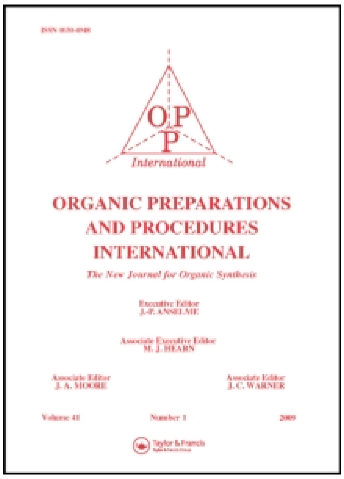

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

USEFUL SYNTHESES OF PYRANO- AND PYRIDOINDOLES

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To cite this Article Mali, Raghao S. and Manekar-Tilve, Anita(1994) 'USEFUL SYNTHESES OF PYRANO- AND PYRIDOINDOLES', Organic Preparations and Procedures International, 26: 5, 573 — 577
To link to this Article: DOI: 10.1080/00304949409458060
URL: http://dx.doi.org/10.1080/00304949409458060

870 and 815 cm^{-1}. PMR ($CDCl_3$): δ 0.90 (distorted t, 3H, CH_3CH_2-), 1.35-1.80 (m, 18H, 9 x -CH_2-), 1.90-2.50 (m, 6H, OHC-C$\underline{H}_2$, -CH_2CH=CH-C$\underline{H}_2$-), 5.37 (m, 2H, -CH=CH-) and 9.84 (t, J = 1.5 Hz, 1H, -CHO); GLC: 3% OV-17 column, 240° flow rate of 50 mL N_2/min., R_t = 10.67 min. (96.3%); TLC (ethyl acetate: pet. ether (20:80), silica gel, DNPH spray): R_f 0.5.

Anal. calcd. for $C_{16}H_{30}O$: C, 80.67; H, 12.60. Found: C, 80.57; H, 12.50

REFERENCES

1. E. H. Smith and D. Pimental, *Pest Control Strategies,* Academic Press, New York, 1978, pp. 23.
2. Y. Konno, K. Arai, S. Kiguchi and Y. Matsumoto, *Appl. Ent. Zool.,* **17**, 207 (1982); *Chem. Abs.,* **97**, 86994q (1982).
3. S. B. Thakur, K. S. Jadhav and S. C. Bhattacharyya, *Indian J. Chem.,* **25B**, 675 (1986).
4. D. Ranganathan, S. Ranganathan and M. M. Mehrotra, *Tetrahedron,* **36**, 1869 (1980).
5. N. N. Joshi, V. R. Mamdapur and M. S. Chadha, *ibid.,* **40**, 3285 (1984).
6. E. J. Corey and J. W. Suggs, *Tetrahedron Lett.,* 2647 (**1975**).
7. S. Mithran and V. R. Mamdapur, *Indian J. Chem.,* **28B**, 755 (1989).
8. I. R. Trehan, R. Vig, V. Singh, S. Sharma and G. L. Kad, *ibid.,* **29B**, 518 (1990).

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USEFUL SYNTHESES OF PYRANO- AND PYRIDOINDOLES

Submitted by (01/18/94)

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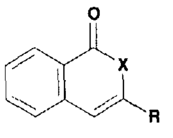
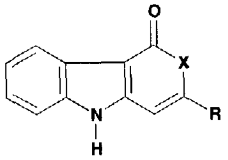
Although isocoumarins (**1**) and isoquinolones (**2**) are well documented in the literature[1,3] their indole analogues of type **3** and **4** have not received much attention. Thus, very few methods have been reported[4,7] for their synthesis. In connection with our work on indole derivatives[8,9] it was decided to synthesize compounds of type **3** and **4**. Reaction of ethyl 1,2-dimethyl-5,6-methylenedioxyindole-3-carboxylate (**6**), obtained in 85% yield by N-methylation of the corresponding indole[8] (**5**), with LDA in THF at -30 to -78° followed by treatment with anisaldehyde (**7a**) gave the hydroxy ester **8a** in 75% yield. The alcohol **8b** was synthesized similarly from **6** in 79% yield using

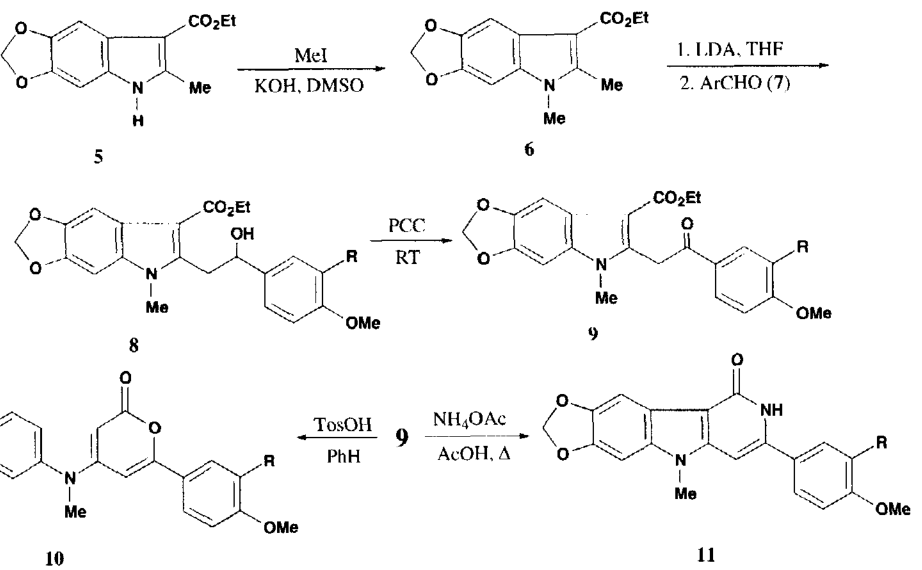


1 X = O
2 X = NH



3 X = O
4 X = NH

veratraldehyde (**7b**) as electrophile. Treatment of alcohols (**8a** and **8b**) with pyridinium chlorochromate in methylene dichloride, at room temperature, provided the keto esters **9a** and **9b**. Treatment of **9a** or of **9b** with *p*-toluenesulfonic acid in refluxing benzene furnished the desired pyranoindoles (**10a** and **10b**) in 75% and 73% yields respectively. The pyridoindoles **11a** (69%) and **11b** (76%), which could be converted to tricyclic analogues[7] of ellipticine, were obtained by treatment of the ketoesters **9a** and **9b** with ammonium acetate in refluxing glacial acetic acid.



7 a) Ar = 4-MeOC_6H_4- b) 3,4-$(OMe)_2C_6H_3$-
8-11 a) R = H b) R = OMe

The present approach could be used for the synthesis of variously substituted pyrano- and pyridoindoles.

EXPERIMENTAL SECTION

All melting points are uncorrected. The IR spectra were recorded on a Perkin-Elmer 337 IR spectrophotometer and 1H NMR, in $CDCl_3$ solutions on Jeol FX 90 Q instrument. Chemical shifts are expressed in δ (ppm) downfield from TMS as an internal standard and coupling constants in Hertz. Analyses were obtained using Holi's rapid carbon-hydrogen analyzer.

Ethyl 1,2-Dimethyl-5,6-methylenedioxyindole-3-carboxylate (6).- To a solution of potassium hydroxide (1.2 g, 0.02 mole) in dimethyl sulfoxide (20 mL) was added indole **5** (1.7 g, 0.007 mole) and the mixture was stirred for 30 min. Then methyl iodide (2.0 g, 0.014 mole) was added dropwise and stirring was continued at room temperature for 3 hrs. Addition of water (10 mL) was followed by extraction with ether (3 x 20 mL). The ethereal layer was washed with water, dried (Na_2SO_4) and evaporated to give a solid which on recrystallization from ether furnished indole **6** (1.54 g, 86%), mp. 124°. IR (nujol): 1685 cm^{-1}. ^1H NMR: δ 1.40 (3H, t, J = 7Hz, $-CH_2-CH_3$), 2.65 (3H, s, C_CH_3), 3.55 (3H, s, $N-CH_3$), 4.30 (2H, q, J = 7Hz, $-CH_2CH_3$), 5.88 (2H, s, $-OCH_2O-$), 6.68 (1H, s, C_7-H), 7.50 (1H, s, C_4-H).

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79. Found: C, 64.56; H, 5.72

Ethyl 1-methyl-2-[2-hydroxy-2-(4-methoxyphenyl)ethyl]-5,6-methylenedioxyindole-3-carboxylate (8a).- A solution of **6** (0.7 g, 0.0026 mole) in THF (15 mL) was added to a solution of LDA (0.0052 mole, prepared from 0.73 mL of diisopropylamine and 3 mL of 1.7 M solution of *n*-butyllithium in hexane) at -78°, under nitrogen atmosphere. The reaction mixture was stirred at -78° for 20 min and a solution of anisaldehyde (**7a**, 0.07 g, 0.0052 mole) in THF (10 mL) was added to it. It was stirred at -78° for 10 min and allowed to warm up to 10°. Dilute acetic acid was added to it, THF removed under reduced pressure and the aqueous layer was extracted with ethyl acetate (3 x 15 mL). The ethyl acetate layer was washed with water, dried (Na_2SO_4) and evaporated to afford a solid which on recrystallization from ethyl acetate-*n*-hexane furnished **8a** (0.8 g, 75%), mp. 136-138°. IR (nujol): 3395, 1675 cm^{-1}. ^1H NMR: δ 1.48 (3H, t, J = 6Hz, $-CH_2-CH_3$) 2.75 (1H, bs, exchangeable with D_2O, OH), 3.25 (3H, s, $N-CH_3$), 3.78 (3H, s, $,OCH_3$), 4.38 (2H, q, J = 6Hz, $-CH_2-CH_3$), 5.10 (2H, m, $-CH_2-$), 5.90 (2H,s, $-OCH_2O-$), 6.68 (1H, s, C_7-H), 6.80 (2H, d, J = 8Hz,2xAr-H), 7.22 (2H, d, J = 8Hz, 2xAr-H), 7.50 (1H,.s, C_4-H).

Anal. Calcd for $C_{22}H_{23}NO_6$: C, 66.49, H, 5.83. Found: C, 66.34; H, 5.73

Ethyl-1-methyl-2-[2-hydroxy-2-(3,4-dimethoxyphenyl)ethyl]-5,6methylenedioxyindole-3-carboxylate (8b).- Indole **6** (1.0 g, 0.0038 mole) on similar reaction with veratraldehyde **7b** (1.26 g, 0.0076 mole) using LDA (0.0076 mole) gave a solid which on recrystallization from chloroform-*n*-hexane yielded **8b** (1.3 g, 79%), mp. 138° IR (nujol): 3435, 1675 cm^{-1} ^1H NMR: δ 1.44 (3H, t, J = 7Hz, $-CH_2CH_3$) 3.12 (3H, s, $-NCH_3$), 3.40 (2H, bd, $-CH_2-CH-$), 3,64 (3H, s, $-OCH_3$), 3.84 (3H, s, $-OCH_3$), 4.07 (1H, bs, exchangeable with D_2O, OH), 4.18 (2H,q, J = 7Hz, $-CH_2-CH_3$), 5.11 (1H, m, $-CH_CH_2$),5.90 (2H, s, $-OCH_2O-$), 6.56-6.88 (4H, m, 3xAr-H + C_7-H), 7.48 (1H, s, C_4-H).

Anal. Calcd for $C_{23}H_{25}NO_7$: C, 64.62; H, 5.90. Found: C, 64.48; H, 5.92

Ethyl 1-Methyl-2-[2-oxo-2-(4-methoxyphenyl)ethyl]-5,6-methylenedioxyindole-3-carboxylate (9a).- A mixture of hydroxyester (**8a**, 0.7 g, 0.002 mole) and pyridinium chlorochromate (1.14 g, 0.005 mole) in methylene dichloride (30 mL) was stirred at room temperature for 24 hrs. It was then passed through a column of alumina using methylene dichloride as an eluent to afford yellowish solid which on recrystallization from methylene dichloride-*n*-hexane furnished **9a** (0.3 g, 43%), mp. 236-238° IR (nujol): 1675, 1650 cm^{-1}. ^1H NMR: δ 1.34 (3H, t, J = 7Hz, $-CH_2CH_3$), 3.58 (3H, s, $-NCH_3$), 3.85 (3H, s, -OCH$_3$) 4.30 (2H, q, J = 7Hz, -CH$_2$CH$_3$), 4.92 (2H, s, Ar-CH$_2$-),5.90 (2H, s, -OCH$_2$O-), 6.73 (1H, s, C$_7$-H), 6.90 (2H, d, J = 9Hz, 2xArH), 7.50 (1H, s, C$_4$-H), 8.05 (2H, d, J = 9Hz, 2xAr-H).

Anal. Calcd for $C_{22}H_{21}NO_6$: C, 66.82; H, 5.35. Found: C, 67.03; H, 5.47

Ethyl 1-Methyl-2-[2-oxo-2-(3,4-dimethoxyphenyl)ethyl]-5,6-methylenedioxyindole-3-carboxylate (9b).- The hydroxyester **8b** (0.25 g, 0.00058 mole) on similar reaction with pyridinium chlorochromate (0.378 g, 0.0017 mole) in methylene dichloride (25 mL) gave a solid which on recrystallization from methylene dichloride-*n*-hexane yielded **9b** (0.08 g, 30%), mp. 237°. IR (nujol): 1655, 1640 cm^{-1}. ^{1}H NMR: δ 1.36 (3H, t, J = 7Hz, -CH$_2$CH$_3$), 3.60 (3H, s, -NCH$_3$), 3.89 and 4.01 (3 H each, s, 2x-OCH$_3$), 4.32 (2H, q, J = 7Hz, -CH$_2$CH$_3$), 4.98 (2H, s, Ar-CH$_2$-), 5.90 (2H, s, -OCH$_2$O-), 6.74 (1H, s, C$_7$-H), 6.89 (1H, d, J = 9Hz, Ar-H), 7.53 (1H, s, C$_4$-H), 7.58 (1H, d, J = 1.5Hz, Ar-H), 7.80 (1H, dd, J = 9 and 1.5Hz, Ar-H).

Anal. Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.45. Found: C, 65.13; H, 5.54

5-Methyl 7,8- methylenedioxy-3-(4-methoxyphenyl)pyrano[4,3-b]indol-1(5H)-one (10a).- To a solution of ketoester **9a** (0.06 g, 0.15 mmole) in benzene(20 mL) was added *p*-TSA (0.1 g, 0.58 m mole), and the reaction mixture was refluxed for 24 hrs. Benzene was removed under reduced pressure, water (10 mL) added and extracted with ethyl acetate (2 x 20 mL). The organic layer was washed with aqueous NaHCO$_3$ solution, water and dried (Na$_2$SO$_4$). On evaporation of solvent gave a solid which on 6 recrystallization from ethyl acetate-*n*-hexane afforded **10a** (0.04 g, 75%), mp. 240° (d). IR (nujol): 1715 cm^{-1}. ^{1}H NMR: δ 3.58 (3H, s, NCH$_3$), 3.83 (3H, s, -OCH$_3$), 5.90 (2H, s, -OCH$_2$O-), 6.90-8.00 (7H, m, 6xAr-H and -CH=).

Anal. Calcd for $C_{20}H_{15}NO_5$: C, 68.76; H, 4.33. Found: C, 68.54; H, 4.23

5-Methyl7,8-methylenedioxy-3-(3,4-dimethoxyphenyl)pyrano[4,3b]indol-1(5H)-one (10b).- The ketoester **9b** (0.08 g, 0.19 mmole) on similar reaction with *p*-TSA gave pyridoindole **10b** (0.055 g, 73%), mp. 155-160° (d). IR (nujol): 1710 cm^{-1}. ^{1}H NMR: δ 3,72 (3H, s, -NCH$_3$), 3.86 (3H, s, -OCH$_3$), 3.92 (3H, s, -OCH$_3$), 6.00 (2H, s, -OCH$_2$O-), 6.70-7.64 (6H, m,5xAr-H and -CH=).

Anal. Calcd for $C_{21}H_{17}NO_6$: C, 66.48; H, 4.52. Found: C, 66.42; H, 4.48

5-Methyl-7,8-methylenedioxy-3-(4-methoxyphenyl)pyrido[4,3-b]indol-1(5H)one (11a).- A mixture of ketoester **9a** (0.09 g, 0.22 mmole), and ammonium acetate (0.5 g, 6.0 m mole) in glacial acetic acid (4 mL) was refluxed for 72 hrs and poured over crushed ice. It was extracted with methylene diochloride (2 x 15 mL). The organic layer was washed with water, dried (Na$_2$SO$_4$) and evaporated to afford a brown solid which on crystallization from acetonitrile furnished **11a** (0.05 g, 69%), mp. 190° (d). IR (nujol): 3300, 1660 cm^{-1}. ^{1}H NMR: δ 3.76 (3H, s, -NCH$_3$), 3.87 (3H, s, -OCH$_3$), 6.00 (2H, s, -OCH$_2$O-), 6.53 (1H, s, -CH=), 6.83 (1H, s, C$_7$-qH),7.02 (2H, d, J = 9Hz, 2xAr-H), 7.58 (2H, d, J = 9Hz, 2xAr-H), 7.78 (1H, s, C$_4$-H).

Anal. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63. Found: C, 68.74; H, 4.68

5-Methyl-7,8-methylenedioxy-3-(3,4-dimethoxyphenyl)pyrido[4,3b]indol-1(5H)one (11b).- The ketoester **9b** (0.075 g, 0.18 mmole) on similar reaction with ammonium acetate (0.4 g, 5.0 mmole) in glacial acetic acid provided **11b** (0.05 g, 76%), mp. 290° (d). IR (nujol): 3310, 1665 cm^{-1}. ^{1}H NMR: δ

3.72 (3H s, $-NCH_3$), 3,85 (3H,s, $-OCH_3$), 3.90 (3H,s, $-OCH_3$), 5.94 (2H, s, $-OCH_2O-$), 6.50 (1H, s, CH=). 6.70-7.02 (4H, m,3x Ar-H and C_7-H), 7.78 (1H, s, C_4-H).
Anal. Calcd for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.80. Found: C, 66.72; H, 4.82

Acknowledgement.- We thank Mrs. J. P. Chaudhari and Mr. A. P. Gadgil for spectral and analytical data. One of us (AMT) thanks the CSIR, New Delhi for the award of a Senior Research Fellowship.

REFERENCES

1. R. D. Barry, *Chem. Rev.*, **64**, 230 (1964).
2. R. A. Hill, H. C. Krebs, R. Verpoorte and R. Wijnama, *Progress in Chemistry of Natural Products*, **49**, Springer Verlag, Wein & New York (1986).
3. S. W. Pelletier, *Chemistry of Alkaloids*, Van Nostrand Reinhold Co. (**1970**).
4. G. A. Bahadur, A. S. Bailey, N. W. Middleton and J. M. Peach, *J. Chem. Soc. Perkin Trans. I*, 1688 (**1980**).
5. Y. Kita, S. I. Mohri, T. Tsugoshi, H. Maeda and Y. Tamura, *Chem. Pharm. Bull. Jpn.*, **33**, 4723 (1985).
6. Y. Kita, S. Akai, N. Ajimura, M.Yoshigi, T. Tsugoshi, H. Yasuda and Y. Tamura, *J. Org. Chem.*, **51**, 4151 (1986).
7. C. H. Naguyen and E. Bisagni, *Tetrahedron*, **43**, 527 (1987).
8. M. S. Wadia, R. S. Mali, S. G. Tilve and V. J. Yadav, *Synthesis*, 401 (**1987**).
9. R. S. Mali and P. G. Jagtap, *Tetrahedron Lett.*, **33**, 1655 (1992).

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