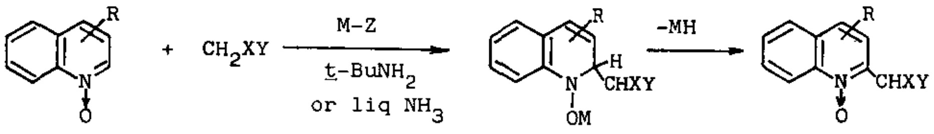
HETEROCYCLES, Vol 22, No. 8, 1984

FACILE FORMATION OF 2,2'-DIQUINOLYLMETHANE N,N'-DIOXIDES AND MONO-N-OXIDES AND RELATED REACTIONS

Genji Iwasaki, Kazuko Wada, Seitaro Saeki and Masatomo Hamana*,[1]
Faculty of Pharmaceutical Sciences, Kyushu University
Maidashi 3-1-1, Higashi-ku, Fukuoka 812, Japan

Abstract —— Reactions of quinoline N-oxides with derivatives of quinaldine or its N-oxide in the presence of t-BuOK in THF at low temperatures afford mono-N-oxides or N,N'-dioxides of 2,2'-diquinolylmethanes, respectively. Some related reactions are also described, which involve reactions of p-chloronitrobenzene giving 2-substituted 4-chloronitrobenzenes.

We previously reported that quinoline N-oxides readily undergo nucleophilic substitution by means of hydride elimination to give 2-substituted quinoline N-oxides, upon treatment with active methylenes and strong bases (t-BuOK, n-BuLi, KNH_2 or $NaNH_2$) in t-$BuNH_2$ or liq. NH_3 at low temperatures as shown below.[2]



R: H, 4-Cl, 3-Br
YXCH-: $-CH_2COMe$, $-CH_2COCMe_3$, $-CH_2COPh$, $-CH_2COOMe$, $-CH_2CN$, etc.
M-Z: t-BuOK, n-BuLi, KNH_2, $NaNH_2$

As an extension of this work, we applied quinaldine and its N-oxide derivatives as active methylenes to quinoline N-oxides under similar conditions, and successfully obtained mono-N-oxides and N,N'-dioxides of 2,2'-diquinolylmethanes.

At first, the reaction of 4-chloroquinoline N-oxide (1b) with quinaldine N-oxide (2a) was investigated in some detail. When 1b was added in small portions to a solution of **2a** (2 equiv) and *t*-BuOK (2.5 equiv) in THF with stirring at -70° C, the reaction mixture immediately turned black. Stirring was continued at the same temperature for 2 h, and the product was purified by chromatography on silica gel with benzene to give *4-chloro-2,2'-diquinolylmethane N,N'-dioxide* (**3b**), *colorless needles*, mp 209-211°C (dec.), in 47.6% yield.[3] The same product **3b** was also obtained from the reaction of quinoline N-oxide (**1a**) with 4-chloroquinaldine N-oxide (**2b**) under the same conditions in 46.5% yield (Chart 1).

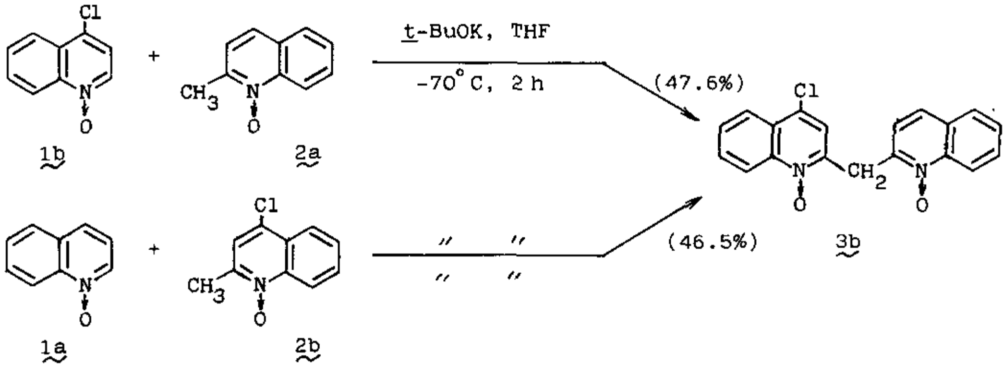


Chart 1

Consecutively, various conditions were examined for the reaction of **1b** with **2a**, and the results summarized in Table were obtained.

Table Reaction of **1b** with **2a**

Solvent	Base	Temp. (° C)	Time(h)	Yield of **3b** (%)
THF	*t*-BuOK	-70	2.0	47.6
	n-BuLi	-70	2.0	13.8
	LDA[a)]	-50	2.5	—
liq NH_3	*t*-BuOK	-70	2.0	45.9
	KNH_2	-60	1.0	35.2
	$NaNH_2$	-60	1.0	29.5
	$LiNH_2$	-60	1.0	5.8
t-$BuNH_2$	*t*-BuOK	-70	2.0	32.1

a) Lithium diisopropylamide

Thus it was found that the ease of the reaction was considerably affected by the nature of both base and solvent. Among the bases so far examined, *t*-BuOK was highly effective, and THF and liq. NH_3 were preferable as the reaction medium. It is noteworthy that the combination of LDA and THF did not give **3b** at all, while that of $LiNH_2$ and liq. NH_3 produced **3b**, though in poor yield.

2,2'-Diquinolylmethane N,N'-dioxide (**3a**), its 3-bromo- (**3c**) and 4-chloro-4'-methyl derivatives (**3d**) were similarly obtained under similar conditions as illustrated in Chart 2.

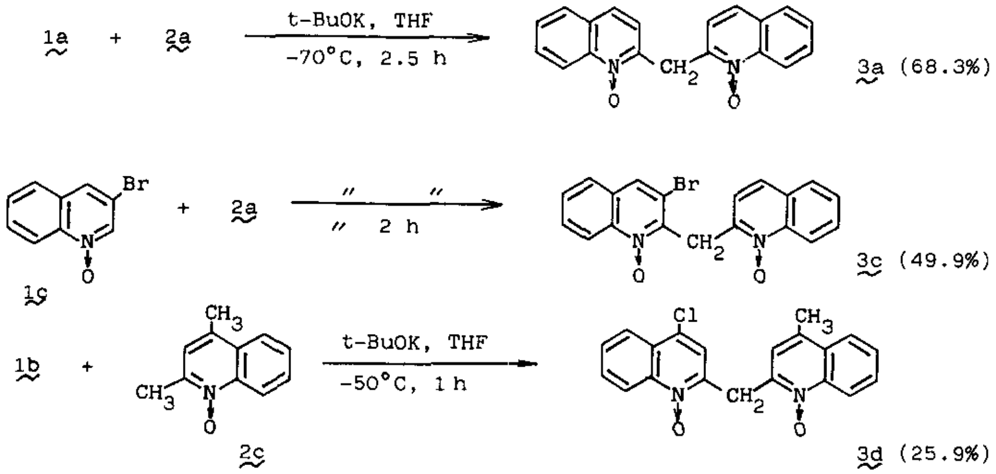


Chart 2

Subsequently, 2,2'-diquinolylmethane mono-N-oxides were obtained from similar reactions with quinaldine or 2,4-dimethylquinoline (Chart 3).

The reactions using 2,4-dimethylquinoline or its N-oxide clearly demonstrate that the 2-methyl group in quinoline ring is much more reactive than the 4-methyl group. However, the reaction of **1b** with lepidine proceeded similarly to give 4-chloro-2,4'-diquinolylmethane N-oxide. Further, 2-picoline N-oxide reacted also smoothly with **1b** to afford 2-pyridyl-2-(4-chloroquinolyl)methane N,N'-dioxide (Chart 3).

While a few methods are known for the preparation of 2,2'-diquinolylmethane and its analogs,[4] there has been no report on the synthesis of their N-oxide or N,N'-dioxide. The N-oxidation of 2,2'-diquinolylmethane is quite unpractical for this purpose because its methylene group is highly susceptible to oxidation.[4,5]

Therefore, the above mentioned reaction is evidently a very promising method for the preparation of 2,2'-diquinolylmethane N-oxide, N,N'-dioxide and their analogs. In addition, this route is also usefull and convenient for the preparation of 2,2'-diquinolylmethane, its analogs and their derivatives, since deoxygenation of aromatic N-oxide can be easily performed by a number of means.

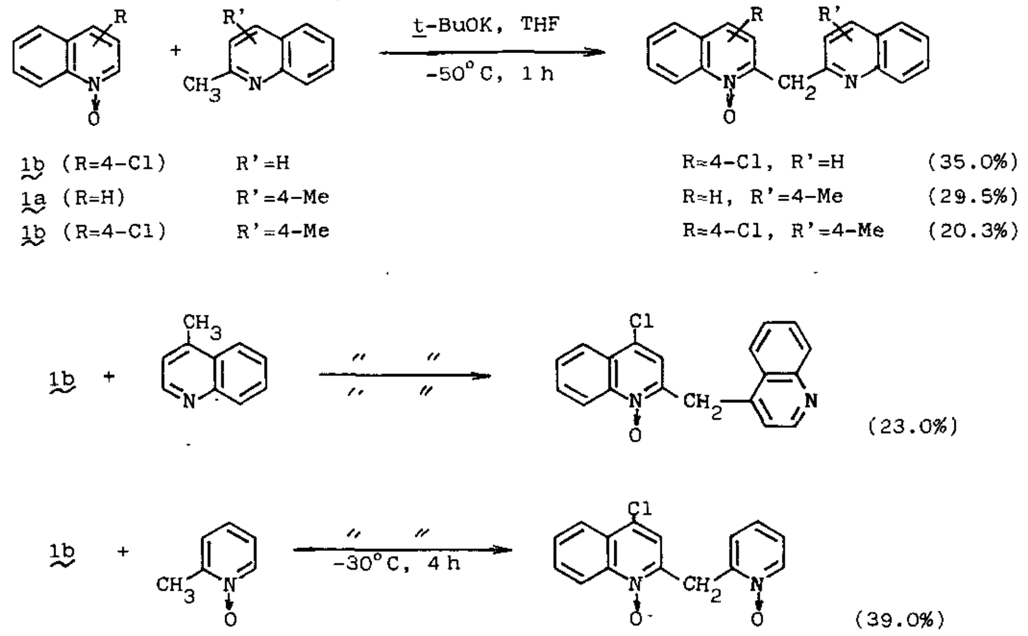


Chart 3

It was previously described that p-chloronitrobenzene is also able to undergo the nucleophilic substitution mentioned at the beginning, giving 2-substituted 4-chloronitrobenzenes.[2] This fact prompted us to investigate the reactivity of p-chloronitrobenzene toward the reaction concerned here, and some attempted reactions were found to give the corresponding 2-substituted 4-chloronitrobenzenes as was expected (Chart 4).

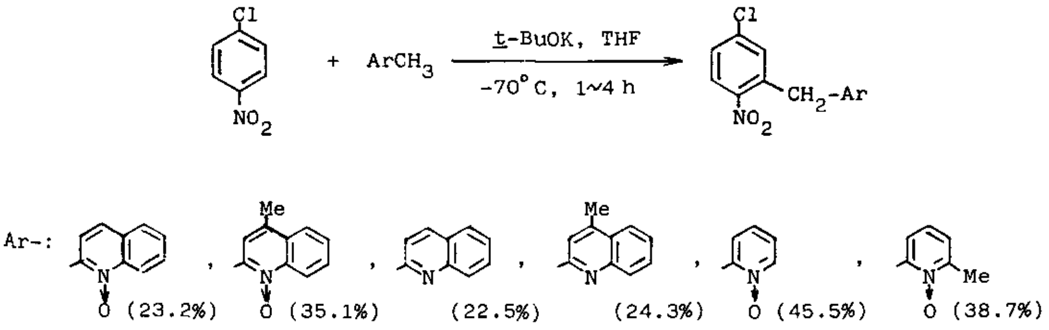


Chart 4

ACKNOWLEDGMENT

We are grateful to a Grant-in Aid for Chemical Research in Development and Utilization of Nitrogen-Organic Resources from the Ministry of Education, Science and Culture, Japan, for partial financial support of this work.

REFERENCES AND NOTES

1. Present address: Central Research Laboratories, Chugai Pharmaceutical Co., Ltd., Takada 3-41-8, Toshima-ku, Tokyo 171, Japan.
2. M. Hamana, G. Iwasaki and S. Saeki, *Heterocycles*, 1982, **17**, 177.
3. All new compounds gave satisfactory microanalytical and spectral data.
4. G. Scheibe and E. Daltrozzo, *Adv. Heterocycl. Chem.*, 1966, **7**, 153.
5. M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.*, 1963, **11**, 415.

Received, 28th April, 1984