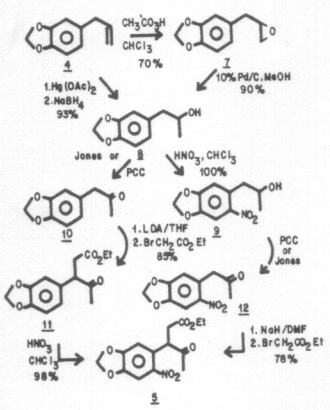
SCHEME II



provide the ketoester 11 (85%) which by nitration gave 5 (98%).

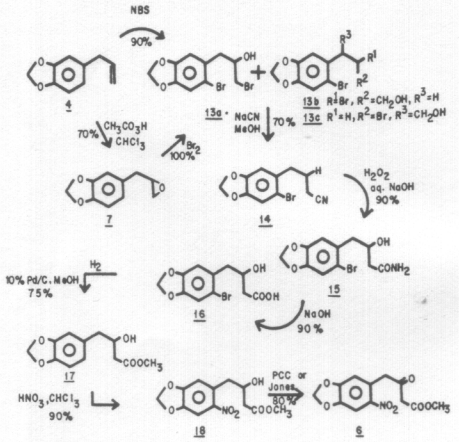
In order to obtain the nitro-β-keto ester 6, we developed the synthetic route described in Scheme III. Thus, reaction of 4 with N-bromosuccinimide (NBS) in acetone/water produced a mixture of isomeric bromohydrins 13a-c[13]. This mixture was treated with sodium cyanide in methanol under reflux, and the crude reaction product 14 submitted to a careful alkaline hydrolysis[14] (H_2O_2, EtOH, 6N NaOH) gave the desired amide 15 as the sole product to crystallize as a clean colourless material from the reaction mixture. This useful sequence can be run on a 30 g scale without isolation of intermediates, in 50% overall yield. Alternatively, the bromohydrin 13a can be prepared in quantitative yield by direct bromination of 7. The formation of this dibromo compound 13a can be understood by initial bromination of the 5-position of the aromatic ring followed by regioselective opening of the oxirane[15] ring by the hydrobromic

[13] The formation of 14c can be explained by the participation of a phenonium ion intermediate: P.R.R. Costa and J.A. Rabi, Tetrahedron Lett., 1975, 4535.

[14] C.R. Hotter, "Organic Synthesis", Coll. II, John Wiley and Sons, Inc., New York, p. 586.

[15] Treatment of epoxyde 7 with hydrobromic acid in acetone:water gives exclusively 4-(3-bromo-2-hydroxypropyl)-1,2-methylenedioxybenzene.

SCHEME III



acid liberated in the reaction medium. A pure sample of 14 could be obtained (65%) by reaction of 13a with sodium cyanide in methanol. The conversion of 15 into hydroxy acid 16 (90%) was attempted by alkaline hydrolysis. A one pot procedure for the transformation of 16 into 17 was accomplished in 75% yield by hydrogenolysis of C-Br bond over Pd/C using methanol as solvent that permits an acid catalytic esterification by action of the hydrobromic acid formed in the reaction vessel. Finally, nitration of 17 gave 18 (90%) which, when submitted to oxidation with PCC[9] or Jones' reagent[10] provided the nitro-β-keto ester 6 in 80% yield.

With the nitro-β-keto esters 5 and 6 in hand we proceeded to the last key step of the synthetic route, viz. the reductive cyclization reaction[16] to provide the indole derivations 2 and 3.

[3] E.J. Corey and W. Sugga, Tetrahedron Lett., 1975, 2647.

[9] The Jones' reagent was prepared as descripted in L.F. Fieser and M. Fieser", Reagents for Organic Synthesis", John Wiley and Sons, Inc., New York, vol. I, p. 142.

[4] We have published previously the cyclization of 12 to 5,6-methylenedioxy-2-methylindole in 60% yield[17]. Using the modified conditions described here this transformation could be accomplished in 90% yield.

[7] cf. E.J. Barreiro, P.R.R. Costa, R.T. de Mello and P.R.V.R. Barros, An. Acad. brasil. Cienc., 1981, 53, 65.

So, when a methanolic solution of 5 was submitted to catalytic reduction (H_2, Pd/C 60 psi) for 15 minutes at room temperature, immediately followed by solvent elimination in vacuum and subsequent "flash" chromatographic filtration over silica gel, the desired indole 2 could be obtained in 80% yield, in the form of a clear oil. On the other hand, catalytic reduction of 6, under identical conditions, afforded 3 as pale yellow crystals (85%).

In conclusion, the synthetic sequence here described is useful for the preparation of indoleacetic esters starting from the allylbenzene moiety present in various abundant natural compounds such as safrole 4. The potential biologically active indole derivatives 2 and 3 can be prepared in high overall yields (46% and 20% respectively) using easily accessible reagents and mild reaction conditions.

We are indebted to the Conselho Nacional de Desenvolvimento Científico e Tecnológico (40.1424/80) for financial support and fellowships to PRVRB and VMQ, to Professor Walter B. Mors (NPPN, UFRJ), for his continuous encouragement and to Professor Timothy J. Brocksom (UFSCar) for his valuable suggestions.

References

[1] J.K. Sugden and T.O. Yoloye, Pharm. Acta Helv., 1978, 53, 65.

[2] J.G. Lombardino, Ann. Rept. Med. Chem., 1978; 13, 167; Y.H. Cahng, Ann. Rept. Med. Chem., 1976, 11, 138; S. Wong, Ann. Rept. Med. Chem., 1975, 10, 172; M.E. Rosenhale, Ann. Rept. Med. Chem., 1974, 9, 193.

[3] T.Y. Shen, U.S. Patent, 3, 241, 185 (Chem. Abstr., 1966, 64, 17555).

[4] Inter-Alia: T.Y. Shen, J. Med. Chem., 1981, 24, 1; G.V. Paris, D.L. Germaise, D.G. Cimon, L. Swett, G.W. Carter and P. Young, J. Med. Chem., 1980, 23, 9; D. Evans, D.W. Kunwell and T.A. Hicks, Australian (1979), 506, 085; (Chem. Abstr., 1980, 92, 169251c); M. Nagakura, T. Oca, M. Shimidzu, K. Kawamura, Y. Eto and Y. Wada, J. Med. Chem., 1979, 22, 48; J. Jeske and K. Stoshka, Acta Pol. Pharm., 1978, 35, 611.

[5] W.B. Mors and C.T. Rizzini, "Botânica Econômica", Epu, São Paulo, S.P., Brazil, 1976, p. 149.

[6] R.L. Augustine, "Catalytic Hydrogenation", E. Arnold (Publishers), LTD, London and M. Dekker, Inc., New York, 1965, p. 137.

[7] cf. D.R. Buckle; D.J. Outred, J.W. Ross, H. Smith, R.J. Smith, B.A. Spicer and B.C. Gasson, J. Med. Chem., 1979, 22, 158.

[8] H.C. Brown and P.G. Georghegan Jr., J. Org. Chem., 1970, 35, 1844.

E.J. Corey and W. Sugga, Tetrahedron Lett., 1975, 2647.

[9] The Jones' reagent was prepared as descripted in L.F. Fieser and M. Fieser", Reagents for Organic Synthesis", John Wiley and Sons, Inc., New York, vol. I, p. 142.

[11] I.K. Stamos, Synthesis, 1980, 664.

[12] J.P. Albarella, J. Org. Chem., 1977, 42, 2009.

[13] The formation of 14c can be explained by the participation of a phenonium ion intermediate: P.R.R. Costa and J.A. Rabi, Tetrahedron Lett., 1975, 4535.

[14] C.R. Hotter, "Organic Synthesis", Coll. II, John Wiley and Sons, Inc., New York, p. 586.

[15] Treatment of epoxyde 7 with hydrobromic acid in acetone: water gives exclusively 4-(3-bromo-2-hydroxypropyl)-1,2-methylenedioxybenzene.

[16] We have published previously the cyclization of 12 to 5,6-methylenedioxy-2-methylindole in 60% yield[17]. Using the modified conditions described here this transformation could be accomplished in 90% yield.

[17] cf. E.J. Barreiro, P.R.R. Costa, R.T. de Mello and P.R.V.R. Barros, An. Acad. brasil. Cienc., 1981, 53, 65.

EXPERIMENTAL

The ^1H NMR spectra were run with Varian XL-100-12 (100 MHz) and Varian EM-360 (60 MHz) instruments, using the indicated solvent and Me_4Si as internal reference. The i.r. spectra were recorded with a Perkin-Elmer 137-B spectrophotometer, using KBr pellets. The u.v. spectra were recorded with a Beckman DGB spectrophotometer using EtOH (Uvasol) as solvent. The mass spectra were obtained with a Varian MAT-CH5-DF instrument coupled to a Varian MAT SS-100 MS computer system. The m.p. were determined in a hoffer apparatus. The hydrogenation reactions were performed in a Parr apparatus. Combustion analyses were carried out by CENPES - Petrobrás (Rio de Janeiro, Brazil).

4-(2-HYDROXYPROPYL)-1,2-METHYLENEDIOXYBENZENE (8) METHOD A - OXYMERCURATION-DEMERCURATION OF SAFROLE (4) - Safrole (12.45 g, 76.7 mmol) was gradually added to a stirred solution of $Hg(OAc)_2$ 25.0 g, 78.6 mmol) in THF (230 mL) : H_2O (75 mL). After 1 h at room temperature the yellow color was discharged and the reaction mixture was alkalinized (3M NaOH aq., 75 mL) followed by addition of a solution of $NaBH_4$ (1.45 g, 38.15 mmol) in 3M aq. NaOH (75 mL). After 1 h the reaction mixture was saturated with NaCl, the organic layer separated and the aqueous layer was extracted with EtOAc (4 x 250 mL). The combined organic layers were then washed successively with H_2O (3 x 100 mL) and saturated brine, dried (anhy. Na_2SO_4) and evaporated to give 8 (12.7 g, 96%) as a clean viscous oil. An analytical sample was