Sodium Dithionite Reduction in the Preparation of Indole Alkaloids of Gambirtannine-type

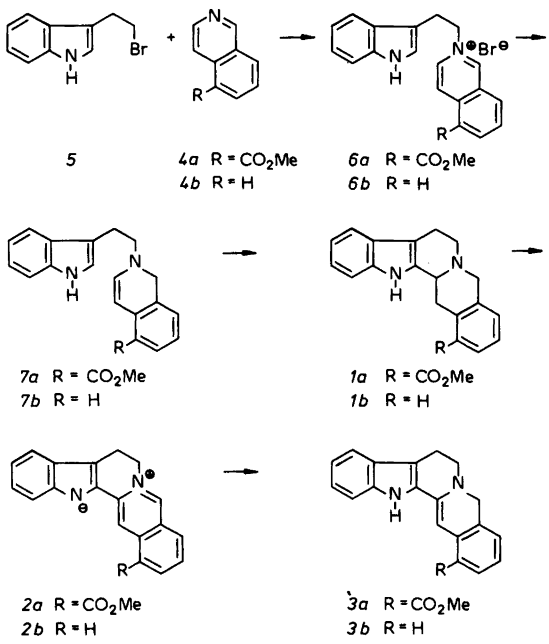
EVA FROSTELL, REIJA JOKELA and MAURI LOUNASMAA *

Technical University of Helsinki, Department of Chemistry, SF-02150 Espoo 15, Finland

The indole alkaloids dihydrogambirtannine *1a*, ourouparine *2a* and gambirtannine *3a* have been isolated from several *Uncaria* species,[1,2] most notably from *Uncaria gambir* Roxb. (*Ourouparia gambir* Baillon) (Rubiaceæ).[3] The corresponding demethoxycarbonyl derivative *1b* has been found in *Ochrosia lifuana* Guill. and *O. miana* H. Bn ex Guill. (Apocynaceæ)[4] as well as in *Strychnos usambarensis* Gilg. (Loganiaceæ).[5] Several essentially different synthetic routes to dihydrogambirtannine *1a*, a useful intermediate in the preparation of ourouparine *2a* and gambirtannine *3a*, have been described.[6,7,8]

In the present communication we describe the use of sodium dithionite reduction in a new and short synthesis of dihydrogambirtannine *1a*, ourouparine *2a* and gambirtannine *3a*, and of the corresponding demethoxycarbonyl derivatives *1b*, *2b* and *3b*.

* To whom correspondence should be sent.



0302-4369/81/090671-02$02.50

Alkylation of 5-methoxycarbonylisoquinoline *4a*[7,9] with tryptophyl bromide *5*[10] yielded the isoquinolinium salt *6a*, and sodium dithionite reduction[11–15] of *6a* effected in a two-phase system (CH_2Cl_2, H_2O) afforded the unstable dihydroisoquinoline derivative *7a*. By acid-induced cyclization *7a* was transformed to dihydrogambirtannine *1a*. Dehydrogenation of *1a* with palladium in aqueous maleic acid solution[16] yielded ourouparine *2a* isolated as the perchlorate. The sodium dithionite reduction of the ourouparine *2a* perchlorate in the same two-phase system afforded gambirtannine *3a*. In analogous manner the isoquinolinium salt *6b*, prepared from *4b* and *5*, afforded the dihydroisoquinoline derivative *7b*, which was transformed first to demethoxycarbonyldihydrogambirtannine *1b*, and then, *via* demethoxycarbonylourouparine *2b* perchlorate, to demethoxycarbonylgambirtannine *3b*.

In accordance with earlier results,[3] it was found that gambirtannine *3a* and demethoxycarbonylgambirtannine *3b* are relatively unstable compounds: they decompose on standing, even in solid state, giving rise to small amounts of corresponding oxygambirtannines.

Experimental. The IR spectra were recorded with a Perkin-Elmer 700 spectrophotometer. The ^1H NMR spectra were measured on a Jeol JNM-FX 60 instrument with TMS as internal standard. The mass spectra were recorded on a Jeol JMS-D-100 Mass Spectrometer at 70 eV using direct sample insertion into the ion source, whose temperature was 100–120 °C. The melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected.

5-Methoxycarbonylisoquinoline 4a. 5-Aminoisoquinoline (EGA-CHEMIE) was transformed to 5-methoxycarbonylisoquinoline *4a* by the Sandmeyer reaction followed by hydrolysis and esterification. Yield 36%. M.p. 66–67 °C (light petroleum) (lit. 66 °C[7,9]).

Isoquinolinium salts 6a *and* 6b. A mixture of 5-methoxycarbonylisoquinoline *4a* (0.77 g) and tryptophyl bromide *5*[10] (1 g) was heated under nitrogen at 100 °C for 3 h. The mixture was allowed to cool, crushed to grains, and stirred in dry ether. The mixture was filtered, yielding 1.55 g (92%) of *6a*. M.p. 245–248 °C (MeOH) (lit. 248 °C[17]). A similar treatment of isoquinoline *4b* (0.56 g) and tryptophyl bromide *5*[10] (1 g) yielded 1.39 g (88%) of *6b*. M.p. 223–227 °C (MeOH) (lit. 207–208 °C[18]).

Dihydrogambirtannine 1a *and demethoxycarbonyldihydrogambirtannine* 1b. Sodium dithionite (200 mg) was quickly added to a magnetically stirred solution of the isoquinolinium salt *6a* (100 mg) and $KHCO_3$ (400 mg) in a two-phase system (H_2O–CH_2Cl_2, 1:1) under nitrogen. After 6 h the CH_2Cl_2 layer was collected and a new lot of CH_2Cl_2 was added. This

procedure was repeated once more. The combined CH_2Cl_2-layers were washed with water, dried over Na_2SO_4, and evaporated under vacuum, yielding 80 mg of *7a*. ^1H NMR ($CDCl_3$): δ 3.93 (3H, s, $-COOCH_3$). MS (IP 70 eV; *m/e*): 332 ($M^{\cdot+}$), 202, 187, 144, 143, 130. Thereafter *7a* in anhydrous MeOH presaturated with dry HCl gas was stirred 48 h at room temperature, and neutralized with $NaHCO_3$ in CH_2Cl_2. The inorganic salts were filtered off and the dried filtrate evaporated under vacuum. Purification on PLC yielded 11.3 mg (14%) of *1a*. M.p. 159–163 °C (benzene–hexane, 1:1) lit. 163 °C,[3] 176–178 °C[6]). IR (KBr): NH 3400 (m), Bohlmann bands at 2805 (w), 2760 (w), C=O 1720 (s) cm^{-1} (lit.[3]). ^1H NMR ($CDCl_3$): δ 3.88 (3H, s, $-COOCH_3$), 4.11 (1 H, d, *J* 16 Hz, C(21)H eq), 6.9–8.0 (arom.), 8.14 (1 H, br s, NH) (lit.[3]). MS (IP 70 eV; *m/e*): 332 ($M^{\cdot+}$), 331, 169 (lit.[3]).

A similar treatment of isoquinolinium salt *6b* (200 mg) with sodium dithionite (400 mg) and $KHCO_3$ (800 mg) afforded 107 mg of *7b*. MS (IP 70 eV; *m/e*): 274 ($M^{\cdot+}$), 144, 143, 130, 129. Acid-induced cyclization of *7b* yielded 40 mg (26%) of *1b*. M.p. 187–190 °C (MeOH–H_2O, 1:1) (lit. 196–197 °C,[19] 191–193 °C[20]). IR (KBr): NH 3400 (m), Bohlmann bands 2815 (w), 2755 (w) cm^{-1} (lit.[4]). ^1H NMR ($CDCl_3$): δ 4.06 (1H, d, *J* 16 Hz, C(21)H eq) 7.05–7.50) (arom.), 8.10 (1H, br s, NH) (lit.[4,18]). MS (IP 70 eV; *m/e*): 274 ($M^{\cdot+}$), 273, 169 (lit.[4]).

Ourouparine (2a) *and demethoxycarbonyl-ourouparine* (2b) *perchlorates*. A mixture of *1a* (17 mg), maleic acid (20 mg) and palladium–charcoal (10%) (15 mg) in 5 ml of water was refluxed for 24 h under nitrogen. The solution was filtered and the filtrate evaporated under vacuum. A saturated solution of sodium perchlorate was added and the salt *2a* separated. Yield 10 mg (45%). M.p. 285–290 °C (dec.). IR (KBr): NH 3400 (m), C=O 1720 (s) cm^{-1}. A similar treatment of *1b* (30 mg), maleic acid (52 mg) and palladium–charcoal (15 mg) in 15 ml of water yielded 22 mg (54%) of *2b*. M.p. 280–283 °C (dec.). IR (KBr): NH 3380 (m), C=C 1630 (m) cm^{-1}.

Gambirtannine 3a *and demethoxycarbonyl-gambirtannine* 3b. Sodium dithionite (80 mg) was quickly added to a magnetically stirred solution of ourouparine *2a* perchlorate (6 mg) and $KHCO_3$ (100 mg) in a two-phase system ($H_2O-CH_2Cl_2$, 1:1) under nitrogen. After 6 h the CH_2Cl_2-layer was collected and a new lot of CH_2Cl_2 was added. This procedure was repeated once more. The combined CH_2Cl_2-layers were washed with water, dried over Na_2SO_4 and evaporated under vacuum. Purification on PLC yielded 1.2 mg (26%) of *3a*. M.p. 146–152 °C (ether–hexane, 1:1) (lit. 150–153 °C[3]). IR ($CHCl_3$): NH 3380 (m), C=O 1720 (s) cm^{-1} (lit.[3]). ^1H NMR ($CDCl_3$): δ 3.90 (3H, s, $-COOCH_3$). MS (IP 70 eV; *m/e*): 330 ($M^{\cdot+}$), 329, (lit.[3]).

A similar treatment of *2b* (20 mg), $Na_2S_2O_4$ (80 mg) and $KHCO_3$ (100 mg) yielded 3.3 mg (22%) of *3b*. M.p. 185–190 °C (MeOH) (lit. 210–215 °C (darkening at 190 °C)[21]). IR ($CHCl_3$): NH 3380 (m) cm^{-1}. MS (IP 70 eV; *m/e*): 272 ($M^{\cdot+}$), 271.

1. Saxton, J. E. In Manske, R. H. F., Ed., *The Alkaloids, Chemistry and Physiology*, Academic, New York 1968, Vol. 10, p. 524 and references therein.
2. Hemingway, S. R. and Phillipson, J. D. In Phillipson, J. D. and Zenk, M. H., Eds., *Indole and Biogenetically Related Alkaloids*, Academic, London 1980, p. 75 and references therein.
3. Merlini, L., Mondelli, R., Nasini, G. and Hesse, M. *Tetrahedron 23* (1967) 3129.
4. Peube-Locou, N., Plat, M. and Koch, M. *Phytochemistry 12* (1973) 199.
5. Angenot, L., Coune, C. and Tits, M. *J. Pharm. Belg. 33* (1978) 284.
6. Wenkert, E., Dave, K. G., Gnewuch, C. T. and Sprague, P. W. *J. Am. Chem. Soc. 90* (1968) 5251. See also Kan-Fan, C. and Husson, H.-P. *Tetrahedron Lett.* (1980) 1463.
7. Beisler, J. A. *Tetrahedron 26* (1970) 1961.
8. Markaryan, E. A., Solomina, L. P., Asatryan, T. O. and Tsatinyan, A. S. *Arm. Khim. Zh. 29* (1976) 326; *Chem. Abstr. 86* (1977) 140, 317.
9. Tyson, F. T. *J. Am. Chem. Soc. 61* (1939) 183.
10. Hoshino, T. and Shimodaira, K. *Justus Liebigs Ann. Chem. 520* (1935) 19.
11. Lounasmaa, M. and Johansson, C.-J. *Tetrahedron 33* (1977) 113.
12. Lounasmaa, M., Juutinen, P. and Kairisalo, P. *Tetrahedron 34* (1978) 2529.
13. Lounasmaa, M. and Jokela, R. *Tetrahedron Lett.* (1978) 3609.
14. Lounasmaa, M. and Husson, H.-P. *Acta Chem. Scand. B 33* (1979) 466.
15. Jokela, R. and Lounasmaa, M. *Tetrahedron. In press.*
16. Lounasmaa, M. and Puhakka, M. *Acta Chem. Scand. B 32* (1978) 77.
17. Elderfield, R. C. and Fisher, B. A. *J. Org. Chem. 23* (1958) 949.
18. Merlini, L., Nasini, G. and Palamareva, M. *Gazz. Chim. Ital. 105* (1975) 339.
19. Clemo, G. R. and Swan, G. A. *J. Chem. Soc.* (1946) 617.
20. Ninomiya, I., Takasugi, H. and Naito, T. *J. Chem. Soc. Chem. Commun.* (1973) 732.
21. Swan, G. A. *J. Chem. Soc.* (1949) 1720.

Received September 10, 1981.