The Monohalogenation of 8-Quinolinols

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In the course of a study of the kinetics of bromination of the chromium(III) chelate of 8-quinolinol by a coulometric method, it was observed that the metal chelate brominated much faster than the free ligand under identical conditions. The same result was obtained with the cobalt(III), aluminum(III), and copper(II) chelates of 8-quinolinol. Although the reaction rates of the metal chelates were too fast to measure by our method,[1] the stoichiometry of the reaction was readily obtained. One mole of bromine reacted rapidly with every mole of 8-quinolinol present in the metal chelate. Further reaction of the metal chelate with bromine did occur, but at a much slower rate. This behavior of the chelated 8-quinolinol is in direct contrast with that of the free ligand, since each mole of 8-quinolinol is known to react quite rapidly with 2 moles of bromine to form the 5,7-dibromo-8-quinolinol.[1] Attempts to monohalogenate 8-quinolinol directly result in low yields and extensive contamination by the dihalo product.

On a preparative scale, halogenation of the metal chelate, rather than of the ligand itself, with 1 mole of halogen/mole of the 8-quinolinol in the metal chelate and subsequent rupture of the metal chelate with acid should give the monohalogenated derivative in good yields and free of dihalogenated products. N-halosuccinimides were used as halogenating agents since they did not release hydrogen ions that can cause rupture of the metal chelate during the course of the reaction. A further means of avoiding chelate dissociation is the use of an organic solvent as reaction medium. If these conditions are met, then it would not be necessary to use inert chelates such as those of Co(III) and Cr(III) which may by their resistance to dissociation present problems in metal ion removal.

The monochloro, monobromo, and monoiodo derivatives of 8-quinolinol, 2-methyl-8-quinolinol, and 4-methyl-8-quinolinol were synthesized by halogenating the copper(II) chelate with N-halosuccinimde (1 mole/mole of the 8-quinolinol in the chelate). Halogenation of the lithium salt under identical conditions always gave the 5,7-dihalo derivative.

An investigation of the effect of the metal ion on the yield of monobromo-8-quinolinol obtained by this method showed that the maximum yield was obtained with the cobalt(II) chelate (69%) followed by the aluminum(III) chelate (66%), the cobalt(III) chelate (52%), and the copper(II) chelate (50%). The similarity of these results indicate that specific metal ion effects are minimal. It was deduced that halogenation occurred in 5-position in all cases by a comparison of the infrared and proton magnetic resonance spectra of the halogenated compounds that were synthesized with available authentic samples of 5-halo-8-quinolinols.

Experimental

5-Bromo-8-Quinolinol.—The copper(II) chelate of 8-quinolinol[2] (0.43 g.) was dissolved in a minimum volume of chloroform and a chloroform solution of N-bromosuccinimide (0.43 g.) was added. After the reaction mixture was allowed to stand for several hours a precipitate of the copper(II) chelate of 5-bromo-8-quinolinol was formed and separated by filtration. About 80% of the copper(II) chelate was recovered in this step. The chelate was dissolved in 50 ml. of 6 *M* HCl and the copper(II) was precipitated by the addition of excess thioacetamide. The solution containing the copper(II) sulfide was filtered and the filtrate was neutralized with $NaHCO_3$ solution. The 5-bromo-8-quinolinol which precipitated was washed with water, recrystallized from ethanol, and finally vacuum sublimed: yield 0.31 g., m.p. 124° (lit.[2] m.p. 124°).

An alternative method that was used for the separation of copper(II) from the 5-bromo-8-quinolinol was as follows. The copper(II) chelate of 5-bromo-8-quinolinol (0.85 g.) was dissolved in 1:1 HCl and a solution containing 1.13 g. of EDTA was added. When the pH of the solution was raised to 4 with ammonium acetate, a yellowish precipitate was formed. The mixture was extracted with 100 ml. of chloroform, the solid obtained by evaporation of the chloroform layer was redissolved in 1:1 HCl, and a solution containing 1.13 g. of EDTA was added. On raising the pH of the solution to 5 with ammonium acetate, a pale yellow precipitate was obtained. The mixture was extracted with 75 ml. of chloroform and on evaporation 0.63 g. of 5-bromo-8-quinolinol was obtained.

The copper(II) chelates of 8-quinolinol, 2-methyl- and 4-methyl-8-quinolinol[3] were halogenated in a similar manner to give the corresponding 5-halo derivatives.

Acknowledgment.—The authors are grateful to the National Institutes of Health for financial assistance.

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(1) G. S. Kozak, Q. Fernando, and H. Freiser, *Anal. Chem.*, **36**, 296 (1964).

(2) R. G. W. Hollingshead, "Oxine and its Derivatives," Vol. I, II, and III, Butterworth and Co., Ltd., London, 1956.

(3) J. P. Phillips, R. L. Elbinger, and L. Merritt, *J. Am. Chem. Soc.*, **71**, 3986 (1949).

The Structure of the Product from Reaction of the Dimedon Formaldehyde Derivative with Base and Iodine. An Example of Coupling through Five Bonds

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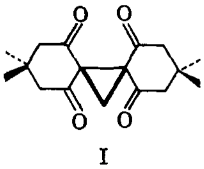
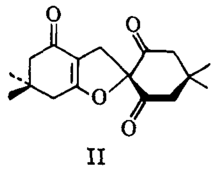
In 1925 and 1927 Radulescu and Georgescu[1,2] proposed the cyclopropane structure I for the product, m.p. 211–212°, obtained by treating iodine with the disodium salt of the dimedon derivative of formaldehyde. Repeating the above authors' procedure we obtained the compound described earlier. However the spectral properties are inconsistent with I and lead to assignment of the isomeric structure II.


I


II

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(1) D. Radulescu and V. Georgescu, *Bull. soc. chim. France*, [4] **37**, 187 (1925).

(2) D. Radulescu and V. Georgescu, *Bul. soc. stiinte Cluj*, **3**, 129 (1927); *Chem. Abstr.*, **21**, 3203 (1927).

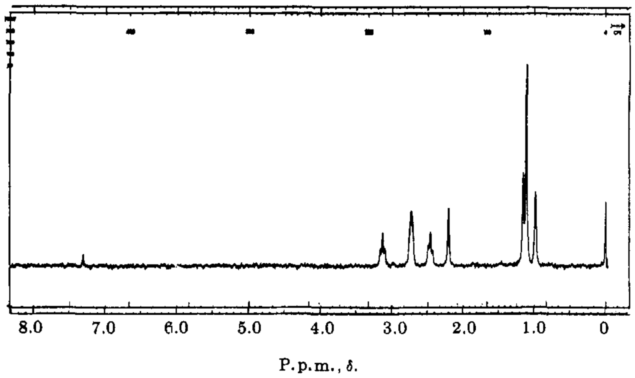


Figure 1.—N.m.r. spectrum of II.

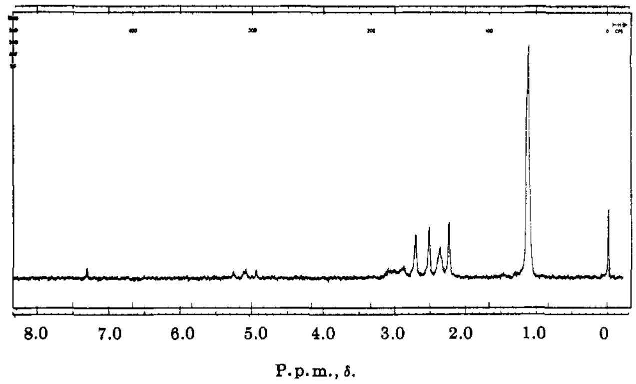
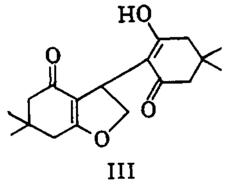


Figure 2.—N.m.r. spectrum of VII.

The n.m.r. spectrum of I would be expected to display four peaks in the area ratio 6:6:8:2. Instead the observed spectrum (Figure 1) in deuteriochloroform exhibits three methyl peaks and four methylene peaks in the ratio 6:3:3:4:2:2:2. This is clearly compatible with II which has nonequivalent methyls attached to the cyclohexanedione ring, equivalent methyls attached to the cyclohexenone ring, and four kinds of methylene groups.

Further evidence for II is gained from the ultraviolet spectrum ($\lambda_{\max}^{\mathrm{EtOH}}$ 267 mμ, ϵ 11,800) which is characteristic of 3-alkoxy-2-alkylcyclohexenones, *e.g.*, 3-ethoxy-2,5,5-trimethylcyclohexenone[3] ($\lambda_{\max}^{\mathrm{EtOH}}$ 268 mμ, ϵ 19,100) and the dimedon derivative obtained from both chloroacetaldehyde and hydroxyacetaldehyde[4] (III, $\lambda_{\max}^{\mathrm{EtOH}}$ 268 mμ, ϵ 24,000). The ultraviolet spectrum of I would be expected to resemble that of 2,2,5,5-tetramethylcyclohexane-1,3-dione[5] ($\lambda_{\max}^{\mathrm{EtOH}}$ 274 mμ, ϵ 240).



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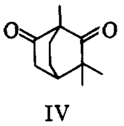
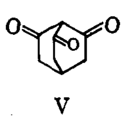


IV

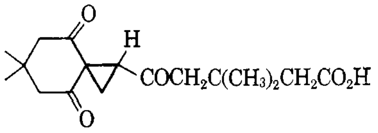


V

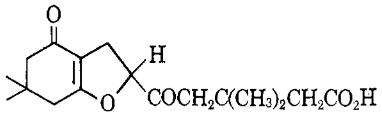
Confirmation of II is given by the infrared spectrum in chloroform which exhibits carbonyl bands due to a 3-alkoxycyclohexenone (1644 cm.$^{-1}$) and a nonenolic 1,3-cyclohexanedione (1722 and 1752 cm.$^{-1}$). Model compounds for comparison are 3-ethoxy-5,5-dimethylcyclohexenone[6] ($CHCl_3$, 1642 cm.$^{-1}$); 2,2,5,5-tetramethylcyclohexane-1,3-dione[6] ($CHCl_3$, 1688 and 1717 cm.$^{-1}$); 1,3,3-trimethylbicyclo[2.2.2]octane-2,6-dione[7] (IV, CS_2, 1712 and 1749 cm.$^{-1}$); and bicyclo[2.2.2]octane-2,6,7-trione[8] (V, KBr, 1725 and 1770 cm.$^{-1}$).

Surprisingly, the n.m.r. spectrum of II displays two methylene groups at δ 3.17 and 2.48 as symmetrical triplets (J = 2.0 ± 0.1 c.p.s.) rather than sharp peaks. The origin of the long-range coupling is demonstrated by the spectrum of II prepared from deuterioformaldehyde. This spectrum is altered from the original (Figure 1) by the disappearance of the 3.17 peaks and the conversion of the 2.48 triplet to a singlet. Therefore, coupling exists between the formaldehyde methylene and one of the methylenes of the cyclohexenone ring. Presumably the methylene involved in this coupling is adjacent to the ring-juncture double bond since protons in the corresponding positions of benzofuran have been found[9] to be coupled.

Radulescu and Georgescu[2] subjected II to basic cleavage and obtained a compound, m.p. 102–103°, which they formulated as VI. We find that treatment of II with sodium hydroxide in aqueous dioxane, followed by acidification, yields an acid with nearly the same melting point, whose spectral properties are those of VII.



VI



VII

The infrared spectrum discloses carbonyl absorptions due to a 3-alkoxycyclohexenone (1637 cm.$^{-1}$), a carboxyl group (1725 cm.$^{-1}$), and an aliphatic ketone (1708 cm.$^{-1}$). The ultraviolet spectrum ($\lambda_{\max}^{\mathrm{EtOH}}$ 269 mμ, ϵ 13,900) is similar to that of II.

The n.m.r. spectrum in deuteriochloroform (Figure 2) reveals two overlapping methyl peaks; four methylene peaks belonging to the side chain and cyclohexenone ring; two poorly resolved multiplets due to the dihydrofuran methylene which is coupled with the adjacent proton and a methylene of the cyclohexenone ring; and a quartet centered at 5.14 (J = 10 c.p.s.) due to the remaining dihydrofuran proton coupled with the adjacent methylene. The low field at which this single proton resonance occurs is consistent with a hydrogen that is bonded to a carbon attached to oxygen. The carboxyl proton occurs at δ 10.08.

The formation of II appears to be the first example of the formation of a dihydrofuran by O-alkylation when the possibility exists for a cyclopropane *via* C-alkyla-

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[3] E. G. Meek, J. H. Turnbull, and W. Wilson, *J. Chem. Soc.*, 811 (1953).

[4] The preparation of III from both aldehydes was originally reported by D. Vörlander, *Z. Anal. Chem.*, **77**, 241 (1929).

[5] E. G. Meek, J. H. Turnbull, and W. Wilson, *J. Chem. Soc.*, 2891 (1953).

[6] K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., and Nankoda Co., Ltd., Tokyo, Japan, 1962, p. 69.

[7] D. Y. Curtin and R. R. Fraser, *J. Am. Chem. Soc.*, **81**, 662 (1959).

[8] W. Theilacker and E. Wegner, *Ann.*, **664**, 125 (1963).

[9] J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, 590 (1960).

tion. The dominant factor leading to the production of II rather than I may be the greater stability of dimedon as the enol rather than the keto form.[10] Thus II with the preferred cyclohexenone ring is the observed product.

Experimental[11]

The Disodium Salt of the Dimedon Formaldehyde Derivative.—This and subsequent procedures were essentially those of Radulescu and Georgescu.[1,2] A mixture of sodium ethoxide (1.00 g of sodium, 0.0435 g.-atom) and the dimedon formaldehyde[12] derivative (5.80 g., 0.0199 mole) in 100 ml. of absolute ethanol was stirred at room temperature for 1.5 hr. affording a finely divided white crystalline precipitate. After filtration and washing with ether and ethanol, the solid was dried under vacuum for 12 hr. and weighed 6.35 g. (95%). The n.m.r. spectrum in D_2O showed three peaks at δ 0.90, 2.05, and 2.97 in the ratio 12:8:2.

Spiro[4-keto-6,6-dimethyltetrahydrobenzofuran-2(5,7,H)-1′-4′,4′-dimethylcyclohexane-2,6-dione](II).—To a suspension of the disodium salt of the dimedon–formaldehyde adduct (4.81 g., 0.0143 mole) in 80 ml. of anhydrous ether was added dropwise with stirring at room temperature during 2 hr. a solution of iodine (3.64 g., 0.0143 mole) in 80 ml. of ether. The deep brown mixture was stirred for 0.5 hr. and filtered; the precipitate was washed with sodium thiosulfate solution and water and dried. The brown solid was then dissolved in 40 ml. of chloroform and successively washed with aqueous sodium thiosulfate and water. After drying ($MgSO_4$) the solvent was evaporated *in vacuo* leaving a yellow-white solid: 3.72 g. (90%); m.p. 207–209°; $\nu_{\max}^{CHCl_3}$ 1644, 1722, and 1752 cm.$^{-1}$; $\nu_{\max}^{KBr}$ 1633, 1713, and 1748 cm.$^{-1}$. Recrystallization from ethanol afforded 2.91 g. (70%), m.p. 211–212°, $\lambda_{\max}^{EtOH}$ 267 mμ (ϵ 11800). The infrared spectra of the crude and recrystallized solids were identical.

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.47; H, 7.62.

The preparation of II-d_2, m.p. 210–211°, was carried out as above employing formaldehyde-d_2 which was obtained by pyrolysis of Eμ-polyoxymethylene-d_2 (Tracerlab, Waltham, Mass.).

Basic Cleavage of II.—To a solution of II (0.324 g., 1.12 mmoles) in 15 ml. of dioxane was added dropwise with stirring at room temperature 35.0 ml. of 0.0314 *N* sodium hydroxide (1.10 mmoles). After stirring 4 hr., the mixture was then acidified with 0.55 ml. of 2 *N* hydrochloric acid and extracted with methylene chloride; the extracts were washed with water and dried (Na_2SO_4); and the solvent was removed at reduced pressure leaving a yellowish white oil (0.316 g.). Crystallization was effected by dissolution in ethyl ether followed by addition of petroleum ether. Several recrystallizations from ethyl ether gave a solid with melting point 98–100°; $\lambda_{\max}^{EtOH}$ 269 mμ (ϵ 13,900); $\nu_{\max}^{KBr}$ 1726 and 1611 cm.$^{-1}$; $\nu_{\max}^{CHCl_3}$ 1637, 1708 and 1725 cm.$^{-1}$.

Dimedon Derivative of Chloroacetaldehyde.—A mixture of dimedon (3.02 g., 0.0215 mole), chloroacetaldehyde diethylacetal (1.62 g., 0.0106 mole), 15 ml. of ethanol, and 25 of ml. water was heated at reflux for 5 hr. After standing overnight the solution deposited a white-yellow solid which was filtered and washed with water. The dried material weighed 0.915 g., m.p. 211–221°. The filtrate deposited an additional 0.277 g. Crystallization of the combined solids (ethanol–acetone) yielded 0.490 g. (8%): m.p. 221–224° (lit.[4] m.p. 237.5°); $\lambda_{\max}^{EtOH}$ 268 mμ (ϵ 24,000)[13]; $\lambda_{\max}^{CHCl_3}$ 1613, 1703 (weak), and 1735 (weak) cm.$^{-1}$; $\nu_{\max}^{KBr}$ 1592, 1629, and 1637 cm.$^{-1}$. The n.m.r. spectrum (dimethyl-d_6 sulfoxide) revealed two methyl peaks at δ 0.98 and 1.07, a dimedon methylene peak at 2.22, and cyclohexenone methylene peaks at 2.29 and 2.05 with the latter a doublet (J = 2 c.p.s.) presumably due to coupling with the lone proton of the dihydrofuran ring; the dihydrofuran methylene is a complex multiplet centered at 4.50 and the single dihydrofuran proton is a multiplet centered at 4.20. A peak due to the hydroxyl proton of the dimedon moiety was not seen.[14]

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 71.34; H, 8.06.

Acknowledgment.—The author wishes to thank Miss Susan Sklar who initiated this study and Drs. H. M. Fales, R. J. Highet, and H. A. Lloyd for many helpful suggestions.

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[10] Dimedon in aqueous solution has been found to be 95% enolic by G. Schwarzenbach and E. Felder, *Helv. Chim. Acta*, **27**, 1044 (1944).

[11] Melting points were obtained on a Kofler hot stage and are corrected. Carbon–hydrogen analyses were performed by Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were determined with a Beckman IR-7 spectrophotometer, ultraviolet spectra with a Cary Model 11 spectrophotometer, and n.m.r. spectra with a Varian A-60 spectrophotometer.

[12] Prepared by the method of R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1959, p. 220.

[13] For 2,5,5-trimethylcyclohexane-1,3-dione, $\lambda_{\max}^{EtOH}$ 264 mμ (ϵ 13,600); ref. 5.

[14] The n.m.r. spectrum of formaldehyde bismethone does not display an enolic hydrogen peak: R. F. Brown, *et al.*, *J. Org. Chem.*, **29**, 146 (1964).

A Convenient Synthesis of Some Haloferrocenes

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Haloferrocenes constitute intermediates of considerable value for the preparation of hydroxy-,[1a–e] amino-,[1a,c] azido-,[2] thio-,[3] and cyanoferrocenes,[1c] as well as biferrocenyls[4,5] and ferrocenyl Grignard reagents.[5] Of the halo derivatives, bromo- and iodoferrocenes were first prepared by Nesmeyanov, Perevalova, and Nesmeyanova in 1955 by the action of the free halogens on mono- and 1,1′-bischloromercuriferrocene.[6] Although relatively simple and direct, the procedure has not found wide application, since, with the possible exception of iodoferrocene, the yields of haloferrocenes obtained in these reactions were poor. In the intervening years, the chloro- and bromoferrocenes have become considerably more accessible through the reaction of cupric halides with ferrocenylboronic and ferrocenyl-1,1′-diboronic acids, a procedure first introduced and largely exploited by the Russian group.[1a,7]

Our interest in the haloferrocenes, in connection with studies related to the possible existence of ferrocynes, prompted us to re-examine the use of the readily accessible chloromercuriferrocenes as potential precursors of these substances. The purpose of the present report is to set forth a general procedure which accomplishes this aim, and which constitutes an attractive alternative method for the preparation of the mono- and disubstituted bromo- and iodoferrocenes.

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[1] (a) A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Ber.*, **93**, 2717 (1960); (b) A. N. Nesmeyanov and V. A. Sazonova, *Dokl. Akad. Nauk SSSR*, **129**, 1060 (1959); (c) *ibid.*, **130**, 1030 (1960); (d) *ibid.*, **133**, 126 (1960); (e) A. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 45 (1962).

[2] A. N. Nesmeyanov, V. N. Drozd, and V. A. Sazonova, *Dokl. Akad. Nauk SSSR*, **150**, 321 (1963).

[3] M. D. Rausch, *J. Org. Chem.*, **26**, 3579 (1961).

[4] E. G. Perevalova and O. A. Nesmeyanova, *Dokl. Akad. Nauk SSSR*, **132**, 1093 (1960); M. D. Rausch, *J. Am. Chem. Soc.*, **82**, 2080 (1960); M. D. Rausch, *J. Org. Chem.*, **26**, 1802 (1962); S. J. Goldberg and R. L. Matteson, *ibid.*, **29**, 323 (1964).

[5] H. Shechter and J. F. Helling, *ibid.*, **26**, 1034 (1961).

[6] A. N. Nesmeyanov, E. G. Perevalova, and O. A. Nesmeyanova, *Dokl. Akad. Nauk SSSR*, **100**, 1099 (1955).

[7] A. N. Nesmeyanov, V. A. Sazonova, and V. N. Drozd, *ibid.*, **126**, 1004 (1959); **131**, 1088 (1960).