HETEROCYCLES, Vol. 24, No.7, 1986

SYNTHESIS OF THE QUINOLINE ALKALOIDS BUCHAPINE AND RAVESILONE+

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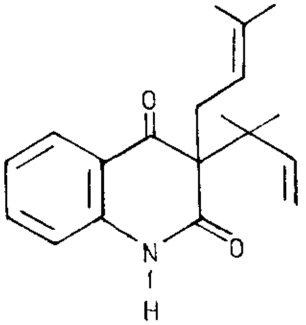
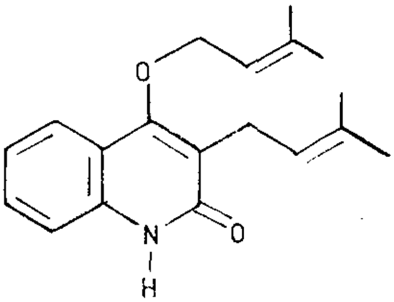
Abstract-Buchapine (I) has been synthesized in one step by a Claisen rearrangement of 3-(γ,γ-dimethylallyl)-4-(γ,γ-dimethylallyloxy)-2-quinolone (III). The total synthesis of ravesilone (II) has been carried out from γ,γ-dimethylallylmalonic acid-2-methoxyanilide (V) in three steps.

In continuation of our studies on the synthesis of quinoline alkaloids occurring in plants of Rutaceae family, we now wish to report the synthesis of (I) and (II). In 1982 Junusov et al. reported[1] the isolation of a new alkaloid,buchapine, from the epigeal part of *Haplophyllum bucaricum*. Buchapine (I),3-(α,α-dimethylallyl)-3-(γ,γ-dimethylallyl)-1,2,3,4-tetrahydroquinoline-2,4-dione,is the only alkaloid possessing the unusual 1,1-dimethylallyl substituent at C-3.From the synthetic viewpoint, we felt that the introduction of 1,1-dimethylallyl group could be efficientely effected by the ortho Claisen rearrangement of a prenyl aryl ether,as in other natural products syntheses[2]



(I)

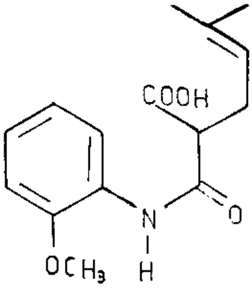


(III)

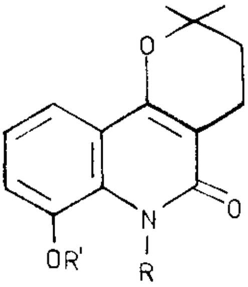
Thus 3-(γ,γ-dimethylallyl)-4-(γ,γ-dimethylallyloxy)-2-quinolone) (III), an alkaloid from *Haplophyllum tuberculatum*[3],is a suitable intermediate for trasformation into buchapine. The compound (III) was already synthesized[4] by the reaction of 3-(γ,γ-dimethylallyl)-4-hydroxy-2-quinolone with 1-bromo-3-methyl-2-butene.

A mixture of (III) (150 mg),acetic anydride (6 ml) and sodium acetate[5] (250 mg) was refluxed under argon for 12 h or in a sealed tube at 200° C for 3 h. The cooled mixture was poured into water (20 ml) and extracted with ether. The ether extract was washed with saturated $NaHCO_3$ solution and water,and dried over $MgSO_4$. After evaporation of the solvent the residue was chromatographed on silica gel column.Elution with hexane-chloroform (3:1) gave (I) (yield 56%);mp 130-131° C (from hexane) (lit.[1] mp 134-135°C). UV and IR spectra of which were identical with published data;NMR-(60 MHz,$CDCl_3$):δ1.10-1.40 and 1.85 (12 H,3s,4-CH_3); 2.72 (2H,d, J=7.5 Hz,$C\underline{H}_2$-CH=);4.65(1H,t,J=7.5 Hz,-CH_2-$C\underline{H}$=);4.80 and 5.75 (3H, CH_2=CH-, system AB);7.5-6.80 (3H,m,aromatic);7.75 (1H,d.J=8.5 Hz, H-5); 8.40 (s,NH).Compound I thus obtained was identical in all respects with the natural buchapine whose structure appears therefore confirmed.

Ravesilone (II) is a phenolic alkaloid isolated in 1984 from *Ravenia spectabilis*[6]. The structure (II) of 3,4,5,6-tetrahydro-7-hydroxy-2,2,6-trimethyl-5-oxo-2H-pyrano [3,2-*c*]quinoline was asgned on the basis of spectroscopic evidences. The synthesis of ravesilone was performed using γ,γ-dimethylallylmalonic acid-2-methoxy-anilide (V) obtained [4,7] by the reaction of o-anisidine and 3-methyl-but-2-enylmalonate.



(V)



(II) R=Me;R'=H
(VI) R=H; R'=Me
(VII) R=R'=Me

A mixture of anilide (V) (300 mg) and PPA[8] (2g) was heated at 140°C for 3h in an oil bath; the cooled mixture was taken up with 1N HCl (50 ml). The solution was adjusted at pH 3 with 10% NaOH to give a precipitate of 3,4,5,6-tetrahydro-7-methoxy-2,2-dimethyl-5-oxo-2H-pyrano-[3,2-*c*]quinoline (VI)(yield 70%),mp 131-132° C (from light petroleum) bp 40-60°)(lit.[9] 134-135° C). A solution of (VI) (100 mg) in dry acetone (30 ml) was treated with anhydrous potassium carbonate (200 mg) and methyl iodide (2 ml) and refluxed for 4h. After conventional work-up, 3,4,5,6-tetrahydro-7-methoxy-2,2,6-trimethyl-5-oxo-2H-pyrano-[3,2-*c*]quinoline (VII)(yield 60%) was obtained. Characteristic of the compound (VII) (UV,IR,NMR) agree with those previously reported[10]. A solution of (VII)(100 mg),hydrobromic acid in acetic acid (3 ml) was heated under reflux for 3 h and then evaporated under reduced pressure. Dilution with water gave a precipitate of ravesilone (II) (yielded 58%),mp 270-271° C (from EtOH-petrol,bp 40-60° C),UV and IR spectra of which were identical with the natural alkaloid. NMR (60 MHz,$CDCl_3$):δ1.45 (6H,s,2-CH_3); 1.84 (2H,t,J=6.5 Hz, Ar-CH_2-$C\underline{H}_2$), 2.70 (2H,t,J=6.5 Hz, Ar-$C\underline{H}_2$-CH_2); 3.88 (3H,s,N-CH_3); 7.0-7.5 (3H,m, aromatic. The structure proposed for ravesilone resulted therefore confirmed.

ACKNOWLEDGEMENT

Financial support for this research came from the Italian Ministry of Education.

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Received, 24th March, 1986