The Institute of Physical
and Chemical Research,
Kamifujimae-cho, Bunkyo-ku, Tokyo.

Akira Tahara (田原　昭)
Osamu Hoshino (星野　修)
Yasuhiko Hamazaki (浜崎泰彦)

Received July 1, 1963

[Chem. Pharm. Bull. 11 (10) 1331 ~ 1333]

UDC 547.831.1 : 547.594.3'831

Reactions of Quinoline 1-Oxide with Enamines of Cyclohexanone

Recent reports[1,2] from this laboratory have shown that quinoline 1-oxide reacts smoothly with compounds containing reactive hydrogens, *e.g.* ethyl cyanoacetate, in the presence of acetic anhydride, producing the corresponding 2-substituted quinolines in good yield, but no reaction occurs with less reactive compounds such as acetone or acetophenone. In an extension of this work we found that cyclohexanone, which was inactive as it was, could readily enter into the reaction under the similar condition when it was modified as an enamine.

When benzoyl chloride (1.2 equiv.) was added to the chloroform solution of quinoline 1-oxide and morpholine enamine of cyclohexanone (2 equiv.) under ice cooling, an exothermic reaction took place and the solution turned to deep red. Treatment of the reaction mixture with 20% hydrochloric acid gave 2-(2-quinolyl)cyclohexanone as a major product (74% yield), which crystallized as orange prisms from methanol, m.p. 121~122°, UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε) : 216.5 (4.57), 278 (3.95), 440 (3.89). $\lambda_{\max}^{N\,\mathrm{HCl}}$ mμ (log ε): 237 (4.52), 317 (4.06). (*Anal.* Calcd. for $C_{15}H_{15}ON$: C, 79.97; H 6.71; N, 6.22. Found : C, 79.95; H, 6.72; N, 5.75). Oxime, white lieflets, m.p. 190~192° (from EtOH, *Anal.* Calcd. for $C_{15}H_{16}ON_2$: C, 74.97; H, 6.71; N, 11.66. Found : C, 75.04; H, 7.00; N, 11.21).

Without benzoyl chloride, quinoline 1-oxide could not react with the enamine of cyclohexanone. The reaction should be considered to proceed through the following couse.

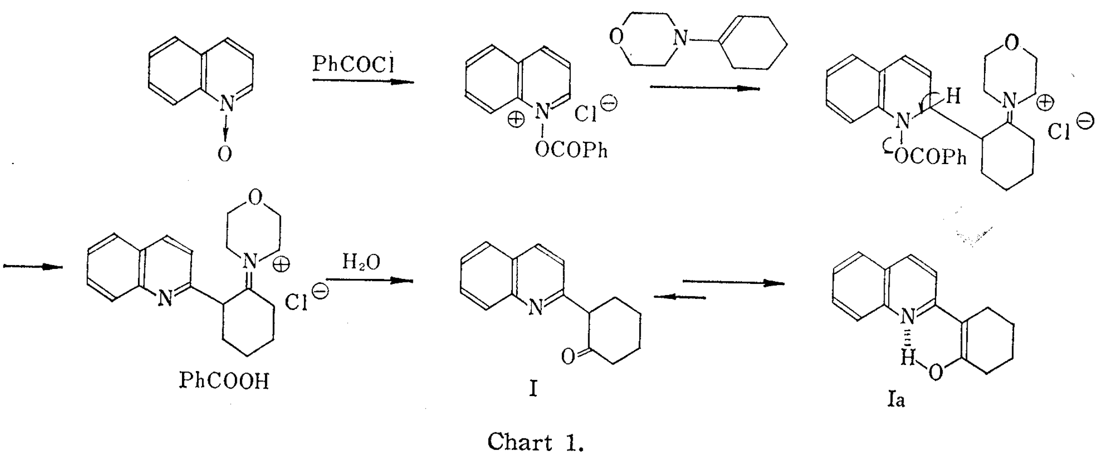

Chart 1.

---

[1] M. Hamana, M. Yamazaki : This Bulletin, **11**, 412 (1963).
[2] *Idem* : *Ibid.*, **11**, 415 (1963).

The compound (I) was obtained likewise in good yields with other acylating agents than benzoyl chloride in contrast to the original reaction,[2)] which was found to be affected profoundly by the nature of acylating agents (Table I). The order of reactivity of enamines was in accordance with that reported in acylation of enamines;[3)] that was, morpholine->piperidine->pyrrolidine-enamine (Table I).

TABLE I.

Quinoline 1-oxide (g.)	Enamine of cyclohexanone (g.)		Acylating agent (g.)		Product (I) (%)
5.43	morpholine	10	PhCOCl	5.06	74
0.6	piperidine	1.1	〃	0.58	61.4
1.81	pyrrolidine	3.02	〃	1.74	49.3
1.81	morpholine	3.34	TsCl	2.29	66.7
1.81	piperidine	3.30	〃	2.29	55.1
1.81	pyrrolidine	3.02	〃	2.29	5.3
0.6	piperidine	1.1	Ac_2O	0.41	53.4
0.6	〃	1.1	AcCl	0.32	54.7

The structure of I was deduced by the reactions formulated below :

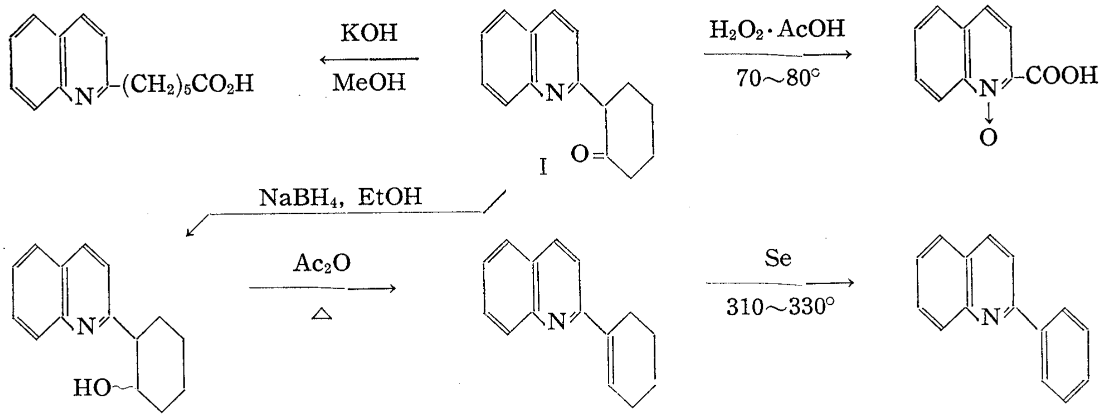

Chart 2.

Its infrared and ultraviolet absorption spectra also supported the assigned structure. The infrared spectrum lacked the absorption bands for ketonic grouping, and the ultraviolet spectrum in alcoholic solution showed absorption in the region of unusually long wave length. These facts show that I exists predominantly as an enol form and an intramolecular hydrogen bonding is formed between the enol hydroxyl group and the nitrogen of quinoline ring (Ia), in the same manner as analogous 2-substituted quinolines.[4),5)]

While the reactivity of pyridine 1-oxide was much lower as compared with that of quinoline 1-oxide in the original reaction,[2)] the new reaction of pyridine 1-oxide using benzoyl chloride and piperidine enamine of cyclohexanone afforded the expected product, 2-(2-pyridyl)cyclohexanone, also in good yield (63%). It was a viscous oil, b.p.$_{0.13}$ 138~140°. Picrate, yellow needles, m.p. 158~160° (*Anal.* Calcd. for $C_{11}H_{13}ON \cdot C_6H_3O_7N_3$: C, 50.50; H, 3.99; N, 13.86. Found : C, 50.40; H, 4.14; N, 14.01).

Kuehne[6)] reported that 2-chloroquinoline reacted with pyrrolidine enamine of cyclohexanone to give none of 2-(2-quinolyl)cyclohexanone but 1-(2-quinolyl)pyrrolidine in unsatisfactory yield. Thus the reaction reported here seems to be a novel method for the synthesis of α-(2-quinolyl or 2-pyridyl) alkanone and analogous compounds.

---

3) S. Hünig, E. Benzing, E. Lücke : Chem. Ber., **90**, 2833 (1957).
4) R.F. Brauch : Nature, **177**, 671 (1956).
5) T. Okamoto, H. Takayama : This Bulletin, **11**, 514 (1963).
6) M.E. Kuehne : J. Am. Chem. Soc., **84**, 837 (1962).

We are now extending this type of reaction to other N-oxides of heterocyclic compounds using various enamines, and the results will be reported in the future.

Institute of Pharmaceutical Sciences,
Faculty of Medicine,
Kyushu University, Katakasu, Fukuoka.

Masatomo Hamana (浜名政和)
Hiroshi Noda (野田浩司)

Received July 6, 1963

Chem. Pharm. Bull.
11 (10) 1333 ~ 1336

UDC 547.918 : 582.938

On the Structure of Metaplexigenin and Benzoylramanone

The isolation of sarcostin (I), metaplexigenin (II) and three other aglycones from the stems and leaves of *Metaplexis japonica* Makino (Asclepiadaceae)[1,2] and benzoylramanone (III) from the roots[3] has been reported previously.

In this communication, experiments leading to the structure determination of metaplexigenin (II) and benzoylramanone (III) are described. Metaplexigenin (II), m.p. 268~275°, $C_{23}H_{34}O_7$ (*Anal.* Calcd.: C, 65.38; H, 8.11. Found: C, 65.44; H, 8.14). IR ν_{max}^{Nujol} cm^{-1}: 1745, 1720, 1240. These data suggest that II has both ester and carbonyl groups. II would not form a semicarbazone, and gave only a monooxime, m.p. 267° (decomp.), $C_{23}H_{35}O_7N$ (*Anal.* Calcd.: C, 63.14; H, 8.06; N, 3.20. Found: C, 63.31; H, 8.04; N, 2.99). Acetylation of II with acetic anhydride-pyridine afforded a monoacetate (IIa), m.p. 262~264°, $C_{25}H_{36}O_8$ (*Anal.* Calcd.: C, 64.63; H, 7.81. Found: C, 64.68; H, 7.23). Hydrolysis of II with 5% methanolic potassium hydroxide gave an acidic substance, which showed only one spot on paper chromatography (1.5*N* NH_3/BuOH) and was identified as acetic acid. As a neutral product, deacetylmetaplexigenin (IIb), m.p. 218~223°, was obtained, which was formulated as $C_{21}H_{32}O_6$ (*Anal.* Calcd.: C, 66.30; H, 8.48. Found: C, 66.32; H, 8.41). Giving the infrared absorption at 1725 and 1690 cm^{-1}. IIb afforded monooxime of m.p. 265° (decomp.), $C_{21}H_{33}O_6N$ (*Anal.* Calcd.: C, 63.77; H, 8.41; N, 3.54. Found: C, 63.81; H, 8.34; N, 3.74), which showed no absorption in carbonyl region of its infrared spectra, implying the existence of only one carbonyl group. Acetylation of IIb afforded a diacetate, m.p. 255~261°, whose identity with monoacetylmetaplexigenin (IIa) was confirmed by mixed fusion and comparison of infrared spectra. This indicates that the monoacetate of IIb is II, and no steric change had occurred during alkaline hydrolysis. II consumed one mole of lead tetraacetate (in dioxane, 164 hr.), and IIb consumed about two moles of the reagent (in dioxane, 192 hr.). I consumed about 3 moles, and VIIa consumed 2 moles of lead tetraacetate. We are not able to reach a reasonable explanation for these results. These observations on II and IIb might be interpreted as follows: II has one carbonyl group, two secondary -OH groups (one -OH group present as an acetate). three tertiary -OH groups, and two hydroxyl groups out of the five exist as a glycol grouping. IIb was reduced by $NaBH_4$, and the product examined

---

[1] H. Mitsuhashi, T. Nomura, Y. Shimizu, I. Takemori, E. Yamada: This Bulletin, **10**, 811 (1962). In the report, metaplexigenin was expressed as crystal 5.

[2] "Rama" is the Chinese name for Metaplexis plant.

[3] H. Mitsuhashi, T. Nomura, Y. Shimizu: Presented as a paper at the 82nd annual meeting of the Pharmaceutical Society of Japan, Nov. 3, 1962, Shizuoka.