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THE REACTION OF HETEROCYCLE N-OXIDES WITH BENZIMIDOYL CHLORIDE[1]

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We wish to report the reaction of a series of pyridine and quinoline N-oxides containing alkyl or ring methylene groups in the α-position with benzimidoyl chloride ($C_6H_5C{-}Cl{=}NC_6H_5$) (1). These reactions provide high yields of widely different products depending upon the structure of the heterocycle employed. The reactions were carried out in refluxing chloroform with a slight excess of benzimidoyl chloride, essentially as described by Abramovitch and Singer[2] for pyridine N-oxides with free α-positions. The results obtained are shown in Table I.

The reaction of quinoline N-oxide (2) with benzimidoyl chloride gave 2-anilinoquinoline (3), the product expected by analogy with the earlier work of Abramovitch and Singer.[2] However, with 2-alkyl quinoline 4 and pyridine 6 the products were the phenolic derivatives 5 and 7.[3] Hydrolysis of 7 with hot methanolic potassium hydroxide gave 2,6-dimethyl-3-pyridinol (mp 211-213° from acetone, lit.[4] mp 209-210°) together with some benzanilide; hydrolysis of 5 with hot sulfuric acid-water (50:50) gave in high yield 2,4-dimethyl-3-quinolinol (mp 204-205.5° from acetone). The benzanilimino ethers 5 and 7 are thought to form as shown in equation 1, by a process analogous to that described by Abramovitch and Rogers[5] in their related studies with quinoline-N-oxide.

(Equation 1)

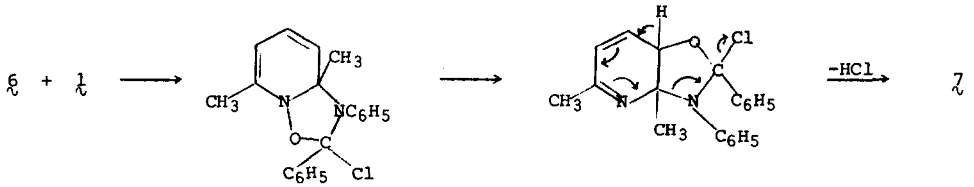
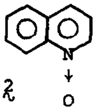
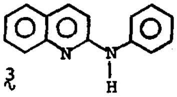
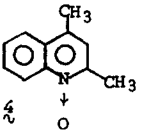
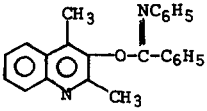
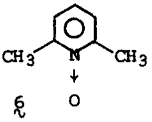
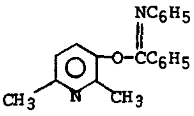
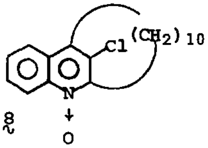
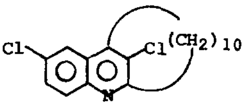
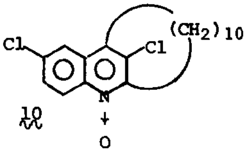
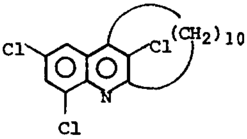
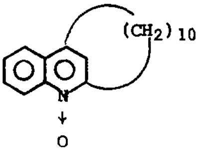
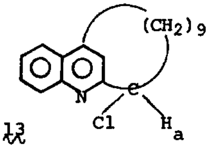


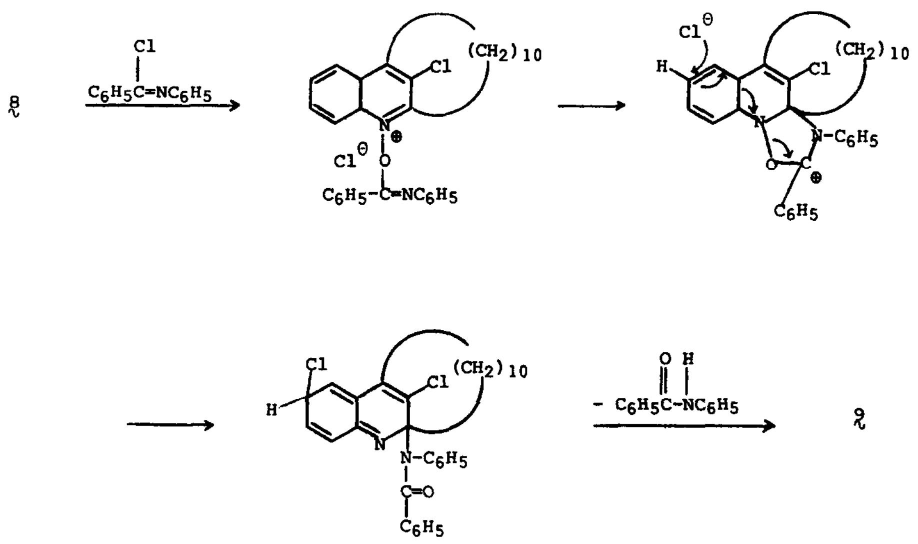
TABLE I

Starting Material[a,b]	Product[a]	Yield	mp
 2	 3	60.5%[c]	95-97° [i]
 4	 5	72.5%[d]	125.5-127.5°
 6	 7	59%[e]	129-131°
 8	 9	80%[f]	77-79°
 10	 11	69%[g]	159-160°
 12	 13	16%[h]	109-110°

(a) All starting materials and products gave satisfactory analyses (± 0.30%). Nmr spectra were run in $CDCl_3$ at 60 MHz. The usual quinoline numbering system is used throughout the table to designate aromatic protons. See ref. 7 for the numbering of metacyclophanes. (b) Compounds 2 and 6 were obtained from Aldrich Chemical Co. Compounds 4 (mp 115-118°), 8 (mp 125-127°), 10 (mp 159-160°) and 12 (mp 119-121°) were prepared essentially according to the method of K. Biemann, G. Buchi and B. H. Walker, *J. Amer. Chem. Soc.*, 79, 5558 (1952). (c) The initially formed N-benzoyl product was purposely hydrolyzed (KOH-methanol). (d) δ 2.63 (s, 3, 4-CH_3), δ 2.80 (s, 3, 2-CH_3). (e) δ 2.50 (s, 3, 6-CH_3), δ 2.58 (s, 3, 2-CH_3). (f) δ 7.83 (AB, 2, J_{AB} = 9 Hz, $\Delta_{\nu AB}$ = 26 Hz, 7- and 8-H), δ 7.93 (X, 1, J_{BX} = 2 Hz, 5-H). (g) δ 7.83 (AB, 2, J_{AB} = 2 Hz, $\Delta_{\nu AB}$ = 6 Hz, 5- and 7-H). (h) δ 5.25 (X, 1, J_{AX} + J_{BX} = 16 Hz, H_a - C-Cl), δ 7.61 (s, 1, 3-H). (i) Lit. mp 98°, *Chem. Abstr.*, 53, 20061b (1959).

Formation of the chlorinated products[b] **9** and **11** may occur as shown in equation 2. The structure of **9** was established by its independent synthesis from p-chlorophenylhydrazine by a procedure similar to that previously reported for the parent metacyclophane.[7] The structure of **11** was assigned from its nmr spectrum and by a logical extention of the scheme outlined in equation 2.

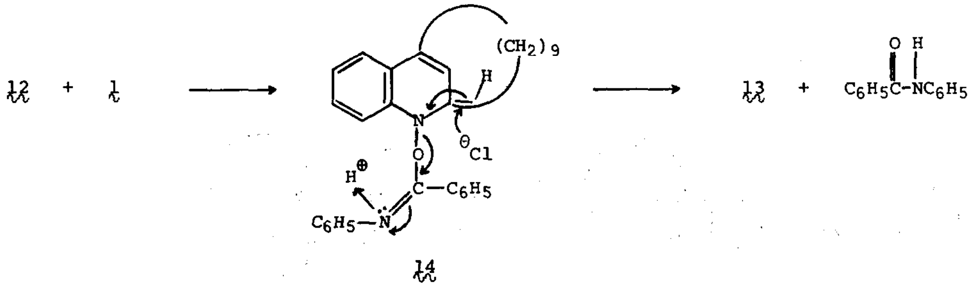
(Equation 2)



The nmr spectrum of the chlorinated product derived from **12** showed the 3-H absorption intact and a benzylic methinyl proton as the X portion of an ABX pattern.[8] Only structure **13** fits these data.[9]

The different course of reaction of the metacyclophanes **8** and **10** as compared with **12** may be a consequence of the resistance of the benzylic carbon atom in **8** (and **10**) to change to sp^2 hybridization. Inspection of models suggests that the removal of halogen from the 3-position of **8** to give **12** relieves the constraint of the methylene bridge.[7] Consequently, formation of a benzylic sp^2 carbon atom as illustrated in equation 3 should be easier in **12** than in **8** or **10** and the formation of **13** may occur as shown in **14**.[10]

(Equation 3)



REFERENCES

(1) Supported by National Science Foundation, Grant GP-11918.

(2) R. A. Abramovitch and G. M. Singer, *J. Amer. Chem. Soc.*, **91**, 5672 (1969).

(3) The nmr spectrum of **5** shows the absence of the 3-*H* absorption at δ 6.93 - 7.02 observed for the free bases corresponding to **4** and **12**. The spectrum of **7** shows a complex multiplet at δ 7.8 - 7.5 for the two remaining aromatic protons which would not be expected if substitution had occurred at C-4. Both **5** and **7** show $\nu_{C=N}$ at 1670 cm^{-1} and base absorption at *m/e* 180 ($C_6H_5\underset{\oplus}{N}{\equiv}CC_6H_5$) in their mass spectra.

(4) N. Naito, T. Yoshikawa, F. Ishikawa, S. Isoda, Y. Omura and I. Takamura, *Chem. Pharm. Bull.* (Tokyo), **13**, 869 (1965); *Chem. Abstr.*, **63**, 11488 (1965).

(5) See R. A. Abramovitch and R. B. Rogers (in press, this journal). We wish to thank Professor Abramovitch for exchange of information prior to publication.

(6) Benzanilide was also isolated in good yield.

(7) Stabilization of the benzylic sp^2 carbon atom is unlikely since the steric bulk of the 3-Cl group prevents the alkyl substituted sp^2 carbon atom from becoming coplanar and being conjugated with the π system of the heterocycle. Cf. W. E. Parham, R. W. Davenport and J. B. Biasotti, *J. Org. Chem.*, **35**, 3775 (1970).

(8) A number of other metacyclophanes substituted in the benzylic position exhibit similar spectra with approximately the same value for J_{AX} + J_{BX} (14-16 Hz). See ref. 7.

(9) An alternate structure with the chlorine atom at the other benzylic carbon atom is not rigorously excluded by these data.

(10) cf. V. J. Traynelis in "Mechanisms of Molecular Migrations," Vol. 2, B.S. Thyagarajan, Ed., Interscience Publishers, New York, N. Y., 1969 for related mechanisms.