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NEW SYNTHESIS OF ISOQUINOLINE ALKALOIDS, THALIFOLINE, CORYPALLINE, AND CHERYLLINE

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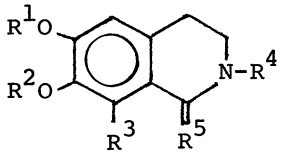
Isoquinoline alkaloids, thalifoline, corypalline, and cherylline, were synthesised by application of the cyclisation reaction of β-phenylethyl isocyanate to N-methylisoquinoline lactam with Magic Methyl and the regioselective cleavage reaction of aromatic methoxyl groups with methionine and methanesulphonic acid.

Although there have been several reports concerning the synthesis of isoquinoline alkaloids, thalifoline (1),[1] corypalline (2),[2] and cherylline (3),[3] we report here a new synthesis of these alkaloids, which has been accomplished by application of a novel cyclisation of β-phenylethyl isocyanate with Magic Methyl (methyl fluorosulphonate) and a regioselective scission of aromatic methyl ethers with methionine and methanesulphonic acid.[4]

The isocyanate (4) (prepared from 3,4-dimethoxyhydrocinnamic acid in the conventional method[5]) was heated in phosphoryl chloride under reflux for 1 h. After removal of the reagent, a solution of the residue in methylene chloride was treated with Magic Methyl (10 molar equivalents) at 0 °C overnight to give a mixture consisting of the N-methyl-lactam (5) and the nor-lactam (6) in 25 and 5% yields, respectively. The latter (6) gave the former by N-methylation with sodium hydride and methyl iodide in benzene in 75% yield. The result provides the first case in which Magic Methyl was used as an initiator for a reaction beyond the methylation reaction.

Application of the cyclisation reaction on 3,4,5-trimethoxyphenylethyl isocyanate (7) furnished the N-methyl-lactam (8) in 25% yield along with the nor-lactam (9) in 17% yield. In the case of 3,4-dimethoxyphenylethyl isocyanate (4), the pre-treatment of it with phosphoryl chloride was not essentially required for



(1) $R^1=R^4=Me$; $R^2=R^3=H$; $R^5=O$

(2) $R^1=R^4=Me$; $R^2=R^3=H$; $R^5=H_2$

(5) $R^1=R^2=R^4=Me$; $R^3=H$; $R^5=O$

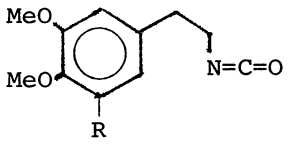
(6) $R^1=R^2=Me$; $R^3=R^4=H$; $R^5=O$

(8) $R^1=R^2=R^4=Me$; $R^3=OMe$; $R^5=O$

(9) $R^1=R^2=Me$; $R^3=OMe$; $R^4=H$; $R^5=O$

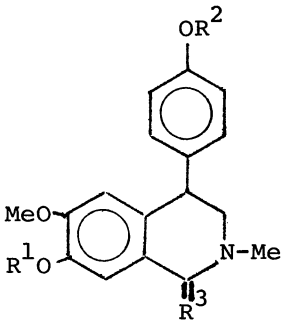
(10) $R^1=R^3=H$; $R^2=R^4=Me$; $R^5=O$

(11) $R^1=R^3=H$; $R^2=R^4=Me$; $R^5=H_2$



(4) R=H

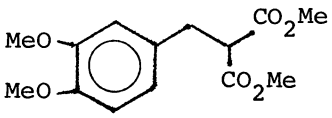
(7) R=OMe



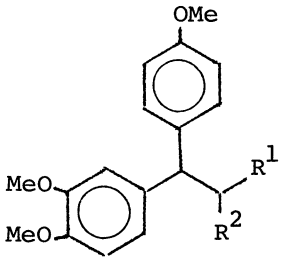
(3) $R^1=R^2=H$; $R^3=H_2$

(17) $R^1=R^2=Me$; $R^3=O$

(18) $R^1=R^2=H$; $R^3=O$



(12)



(13) $R^1=R^2=CO_2Me$

(14) $R^1=R^2=CO_2H$

(15) $R^1=H$; $R^2=CO_2H$

(16) $R^1=H$; $R^2=N=C=O$

the methylation-cyclisation reaction,[6] while, in the case of 3,4,5-trimethoxyphenylethyl isocyanate (7), the pre-treatment was indispensable. The result was thought to be due to subtle difference between the nucleophilicity of each benzene ring in (4) and (7).

Treatment of the N-methyl-lactam (5) with 1.5 molar equivalents of methionine in methanesulphonic acid (neat) gave thalifoline (1) and its isomer (10) in 65 and 5% yields respectively. Reduction of the former (1) with lithium aluminium hydride in tetrahydrofuran gave corypalline (2) in 75% yield. These synthetic alkaloids (1) and (2) were identical with the respective authentic samples[7] in their i.r.

and n.m.r. spectra. Reduction of the isomeric lactam (10) with the same reagent gave the phenolic base (11), which was identical with the authentic sample.[8)]

From the result described above, it is clear that the alkaloid, cherylline (3) is a suitable target for the synthesis to realise the applicability of the new cyclisation and regioselective demethylation reactions. Condensation of 3,4-dimethoxybenzaldehyde and dimethyl malonate in benzene in the presence of benzoic acid and piperidine gave the diester (12) in 80% yield. The diester (12) was treated with p-methoxyphenylmagnesium bromide in ether and tetrahydrofuran in the presence of copper(I) iodide to give the trimethoxy-diester (13) in 65% yield. Hydolysis of the ester (13) with 5% aqueous sodium hydroxide gave the diacid (14) which was smoothly decarboxylated to the monoacid (15) at 205-210 °C (bath temperature) in 87% yield from the diester (13). Instead hydrolysis of (13) with hydrochloric acid in acetic acid did not give the acid in pure form. The acid (15) was transformed to the isocyanate (16) in the conventional way. After heating the isocyanate (16) with phosphoryl chloride and evaporating the reagent under reduced pressure, the residue was treated with Magic Methyl in methylene chloride at 5 °C overnight to give the lactam (17) in 45% yield. In this case, the pre-treatment of (16) with phosphoryl chloride was indispensable. Without the pre-treatment, the isocyanate (16) gave an inseparable mixture with Magic Methyl in methylene chloride. The n.m.r. spectrum of the lactam (17) showed a typical A_2B_2-type pattern at δ ($CDCl_3$) 6.82 (2H, d, J=8.8Hz), 7.04 (2H, d, J=8.8Hz), and two singlets at δ 6.36 and 7.64 (1H each, s), confirmimg the structure. Treatment of the lactam (17) with 2.5 molar equivalents of methionine in methanesulphonic acid at 45 °C for 16 h gave cherylline lactam (18) in 60% yield. Reduction of (18) with lithium aluminium hydride in tetrahydrofuran furnished (±)-cherylline in 60% yield. All the spectral data of the synthetic (±)-cherylline exhibited good accordance with those of cherylline reported in literature,[3)] indicating accomplishment of the synthesis of the alkaloid.

References and Notes

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5) T. Fushimi, H. Ikuta, H. Irie, K. Nakadachi, and S. Uyeo, Heterocycles, 12, 1311 (1979).

6) Without the pre-treatment with phosphoryl chloride, the isocyanate (4) gave the same mixture consisting of the N-methyl- (5) and N-nor-lactam (6) in the same yields by treatment with Magic Methyl and although the reaction mixture of the isocyanate with phosphoryl chloride was monitored by a thin layer chromatography, the spot corresponding to the nor-lactam (6) was hardly observed.

7) We are grateful to Professors J.M. Bobbitt (Department of Chemistry, University of Connecticut) and H. Ishii (Faculty of Pharmaceutical Sciences, Chiba University) for their generous supplies of the authentic specimens of corypalline and thalifoline, respectively.

8) O. Hoshino, K. Ohyama, M. Taga, and B. Umezawa, Chem. Pharm. Bull., 22, 2587 (1974). We are also grateful to Professor B. Umezawa (Faculty of Pharmaceutical Sciences, Science University of Tokyo) for his kind supply of the phenolic base (11).

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