

Studies on the Syntheses of Heterocyclic Compounds. Part DLXXXVII (1).  
A Modified Synthesis of the Spirobenzylisoquinolines

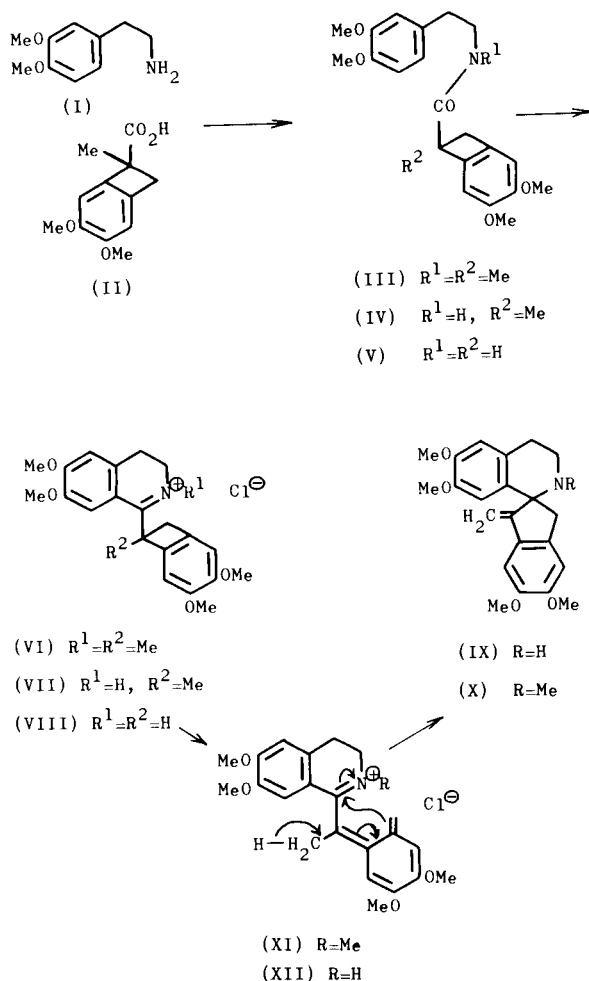
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Previously we reported the synthesis of a spirobenzylisoquinoline (X) from the benzocyclobutenyl precursor (III) as shown in Chart 1 (3).<sup>1</sup> This method is a simple and novel reaction, but has the defects of poor yield and difficult separation of the product. Therefore we have investigated an alternative synthesis of the spirobenzylisoquinolines and here wish to report the modified synthesis of this type of compound.

Chart 1



Condensation of the known 1-carboxy-4,5-dimethoxy-1-methylbenzocyclobutene (II) (3) with homoveratrylamine (I) in the presence of dicyclohexylcarbodiimide in chloroform at room temperature gave the amide IV in 49% yield. Treatment of IV with phosphoryl chloride in boiling benzene for 3 hours afforded directly the spirobenzylisoquinoline IX in 45% yield. The structure was easily confirmed by uv [ $\lambda$  max (methanol 325 sh, 314, 294, 273 and 267 sh nm;  $\lambda$  max (methanolic hydrogen chloride) 325 sh, 312, 294, 270, 265 nm] and nmr ( $\delta$ ) spectra, which showed two sharp singlets at 4.62 and 5.36, typical of the exocyclic methylene group of octotensine type compounds (4). The methylation of this product (IX) with formalin and sodium borohydride gave the *N*-methylspirobenzylisoquinoline (X) in 72.5% yield, which was identical with the authentic sample (3) in ir and nmr spectral comparisons and the behaviors in several systems.

The amides (III and IV) having a methyl substituent at the 1 position of the benzocyclobutene ring gave the spirobenzylisoquinolines by the Bischler-Napieralski reaction (3), but the amide (V) having no methyl substituent at the same position afforded the corresponding 3,4-dihydroisoquinoline hydrochlorides (VIII) (5).

Therefore, the different chemical behavior in the above two types of amides must arise from the hyperconjugation and steric effect of the methyl group. Thus, the 3,4-dihydroisoquinoline hydrochlorides (VI and VII) formed by Bischler-Napieralski reaction are unstable due to the steric influence of the methyl substituent (6) causing opening of the cyclobutene ring on heating and the generated *o*-quinodimethanes (XI and XII) cyclise by the electrocyclic process indicated to form the spirobenzylisoquinolines (IX and X).

According to the previous method (3), the conversion of homoveratrylamine (I) into *N*-methylhomoveratrylamine and then amide (III) formation followed by synthesis of the spirobenzylisoquinoline (X) proceeded in 3.1% yield. The synthesis of X from homoveratrylamine (I) in the present method has been achieved in 16% yield. Thus, we have modified the synthetic method of the spirobenzylisoquinolines from the benzocyclobutenylisoquinolines *via* the *o*-quinodimethane intermediates.

## EXPERIMENTAL

Nmr spectra were measured with a Hitachi H-60 spectrometer with tetramethylsilane as an internal standard. Ir spectra were taken with a Hitachi 215 grating spectrometer, and uv spectra with a Hitachi recording spectrophotometer (EPS-3).

*N*-3,4-Dimethoxyphenethyl-4,5-dimethoxy-1-methylbenzocyclobutene-1-carboxamide (IV).

To a solution of 820 mg. of homoveratrylamine (I) and 1 g. of 4,5-dimethoxy-1-methylbenzocyclobutene-1-carboxylic acid (II) in 30 ml. of chloroform was added 1 g. of dicyclohexylcarbodiimide, and the mixture was stirred for 6 hours at room temperature. After separation of the undissolved material, the filtrate was washed with 2% hydrochloric acid, 5% sodium hydrogen carbonate, and water, dried over sodium sulfate, and evaporated to leave 2.2 g. of an oil, which was chromatographed on 44 g. of silica gel with chloroform to afford 850 mg. of the amide (IV) as a pale yellow oil;  $\nu$  max (chloroform) 3410 (NH) and 1640  $\text{cm}^{-1}$  (CO);  $\delta$  (deuteriochloroform) 1.60 (3H, s,  $\geq$ CMe), 2.60-3.65 (6H, m, 3 x CH<sub>2</sub>), 3.75 (3H, s, OMe), 3.81 (9H, s, 2 x OMe), 6.48 (1H, s, ArH), and 6.58-6.80 (4H, m, ArH).

1',2,2',3,3',4'-Hexahydro-5,6,6',7'-tetramethoxy-1-methylenespiro-(indene-2,1'-isoquinoline) (IX).

A mixture of 200 mg. of the amide (IV), 200 mg. of phosphoryl chloride, and 20 ml. of dry benzene was refluxed for 3 hours. To this solution was added an excess of hexane, and the separated oil was collected by decantation, made alkaline with ammonia and extracted with chloroform. The extract was washed with water, dried over potassium carbonate, and evaporated to leave 200 mg. of an oil, which was chromatographed on 4 g. of silica gel. Elution with chloroform-methanol (99.5:0.5 v/v) gave 85 mg. of the spirobenzylisoquinoline (IX), characterized as hydrochloride as pale yellow prisms, m.p. 186-187° (from ethanol);  $\nu$  max (chloroform) 850  $\text{cm}^{-1}$  (exomethylene);  $[\lambda$  max (methanol) 325 sh, 314, 294, 273 and 267 sh nm,  $\lambda$  max (methanol-hydrochloric acid) 325 sh, 312, 294, 270, and 265 nm],  $\delta$  (deuteriochloroform) 2.65-3.40 (6H, m, 3 x CH<sub>2</sub>), 3.70 (3H, s, OMe), 3.88 (3H, s, OMe), 3.90 (3H, s, OMe), 4.62 (1H, s, vinylic H), 5.36 (1H, s, vinylic H), and 6.40, 6.51, 6.74, and 6.98 (each 1H, each s, ArH).

*Anal.* Calcd. for C<sub>22</sub>H<sub>26</sub>ClO<sub>4</sub>N<sub>0.5</sub>H<sub>2</sub>O: C, 63.98; H, 6.54; N, 3.46. Found: C, 63.93; H, 6.80; N, 3.42.

1',2,2',3,3',4'-Hexahydro-5,6,6',7'-tetramethoxy-2'-methyl-1-methylenespiro(inden-2,1'-isoquinoline) (X).

The mixture of 40 mg. of the above spirobenzylisoquinoline (IX), 5 ml. of 38% formalin, and 30 ml. of methanol was set aside for 2 hours at room temperature, and to this solution was added 100 mg. of sodium borohydride with stirring under cooling. The reaction mixture was stirred for 3 hours at room temperature and then methanol was distilled off *in vacuo*. The residue was decomposed with water and extracted with chloroform. The extract was washed with water, dried over potassium carbonate, and evaporated *in vacuo* to give 30 mg. of the *N*-methylspirobenzylisoquinoline (X) as a pale brown amorphous powder, which was characterized as hydrochloride as colorless needles, m.p. 175-177° (from ethanol). The ir and nmr spectra of the free base were superimposable upon those of the authentic sample (3).

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