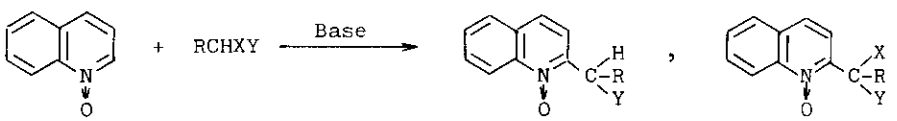
REACTIONS OF QUINOLINE 1-OXIDE WITH CYANOACETIC ACID DERIVATIVES BEARING LEAVING GROUPS[1]

Masatomo Hamana,* Yasuo Fujimura, and Yoshiharu Nawata
Central Research Laboratories, Chugai Pharmaceutical Co., Ltd.,
Takada 3-41-8, Toshima-ku, Tokyo 171, Japan

Abstract —— Quinoline 1-oxide reacts with bromocyanoacetic acid derivative (1a, 1b and 2a) in the presence of acetic anhydride to afford 2-substituted quinolines (3a, 3b and 6) through the vicarious nucleophilic substitution and the subsequent deoxygenation. From reactions with phenylthiocyanoacetic acid derivatives (1c, 1d and 2b), the deoxygenated α-substitution products (8c and 8d) are formed in addition to 3a, 3b and 6.

The preceding paper has described that quinoline 1-oxides react with some rather weakly acidic active methylenes bearing leaving groups in the presence of strong bases to give 2-substituted quinoline 1-oxides through the vicarious nucleophilic substitution or through hydride elimination.[2]



X: Leaving group, PhO, Cl, MeS
Y: Carbanion stabilizing group, CN, SO_2

As a continuation of this work, reactions of quinoline 1-oxides with highly active methylenes bearing leaving groups were investigated. We now wish to report novel reactions of quinoline 1-oxide with bromo- and phenylthio-cyanoacetic acid derivatives in the presence of acetic anhydride (Ac_2O).

During the course of studies of the Ac_2O-mediated reaction of aromatic N-oxide with active methylenes, the reaction of quinoline 1-oxide (A) with ethyl bromocyanoacetate (2a) was found to give ethyl 2-quinolinecyanoacetate[3] (6) in fair yield.[4] This reaction cannot be explained either by the deoxygenative α-substitution or the vicarious nucleophilic substitution.

In order to elucidate the mechanism of this reaction, we examined reactions of A with bromocyanoacetamide (1a) and N-propylbromocyanoacetamide (1b) in some details. A solution of A (0.01 mol), 1a[5] (0.01 mol) and Ac_2O (0.02 mol) in DMF (10 ml) was stirred at room temperature for 12 h to deposit yellow crystals, which were filtered and recrystallized from ethanol to give 2-quinolinecyanoacetamide[6] (3a) [yellow needles, mp 256-257°C] in 40% yield. The residue from the filtrate was chromatographed on silica gel with 1% MeOH-$CHCl_3$ to give 2-acetoxy-8-cyano-8,11-dibromo-9-oxo-2,10-diazabenzo[c]bicyclo[3.3.1]nonane (4a) [pale yellow crystals, mp 196°C (dec.) (MeOH)] in 16.1% yield. The structure of 4a was deduced from the elemental analysis ($C_{14}H_{11}Br_2N_3O_3$), the ms and ^1H nmr spectroscopies,[7] and confirmed by X-ray analysis (Fig.). From the reaction of A with 1b[8] under the same conditions, not only the corresponding 2-substituted quinoline (3b) [yellow flocculent crystals, mp 147°C (EtOH)] and tricyclic compound (4b)[9] [pale yellow crystals, mp 154-155°C (EtOH)] but also N-propyldibromoacetamide (5b)[10] [colorless needles, mp 37°C (hexane)] were isolated in 45, 4.2 and 14.4% yield, respectively (Chart 1).

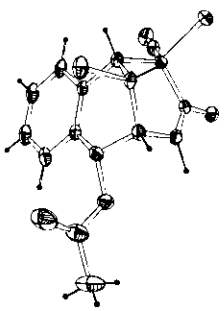
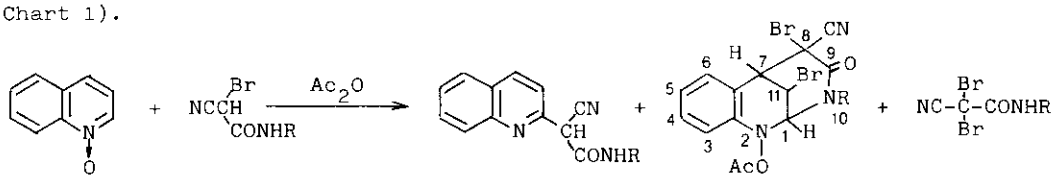


Fig. ORTEP drawing of 4a

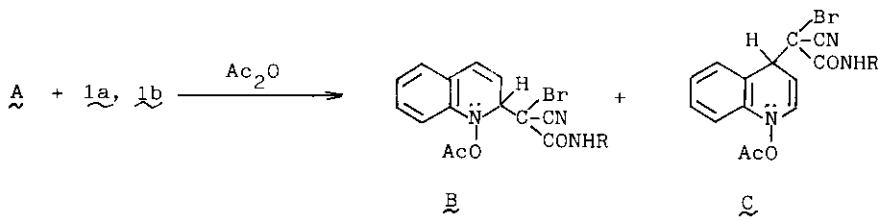


A	1a: R=H	3a (40%)	4a (16.1%)	—
	1b: R=n-Pr	3b (45%)	4b (4.2%)	5b (14.4%)

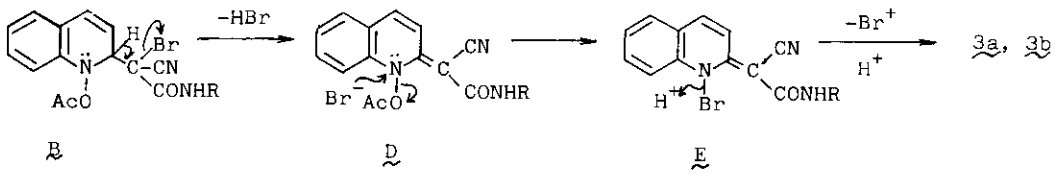
Chart 1

The formation of 4a, 4b and 5b indicates the intermediary generation of Br^+, and the reaction may be rationalized by the courses shown in Chart 2. N-Acetoxy-1,2- and -1,4-dihydroquinolines (B and C) are initially formed in the usual way. Elimination of hydrogen bromide from B gives an anhydro base intermediate[11] (D) in a similar manner to the vicarious nucleophilic substitution.[12] The next step is the extrusion of AcO^- from D and the consecutive attack by Br^- at N^+ to give N-bromo-intermediate (E), which is converted to 3a or 3b by releasing of Br^+ (course a). The formation of 4a and 4b can be explained by course b involving bromination of the enamine-like moiety of C with Br^+ originated from E to give the 3-bromo-immonium compound (F), followed by the intramolecular attack by the amide-nitrogen at the

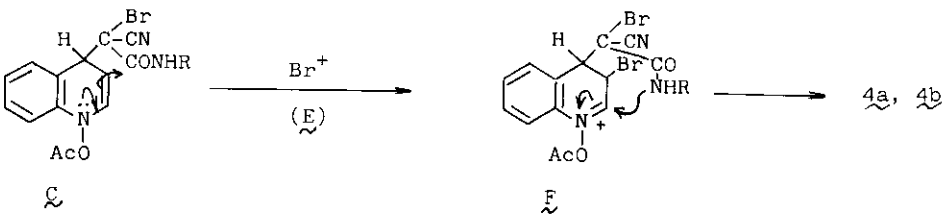
immonium moiety in F[13] (course b). Bromination of 1b gives 5b (course c).



Course a



Course b



Course c

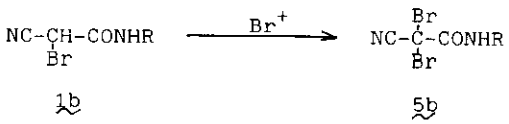
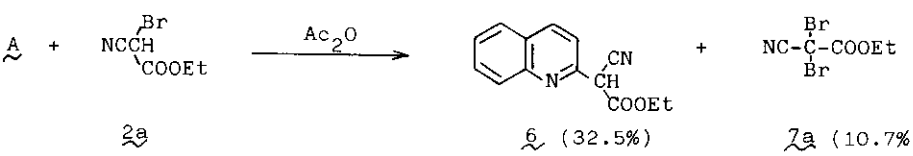


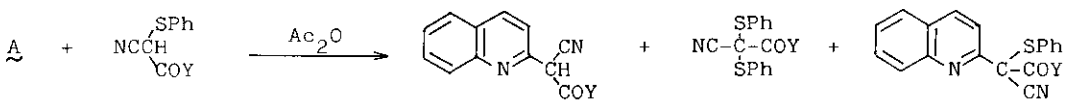
Chart 2

Considering these findings, the reaction of A with ethyl bromocyanoacetate (2a) was re-examined. Treatment of A (dihydrate, 0.01 mol) with 2a (0.01 mol) in Ac_2O (0.024 mol) at room temperature for 12 h gave 6 and ethyl dibromocyanoacetate[14] (7a) in 32.5 and 10.7% yields, respectively, after purification by silica gel chromatography with chloroform; thus, it was disclosed that course a and c reactions occurred in this case.



Subsequently, reactions of A with cyanoacetamides (1c[15] and 1d[16]) and ethyl cyano-

acetate[17] (2b) having phenylthio group as a leaving group were carried out in Ac_2O.[18] In reactions with amides, 1c and 1d, the deoxygenated α-substitution products, 8c [colorless needles, mp 140-160°C (dec.) (MeOH), 46.8%] and 8d [colorless needles, mp 87-88°C (acetone-hexane), 42%] were produced as the main products in addition to course a reaction products, 3a (22.8%) and 3b (33%), and course c reaction products, 5c [colorless crystals, mp 145-147°C (EtOH), 10.7%] and 5d [colorless needles, mp 124°C (acetone-hexane), 9.3%]. On the other hand, the reaction with 2b gave 6 (34%) and 7b[19] (41.6%), respectively through course a and c, as the reaction with 2a, no product by deoxygenative α-substitution being obtained.



1c: Y=NH_2	3a (22.8%)	5c (trace)	8c (46.8%)
1d: Y=NHPr	3b (33.0%)	5d (9.3%)	8d (42.0%)
2b: Y=OEt	6 (34.0%)	7b (41.6%)	——

In the preceding paper,[2] we have postulated three types for the reaction of quinoline 1-oxide with active methylene compounds bearing leaving groups, and the vicarious nucleophilic substitution (type II) and the nucleophilic substitution by means of hydride elimination (type III) have been successfully realized. Now, the deoxygenative α-substitution, type I reaction, has been verified by the formation of 8c and 8d. The formation of 3a, 3b and 6 does not fall in these categories, and should be accounted for by a new course a shown in Chart 2 (IV type reaction). The following points are of particularly significant in course a reaction: 1) the elimination of acetic acid from B does not occur; 2) D does not undergo the rearrangement of acetoxy anion[11]; 3) a vicarious nucleophilic substitution product is not isolated from D.

Further work on extending these observation is in progress.

REFERENCES AND NOTES

1. We wish to dedicate this paper to Professor Dr. G. Stork on the occasion of his 65th birthday.
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3. M. Hamana and M. Yamazaki, Chem. Pharm. Bull., 1963, 11, 415.
4. Private communication by S. Saeki, Y. Kaku, and M. Hamana (Kyushu University).
5. T. Hata and T. Mukaiyama, Bull. Chem. Soc. Jap., 1962, 35, 1106.

6. J.D. Baty, G. Jones, and C. Moore, J. Org. Chem., 1969, 34, 3295.

7. 4a: ms m/z: 427 (M^+), 385 (M^+-42); ir (Nujol) cm^{-1}: 2180 (CN), 1780, 1685 (CO); ^1H nmr ($CDCl_3$) δ ; 2.28 (3H, s, CH_3), 3.81 (1H, t, H_7), 5.05-5.11 (1H, m, H_1), 5.26-5.29 (1H, m, H_{11}), 6.95-7.52 (4H, m, Ar-H), 9.45 (1H, d, NH).

8. Prepared according to Hata's procedure (Bull. Chem. Soc. Jap., 1964, 37, 547), colorless needles, mp 76-78°C (EtOH-H_2O).

9. 4b: $C_{17}H_{17}Br_2N_3O_3$; ms m/z: 469 (M^+), 427 (M^+-42); ^1H nmr ($CDCl_3$) δ : 0.95 (3H, t, $CH_2CH_2CH_3$), 1.60-1.74 (2H, m, $CH_2CH_2CH_3$), 2.26 (3H, s, $COCH_3$), 3.20-3.36 (1H, m, N-$CHCH_2CH_3$), 3.83 (1H, t, H_7), 3.95-4.08 (1H, m, N-$CHCH_2CH_3$), 5.06-5.11 (1H, m, H_1), 5.26-5.29 (1H, m, H_{11}), 6.90-7.49 (4H, m, Ar-H).

10. 5b: $C_6H_8Br_2N_2O$; ms m/z: 282 (M^+), 253 (M^+-CH_2CH_3); ir (KBr) cm^{-1}: 3350 (NH), 1680, 1520 (CO); ^1H nmr ($CDCl_3$) δ : 0.99 (3H, t, $CH_2CH_2CH_3$), 1.65 (2H, m, $CH_2CH_2CH_3$), 3.34 (2H, q, $NHCH_2CH_2CH_3$), 6.95 (1H, br-s, NH); ^{13}C nmr ($CDCl_3$) δ : 11.08 (q, CH_3), 21.13 (t, $CH_2CH_2CH_3$), 26.80 (s, CBr_2), 43.16 (t, $NHCH_2$), 114.05 (s, CN), 159.89 (s, CO).

11. S. Oae and K. Ogiso, Heterocycles, 1977, 6, 583.

12. M. Makosza and T. Glinka, J. Org. Chem., 1983, 43, 3860.

13. cf. S. Saeki, Y. Kaku, M. Hamana, and H. Noda, Heterocycles, 1980, 14, 809.

14. 7a: an oil; ^{13}C nmr ($CDCl_3$) δ : 13.61 (q, CH_3), 23.41 (s, CBr_2), 66.20 (t, CH_2), 113.44 (s, CN), 160.29 (s, CO).

15. S. Hayashi, M. Furukawa, Y. Fujino, and H. Matsukura, Chem. Pharm. Bull., 1969, 17, 419.

16. Prepared according to the method of ref. 15, colorless needles, mp 72-73°C.

17. Prepared according to the method of ref. 15, an oil.

18. For example, a solution of A (1.017g), 1c (1.08g, 1 eq.) and Ac_2O (1.15g, 2 eq.) in DMF (5 ml) was stirred at room temperature for 12 h.

19. 7b: a colorless oil; ^{13}C nmr ($CDCl_3$) δ : 13.73 (q, CH_3), 57.16 (s, $C(SPh)_2$), 64.06 (t, CH_2), 114.54 (s, CN), 163.89 (s, CO), 128.61, 129.37, 136.94 (Ph).

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