J. Indian Inst. Sci., Mar.–Apr. 2001, **81**, 135–138.

Short Communication

An efficient synthesis of olivacine

N. S. NARASIMHAN* AND S. M. GOKHALE
Department of Chemistry, University of Pune, Pune 411 007.
email: nsn@chem.unipune.ernet.in; Fax: 91-20-5693899/5691728.

Received on October 5, 2000.

Abstract

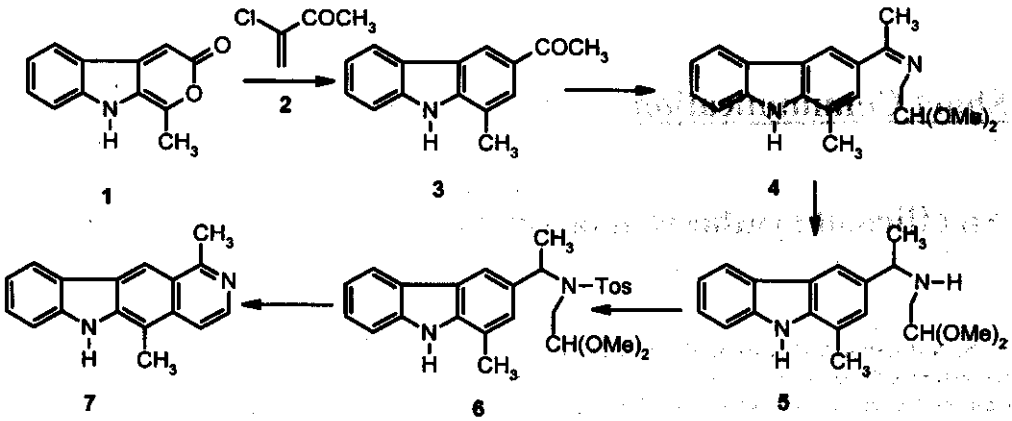
The key intermediate, 3-acetyl-1-methylcarbazole (**3**), has been synthesized in a Diels–Alder reaction of 1-methylindolo[3,4-b]pyran-3-one (**1**) with 1-chlorovinyl methyl ketone (**2**), which was then converted to olivacine (**7**).

Keywords: Indolopyrone, Diels–Alder reaction, regioselectivity.

Olivacine, 1,5-dimethyl-6*H*-pyrido[4,3-b]carbazole (**7**), was isolated in 1959 from *Aspidosperma olivaeum*.[1] The alkaloid was reported to have anticancer activities, specifically inhibition of tumours, such as adenocarcinoma, leukaemia L-1210, myeloblastic leukaemia, etc.[2] It was shown that the anticancer activity was due to the binding of the carbazole with the base pairs of the double-stranded DNA of the cancerous cells which then prevented their duplication.[3]

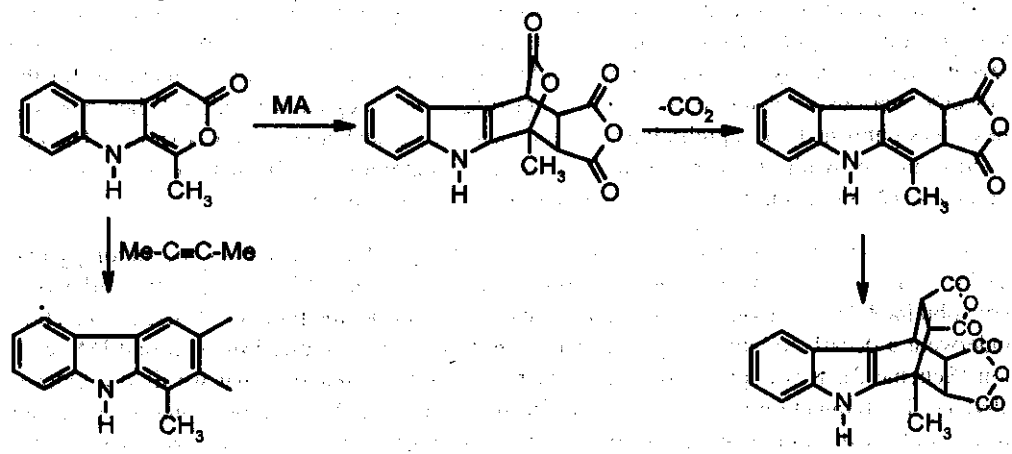
Due to its anticancer activity olivacine has been a subject of synthesis in several laboratories. Several analogues of olivacine have been made by different routes.[4] We describe here a new method for the synthesis of the molecule, which would make available analogues of the molecule, variously substituted in the different rings, for biological screening. When our synthesis was published,[5] as a preliminary communication, no such approach was known. The key reaction in our synthesis is the cycloaddition of the indolopyrone (**1**) with a chloroethylene dienophile (**2**) and completing the synthesis according to Scheme 1.

At the time when we had planned the Diels–Alder (DA) reaction of the indolopyrone (1984), only one report on such reactions had appeared.[6] With acetylenes, carbazoles were obtained. With ethylenes, for example, maleic anhydride, the product of first DA reaction underwent a decarboxylation to give a diene, which was then followed by a second DA reaction (Scheme 2). It was precisely to prevent the second DA reaction that we used a chloroethylene. In conjunction with a base (hindered base) the first DA reaction would be followed by not only a decarboxylation but also a dehydrohalogenation to give a carbazole directly (Scheme 1).



Scheme 1.

With the above considerations in mind and towards the synthesis of olivacine, the 1-methylindolopyrone (**1**) was prepared according to the procedure of Plieninger *et al.*[6] with some modifications by changing the quantities of acetic anhydride and boron trifluoride etherate. The DA reaction with 1-chlorovinyl methyl ketone (**2**) in the presence of collidine furnished 3-acetyl-1-methylcarbazole (**3**) in 72% yield. The carbazole (**3**) was condensed with aminoacetaldehyde dimethylacetal in toluene at 100°C. In this reaction, the water droplets formed at the sides of the flask after 20 min heating were removed and fresh amino acetaldehyde dimethylacetal was added. This process was repeated twice, when a thick oil was obtained. The oil had the ^{1}H NMR corresponding to the expected imine (**4**). It was not purified, but was reduced in ethanol using Raney nickel catalyst at 85 psi pressure of hydrogen to obtain the amine (**5**), which on tosylation furnished the tosyl derivative (**6**). Various conditions were tried for the cyclisation of the tosyl derivative to olivacine. The best condition was treating at room temperature in dioxane solution with a few drops of conc. HCl. Olivacine (**7**) was obtained in 65% yield.



Scheme 2.

Experimental

M.p.s are uncorrected. The ^{1}H NMR spectra were recorded on a Perkin–Elmer R-32 (90 MHz) instrument.

3-Acetyl-1-methylcarbazole (3)

1-Methylindolo[3,4-b]pyran-3-one (**1**) (0.6 g, 0.003 mol) was suspended in collidine (2 eq.) and THF (20 ml, freshly distilled over LAH) in a round bottom flask provided with a reflux condenser and a calcium chloride guard tube. 1-Chlorovinyl methyl ketone (**2**) (1 g) was added to it. The reddish suspension with bright fluorescence was heated, with constant stirring at 75°C (bath temperature). Within 10 min, the entire solid gets dissolved. Heating and stirring was continued for a further period of 6 h. The reaction mixture was cooled and diluted with water, concentrated under reduced pressure, cooled, acidified with dilute hydrochloric acid and extracted with ether (3 × 25 ml). The ether layer was washed with water (2 × 15 ml) and dried (sodium sulphate). Ether was removed under reduced pressure to give a brownish solid. It was purified by column chromatography over silica gel using hexane–12% ethyl acetate as eluant. 3-Acetyl-1-methylcarbazole (**3**) was obtained as a yellow solid and was crystallised from hexane–ethyl acetate (0.048 g, 72%), m.p.169°C. Analysis: Found: C, 80.45; H, 5.74. Calc. for $C_{15}H_{13}NO$: C, 80.69; H, 5.87%. ^{1}H NMR ($CDCl_3$+DMSO-d_6), 9.7 (1H, bs, exchanges with D_2O, NH), 8.52 (1H, d, J = 1.5 Hz, Ar-H4), 8,09 (1H, dd, J = 6 and 1.5 Hz, Ar-H5), 7.88 (1H, d, J = 1.5 Hz, Ar-H2), 7.12–7.6 (3H, m, Ar-H6,7,8), 2.7 (3H, s), 2.6 (3H, s).

Condensation of 3-acetyl-1-methylcarbazole (3) with aminoacetaldehyde dimethylacetal

A mixture of 3-acetyl-1-methylcarbazole (**3**) (0.43 g, 0.002 mol) and aminoacetaldehyde dimethylacetal (0.5 ml, 0.005 mol) in dry toluene was heated at 100°C (oil bath). After heating for 20 min, water droplets which collected on the sides were removed. Fresh aminoacetaldehyde dimethylacetal (0.5 ml) was added and the reaction mixture heated. The procedure was repeated twice more and then toluene was removed under reduced pressure. The imine **4** (0.58 g) was obtained as a thick yellow oil. The compound was sufficiently pure and was used as such for the next experiment. ^{1}H NMR ($CDCl_3$): 8.5 (1H, d, J = 1 Hz, Ar-H4), 8.06 (1H, dd, J = 7 and 1.5 Hz, Ar-H5), 7.82 (1H, d, J = 1 Hz, Ar-H2), 7.2–7.58 (3H, m, Ar-H 6,7,8), 4.4 (1H, t, J = 5 Hz, $CH(OCH_3)_2$), 3.4 (6H, s, 2 × OCH_3), 2.88 (2H, d, J = 5 Hz, NCH_2), 2.7 and 2.6 (2 × 3H, 2 × s, CH_3C=N and Ar-CH_3).

Reduction of the imine (4)

The faint yellow imine **4** (0.6 g) in absolute ethanol was hydrogenated using Raney nickel as catalyst at 85 psi pressure of hydrogen. After 10 h of shaking at room temperature, a colourless solution was obtained. Filtration and evaporation of solvent gave the amine (**5**) as a thick faint yellow oil (0.575 g, 96%). The compound was sufficiently pure and was converted into the tosyl derivative. ^{1}H NMR ($CDCl_3$): 7.7–8.0 (2H, m, Ar-H4 and H5), 7.1–7.4 (4H, m, Ar-H 2,6,7,8), 4.48 (2H, m, C*H*(OCH_3)$_2$ and Ar-CH-N), 3.91 (3H, bd-sharp doublet after D_2O J = 4 Hz, NH and N-CH_2), 3.32 (6H, s, 2 × OCH_3), 2.75 (3H, bd, sharp after D_2O, J = 7 Hz, Ar-C-CH_3), 2.45 (3H, s, Ar-CH_3).

Tosylation of the amine (5)

To a solution of the amine **5** (0.315 g, 0.001 mol) in dry THF (8 ml) was added distilled water (5 ml) and a pinch (0.3 g) of sodium carbonate. To the stirred solution freshly crystallised *p*-toluenesulfonyl chloride (0.6 g, 0.003 mol) was added. The flask was protected from light and stirred for 12 h. Usual work up gave the tosyl derivative (**6**), which was crystallised from dichloromethane (0.35 g, 67%), m. p.148°C. Analysis: Found: C, 66.9; H, 6.51. Calc. for $C_{26}H_{30}N_2O_4S$: C, 66.93; H, 6.48%.

Olivacine (7)

To a solution of the *N*-tosylated amine **6** (0.47 g, 0.001 mol) in dry dioxane (0.2 ml) was added 3 drops of 6N HCl and the solution stirred, protected from light, at room temperature (25°C). After 6 h an yellowish solid separated. Stirring was continued for 48 h. The solid was filtered and the reaction mixture poured in water (5 ml), neutralised with sodium hydroxide and extracted with dichloromethane. The extract was washed, dried (sodium sulphate) and the solvent removed. The residue, together with the solid obtained earlier, was chromatographed on alumina using hexane–20% ethyl acetate as the eluant. Crystallization of the solid obtained, from methylene chloride, gave olivacine **7** (0.16 g, 65%); m. p. 318–320°C (lit.[7] m. p. 318–322°C). Analysis: Found: C, 82.72, H, 5.82; Calc. for $C_{17}H_{14}N_2$: C, 82.90, H, 5.73%. ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 9.5 (1H, bd, Ar-H), 9.2 (1H, brs, exchanges with D_2O, NH), 8.4 (1H, bd, Ar-H), 8.3 (1H, s, Ar-H11), 8.1 (1H, bd, Ar-H3), 7.75 (1H, d, J = 6 Hz, Ar-H4), 7.45 (1H, d, J = 6 Hz, Ar H), 7.2 (1H, m, Ar-H), 3.6 (3H, s, N=CCH_3), 2.8 (3H, s, $ArCH_3$).

References

1. Morini-Bettolo, G. B. and Schmutz, J. — *Helv. Chim. Acta*, 1959, **42**, 2146.
2. Svoboda, G. H., Poore, G. A. and Montfort, M. L. — *J. Pharm. Sci.*, 1968, **57**, 1720.
3. a. Le Pecq, J. B., Goose, C., N-Dat Xuong and Paoletti, C. — *Proc. Natn. Acad. Sci. USA*, 1974, **71**, 5078.
   b. Hansch, G. — *Canc. Chem. Rep.*, 1972, **56**, 433.
4. Reviews
   a. Sainsbury, M. — *Synthesis*, 1977, **7**, 437.
   b. Kansol, V. K. and Potier, P. — *Tetrahedron*, 1986, **42**, 2389.
   c. Hogan, I., Jenkings, P. and Sainsbury, M. — *Tetrahedron*, 1990, **46**, 2943.
5. a. Narasimhan, N. S. and Gokhale, S. M. — *J. Chem. Soc., Chem. Commun.*, 1985, 86.
   b. Gokhale, S. M. — Ph.D. Thesis, University of Poona, 1984.
6. Plieninger, H., Muller, W. and Weinerth, K. — *Chem. Ber.*, 1964, **97**, 667.
7. Schmutz, J. and Wittewer, H. — *Helv. Chim. Acta*, 1960, **43**, 793.