[Chem. Pharm. Bull. 15(9)1380~1384(1967)]

UDC 547.831.1.04 : 615.754.5-011

177. Masatomo Hamana and Hiroshi Noda : Studies on Tertiary Amine Oxides. XXXI.*1 Reactions of Aromatic N-Oxides with Antipyrine in the Presence of Acylating Agents.

(*Faculty of Pharmaceutical Sciences, Kyushu University**2)

Antipyrine (I) was shown to react smoothly with quinoline 1-oxide (II), 4-chloroquinoline 1-oxide (VII) and isoquinoline 2-oxide (IX) in the presence of benzoyl chloride, producing 4-(2-quinolyl)antipyrine (III) (63.4%) together with 4-(4-quinolyl)antipyrine (IV) (16.4%), 4-(4-chloro-2-quinolyl)antipyrine (VIII) (88%) and 4-(1-isoquinolyl)antipyrine (X) (79%), respectively. Although tosyl chloride was not effective as an acylating agent for these reactions, methosulfate of II could enter into reaction with I to give III in 38.4% yield. Nucleophilic reactivity of I was considerably lower compared with that of cyclohexanone enamine, and no satisfactory result was obtained from similay treatment of pyridine 1-oxide.

(Received December 15, 1966)

Previous papers*1,1) from this Laboratory have described that treatment of the acyl-adducts of N-oxides of pyridine series with enamines of cyclohexanone followed by hydrolysis of the reaction mixtures leads to introduction of α-cyclohexanonyl group into the pyridine ring in fairly good yields. Although there is multiplicity in the position undergone substitution as well as in the detailed reaction mechanism depending upon the structure of N-oxide, all the reactions can be assumed to proceed by nucleophilic attack of the enamine at the pyridine nucleus accompanied by elimination of acyloxy group from the ring nitrogen. Since no reaction occurs wih cyclohexanone itself under comparable conditions, it is clear that the high nucleophilic activity of the enamine caused by the following polarization plays an essential role in such reactions. This fact suggests the possibility that besides enamines an appropriate system including similar polarization would enter into reaction with acyl-adducts of aromatic N-oxides. In fact, it was previously shown that N,N-dimethylaniline reacted with quinoline 1-oxide in the presence of benzoyl chloride to produce 2-(*p*-dimethylaminophenyl)quinoline.2) In order to ascertain this possibility and also to widen the scope of this kind of reaction, antipyrine, indoles and enol ethers were applied to some aromatic N-oxides in the presence of an acylating agent. The present communication deals with our observations using antipyrine as an analogue of enamine.

When a solution of antipyrine (I), quinoline 1-oxide (II) and benzoyl chloride in chloroform was refluxed on a water-bath, a reaction ensued and the color of the solution turned from pale yellow to deep orange, while no reaction was observed at room temperatures. After heating for fourteen and a half hours, the reaction mixture was treated with potassium carbonate solution and the products were extracted with chloroform to give colorless needles (III) of m.p. 162~163° as the major product (63.4%) together with a small amount of pale yellow crystals (IV), m.p. 204~206° (16%). Both

*1 Part XXX. M. Hamana, H. Noda : This Bulletin, **15**, 474 (1967).
*2 Katakasu, Fukuoka (浜名政和, 野田浩司).
1) *a*) M. Hamana, H. Noda : This Bulletin, **13**, 912 (1965). *b*) *Idem* : *Ibid.*, **14**, 762 (1966).
2) M. Hamana, O. Hoshino : Yakugaku Zasshi, **81**, 35 (1964).

TABLE I. Reaction of Quinoline 1-Oxide (II) with Antipyrine (I) in the Presence of an Acylating Agent

II (g.)	I (g.)	Acylating agent	Solvent	Reaction conditions: temp. (°C)	Reaction conditions: time (hr.)	Products (g.) (%): III	Products (g.) (%): IV	Recovered I (g.) (%)
1.45	2.26	PhCOCl (1.6 g.)	$CHCl_3$	R.T. reflux	0.5 2	0.942 (29.9)	0.452 (14.3)	1.08 (47.8)
1.45	2.26	PhCOCl (1.6 g.)	$CHCl_3$	R.T. reflux	12 9	1.34 (42.6)	0.4 (12.7)	0.46 (20.4)
1.45	2.26	PhCOCl (1.6 g.)	$CHCl_3$	reflux	14.5	2.0 (63.4)	0.5 (19.5)	—
1.45	2.07	Me_2SO_4 (1.26)	MeCN	reflux	7	1.21[a] (38.4)	—	—
						V	VI	
1.45	2.07	TsCl (2.1)	$CHCl_3$	R.T. reflux	0.5 7	0.85 (52)	0.55 (38)	2.06 (*ca.* 100)

a) Besides III, 0.202 g. (16%) of quinoline was recovered.

TABLE II. Nuclear Magnetic Resonance Spectra of I, III, IV and X

Compound	Chemical shifts (τ)[a]: quinoline ring: C_2–H	C_3–H	C_4–H	C_8–H	$C_{5,6,7}$–H	antipyrine ring: C–CH_3	N–CH_3	C_4–H	Phenyl–H
I	—	—	—	—	—	7.8	6.98	4.63	2.62
III	—	2.53 or 2.58 (d; J=8.25[b])	1.46[c] (d; J=8.25)		1.83~2.37[d] (m)	7.16[g]	6.83	—	2.60
IV	1.08 (d) (J=4.5)	2.71 (d) (J=4.5)	—	1.89 (m)	2.07~2.5 (m)	7.85	6.8	—	2.53
X	—[e]	1.45 (d) (J=6)	1.72~2.7 (m)[f]			7.7	6.83	—	2.56

a) Spectra were determined on solution in $CDCl_3$, using TMS as internal reference by JMN-3H-60 spectrometers operated at 60 Mc. d: doublet, m: multiplet
b) J value in c.p.s. *c*) τ values of C_4–H or C_8–H *d*) τ values of C_4–H or C_8–H, and $C_{5\sim7}$–H
e) C_1–H of isoquinoline ring *f*) $C_{4\sim7}$ and 8-H
g) The reason why the C-methyl resonance of III appears in 0.64 p.p.m. lower fields compared with that of antipyrine itself is considered to be as follows. Inspection of the Stuart model indicates that the C-methyl group of III lies so closely to the quinoline ring in the same plane to be appreciably deshielded by the ring current effect of quinoline ring. On the other hand, this situation can not be applied to IV and X, because of the steric hindrance by the hydrogen atom at the 5-position of quinoline or that at the 8-position of isoquinoline, respectively; thus, these C-methyl groups are not affected by the above-mentioned effect.

compounds gave the same analytical values in agreement with that of quinolylantipyrine, $C_{20}H_{17}ON_3$.

Similar reaction with 4-chloroquinoline 1-oxide (VII) resulted in formation of pale yellow needles (VIII) of m.p. 200~202° in a high yield of 88%. This compound corresponded to a chlorinated derivative of III or IV, and was reduced catalytically to III in 91% yield. From these results as well as analogy with the reactions of cyclohexanone enamines, III, IV and VIII were assumed to be 4-(2-quinolyl)-, 4-(4-quinolyl)- and 4-(4-chloro-2-quinolyl)-antipyrine, respectively. These structural assignments were confirmed by examination of the nuclear magnetic resonance spectra (Table II).

It is interesting to note that in the above reaction with II using benzoyl chloride, the longer the period of heating, the better yields of III were obtained, while that of IV

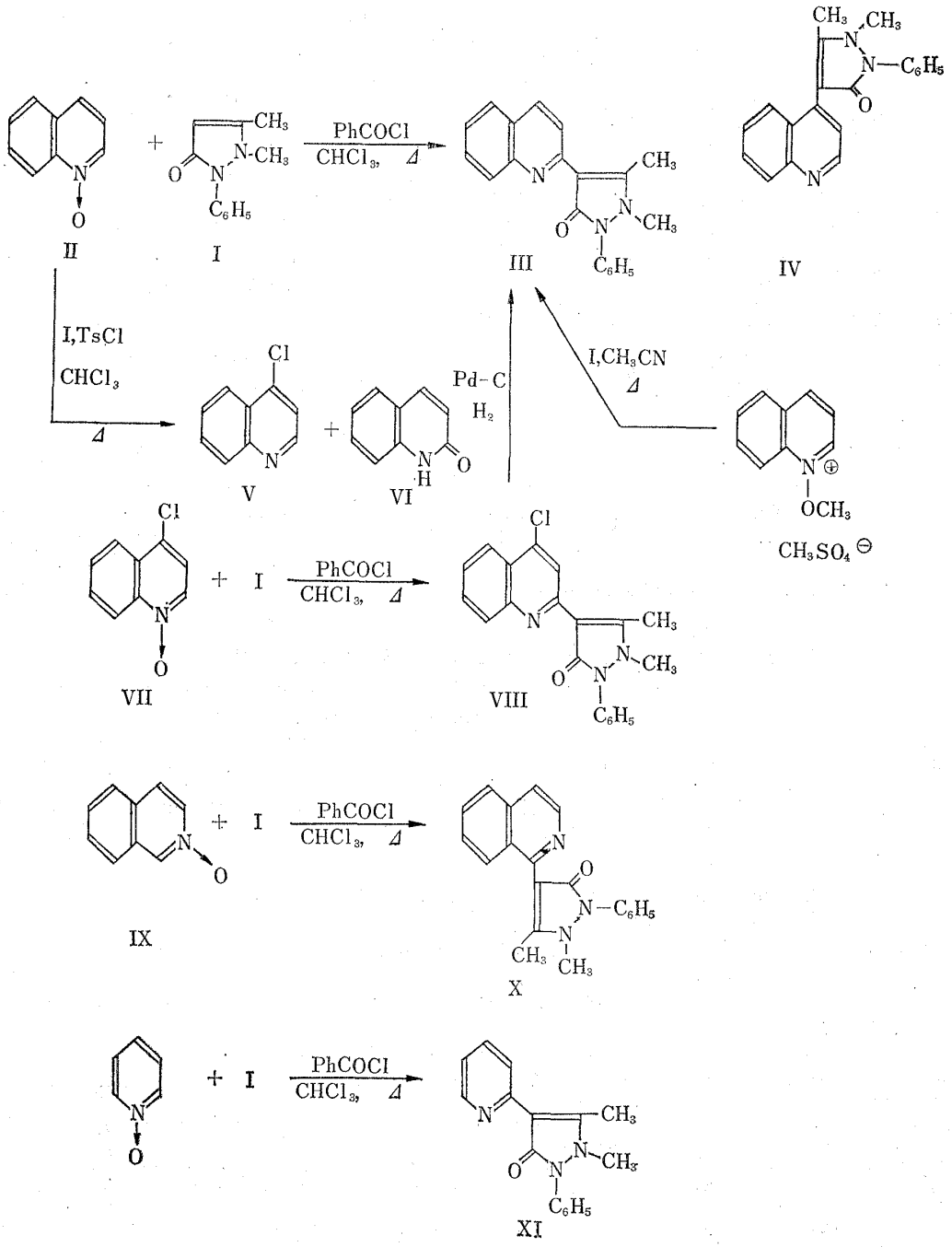

Chart 1.

remained almost the same. On the other hand, the use of *p*-toluenesulfonyl chloride as an acylating agent in place of benzoyl chloride resulted in formation of 4-chloroquinoline (V) and carbostyril (VI) in 52 and 38% yields, respectively, accompanied by recovery of antipyrine in a practically theoretical amount. However, N-methoxyquinolinium methosulfate[3] was found to react with I in hot acetonitrile and III was formed in 38.4% yield together with a small amount of quinoline after seven hours' heating. These results are summarized in Table I.

The reaction of isoquinoline 2-oxide (IX) also progressed in the presence of benzoyl chloride, and 4-(1-isoquinolyl)antipyrine (X) was obtained as colorless needles of m.p.

3) T. Okamoto, H. Takayama: This Bulletin, **11**, 514 (1963).

172~173°, in 79% yield, after fifteen hours' heating. The structure of X was deduced from the NMR spectrum.

In spite of the ease reaction with the enamine, pyridine 1-oxide was so feebly reactive with antipyrine that a compound conceivable to be 4-(2-pyridyl)antipyrine (XI), colorless needles of m.p. 142~144°, was obtained in only 5% yield accompanied by 95% recovery of I, even when heating was continued for fourteen hours in the presence of benzoyl chloride. Similarly, no expected product was detected from 4-chloropyridine 1-oxide, I being recovered besides some black resine.

Chart 1 shows the reactions mentioned above.

As a consequence of the experiments described above it is now shown that antipyrine is capable of reacting as an analogue of enamine with quinoline and isoquinoline N-oxides in the presence of benzoyl chloride. However, its reactivity is considerably lower compared with cyclohexanone enamines, and for the smooth progress of the reaction it is required somewhat prolonged heating and the presence of naphthoid structure in aromatic N-oxide. On the other hand, it is favorable for the preparative procedure that antipyrine is far more stable toward heating. The fact that the reaction of quinoline 1-oxide using *p*-toluenesulfonylchloride follows a quite different course from that using benzoyl chloride is analogous to the results obtained in the reaction of the acyl-adduct of the same N-oxide with N,N-dimethylaniline.[2] These observations apparently demonstrate that the nature of acylating agent is very important for the pattern of the reaction of aromatic N-oxide involving a N-acyloxy compound as an intermediate.

Experimental*4

Reactions of Quinoline 1-Oxide (II) with Antipyrine (I)——1) To a solution of quinoline 1-oxide (II) (1.45 g.) and antipyrine (I) (2.26 g.) in $CHCl_3$ (20 ml.), PhCOCl (1.69 g.) was added at room temperature, and the whole was refluxed on a water-bath for 14.5 hr. The resulted deep orange mixture was cooled to give a solid mass, to which was added 20% K_2CO_3 solution and $CHCl_3$ layer was separated and the residual aqueous layer was further extracted with $CHCl_3$. The combined $CHCl_3$ solution was concentrated into a small volume and poured onto an alumina column followed by eluting successively with benzene and ether to afford 2 g. of 4-(2-quinolyl)antipyrine (III), and 0.5 g. of 4-(4-quinolyl)antipyrine (IV). The former, III, colorless needles of m.p. 162~163°(AcOEt). *Anal.* Calcd. for $C_{20}H_{17}ON_3$: C, 76.17; H, 5.43; N, 13.33. Found: C, 76.17; H, 5.65; N, 13.21. The latter, IV, formed colorless scales of m.p. 203~204°. *Anal.* Calcd. for $C_{20}H_{17}ON_3$: C, 76.17; H, 5.43; N, 13.33. Found: C, 76.01; H, 5.31; N, 13.27.

2) A mixture of II (1.45 g.), I (2.26 g.) and PhCOCl (1.69 g.) in $CHCl_3$ (20 ml.) was kept overnight at room temperatures, no sign of reaction being observed. After refluxing for 9 hr., the reaction mixture was treated in a similar manner as described above. The crude products were dissolved in as small amount of $CHCl_3$ as possible, and this $CHCl_3$ solution poured onto an alumina column and eluted successively with ether, $CHCl_3$ and AcOEt to yield 1.34 g. of III, and 0.4 g. of IV and then 0.46 g. of recovered I.

3) A mixture of II (1.45 g.) and Me_2SO_4 (1.26 g.) was heated for 2 hr. on a water-bath, followed by keeping overnight at room temperature. This was dissolved in MeCN (20 ml.) to give a homogeneous solution, to which was added I (2.07 g.). The whole was refluxed for 7 hr., concentrated *in vacuo*, made alkaline with 20% K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ solution was passed through an alumina column to yield 0.20 g. of quinoline, b.p_{25} 160°(bath temp.) and then 1.21 g. of III.

4) To a solution of II (1.45 g.) and I (2.07 g.) in $CHCl_3$ (20 ml.) was added TsCl (2.1 g.). Some heat of reaction was observed and the solution turned to yellow. After standing for 30 min. at room temperature, the solution was refluxed for 7 hr. After cooling, 20% K_2CO_3 solution was added to the solution and $CHCl_3$ layer was separated and the H_2O layer was extracted further with $CHCl_3$. Evaporation of the combined $CHCl_3$ extract left a solid, which was recrystallized from EtOH to give 0.11 g. of carbostyril, m.p. 194~196°. The mother liquor was evaporated and the residue was purified by chromatography in benzene on an alumina column to afford 0.85 g. of colorless oil, which was identified as 4-chloroquinoline by converting to its picrate, m.p. 205~207°. The column was further eluted with $CHCl_3$ and AcOEt to yield 2.06 g. of I and then additional 0.44 g. of carbostyril.

Reaction of 4-Chloroquinoline 1-Oxide (VII)——1) A solution of VII (0.54 g.), I (0.68 g.) and PhCOCl (0.51 g.) in $CHCl_3$ (10 ml.) was refluxed for 12 hr. and then worked up in an usual way. Recrystallization of

*4 All melting points and boiling points are uncorrected.

the crude product from EtOH gave 0.49 g. of 4-(4-chloro-2-quinolyl)antipyrine (Ⅷ), pale yellow needles, m.p. 199~201°. The mother liquor was evaporated and the residue was dissolved in $CHCl_3$ and chromatographed on an alumina column to afford an additional 0.48 g. of Ⅷ. Ⅷ was further purified by recrystallization from AcOEt to melt at 201~202°. *Anal.* Calcd. for $C_{20}H_{16}ON_3Cl$: C, 68.40; H, 4.65; N, 11.97. Found: C, 68.64; H, 4.46; N, 11.72.

2) A solution of Ⅷ (0.45 g.) in MeOH (30 ml.) was hydrogenated at ordinary temperature and pressure over 10% Pd-C (0.1 g.) to give 0.37 g. of Ⅲ.

Reaction of Isoquinoline 2-Oxide (IX)——A solution of Ⅸ (1.45 g.), I (2.26 g.) and PhCOCl (1.69 g.) in $CHCl_3$ (20 ml.) was refluxed for 15 hr., and the resulted deep orange solution was quite similarly treated. Purification of the products was carried out by chromatography on alumina. Elution with $CHCl_3$ gave 2.49 g. of 4-(1-isoquinolyl)antipyrine (X), colorless needles, m.p. 172~173°(AcOEt). *Anal.* Calcd. for $C_{20}H_{17}ON_3$: C, 76.17; H, 5.43; N, 13.33. Found: C, 76.15; H, 5.58; N, 13.16. Subsequent elution with AcOEt afforded 0.68 g. of unchanged I.

Reaction of Pyridine 1-Oxide——A solution of pyridine 1-oxide (1.9 g.), I (4.14 g.) and PhCOCl (3.38 g.) in $CHCl_3$ (20 ml.) was refluxed for 14 hr. on a water-bath. To the cooled reaction mixture was added K_2CO_3 solution. The $CHCl_3$ layer was separated and the residual H_2O layer was extracted with $CHCl_3$. Evaporation of the combined $CHCl_3$ extract left a solidified residue, to which was added cold ether, and undissolved I (1.46 g.) was collected. The ether solution was poured onto an alumina column, followed by eluting with $CHCl_3$ to afford an additional 2.46 g. of I. Subsequent elution of the column with AcOEt yielded 0.22 g. of Ⅺ, colorless needles, m.p. 142~143°(benzene). *Anal.* Calcd. for $C_{16}H_{15}ON_3$: C, 72.43; H, 5.70. Found: C, 72.31; H, 5.68. Further, 0.43 g. of pyridine 1-oxide was obtained, $b.p_4$ 130~140°(bath temp.), picrate, m.p. 181~183°(EtOH).