[Chem. Pharm. Bull.
36(5)1869—1871(1988)]

Studies on Tetrahydroisoquinolines. XXXI.[1] A Synthesis of Tetrahydroisoquinoline Dimers by Intermolecular C–O Coupling

Hiroshi Hara,[a] Masatoshi Murakata,[a] Osamu Hoshino,[a]
Bunsuke Umezawa,*,[a] and Tsutomu Inoue[b]

Faculty of Pharmaceutical Sciences, Science University of Tokyo,[a] 12,
Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo 162, Japan and
Ohmori Research Laboratory, Tobishi Pharmaceutical
Co., Ltd.,[b] 1-16-18 Ohmori Nishi,
Ohta-ku, Tokyo 143, Japan

(Received September 17, 1987)

Reaction of 8,8a-epoxy-1,2,3,4,4a,7,8,8a-octahydro-4a-hydroxy-6-methoxy-2-methylisoquinolin-7-one (**6**), derived from the *p*-quinol acetate (**1**), with phenols gave the bistetrahydroisoquinolines (**10**—**13**).

Keywords——*p*-quinol monoepoxide; epoxide cleavage; bistetrahydroisoquinoline; diaryl ether; C–O bond formation

In a preceding paper,[1] we described a synthesis of some tetrahydroisoquinoline dimers having an intermolecularly formed C–C bond between two aromatic rings by the use of the *p*-quinol acetate (**1**) derived from corypalline (**2**). On the other hand, Inoue *et al.*[2] have reported a convenient construction of a diphenyl ether linkage involving a tyrosine moiety by a novel method; the cross-conjugated dienone (**3**) was transformed to the diphenyl ether (**4**) *via* the formation of the monoepoxide (**5**) and its cleavage.

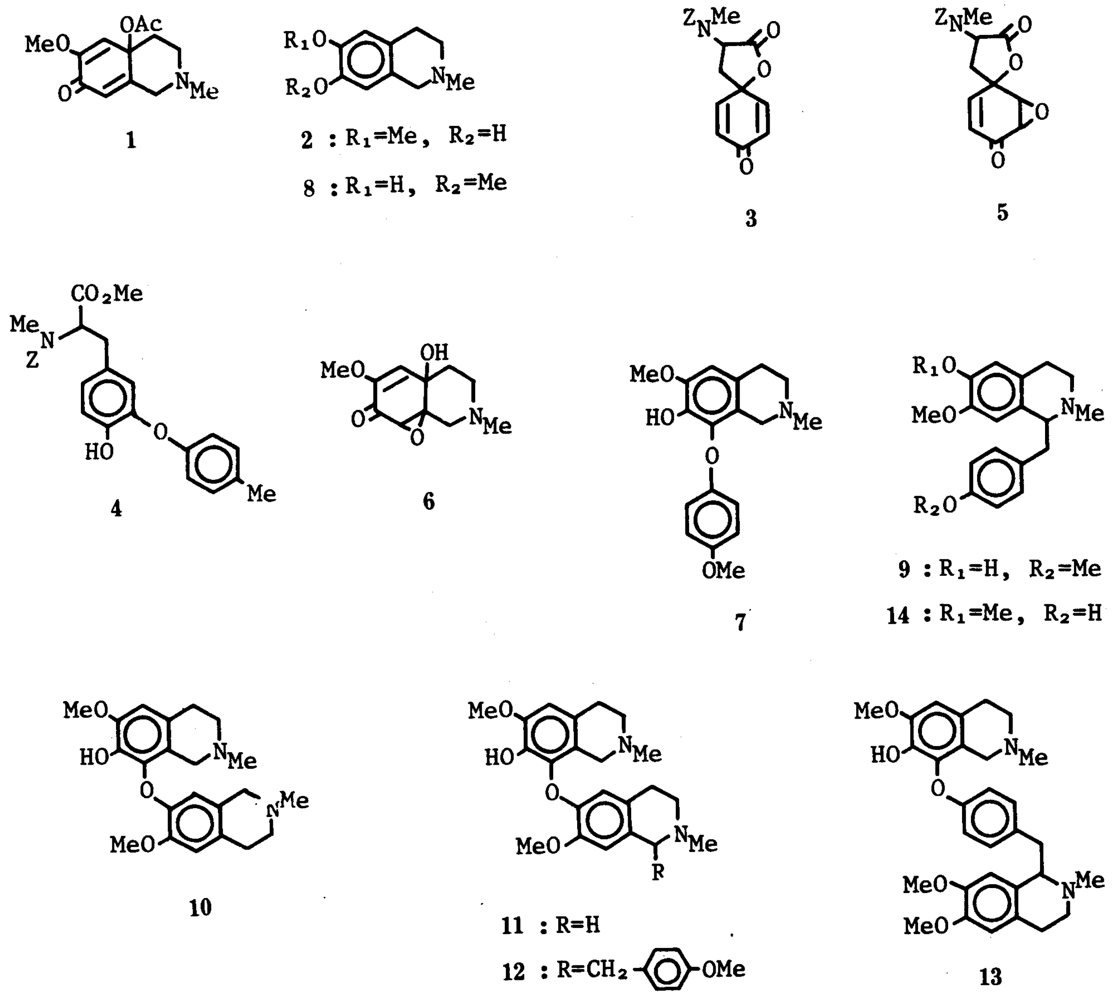
The same methodology as above was applied to the *p*-quinol monoepoxide (**6**), aiming at the preparation of several tetrahydroisoquinoline dimers having a diaryl ether linkage. This paper deals with the synthesis of **6** and its reactions with several phenoxide ions.

The starting monoepoxide (**6**) was easily prepared by epoxidation of **1** with a limited amount of alkaline 3.5% hydrogen peroxide[3] in a yield of 62% from corypalline (**2**). As expected, the double bond at the C-8 and C-8a positions was epoxidized.

Cleavage of **6** was then investigated, and it was found that the cleavage of the epoxide ring proceeded smoothly in the presence of lithium phenoxide. Thus, reaction of **6** and *p*-methoxyphenol with LiOH in dimethylformamide (DMF) and subsequent treatment of the product with zinc in acetic acid gave the 8-(4-methoxyphenoxy)-tetrahydroisoquinoline (**7**) in a yield of 39%. The structure of **7** was supported by the proton nuclear magnetic resonance (^{1}H-NMR) and infrared (IR) spectra.

Compound **6** was similarly reacted with corypalline (**2**), isocorypalline (**8**), and 1,2,3,4-tetrahydro-6-hydroxy-7-methoxy-1-(4-methoxybenzyl)-2-methylisoquinoline (**9**) to give 1,2,3,4-tetrahydro-7-hydroxy-8-(1,2,3,4-tetrahydro-6-methoxy-2-methyl-7-isoquinolyloxy)-6-methoxy-2-methylisoquinoline (**10**), 1,2,3,4-tetrahydro-7-hydroxy-8-(1,2,3,4-tetrahydro-7-methoxy-2-methyl-6-isoquinolyloxy)-6-methoxy-2-methylisoquinoline (**11**), and 1,2,3,4-tetrahydro-6-(1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methyl-8-isoquinolyloxy)-7-methoxy-1-(4-methoxybenzyl)-2-methylisoquinoline (**12**) in 28%, 32%, and 12% yeilds, respectively.

The dimer (**10**) was identical with Bobbitt's sample[4] by comparison of the respective ^{1}H-



1

2 : R_1=Me, R_2=H

8 : R_1=H, R_2=Me

3

5

4

6

7

9 : R_1=H, R_2=Me

14 : R_1=Me, R_2=H

10

11 : R=H

12 : R=CH_2-C$_6$H$_4$-OMe

13

Chart 1

NMR spectra. Structural assignments of **11** and **12** were analogously performed. Thus, the head-to-head dimers having a C–O linkage could be prepared, though in low yields.

By the same methodology as above, we tried to prepare the head-to-tail dimer, such as **13**. A similar sequence of reactions of **6** with (±)-armepavine (**14**) gave the expected 1,2,3,4-tetrahydro-1-[4-(1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methyl-8-isoquinolyloxy)benzyl]-6,7-dimethoxy-2-methylisoquinoline (**13**) in a yield of 5.4%. The reason for the very low yield of **13** seemed to be the absence of an *ortho* or *para* methoxy group in **14** that would enhance the reactivity of the phenoxide ion.

In any event, a promising route to both the head-to-head and the head-to-tail dimers having an intermolecularly formed C–O linkage in the field of 1,2,3,4-tetrahydroisoquinolines has been exploited.

Experimental

All melting points were measured on a Büchi melting point apparatus and are uncorrected. ^{1}H-NMR spectra were taken with a JEOL JNX-FX-100 (100 MHz) or with a Hitachi R-24B (60 MHz) instrument in $CDCl_3$ solution with Me_4Si as an internal standard. IR spectra were run on a Hitachi 260 spectrometer. Mass spectra (MS) were run on a Hitachi RMU-7M mass spectrometer. Preparative thin layer chromatography (TLC) was performed on Silica gel 60F_{254} plates (Merck), 2.0 mm thick.

Preparation of the *p*-Quinol Monoepoxide (6) from Corypalline (2)——*p*-Quinol acetate (1)[5] derived from 2 (100 mg) was dissolved in MeOH (1 ml). A mixture of 1 N NaOH solution in MeOH and H_2O (3 : 1) (0.52 ml) was added to the ice-cooled solution and the whole was stirred for 15 min. To the ice-cooled solution, 3.5% H_2O_2 (0.38 ml) was slowly added over a period of 30 min.[6] Excess H_2O_2 was decomposed by adding excess $Na_2S_2O_3$ (powder) under vigorous stirring. The product was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with brine and dried over K_2CO_3. Usual work-up of the organic layer gave the monoepoxide (**6**) [73 mg (63%), mp 208—210 °C (dec.) (MeOH)]: ^{1}H-NMR δ: 2.35 (3H, s, NMe), 3.56 (1H, s, 8-H), 3.61 (3H, s, OMe), 5.35 (1H, s, 5-H). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1685 (C=O), 1250, 870 (epoxide). *Anal.* Calcd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.71; H, 6.78; N, 6.19.

A Typical Procedure for the Synthesis of the Diphenyl Ethers (7, 10, 11, 12, and 13)——LiOH·H_2O (112 mg) was added to a solution of **6** (200 mg, 8.89×10^{-1} mmol) and hydroquinone monomethyl ether (331 mg, 2.67 mmol) in warm DMF (10 ml), and the whole was warmed at 50 °C for 3 h. The solvent was evaporated off to leave a residue, which was extracted with CH_2Cl_2. The organic layer was washed successively with 5% aqueous NaOH and brine, and dried over K_2CO_3. Usual work-up of the organic layer gave an oil (152.1 mg), which was dissolved in AcOH (1.5 ml) and treated with Zn powder (179.2 mg, 2.76 mmol) under stirring at room temperature for 2 h. The reaction mixture was made alkaline with saturated aqueous $NaHCO_3$ and the product was extracted with CH_2Cl_2. Usual work-up of the organic layer gave an oil (134.2 mg), which was purified by preparative TLC [developing solvent, $CHCl_3$–MeOH–AcOEt (30 : 4 : 3)] to give oily **7** (108.9 mg, 39%). ^{1}H-NMR δ: 2.36 (3H, s, NMe), 3.74, 3.83 (each 3H, s, OMe), 6.45 (1H, s, 5-H), 6.75 (4H, s, ArH). IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3520 (OH), 1230 (ArOAr). Methiodide: prisms (MeOH–AcOEt), mp 177—180 °C, *Anal.* Calcd for $C_{19}H_{24}INO_4$ (457.31): C, 49.90; H, 5.29; N, 3.06. Found: C, 49.84; H, 5.40; N, 2.99.

In other cases, the ratio of a given phenol to **6** was 1.2 to 2.7. Spectral data (^{1}H-NMR and IR) and analytical data (elemental analysis or high-resolution MS) are given below. **10**: Prisms (AcOEt), mp 177 °C (lit.[4] oil). *Anal.* Calcd for $C_{22}H_{28}N_2O_4$ (384.36): C, 68.72; H, 7.34; N, 7.29. Found: C, 68.47; H, 7.22; N, 7.28. ^{1}H-NMR δ: 2.36 (6H, s, 2 × NMe), 3.82, 3.89 (each 3H, s, OMe), 6.15, 6.46, 6.63 (each 1H, s, ArH). IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3550 (OH), 1260 (ArOAr). **11**: Colorless oil. High-resolution MS Calcd for $C_{22}H_{28}N_2O_4$: 384.2047. Found: 384.2024 (M^+). ^{1}H-NMR δ: 2.36, 2.40 (each 3H, s, NMe), 3.84, 3.90 (each 3H, s, OMe), 6.26, 6.47, 6.55 (each 1H, s, ArH). IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3550 (OH), 1260 (ArOAr). Dimethiodide: Prisms, mp 204—206 °C (MeOH). *Anal.* Calcd for $C_{24}H_{34}I_2N_2O_4 \cdot 2H_2O$ (704.38): C, 40.92; H, 5.43; N, 4.08. Found: C, 41.11; H, 5.18; N, 3.78. **12**: Colorless oil. MS *m/z*: 504 (M^+), 383 ($M^+ - 121$, base peak). ^{1}H-NMR δ: 2.40, 2.50 (each 3H, s, NMe), 3.63, 3.78, 3.85 (each 3H, s, OMe), 6.04, 6.24, 6.48 (each 1H, s, ArH), 6.77, 6.99 (each 2H, d, $J = 9$ Hz, 2 × ArH). IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3550 (OH), 1245 (ArOAr). Dimethiodide: Prisms (MeOH), mp 250—252 °C (dec.). *Anal.* Calcd for $C_{32}H_{42}I_2N_2O_5 \cdot H_2O$ (806.508): C, 47.65; H, 5.50; N, 3.47. Found: C, 47.68; H, 5.49; N, 3.70. **13**: Colorless oil. High-resolution MS Calcd for $C_{30}H_{35}N_2O_5$: 503.2544 ($M^+ - 1$). Found: 503.2588. ^{1}H-NMR δ: 2.36, 2.52 (each 3H, s, NMe), 3.55, 3.82, 3.86 (each 3H, s, OMe), 5.91, 6.49, 6.51 (each 1H, s, ArH), 6.73, 6.93 (each 2H, d, $J = 9$ Hz, 2 × ArH). IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3525 (OH), 1240 (ArOAr).

Acknowledgements We thank Dr. T. Moroe of Takasago Perfumery Co., Ltd. for providing the starting vanillin, Miss T. Kanbara for her technical assistance, Sankyo Co., Ltd. for elemental analyses, and Miss N. Sawabe and Mrs. N. Yamatani of this Faculty for ^{1}H-NMR and mass spectral measurements.

References and Notes

1) Part XXX: H. Hara, M. Murakata, O. Hoshino, B. Umezawa, and Y. Iitaka, *Chem. Pharm. Bull.*, **36**, 1627 (1988).

2) T. Inoue, K. Naitoh, S. Kosemura, I. Umezawa, T. Sonobe, N. Serizawa, N. Mori, and H. Itokawa, *Heterocycles*, **20**, 397 (1983).

3) K. Uba, N. Miyata, K. Watanabe, and M. Hirobe, *Chem. Pharm. Bull.*, **27**, 2257 (1979).

4) J. M. Bobbitt, K. H. Weisgraber, A. S. Steinfeld, and S. G. Weiss, *J. Org. Chem.*, **35**, 2884 (1970).

5) B. Umezawa, O. Hoshino, Y. Terayama, K. Ohyama, Y. Yamanashi, T. Inoue, and T. Toshioka, *Chem. Pharm. Bull.*, **19**, 2138 (1971).

6) The use of excess oxidant and elongation of the reaction time should be avoided. The best yield of the monoepoxide (**6**) was obtained when the amount of hydrogen peroxide was at most 0.75 equivalent and the reaction mixture was quenched immediately after disappearance of the spot of the *p*-quinol[5] on TLC.