Chem. Pharm. Bull. 29(1) 51—54 (1981)

Studies on Tetrahydroisoquinolines. XVII.[1] A Synthesis of 8-Halo-1,2,3,4-tetrahydroisoquinolines[2]

Hiroshi Hara, Osamu Hoshino, and Bunsuke Umezawa*

Faculty of Pharmaceutical Sciences, Science University of Tokyo,[3] 12, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo, 162, Japan

(Received June 20, 1980)

Treatment with conc. hydrochloric acid of *p*-quinol acetates (**1**) obtained from 7-hydroxy-1,2,3,4-tetrahydroisoquinolines (**4**) gave the corresponding 8-chloro-7-hydroxy-1,2,3,4-tetrahydroisoquinolines (**5**) in good yields.

Similarly, by using conc. hydrobromic acid or 38% hydriodic acid, 8-bromo (**6**)- or 8-iodo-corypalline (**7**) was obtained.

Keywords——oxidation; lead tetraacetate; chlorination; halogenation; nucleophilic substitution; tetrahydroisoquinoline; NOE

We have already demonstrated that *p*-quinol acetates (**1**)[4] yield 4,7-diacetates (**2**) when treated under Thiele's conditions.

On the other hand, if an *o*-quinonoid intermediate such as (**3**) could be produced from the acetate (**1**) in the presence of a suitable nucleophile and under appropriate acidic conditions, this might provide a new route to 5- or 8-substituted derivatives, because *p*-benzoquinone is known to be transformed to 2-chlorohydroquinone by treatment with hydrochloric acid.[5]

We now wish to report a method for halogenation of the benzene ring in a phenolic 1,2,3,4-tetrahydroisoquinoline by hydrogen halide treatment of *p*-quinol acetate (**1**), which is easily obtainable from 7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**4**).

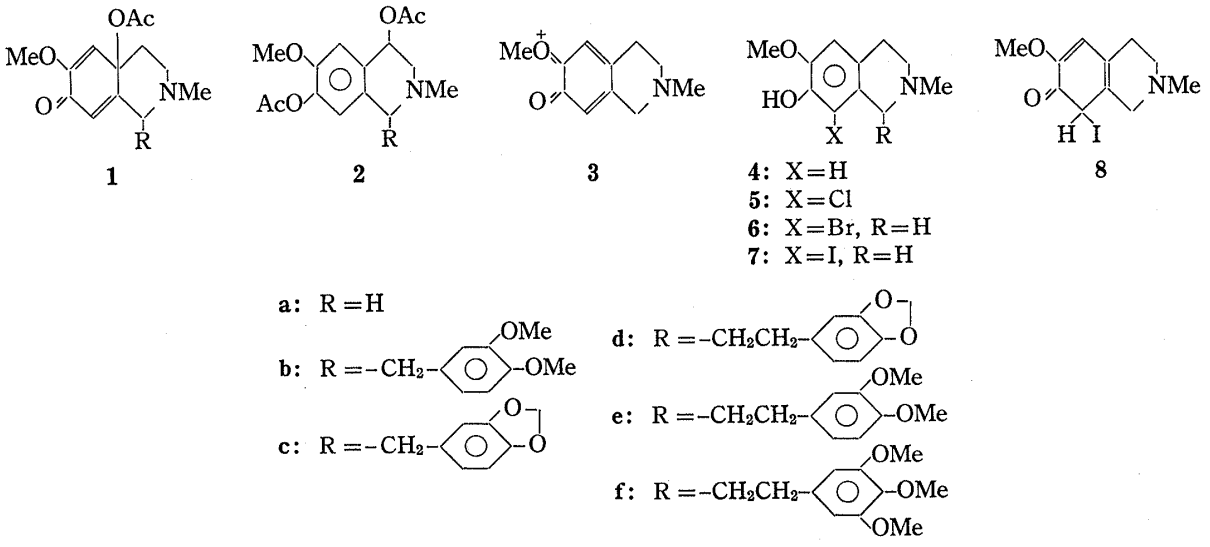

Chart 1

p-Quinol acetate (**1a**) was treated with conc. hydrochloric acid at room temperature for 1 hr, and usual work-up gave a crystalline compound in high yield. Its infrared (IR), nuclear magnetic resonance (NMR), and mass (MS) spectra showed a phenolic hydroxyl group, one aromatic proton (δ 6.51, singlet), and a pair of parent peaks [229 ($M^+ +2$) and 227 (M^+) in a 1:3 ratio]. Thus, this compound was presumed to be 5- or 8-chlorocorypalline; the 4-chloro

isomer was ruled out. The structure of the chloro derivative was determined to be 8-chlorocorypalline (**5a**) on the basis of nuclear Overhauser effect (NOE)[6] and by analogy with the result of bromination, as described below. Namely, proximity of the aromatic proton at δ 6.50 and the methoxyl protons at δ 3.83 was clearly indicated by a positive NOE (16%). On the other hand, the effect between the former proton and the protons at C-1 (δ 3.50) was negligible.

Similarly, conc. hydrobromic acid treatment of **1a** gave 8-bromocorypalline (**6**) (78% yield), mp 193.5—194.5°, which was identical with an authentic sample prepared from corypalline (**4a**) by bromination[7] (mixed mp and IR spectrum comparison).

With 38% hydriodic acid, however, **1a** was converted to 8-iodocorypalline (**7**) (11% yield), mp 159—160°, accompanied by a considerable amount of corypalline (**4a**) (17% yield). No phenol (**4a**) was included in the crude *p*-quinol acetate (**1a**), indicating that the two products (**7** and **4a**) had undoubtedly originated from *p*-quinol acetate (**1a**). A rational interpretation of this result was possible by assuming an intermediate (**8**) derivable from *p*-quinol acetate (**1a**). Namely, protonation at the carbonyl oxygen was presumably followed by normal deprotonation or loss of an iodonium ion at the 8 position.

Thus, it was found that treatment of *p*-quinol acetate (**1a**) with aqueous hydrogen halides gave 8-halocorypalline (**5a**, **6**, and **7**); this represents a novel halogenation of corypalline (**4a**).

In order to examine the generality of the reaction, morever, chlorination of various 1-substituted *p*-quinol acetates (**1b**—**f**) was carried out.

Treatment of 1-veratryl *p*-quinol acetate (**1b**) with conc. hydrochloric acid gave 8-chlorocodamine (**5b**) (43% yield), as expected, and no cyclization to aporphine[8] occurred. Similar treatment of 1-piperonyl (**1c**) and three 1-phenethyl *p*-quinol acetates (**1d**, **1e**, and **1f**) furnished the corresponding 8-chloro phenols (**5c** and **5d**, **5e**, and **5f**, respectively). The structures of **5b** and **5c** were confirmed by inspection of their NMR data (Table I). Thus, disappearance of the signals due to the aromatic protons (δ 6.44 and δ 6.37) assignable to C_8–H and the up-field shift of the N-methyl protons (δ 2.44 and δ 2.40) in the starting materials (**4b** and **4c**) indicated

Table I. Spectral Data for New Compounds

	IR (cm^{-1})	NMR (δ)				Mass (m/e)
	OH	NMe	OMe	ArH	Others	
5a	3520	2.48[a]	3.83[a]	6.50[a]	3.50[a] ($ArCH_2N$)	229 (M^++2), 228 (M^++2−1), 227 (M^+), 226 (M^+−1)
5b	3520	2.34	3.82 (6H) 3.86	6.53 6.81 (3H)		379 (M^++2), 377 (M^+), 228, 226
5c	3520	2.34	3.81	6.53 6.72 (2H) 6.86	5.88 (OCH_2O)	363 (M^++2), 361 (M^+), 228, 226
5d	3530	2.40	3.82	6.48 6.66 (2H) 6.70	5.86 (OCH_2O)	377 (M^++2), 275 (M^+), 228, 226
5e	3530	2.44	3.83 (9H)	6.50 6.76 (3H)		393 (M^++2), 391 (M^+), 228, 226
5f	3520	2.42	3.82 (12H)	6.47 (2H) 6.50		423 (M^++2), 421 (M^+), 228, 226
7	3520	2.49	3.83	6.59	3.43 ($ArCH_2N$)	319 (M^+), 318 (M^+−1)

a) Measured with a Varian HA-100 spectrometer in $CDCl_3$.

Table II. Yields and Melting Points of Chlorinated Products

	Yield (%)	mp
5a	78	196—198°
5b	43	162—164°
5c	70.5	145—147°
5d	49	109—111°
5e	44	100—103°
5f	57	145—146°

Table III. Analytical Data for New Compounds

	Formula	m.w.	Analysis (%) Calcd C	H	N	Found C	H	N
5a	$C_{11}H_{14}ClNO_2$	227.687	58.02	6.20	6.15	58.01	6.19	6.20
5b	$C_{20}H_{24}ClNO_4$	377.857	63.57	6.40	3.71	63.24	6.46	3.57
5c	$C_{19}H_{20}ClNO_4$	361.815	63.07	5.57	3.87	62.88	5.54	3.72
5d	$C_{20}H_{22}ClNO_4$	375.841	63.90	5.90	3.73	63.94	6.05	3.67
5e	$C_{21}H_{26}ClNO_4$	391.904	64.36	6.69	3.57	64.17	6.91	3.26
5f	$C_{22}H_{28}ClNO_5$	421.929	62.74	6.69	3.32	62.62	6.62	3.56
7	$C_{11}H_{14}INO_2$	319.145	41.40	4.42	4.39	41.51	4.46	4.35

that 1-veratryl and 1-piperonyl groups originally located in the neighborhood of C_8–H were brought closer to the N-methyl groups on account of the newly introduced chlorine atoms.

Yields and melting points of these products are listed in Table II.

Since the usual chlorination of phenols in general is troublesome, the present methodology for chlorination should constitute a useful alternative.

Thus, a regiospecific halogenation of phenolic tetrahydroisoquinolines was achieved as described above by way of *p*-quinol acetate.[9]

Experimental[10]

General Procedure for Chlorination——Conc. HCl (5 ml) was added to *p*-quinol acetate (**1**) obtained from **4** (100 mg) as described previously,[8,11] and the whole was stirred at room temperature for 2 hr. The acidic solution was cautiously basified with $NaHCO_3$ (powder). Usual work-up gave a crystalline or an amorphous mass, which was purified by recrystallization (from iso-PrOH) or by preparative TLC.

8-Bromocorypalline (**6**)——48% HBr (5 ml) was added to a *p*-quinol acetate (**1a**) obtained from **4a** (100 mg) as described above and the whole was stirred at room temperature for 2 hr. Work-up as usual afforded a pale yellow sand (**6**) (106 mg, 75%), mp 189—191°, which was recrystallized from iso-PrOH to give pale yellow needles (84 mg, 67%), mp 193.5—194.5°; this product was identical with an authentic sample [mp 189—191° (lit.[7] 185°)] as judged by comparison of their IR spectra and by mixed melting point determination.

Treatment of 1a with 38% HI——38% HI (10 ml) was added to a *p*-quinol acetate (**1a**) obtained from **4a** (100 mg) as described above and the whole was stirred at room temperature for 2 hr. Usual work-up yielded a crystalline mass (40 mg), which was separated into two products by preparative TLC. Elution of the upper zone gave pale yellow crystals (**7**: 18 mg, 11%), mp 147—153°, which were recrystallized from iso-PrOH to afford pale yellow prisms (9 mg, 5.5%), mp 159—160°. Elution of the lower zone gave colorless needles (**4a**: 17 mg, 17%), mp 161—166°, which were identical with corypalline (**4a**), as judged by comparison of the IR spectra and TLC behavior.

Acknowledgement We thank Dr. T. Moroe of Takasago Perfumery Co., Ltd. for his kind gift of the starting material and Sankyo Co., Ltd. for elemental analysis. Thanks are also due to Miss T. Kawana and Mrs. S. Toshioka of this Faculty for NMR and MS measurements.

References and Notes

1) Part XVI: O. Hoshino, M. Ohtani, and B. Umezawa, *Chem. Pharm. Bull.*, **27**, 3101 (1979).
2) A preliminary communication has appeared: H. Hara, O. Hoshino, and B. Umezawa, *Heterocycles*, **3**, 123 (1975).
3) Location: *12, Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo, 162, Japan.*
4) B. Umezawa and O. Hoshino, *Heterocycles*, **3**, 1005 (1975).
5) A. Schönberg, G. Shütz, and N. Latif, *Chem. Ber.*, **94**, 2540 (1961).
6) We thank Dr. H. Mishima of Sankyo Co., Ltd. for the measurement, which was performed on a Varian HA-100 spectrometer in $CDCl_3$.
7) M. Tomita and H. Watanabe, *Yakugaku Zasshi*, **58**, 783 (1938).
8) H. Hara, O. Hoshino, and B. Umezawa, *Chem. Pharm. Bull.*, **24**, 262 (1976).
9) We are also interested in the pharmacological activities [A. Brossi, H. Besendorf, L.A. Pirk, and A. Rheiner, *Med. Chem.*, **5**, 281 (1965)] of these products and of haloisoquinoline alkaloids obtainable from them. Details will be published shortly.
10) All melting points were measured on a Büchi melting point measuring apparatus and are uncorrected. IR spectra were taken on a Hitachi 215 infrared spectrometer in $CHCl_3$ solution. NMR spectra were run on a JNR-4H-100 spectrometer in $CDCl_3$ solution with $(CH_3)_4Si$ as an internal standard. TLC or preparative TLC was run on silica gel G or GF_{254} (Merck); developing solvent, $CHCl_3$–MeOH=20: 1. Spectral data and analytical data for all new compounds are listed in Tables I and III, respectively.
11) H. Hara, O. Hoshino, and B. Umezawa, *J. Chem. Soc. Perkin I*, **1979**, 2657.