AN IMPROVED SYNTHESIS OF THE PYRIDOCARBAZOLE INDOLE ALKALOID OLIVACINE

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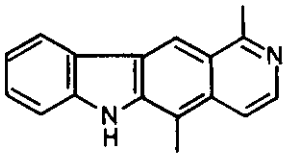
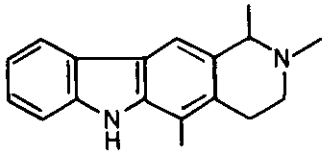
An improved synthesis of the alkaloid olivacine (I) has been developed. Employing tryptophol (III) as starting material, the synthetic sequence provides, in three high-yielding steps, the important aldehyde intermediate X. The latter has been previously converted in an efficient manner to the desired alkaloid.

In connection with our present investigation into the biosynthesis of the pyrido- and tetrahydropyridocarbazole class of indole alkaloids exemplified by the structures of olivacine (I) and guatambuine (II), it became necessary to undertake some synthetic studies which could be directly applicable to the biosynthetic experiments.



I



II

None of the previously developed syntheses of olivacine[1,2,3], or the work recently published on olivacine-like systems[4] could adequately be adapted to our needs for a large scale preparation of this compound or its N-methyl tetrahydro form, guatambuine. The synthesis by Mosher et al[3] which constituted an improvement of the initial olivacine synthesis by Schmutz and Wittwer[1] was best suited for large scale work. However, it was inefficient due to its excessive length. Following the theme developed by these workers we centered our efforts on an efficient synthesis of the carbazole intermediate X which could subsequently be elaborated into the olivacine skeleton by a series of well known high yielding reactions.

We chose tryptophol (III) as our starting material because it is readily available both commercially and via simple synthesis[5,6]. Condensation of the bromide IV , obtained by PBr_3 treatment of III, with the sodium anion of methyl acetoacetate in dimethylformamide (3.5 hours, 100°C) produced, in 80% yield, an alkylation product which from spectral data[7] (nmr: 2.12, s, 3H, $\underline{CH_3}CO$; 3.66, s, 3H, $COO\underline{CH_3}$; mass spectrometry: 259.120, $C_{15}H_{17}O_3N$ requires 259.120) could be assigned the desired structure V (Figure 1).

Cyclization of the ketone carbonyl of the alkylation product onto the C_2 position of the indole ring was initially accomplished by reaction in a solution of 2% HCl in methanol at 0°C. The cyclization was instantaneous providing a quantitative yield of a reaction mixture consisting of two products in approximately a 1:1 ratio. Analysis of the spectral data for the mixture showed neither of the products to be the expected 3,4-dihydrocarbazole derivative VI but the tetrahydro carbazole VII and the fully oxidized carbazole VIII. It was apparent that these products were arising from the disproportionation of VI.[8,9]

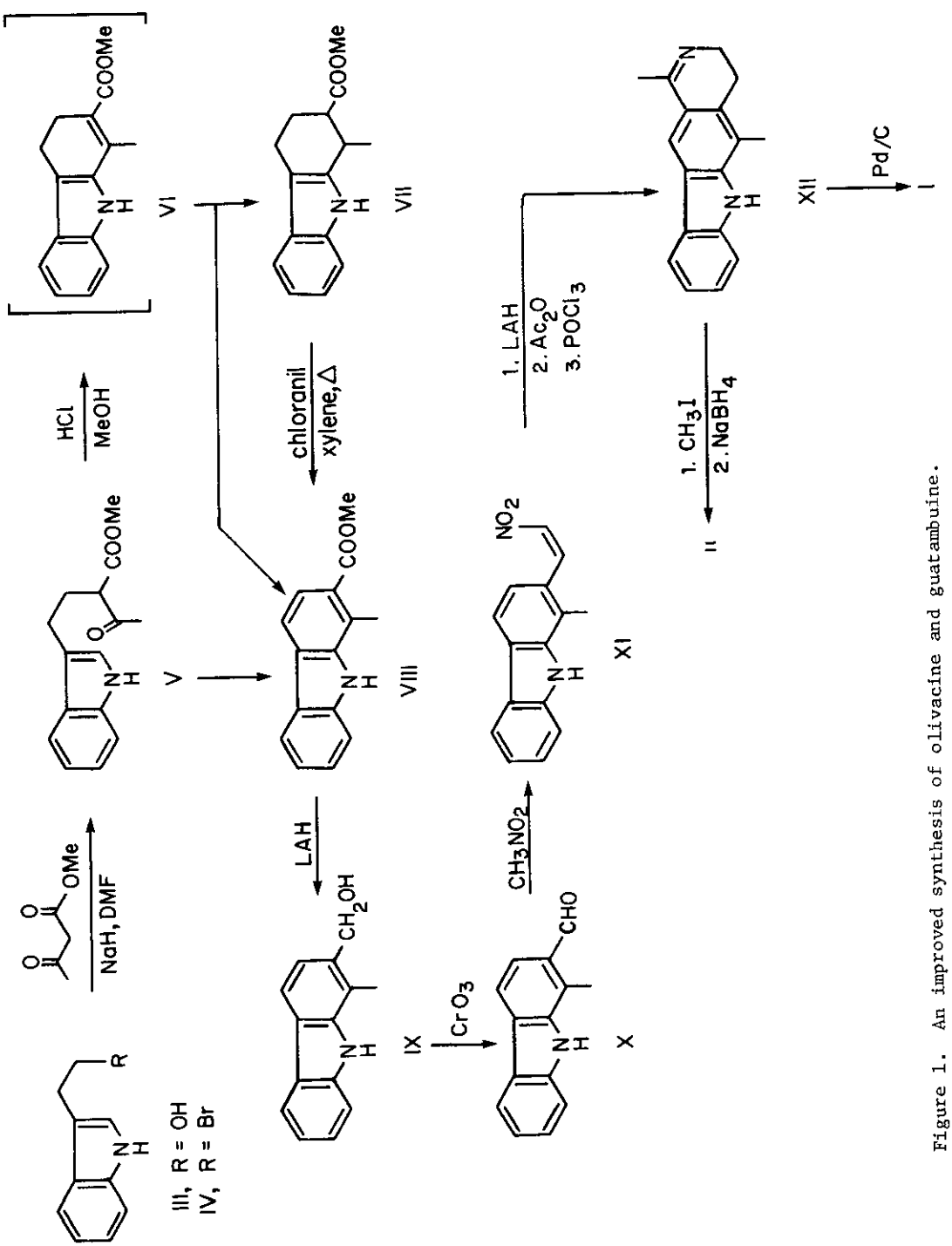


Figure 1. An improved synthesis of olivacine and guatambuine.

Separation of VII and VIII for spectral identification was accomplished with difficulty using column and thick layer chromatography on alumina. For preparative purposes however no attempt was made to separate these components. Instead the component mixture was converted to a homogeneous product by means of dehydrogenation.

Dehydrogenation of the above mixture employing Pd/C did not give uniformly reproducible results but optimum conditions were obtained with chloranil as the reagent.[10,11] Thus reaction of the cyclization material with an equimolar quantity of chloranil in refluxing toluene (24 hours) provided the carbazole VIII in high yield (about 80%).

Advantage was taken of the disproportionation reaction to achieve the direct conversion of V to the carbazole VIII in one step by conducting the cyclization reaction in the presence of an excess of chloranil as the hydrogen acceptor. Thus V was converted to VIII by dropwise addition of a solution of 2% HCl in methanol to a benzene solution of V containing 1.5 mole equivalents of chloranil. In this way the desired product VIII was isolated in an overall 84% yield. The ultraviolet data of VIII (λ_{max} 303 and 246 nm) was in good agreement with that of the corresponding ethyl ester reported by Schmutz[1] while the nmr (3.95, s, 3H, $COO\underline{CH_3}$; 2.84, s, 3H, aromatic $\underline{CH_3}$) and mass spectral data (base peak at m/e 239 (M^+), 239.094, $C_{15}H_{13}O_2N$ requires 239.094) were in complete agreement with the assigned structure.

Lithium aluminum hydride reduction of the ester group in VIII was accomplished in ether at room temperature (0.5 hours). The isolated product (95% yield) was the known crystalline alcohol IX, m.p. 184-186° (lit., m.p. 187-188°).[1]

It was hoped that through the use of more efficient oxidizing media that the yields for the synthesis of the desired aldehyde intermediate X might be increased over those previously obtained by Sarett oxidation (60%) of the benzylic carbazole alcohol IX.[3,12] A variety of alternate methods including Collins[13], $Ag^{(II)}$[14] and $Ce^{(IV)}$ oxidations[15], CrO_3/HOAc-pyr[16], DMSO/pyr-SO_3[17] and $Pb(OAc)_4$/pyr[18] were tried. However, all proved of little utility as a consequence of either of two drawbacks, poor solubility of the alcohol in the reaction medium, or complications on workup. Jones oxidation[19] conditions eventually provided a facile means of effecting the desired conversion. The yields were not enhanced greatly (70%), however the reaction was instantaneous and workup was greatly simplified when compared to the Sarett reaction. The desired aldehyde was obtained as yellow needles by recrystallization from chloroform (m.p. 165-166°C, lit. 164-165°).[3]

The overall synthesis of the aldehyde intermediate X was thus effected in three high yielding steps starting from tryptophol (III) thereby representing a substantial improvement over the previously employed approaches.[1,3]

The subsequent construction of the "D" rings of olivacine and guatambuine via the sequences, X → XI → XII → I and/or II proceeded without complication and in an efficient manner according to the established procedures.[1,3,12] It should be noted that in the synthesis of guatambuine, the final step XII → II involves a sodium borohydride reduction of the methiodide derivative of XII. We found this method to be as convenient as the catalytic reduction technique employed by Schmutz.[1] The yield in this conversion is essentially quantitative.

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