PUBLICATIONS

List of Publications :

1. Chemically modified teflon as an effective humidity sensor
   S. B. Dake, S. V. Bhoraskar, N. S. Narasimhan and P. A. Patil
   Polymer, 27, 910 (1986).

2. A novel cyclopentane annulation reaction : New synthesis of estrone
   N. S. Narasimhan and P. A. Patil
   Tetrahedron Lett., 27, 5133 (1986).

3. An efficient synthesis of 4-aryl-1,2,3,4-tetrahydroisoqinolines
   N. S. Narasimhan and P. A. Patil
   J. Chem. Soc., Chem. Commun., 191 (1987).

4. A novel synthesis of naphthelenic lignan lactones
   P. A. Patil, R. R. Joshi and N. S. Narasimhan
   Ind. J. Chem., 0000 (1987).

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A NOVEL CYCLOPENTANE ANNULATION REACTION : NEW SYNTHESIS OF ESTRONE

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Abstract : Novel cyclopropanol synthesis and cyclopentane annulation reaction lead to a new synthesis of estrone.

A new, simple and commercially viable synthesis of estrone[1], the starting material for important contraceptic drugs, is described in the present communication.

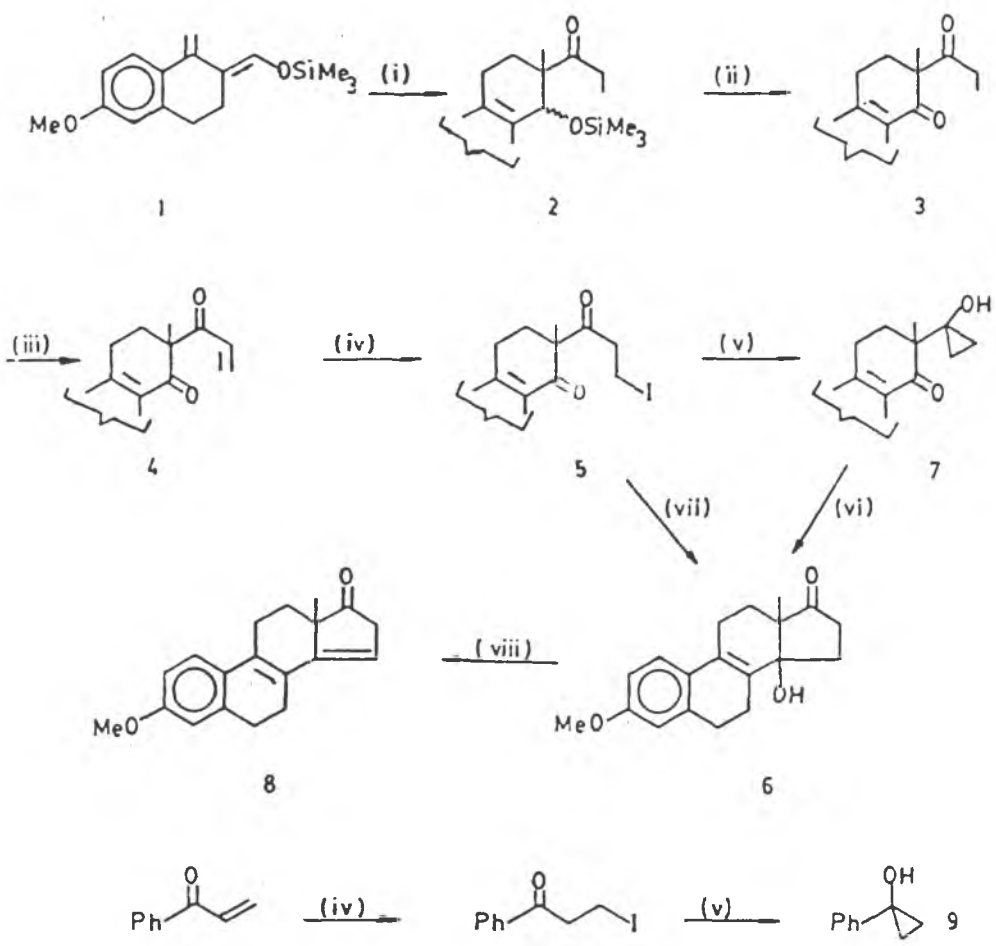
The key steps in the synthesis, delineated below, are :
(i) formation of the C ring by a Diels-Alder reaction on the diene (1) using ethyl isopropenyl ketone as the dienophile, a strategy similar to the one used earlier by us for the synthesis of equilenin[2], leading to an adduct which had all the carbon atoms needed for the construction of ring D, (ii) formation of a cyclopropanol derivative from an α,β-unsaturated ketone via the β-iodo compound (5), by treatment of the latter with $Zn/ClSiMe_3$ in refluxing THF[3], and (iii) ring expansion of the cyclopropanol (7) to the hydroxy cyclopentanone (6) by treatment with NaH in THF.

The new cyclopentane annulation reaction lead to construction of the D ring, by cyclisation between C-14 and C-15 (steroid numbering), not reported so far in estrone synthesis. The synthesis is of significance since dehydration of the cyclopentanol followed by reduction would lead to transfused cyclopentanone, especially when an alkyl group is present at the ring junction.

Cyclopentane annulation via cyclopropyl derivatives has been reported by others[4]. The methodology reported here, however, is new.

The cyclopropanol formation, reported here, is also new and general. Thus phenylvinylketone, was converted to the phenyl cyclopropanol (9) via the corresponding β-iodoketone.

It was also possible to obtain the hydroxy cyclopentanone (6), from the β-iodoketone (5), by an intramolecular Grignard reaction, using active Mg[5]. However the yield was only 30%.



(i) $H_2C{=}C(CH_3)COCH_2CH_3$, PhH, △, 40 h; 95% (ii) DDQ; 95% (iii) a. PhSeCl, CH_2Cl_2, RT, 20 h b. 30% H_2O_2-AcOH; 80% (iv) 57% HI; quant. (v) Zn, TMSCl, THF, △, 2 h, 68% (vi) NaH, THF, RT, 3 h, 90% (vii) active Mg, THF, 10°, 30% (viii) p-TSA, PhH, △, 2 min, quant.

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6. Satisfactory IR, PMR, and analytical data were obtained for all new compounds.

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An Efficient Synthesis of 4-Aryl-1,2,3,4-tetrahydroisoquinolines

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A general synthesis of *N*-methyl-1,2,3,4-tetrahydroisoquinolines from 3-aryl phthalides is described.

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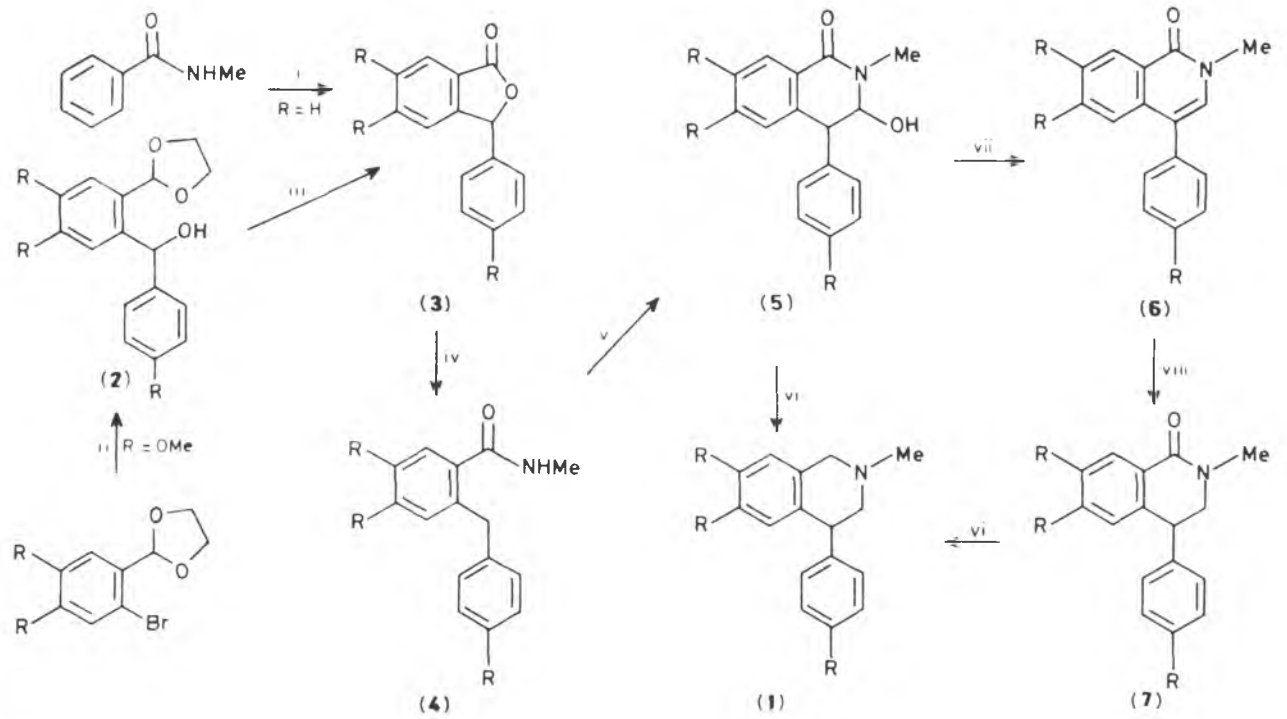
A general synthesis of *N*-methyl-1,2,3,4-tetrahydroisoquinolines from 3-aryl phthalides is described.

In this communication we describe a general synthesis of *N*-methyl-4-aryl-1,2,3,4-tetrahydroisoquinolines. Our synthesis is illustrated for *N*-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**), which is an agonist for the dopamine receptor[1] and the methyl ether of cherylline (**1b**), a rare phenolic isoquinoline alkaloid[2] with an aryl substituent at the 4 position.

The starting compounds are the 3-aryl phthalides (**3**), which are obtained as shown.[3] On hydrogenolysis, the phthalides provided the *ortho*-benzyl benzoic acids. The *N*-methyl

Table 1.

		(2)	(3)	(4)	(5)	(6)	(7)	(1)
a; R = H	M.p./°C		114 (EtOH–C_6H_{14})	102—103 (C_6H_{14}–EtOAc)	135—136	181—182 (C_6H_{14}–EtOAc)	79—80	178—179 (HCl), (EtOH–Et_2O) Lit.,[5] 178—179
	% Yield		70	75	80	90	75	50
b; R = OMe	M.p./°C	106—108 (Et_2O)	128—129 (EtOH)	131—132 (C_6H_{14}–EtOAc)	123—126	179—180 (EtOAc)		227—228 (HCl) (MeOH–Et_2O) Lit.,[6] 228—229
	% Yield	80	65	80	75	90		45



Scheme 1. i, Bu^nLi–diethyl ether, tetrahydrofuran (THF), heat; PhCHO, 0 °C; 50% HCl; ii, Bu^nLi–diethyl ether, −78 °C; ArCHO, −78 °C; H_2O; iii, 1 M H_2SO_4, C_6H_6, room temp., 3 h; $Na_2Cr_2O_7$, room temp., 3 h; iv, H_2–Pd/C, 90 psi; for **a**, room temp., 18 h, for **b**, 80 °C, 3 h; $SOCl_2$; for **a**, 10 min, room temp., for **b**, THF, 0 °C, 1 h; aq. $MeNH_2$, 0 °C; v, Bu^nLi–diethyl ether, 0 °C; DMF, 0 °C; H_2O; vi, $LiAlH_4$–THF, room temp., 2 h; vii, 1 M H_2SO_4, heat, 10 min; viii, H_2–Pd/C, 90 psi, 80 °C, 3 h (only for **a**).

benzamides (**4**) of the acids, on lithiation with Bu^nLi followed by treatment with dimethylformamide (DMF), gave the *N*-methyl-3-hydroxy-1,2,3,4-tetrahydroisoquinolone (**5**), which on dehydration and reduction or direct reduction furnished the target compounds (Table 1).†

The synthesis described above is potentially very useful, since the 3-aryl phthalides, in which the aromatic ring may be unsubstituted or substituted at any position with methoxy groups, are readily available through aromatic lithiation reactions[3] or through halogen–metal exchange reactions.[4]

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† Satisfactory i.r., ^1H n.m.r., and analytical data were obtained for all new compounds.

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