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SYNTHESIS OF 2-METHYL-6,7-BENZOMORPHANE[1] VIA RADICAL CYCLISATION

Lucien Stella, Bernard Raynier, Jean-Marie Surzur

Laboratoire de Chimie Organique B
LA 109-CNRS. Faculté des Sciences St Jérôme
13397 Marseille Cedex 4 - France

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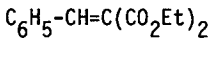
Synthesis of compounds structurally related to morphine is a field of lasting interest to many chemists. These substances form a well-known class of analgesics[2] which can possess properties of antagonism to narcotics[3] and which includes phenazocine[4] and pentazocine[5] of medicinal use.

The Grewe synthesis[6] has been extended to the preparation of a number of morphinans, isomorphans and benzomorphans[2], but this route and other conventional methods have failed on occasion [7] for the synthesis of 6,7-benzomorphans. The use of N-chloroamines in the synthesis of cyclic amines via intramolecular addition to olefins has been described in recent years. Thus, for example, Belleau has used a chloroamine solvolysis for the synthesis of D-normorphinans[8].

We wish to report a new route to 2-methyl-6,7-benzomorphan, utilising as a key step an intramolecular addition of an amino radical to an olefinic double bond [9]. An 8-step sequence from benzaldehyde has been developed (overall yield about 19%) and is described below.

The addition of diethyl benzylidenemalonate 1, (90% yield, bp 120°/0.1 Torr) from a Knoevenagel condensation [10] between benzaldehyde and diethyl malonate to a tetrahydrofuran solution of diallyl-zinc (room temperature, dry nitrogen)[11] led to a 1,4-addition product 2 (75%, bp 120-122°/0.1 Torr)[12], whose decarboethoxylation (0.1 mole) in dimethyl sulfoxide (85 ml) and water (0.2 mole), containing sodium chloride (0.1 mole)[13], produced monoester 3 (85%, bp 95°/0.1 Torr). The latter was converted into amide 4 (85%) on standing for 3 days in a methanolic solution of methylamine and sodium methoxide [14]. Lithium aluminium hydride reduction of 4 yielded amine 5 (80%, bp 82°/0,1 Torr). Replacement of hydrogen attached to nitrogen atom by Chlorination in heterogenous medium [15] (excess of aqueous 1M sodium hypochlorite solution, methylene chloride, room temperature, 90 min strongly strirring) gave N-chloroamine 6 (95%, undistilled), a good amino-radical precursor [16].



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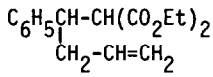

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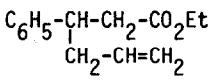

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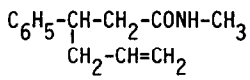

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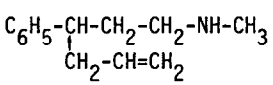

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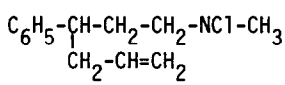

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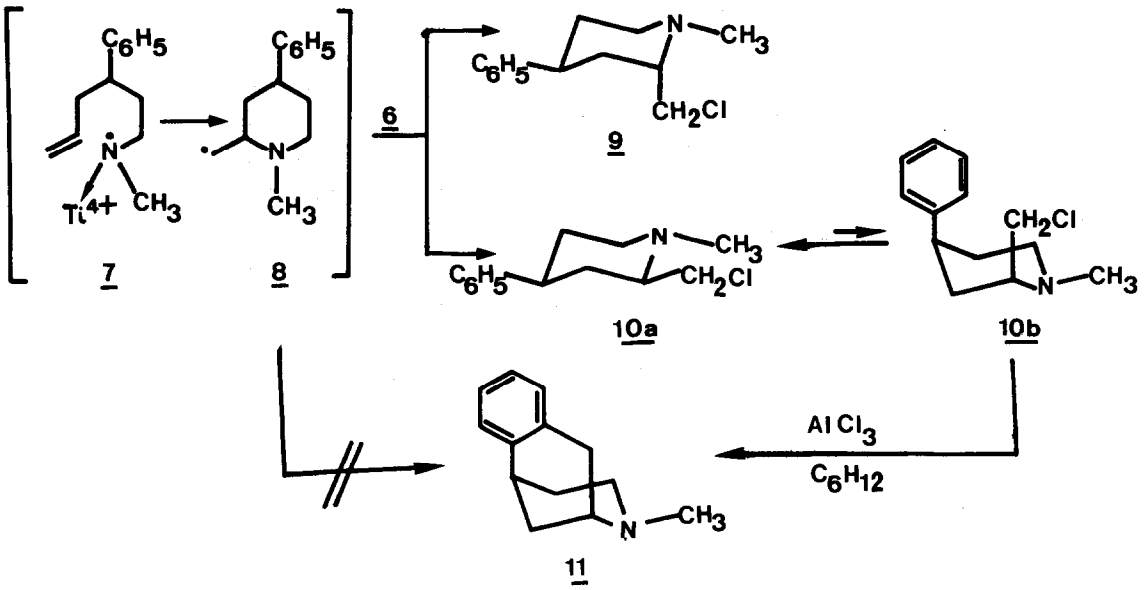
Homolytic fission of the nitrogen-chlorine bond, effected by slow addition of 15% aqueous titanium trichloride solution (0°, nitrogen stream) to a 1:1 acetic acid-water solution of chloride 6, produced the amino radical-titanium complex 7 which underwent cyclisation [17] by intramolecular addition to the well situated olefinic double bond. The resultant carbon radical 8 abstracted a chlorine atom from 6, in a chain reaction, giving 2-chloromethyl-1-methyl-4-phenylpiperidine as a mixture of trans 9 [$\delta(CDCl_3)$ 2.45 ppm (s, 3, NCH_3) (20%)] and cis 10 [$\delta(CDCl_3)$ 2.30 ppm (s, 3, NCH_3) (80%)] stereoisomers, in overall yield 92%. We believe that the amino radical, formed in the chain-propagating step, also complexes with titanium and that this complexed form 7 shows a strong preference for the double bond rather than the benzene ring [18].



While, in principle, the intermediate radical 8 might have cyclised by homolytic aromatic substitution to give the tricycle 11 directly, the formation of only the monocyclisation products 9 and 10 suggests an easy chlorine atom transfer from 6 to 8 and the presence of an unfavorable conformation (the 2,4-diequatorial isomer) for cyclisation. However, inversion of 10a to the 2,4-diaxial piperidine 10b, a favorable conformer for cyclisation, took place in the presence of aluminium trichloride in boiling cyclohexane, since under these conditions the mixture of stereoisomers 9 and 10 produced 2-methyl-6,7-benzomorphan 11 in 60% yield [bp 90°/0.05 Torr, m/e 187, $\delta(CDCl_3)$ 2.37 (s, 3, NCH_3), 7.08 (s, 4, C_6H_4) ; hydrochloride ($iPrOH-Et_2O$) mp 224°, $\delta(D_2O)$ 2.92 ppm (s, 3, NCH_3), 7,32 (s, 4, C_6H_4)[7b] ,][19].
The new cyclisation method appears to be useful for the synthesis of various substitued benzomorphans and results will be presented later.

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19 - Compounds reported gave correct elemental analyses. Mass spectral, ir and nmr data confirmed their structures.