (15 ml) were added dropwise under ice-cooling and stirring. After 30 min's stirring, the reaction mixture was shaken with 10% Na_2CO_3 for 2 hr and extracted with $CHCl_3$. The extract was dried over Na_2SO_4, concentrated and passed through an alumina column in $CHCl_3$–CCl_4. Recrystallization of the fraction eluted with $CHCl_3$–CCl_4 (1:2) from MeOH to give 1.25 g of 1-methyl-2-ethoxy-3-(4-chloro-2-quinolyl)indole (XIV), faint yellow leaflets, mp 127.5—128°. IR cm^{-1}: $\nu_{c=c}$ (indole), 1590 (Nujol). *Anal.* Calcd. for $C_{20}H_{17}ON_2Cl$: C, 71.45; H, 5.08; N, 8.32. Found: C, 71.45; H, 5.13; N, 8.09.

Recrystallization of the fraction eluted with $CHCl_3$ from $CHCl_3$–MeOH to yield 0.2 g of 1-methyl-3-(4-chloro-2-quinolyl)oxindole (XV),[4] red needles, mp 245—248°.

15) All melting and boiling points are uncorrected. All the known compounds reported in ref. 3) and 4) were identified by comparison of IR spactra and admixtures with the authentic samples.

2) The similar reaction using C_6H_5COCl (0.9 g) instead of TsCl was carried out for 1 hr to give 0.32 g of XIV and 0.08 g of XV.

Reaction of 1-Methyl-2-ethoxy-3-(2-chloro-4-quinolyl)indole (XI)——1) A mixture of XI (0.2 g) and MeOH (10 ml)–10% HCl (7 ml) was refluxed for 3 hr, concentrated *in vacuo*, neutralized with 10% Na_2CO_3 and extracted with $CHCl_3$–EtOH (9:1). The extract was dried over Na_2SO_4 and evaporated, and the residue was recrystallized from MeOH to give 0.13 g of 1-methyl-3-(2-hydroxy-4-quinolyl)-oxindole (XVI), colorless powder, mp 279—280°. IR cm^{-1}: ν_{OH}—3100—(broad); $\nu_{C=C}$ (oxindole) 1705; $\nu_{C=O}$ (carbostyril) 1675 (Nujol). *Anal.* Calcd. for $C_{18}H_{14}ON_2 \cdot H_2O$: C, 70.11; H, 5.23; N, 9.19. Found: C, 69.52; H, 5.37; N, 9.09.

A mixture of XVI (0.1 g) and $POCl_3$ (3 ml) was refluxed for 1 hr, concentrated *in vacuo*, poured on ice, neutralized with Na_2CO_3 solution and extracted with $CHCl_3$. A solution of the extracted substance (XVII) in MeOH (20 ml) was hydrogenated over 20% Pd-C (0.1 g) at 30° for 3 hr. The catalyst was filtered and washed with MeOH. The combined filtrate and washings were concentrated *in vacuo*, neutralized with 10% Na_2CO_3 and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and passed through an alumina column to give 0.02 g of 1-methyl-3-(4-quinolyl)indole (XX),[3] yellow needles, mp 147—148°.

2) A mixture of XI (0.3 g) and $LiAlH_4$ (0.2 g) in ether (30 ml) was refluxed for 6 hr. The excess $LiAlH_4$ was decomposed with AcOEt and H_2O, and the precipitate was filtered and washed with ether. The combined filtrate and washings were evaporated, and the residue[16] was treated with EtOH (15 ml)–10% HCl (2 ml) for 3 hr under reflux. The reaction mixture was concentrated *in vacuo*, treated with 10% Na_2CO_3 and extracted with $CHCl_3$. Recrystallization of the extracted substance from EtOH gave 0.15 g of 1-methyl-3-(4-quinolyl)oxindole (XIX),[4] colorless needles, mp 132—135°.

Reaction of 1-Methyl-2-ethoxy-3-(4-chloro-2-quinolyl)indole (XIV)——1) A solution of XIV (0.2 g) in MeOH (30 ml) was hydrogenated over 20% Pd-C (0.2 g) for 1 hr. The catalyst was filtered and washed with MeOH. The filtrate and washings were combined, concentrated, neutralized with 10% Na_2CO_3 and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and purified by chromatography on alumina with $CHCl_3$ to give 0.11 g of V.

2) A solution of XIV (0.2 g) in MeOH (10 ml)–10% HCl (7 ml) was refluxed for 3 hr. The reaction mixture was concentrated *in vacuo*, treated with 10% Na_2CO_3 (10 ml) and extracted with $CHCl_3$ to give 0.15 g of 1-methyl-3-(4-chloro-2-quinolyl)oxindole (XV),[4] red needles, mp 245—247° (MeOH).

3) A mixture of XIV (0.3 g) and $LiAlH_4$ (0.2 g) in ether (50 ml) was refluxed for 5 hr. The reaction mixture was treated with AcOEt and H_2O (0.2 ml), and the precipitate was filtered and washed with ether. The filtrate and washings were combined, dried over Na_2SO_4 and evaporated. The residue was purified by chromatography on alumina with CCl_4 to give 0.09 g of 1-methyl-3-(4-chloro-2-quinolyl)indole (XXI).[3]

Reaction of Pyridine 1-Oxide (XXII) with I——1) Pyridine 1-oxide (XXII) (0.7 g) was dehydrated azeotropically with $CHCl_3$ and dissolved in $CHCl_3$ (10 ml), and TsCl (1.5 g)–$CHCl_3$ (15 ml) and I (1.35 g)–$CHCl_3$ (20 ml) was added dropwise under ice-cooling and stirring. After stirring was continued at 10—20° overnight, the reaction mixture was shaken with 10% Na_2CO_3 (15 ml) for 0.5 hr and extracted with $CHCl_3$. The extract was dried over Na_2SO_4, concentrated and the residue was chromatographed on alumina with $CHCl_3$–CCl_4 (1:2). The elute fluorescent with ultraviolet (UV) lump was collected to afford 1-methyl-2-ethoxy-3-(2-pyridyl)indole (XXIII) as an oil. A solution of XXIII in EtOH (10 ml) containing conc. HCl (1 ml) was refluxed for 3 hr, concentrated *in vacuo*, treated with 10% Na_2CO_3 and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated. The residue was chromatographed over alumina with $CHCl_3$–CCl_4 (1:1) and the effuluent was recrystallized from benzene to give 0.37 g of 1-methyl-3-(2-pyridyl) oxindole (XXIV),[4] orange-yellow needles, mp 173—174°.

2) The product (XXIII) obtained from another run was divided into halves. The first one was derived to a picrate by adding picric acid to its EtOH solution; yellow needles, mp 179—180° (from EtOH). *Anal.* Calcd. for $C_{16}H_{16}ON_2 \cdot C_6H_3O_7N_3$: C, 55.48; H, 3.98; N, 14.55. Found: C, 55.75; H, 3.96; N, 14.84.

Another half was dissolved in ether (20 ml) containing $LiAlH_4$ (0.2 g) and the whole was refluxed for 5 hr. The reaction mixture was treated with AcOEt and H_2O (0.1 ml), and the precipitate was filtered and washed with ether. The filtrate and washings were combined, dried over Na_2SO_4 and concentrated, and the residue was chromatographed on alumina in $CHCl_3$–CCl_4 (1:1). Recrystallization of the first effluent from benzene–petr. ether gave 0.06 g of 1-methyl-3-(2-pyridyl)indole (XXV),[4] yellow crystals, mp 83—84°.

3) To a solution of XXII (1 g) in $CHCl_3$ (5 ml), C_6H_5COCl (1.5 g)–$CHCl_3$ (10 ml) and then I (1.5 g)–$CHCl_3$ (15 ml) were added dropwise with ice-cooling and stirring. After 10 hr's stirring, the reaction mixture was shaken with 10% Na_2CO_3 (15 ml) for 1 hr and extract with $CHCl_3$. The extract was dried over Na_2SO_4, concentrated and chromatographed on alumina using $CHCl_3$–CCl_4 (2:3) as the solvent. The first fraction was recrystallized from EtOH to afford 0.94 g of I. Recrystallization of the second fraction from EtOH gave 0.43 g of colorless needles, mp 109—110°, which was assumed to be 1-methyl-2-ethoxy-3-benzoylindole (XXVI) from the elemental analysis. *Anal.* Calcd. for $C_{18}H_{17}O_2N$: C, 77.39; H, 6.13; H, 5.01. Found: C, 77.64; H, 6.28; H, 4.90. Recrystallization of the third effluent from EtOH–H_2O gave 0.15 g of 1-methyl-oxindole (IX).

16) Attempted re-treatment of this residue containing XVIII with $LiAlH_4$ in hot ether was unsuccessful, XX being not obtained.

Reaction of 4-Chloropyridine 1-Oxide (XXVII) with I——1) To a solution of XXVII (0.7 g) in $CHCl_3$ (10 ml), TsCl (1 g)–$CHCl_3$ (10 ml) and I (1 g)–$CHCl_3$ (10 ml) were added under ice-cooling and stirring. After 1 hr's stirring under reflux, the reaction mixture was shaken with 10% Na_2CO_3 and extracted with $CHCl_3$. The extract was dried over Na_2SO_4, concentrated and the residue was dissolved in $CHCl_3$–CCl_4 (1:2), which was passed through an alumina column. The first effluent containing 1-methyl-2-ethoxy-3-(4-chloro-2-pyridyl)indole (XXVIII) was treated for 2 hr with EtOH (10 ml)–conc. HCl (2 ml) under reflux. The reaction mixture was concentrated *in vacuo*, treated with 10% Na_2CO_3 and extracted with $CHCl_3$. The extracted substances was purified by chromatography over alumina in $CHCl_3$–CCl_4 (1:2) and recrystallized from benzene to give 0.15 g of 1-methyl-3-(4-chloro-2-pyridyl)oxindole (XXIX), orange yellow sands, mp 213—215°. IR cm^{-1}: $\nu_{C=O}$ 1630 (Nujol). *Anal.* Calcd. for $C_{14}H_{11}ON_2Cl$: C, 64.99; H, 4.27; N, 10.83. Found: C, 64.95; H, 4.13; N, 11.18.

A solution of XXIX (0.1 g) in MeOH (30 ml) was hydrogenated at 30° over 20% Pd-C (0.1 g). After absorption of H_2 had stopped, the catalyst was filtered and washed with MeOH. The filtrate and washings were combined, concentrated *in vacuo*, treated with 10% Na_2CO_3 and extracted with $CHCl_3$. The extracted substance was recrystallized from benzene to give 0.03 g of XIV.

2) A same solution of XXVII, TsCl and I in $CHCl_3$ as above was refluxed for 8 hr and treated in the same way. The product (XXVIII) was dissolved in MeOH (20 ml) and hydrogenated over 20% Pd-C (0.2 g) for 2 hr. The catalyst was filtered and washed with MeOH. The combined MeOH solution was concentrated to 10 ml and treated for 3 hr with 10% HCl (2 ml) under reflux. The reaction mixture was concentrated *in vacuo*, treated with 10% Na_2CO_3 and extracted with $CHCl_3$. The extracted substance was purified by chromatography on alumina with $CHCl_3$–CCl_4, and recrystallized from benzene to give 0.07 g of XXIV.

Reaction of 2-Ethoxyindole (II) with IV——To a solution of IV (0.8 g) in $CHCl_3$ (5 ml), TsCl (1.1 g)–$CHCl_3$ (10 ml) and II (1 g)–$CHCl_3$ (20 ml) were added dropwise under ice-cooling and stirring. After 5 hr's stirring, the reaction mixture was shaken with 10% Na_2CO_3 (10 ml) and extracted with $CHCl_3$. The extracted substance was chromatographed on alumina with $CHCl_3$–CCl_4 (1:1) and the first effluent was recrystallized from EtOH to give 0.45 g of 2-ethoxy-3-(2-quinolyl)indole (XXX), yellow needles, mp 178—180°. IR cm^{-1}: ν_{N-H} 3180; $\nu_{C=C}$ (indole) 1600 (Nujol). *Anal.* Calcd. for $C_{19}H_{16}ON_2 \cdot \frac{1}{2}C_2H_5OH \cdot \frac{1}{2}H_2O$: C, 74.97; H, 6.29; N, 8.74. Found: C, 74.92; H, 6.47; N, 8.71.

Reaction of 2-Ethoxy-3-(2-quinolyl)indole (XXX)——1) A mixture of XXX (0.1 g) and EtOH (10 ml)–10% HCl (2 ml) was refluxed for 3 hr, concentrated *in vacuo*, treated with 10% Na_2CO_3 and extracted with $CHCl_3$. Recrystallization of the extracted substance from EtOH gave 0.06 g of 3-(2-quinolyl)oxindole (XXXI),[4] red needles, mp 275—280°.

2) A mixture of XXX (0.1 g) and $LiAlH_4$ (0.1 g) in ether (20 ml) was refluxed for 5 hr. After addition of AcOEt (1 ml) and H_2O (0.3 ml), the resulting precipitate was filtered and washed with ether. The filtrate and washings were combined, dried over Na_2SO_4 and concentrated. The residue was chromatographed on alumina with $CHCl_3$–CCl_4 (1:1). Recrystallization of the first effluent from EtOH afforded 0.05 g of XXX. TLC of the mother liquor showed a spot which agreeded with that of 3-(2-quinolyl)indole (XXXII).[3]

Reaction of 3-Methoxyindole (III) with IV——1) To a solution of IV (0.8 g) in $CHCl_3$ (15 ml), C_6H_5COCl (0.8 g)–$CHCl_3$ (10 ml) and III (0.8 g)–$CHCl_3$ (15 ml) were added dropwise under ice-cooling and stirring. After 7 hr's stirring, the reaction mixture was shaken with 10% Na_2CO_3 (10 ml) for 2 hr and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and passed through an alumina column. The first effluent was recrystallized from EtOH to give 0.44 g of 2-(2-quinolyl)-3-methoxy-indole (XXXIII), yellow needles, mp 138—139°. IR cm^{-1}: ν_{N-H} 3200; $\nu_{C=C}$ (indole) 1600 (Nujol). *Anal.* Calcd. for $C_{18}H_{14}ON_2$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.41; H, 5.19; N, 10.17.

2) The similar reaction using TsCl (1.2 g) instead of C_6H_5COCl was carried out for 4 hr, and the products were chromatographed on alumina in $CHCl_3$–CCl_4. From the first elute 0.05 g of XXXIII was obtained. The second effluent was recrystallized from MeOH to yield 0.09 g of 3-methoxy-1,2-bis(2-quinolyl) indole (XXXIV), pale yellow needles, mp 116—117.5°. IR cm^{-1}: $\nu_{C=C}$(indole) 1600; no N-H stretching band was observed (Nujol). *Anal.* Calcd. for $C_{27}H_{19}ON_3$: C, 80.77; H, 4.77; N, 10.48. Found: C, 80.56; H, 5.27; N, 10.47.

3) A solution of IV (0.8 g) and III (0.8 g) in Ac_2O (8 ml) was kept at 50° for 24 hr, concentrated *in vacuo*, treated with 10% Na_2CO_3 and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and passed through an alumina column to give 0.48 g of XXXIV.

Reaction of 2-(2-Quinolyl)-3-methoxy-indole (XXXIII)——1) A mixture of XXXIII (0.5 g) and pyridine hydrochloride (2 g) was heated at 180—210° for 30 min. The reaction mixture was cooled and triturated with $CHCl_3$ and H_2O, and the insoluble substance was filtered and recrystallized from EtOH to give 0.2 g of black-violet sands, mp 230° (XXXVII).

This was heated under reflux with $POCl_3$ (5 ml) for 7 hr, and the resulting solution was concentrated *in vacuo*, poured on ice-water, neutralized with 10% Na_2CO_3 and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated. The residue (XXXVIII) was dissolved in MeOH (40 ml) and hydrogenated over 25% Pd-C (0.25 g). The catalyst was filtered and washed successively with 10% Na_2CO_3 (2 ml), H_2O, MeOH and $CHCl_3$. The filtrate and washings were combined and evaporated *in vacuo*. The residue was treated with H_2O and $CHCl_3$, and the fraction soluble in $CHCl_3$ was chromatographed on alumina

in $CHCl_3$–CCl_4 (1:2). Recrystallization of the effluent from EtOH to give 0.03 g of 2-(2-quinolyl)indole (XXXIX),[3] yellow needles, mp 184—186°.

2) A solution of XXXIII (0.32 g) and $KMnO_4$ (1.1 g) in acetone (60 ml) was stirred at room temperatures for 6 hr, and EtOH (5 ml) was added to this solution to decompose excess $KMnO_4$. The precipitated MnO_2 was filtered and washed with acetone, and the combined filtrate and washings were evaporated *in vacuo*. The residue was shaken with 5% KOH and $CHCl_3$, and the $CHCl_3$ layer was washed with H_2O, dried over Na_2SO_4 and passed through an alumina column. Recrystallization of the effluent from EtOH gave 0.2 g of methyl N-quinaldylanthranilate (XXXV), colorless leaflets, mp 147—151°. IR cm^{-1}: ν_{N-H} 3200; $\nu_{C=O}$(ester) 1703; $\nu_{C=O}$(amide) 1680 (Nujol). *Anal.* Calcd. for $C_{18}H_{14}O_3N_2$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.63; H, 4.66; N, 9.35.

A mixture of XXXV (0.07 g), 2% NaOH (10 ml) and EtOH (4 ml) was refluxed for 2 hr. The cooled solution was neutralized with AcOH, and the resultant precipitate was filtered and recrystallized from EtOH to give 0.06 g of N-quinaldylanthranilic acid (XXXVI), colorless crystals, mp 255—255.5°. This was proved identical with an authentic sample prepared from quinaldyl chloride and anthranilic acid.[13]

A solution of XXXVI (0.17 g) in MeOH (20 ml) was saturated with HCl gas and refluxed for 3 hr. After evaporation of MeOH *in vacuo*, the residue was made alkaline with $NaHCO_3$ solution and extracted with $CHCl_3$. The extracted substance was recrystallized from EtOH to give a few miligrams of XXXV, colorless leaflets, mp 148—150°. This was identified with the above sample obtained from XXXIII by comparison of IR spectra and the admixture.

Reaction of 3-Methoxy-1,2-bis(2-quinolyl)indole (XXXIV)——A solution of XXXIV (0.46 g) and $KMnO_4$ (2 g) in acetone (70 ml) was stirred at room temperatures for 15 hr. After addition of EtOH, the precipitated MnO_2 was filtered and washed with acetone. The combined filtrate and washings were concentrated *in vacuo*, and the residue was treated with H_2O and $CHCl_3$. The $CHCl_3$ layer was separated, dried over Na_2SO_4 and evaporated. The residue was purified by chromatography on alumina in $CHCl_3$–CCl_4 (1:5) and recrystallized from MeOH to give 0.08 g of methyl N-(2-quinolyl)anthranilate (XLI), colorless cubes, mp 133—135°. IR cm^{-1}: ν_{N-H} 3280; $\nu_{C=O}$ 1695 (Nujol). *Anal.* Calcd. for $C_{17}H_{14}O_2N_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.62; H, 5.08; N, 10.04.

Reaction of Methyl Anthranilate with 2-Chloroquinoline——When a mixture of methyl anthranilate (1.4 g) and 2-chloroquinolne (1.2 g) was melted at 160°, a violent reaction ensued. Afetr the evolution of gas had ceaced, the mixture was cooled and shaken with 10% Na_2CO_3 and $CHCl_3$. The $CHCl_3$ layer was separated, dried over Na_2SO_4 and evaporated, and the residue was recrystallized from $CHCl_3$–MeOH to give colorless crystals of mp 168—169°, which agreed with the reported melting point of 12-H-quinolino[2, 1-*b*]quinazolone-12 (XLII).[14] *Anal.* Calcd. for $C_{16}H_{10}ON_2$: C, 78.03; H, 4.09; N, 11.38. Found: C, 78.38; H, 4.33; N, 11.55. The mother liquor was concentrated and the residue was recrystallized from MeOH to give 0.03 g of XLI, mp 134—135°.

Reaction of Ethyl Nicotinate 1-Oxide (XLIII) with III——1) To a solution of XLIII (1 g) and III (0.9 g) in $CHCl_3$ (15 ml), C_6H_5COCl (0.9 g)–$CHCl_3$ (10 ml) was added under ice-cooling and stirring. Stirring was continued for 3 hr, during which the temperature rised to room temperatures. The reaction mixture was shaken with 10% Na_2CO_3 (13 ml) for 40 min and extracted with $CHCl_3$. The extracted substance was purified by chromatography on alumina in $CHCl_3$–CCl_4 (1:3) and recrystallized from MeOH to give 0.07 g of 2-(5-methoxycarbonyl-2-pyridyl)-3-methoxy-indole (XLIV), yellow needles, mp 151—153°. IR cm^{-1}: ν_{N-H} 3400; $\nu_{C=O}$ 1704 (Nujol). *Anal.* Calcd. for $C_{17}H_{16}O_3N_2$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.52; H, 5.25; N, 9.17.

2) A mixture of XLIII (1 g) and II (0.9 g) in Ac_2O (4 ml) was refluxed for 7 hr. The reaction mixture was evaporated *in vacuo* and the residue was shaken with 10% Na_2CO_3 and $CHCl_3$. The $CHCl_3$ layer was separated and the extracted substance was recrystallized from MeOH to give 0.32 g of 1-acetyl-3-methoxy-indole (XLV), colorless sands, mp 102—103°. IR cm^{-1}: $\nu_{C=O}$ 1670; ν_{N-H} was not observed (Nujol). *Anal.* Calcd. for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.82; H, 6.05; N, 7.82.

Reaction of 1-Methyl-2-chloro-3-(2-quinolyl)indole (XLVI) with Lithium Aluminium Hydride——To a solution of $LiAlH_4$ (0.1 g) in ether (15 ml), XLVI (0.1 g)–ether (20 ml) was added with stirring, and the solution was refluxed for 6 hr and treated with AcOEt and H_2O (0.2 ml). The resultant precipitate was filtered and washed with ether. The combined filtrate and washings were evaporated, and the residue was recrystallized from acetone–MeOH to give 0.05 g of VIII.[3]

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