Studies on the Syntheses of Heterocyclic Compounds. Part DXIV.[1] Synthesis of 6a,7-Didehydroaporphine and Indolo[2,1-*a*]isoquinoline Systems by Benzyne Reactions

By **Tetsuji Kametani,*** Pharmaceutical Institute, Tokoku University, Aobayama, Sendai, Japan
Shiroshi Shibuya and **Shinzo Kano,** Tokyo College of Pharmacy, 3-20-1, Kitashinjuku Shinjuku, Tokyo, Japan

The benzyne reaction of 1-(2-bromo-4,5-dimethoxybenzyl)-3,4-dihydro-7-hydroxy-6-methoxyisoquinoline (3) methiodide with sodium methylsulphinylmethanide in dimethyl sulphoxide afforded 6a,7-didehydro-2,9,10-trimethoxyaporphin-1-ol (7), which on reduction gave (±)-thaliporphine (2). 5,6-Dihydro-2,3,9,10-tetramethoxyindolo[2,1-*a*]isoquinoline (6) and its 2-hydroxy-analogue (5) were also obtained through benzyne reactions of 1-(2-bromobenzyl)-3,4-dihydroisoquinolines under similar conditions.

THE benzyne reaction has been used for the syntheses of numerous synthetic intermediates and natural products, usually with sodium amide or potassium t-butoxide as base [*e.g.* the synthesis of the aporphine alkaloid, domesticine (1) [2]. We report here the benzyne reaction of 1-(2-bromobenzyl)-3,4-dihydroisoquinoline derivatives with sodium methylsulphinylmethanide as base to give indoloisoquinoline and didehydroaporphine systems.

The benzyne reaction of 1-(2-bromo-4,5-dimethoxy-

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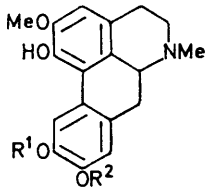
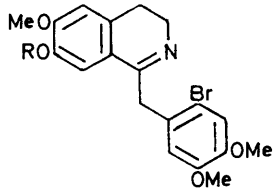
[2] T. Kametani, S. Shibuya, K. Kigasawa, M. Hiiragi, and O. Kusama, *J. Chem. Soc.* (*C*), 1971, 2712.

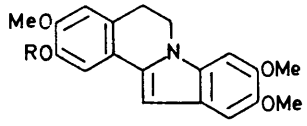
benzyl)-3,4-dihydro-7-hydroxy-6-methoxyisoquinoline (3) with sodium methylsulphinylmethanide [3] in dimethyl sulphoxide gave the indolo[2,1-*a*]isoquinoline (5). Mass spectrometry (M^+ 325) and microanalysis verified the



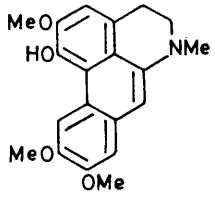
(1) $R^1R^2 = CH_2$
(2) $R^1 = R^2 = Me$



(3) R = H
(4) R = Me



(5) R = H
(6) R = Me



(7)

molecular formula as $C_{19}H_{19}NO_4$, and the n.m.r. spectrum revealed resonances at δ($CDCl_3$) 3·90 (2 × OMe), 3·92 (OMe), and 6·63 (12-H) but no characteristic 1-$ArCH_2$ signal. Under similar conditions, 1-(2-bromo-4,5-dimethoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (4) afforded the indoloisoquinoline (6), identical spectroscopically with an authentic specimen.[4]

However, the benzyne reaction of 1-(2-bromo-4,5-dimethoxybenzyl)-3,4-dihydro-7-hydroxy-6-methoxyisoquinoline (3) methiodide gave the didehydroaporphine (7), identified by mass spectrometry (M^+ 339), microanalysis, n.m.r. spectroscopy, and reduction with zinc amalgam to afford (±)-thaliporphine (2) [5] an alkaloid from *Thalictrum fendleri*.[6] The n.m.r. spectrum of compound (7) showed aromatic protons at low field [δ($CDCl_3$) 8·85] and an unusually deshielded *N*-methyl group (3·02), typical pattern of an 11-proton and an *N*-methyl group of a didehydroaporphine system.[7,8]

EXPERIMENTAL

N.m.r. spectra were determined with a Varian T-60 instrument (tetramethylsilane as internal reference) and mass spectra with a Hitachi RMU-7L at 70 eV.

1-(2-*Bromo*-4,5-*dimethoxybenzyl*)-3,4-*dihydro*-7-*hydroxy*-6-*methoxyisoquinoline* (3).—A solution of 7-benzyloxy-1-(2-bromo-3,4-dimethoxybenzyl)-3,4-dihydro-6-methoxyisoquinoline [4] (10 g) in ethanol (50 ml) and concentrated hydrochloric acid (50 ml) was refluxed for 2 h. The solvent was evaporated off and the residue was made basic with 28% ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4) and evaporated. The solid was recrystallised from methanol to give *needles* (7 g) (Found: C, 56·45; H, 3·6; N, 5·05. $C_{19}H_{20}BrNO_4$ requires C, 56·15; H, 3·45; N, 4·95%), δ($CDCl_3$) 3·69, 3·77, and 3·85 (9H, each s, 3 × O·CH_3), 4·0 (2H, s, 1-CH_2Ph), and 6·55, 6·67, 6·9, and 6·97 (4H, each s, ArH).

A solution of the product (3) (5 g) in methyl iodide (10 ml) and methanol (20 ml) was refluxed for 4·5 h. Removal of the solvent and recrystallisation of the residue from methanol gave the methiodide (6 g) as pale yellow *needles*, m.p. 210—212° (decomp.) (Found: C, 43·8; H, 2·55; N, 4·05. $C_{20}H_{23}BrINO_4$ requires C, 43·75; H, 2·55; N, 4·05%).

Reaction of 1-(2-*Bromo*-4,5-*dimethoxybenzyl*)-3,4-*dihydro*-6,7-*dimethoxyisoquinoline* (4) *with Sodium Methylsulphinylmethanide*.—To a solution of sodium methylsulphinylmethanide [from sodium hydride (0·7 g) and dimethyl sulphoxide (10 ml)], the isoquinoline (4) (2 g) in dimethyl sulphoxide (15 ml) was added with stirring at 40° within a few minutes. The mixture was stirred for 3 h at the same temperature, poured into cold water (150 ml), and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to leave an oil (1·5 g), which was chromatographed on silica gel (30 g) (chloroform as eluant). The product (0·8 g) was further chromatographed on silica gel (20 g), again with chloroform. The product afforded needles (0·6 g), m.p. 202—203° (from ethanol), identical with authentic 5,6-dihydro-2,3,9,10-tetramethoxyindolo[2,1-*a*]isoquinoline (6) [4] (spectroscopic data).

5,6-*Dihydro*-2-*hydroxy*-3,9,10-*trimethoxyindolo*[2,1-*a*]*isoquinoline* (5).—To a solution of sodium methylsulphinylmethanide [from sodium hydride (1 g) and dimethyl sulphoxide (15 ml)] a solution of the isoquinoline (3) (2 g) in dimethyl sulphoxide (15 ml) was added within 10 min with stirring at 40°. Stirring was continued for 3 h, and the mixture was then poured into ice–water (150 ml) containing ammonium chloride (5 g) and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residue (1·5 g) was chromatographed on silica gel (40 g) (chloroform as eluant). to afford *needles* (5), m.p. 224—225° (from chloroform–methanol) (Found: C, 69·85; H, 6·0; N, 4·25. $C_{19}H_{19}NO_4$ requires C, 70·15; H, 5·9; N, 4·3%), δ($CDCl_3$) 3·05 (2H, t, 5-H_2), 3·9 (6H, s, O·CH_3), 3·92 (3H, s, O·CH_3), 4·13 (2H, t, 6-H_2), and 6·63 (1H, s, 12-H), *m/e* 325 (M^+, base peak).

6a,7-*Didehydro*-2,9,10-*trimethoxyaporphin*-1-*ol* (7).—To a solution of sodium methylsulphinylmethanide [from sodium hydride (2 g) and dimethyl sulphoxide (20 ml)] a solution of the isoquinoline (3) methiodide (4 g) in dimethyl sulphoxide (30 ml) was added with stirring at 40° within 10 min. Stirring was continued for 4 h, then the mixture was poured into ice–water, made basic with crystalline ammonium chloride, and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and

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[7] M. P. Cava, Y. Watanabe, K. Bessho, M. J. Mitchell, A. I. da Rocha, B. Hwang, B. Douglas, and J. A. Weisbach, *Tetrahedron Letters*, 1968, 2437.
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evaporated to leave a syrup (2·5 g), which was chromatographed on silica gel (50 g) (chloroform as eluant). The product afforded *needles* (7) (0·9 g), m.p. 157—160° (decomp.) (from methanol–ether) (Found: C, 70·4; H, 6·3; N, 3·85. $C_{20}H_{21}NO_4$ requires C, 70·75; H, 6·25; N, 4·15%), δ($CDCl_3$), 3·02 (3H, s, N·CH_3), 3·23br (4H, s, 4-H_2, 5-H_2), 3·98 (6H, s, 2 × O·CH_3), 4·0 (3H, s, O·CH_3), 6·57 (1H, s, 7-H), 6·85 and 6·98 (2H, each s, ArH), and 8·85 (1H, s, 11-H), *m/e* 339 (M^+), 325 ($M^+ - 14$).

(±)-*Thaliprophine* (2).—A mixture of compound (7) (0·2 g), zinc amalgam [prepared from 5% mercuric chloride (10 ml) and zinc (7 g)], 50% acetic acid (20 ml), and concentrated hydrochloric acid (10 ml) was heated on a steam-bath for 2 h. After removal of inorganic substances, the solution was made basic with 28% ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residual solid was recrystallised from ether to give compound (2) (110 mg) as *needles*, m.p. 192—193° (lit.,[5] 192—194°) (Found: C, 70·6; H, 6·9; N, 3·85. $C_{20}H_{23}NO_4$ requires C, 70·35; H, 6·8; N, 4·1%), δ($CDCl_3$), 2·53 (3H, s, N·CH_3), 6·52 and 6·78 (2H, each s, ArH), and 8·02 (1H, s, 11-H).

We thank the Analytical Center, Tokyo College of Pharmacy, and Miss C. Yoshida, Miss R. Kato, and Miss F. Yoshinaka for microanalyses, spectral measurements, and technical assistance.

[2/2827 *Received*, 15*th December*, 1972]