CYCLISATION OF γ-PHENYLPROPYL ISOCYANATE TO 1H-2-BENZAZEPIN-1-ONE: AN IMPROVED SYNTHESIS OF ALKALOID ELWESINE

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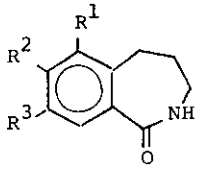
Treatment of γ-(3,4-dimethoxyphenyl)propyl isocyanate with phosphorous oxychloride followed by stannic chloride gave 1H-7,8-dimethoxy-2-benzazepin-1-one in fair yield, providing a convenient method for constructing 1H-benzazepin-1-one derivatives. Application of the procedure on β-[4-acetoxy-1-(3,4-methylenedioxyphenyl)cyclohexyl]propionic acid furnished an improved synthesis of alkaloid elwesine (dihydrocrinine) isolated from Amaryllidaceae plant.

In 1976 Tsuda and his co-workers reported a simple method for constructing isoquinoline lactam starting from some β-arylethyl urethane or β-arylethyl isocyanate by sequential treatment with phosphorous oxychloride and stannic chloride[1]. Recent report concerning the intramolecular cyclisation of 2-phenylethyl isocyanate by Iddon and his co-workers[2] prompted us to report here our result on cyclisation of some γ-phenylpropyl isocyanates to 1H-2-benzazepin-1-ones[3] by application of Tsuda's two stage procedure.

First, attempt to obtain the benzazepinone (1) from the urethane (2), prepared easily by treatment of the amine (3)[4] with methyl chloroformate, was made by applying Tsuda's two stage procedure but the usual work-up gave no benzazepinone (1) expected. On the other hand, treatment of the isocyanate (4), derived from the acid (5)[5] under Curtius condition ((1) thionyl chloride, (2) sodium azide, and (3) refluxing in benzene), with phosphorous oxychloride followed by stannic chloride yielded smoothly the benzazepinone (1), m.p. 192-194°, $\nu_{max.}$ 3130 (NH) and 1645cm^{-1} (CO), δ ($CDCl_3$), 7.29 (1H, s, ar-H), 6.71 (1H, s, ar-H), and 3.92 (6H, s, OMe) in 80% yield. In the cyclisation reaction, pre-treatment of the isocyanate with phosphorous oxychloride was indispensable, because the isocyanate gave a serious mixture without the pre-treatment. Congeners (6)

and (7) also yielded the lactam (8), m.p. 175-177°, $\nu_{max.}$ 3150 (NH) and 1645cm^{-1}, δ ($CDCl_3$) 7.44 (1H, d, J=9Hz, ar-H), 6.89 (1H, d, J=9Hz, ar-H), and 3.90 and 3.80 (3H each, s, OMe) and (9) m.p. 160-163° (lit.[6] m.p. 160-161°) in 30 and 65% yield, respectively. However, attempt to obtain the benzazepinone (10) from γ-phenylpropyl isocyanate was fruitless with the same reagent system. This fact indicated that the benzene ring of the isocyanate should be activated by the electron-donating substituent(s) when the two stage procedure was used.

Based on the above results, the synthesis of elwesine (dihydrocrinine)[7] was undertaken. Previously we synthesised the lactam (12) from the tetralone (13) by the Schmidt rearrangement in 20% yield[8]. Application of the reagent system mentioned above to the cyclohexane propionic acid (14) gave the lactam (12) in 70% yield, which was identical with the sample synthesised by the Schmidt rearrangement, providing an improved synthesis of elwesine (11), since the lactam (12) has been transformed into elwesine in optically active form[8].

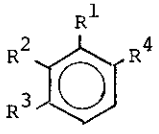


(1) R^1=H; R^2=R^3=OMe

(8) R^1=R^2=OMe; R^3=H

(9) R^1=R^3=H; R^2=OMe

(10) R^1=R^2=R^3=H



(2) R^1=H; R^2=R^3=OMe; R^4=$(CH_2)_3NHCO_2Me$

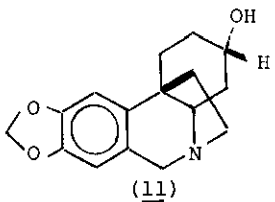
(3) R^1=H; R^2=R^3=OMe; R^4=$(CH_2)_3NH_2$

(4) R^1=H; R^2=R^3=OMe; R^4=$(CH_2)_3NCO$

(5) R^1=H; R^2=R^3=OMe; R^4=$(CH_2)_3CO_2H$

(6) R^1=R^2=OMe; R^3=H; R^4=$(CH_2)_3CO_2H$

(7) R^1=R^3=H; R^2=OMe; R^4=$(CH_2)_3CO_2H$



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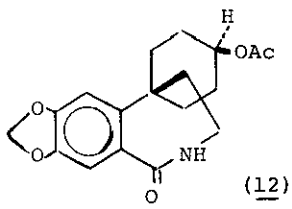

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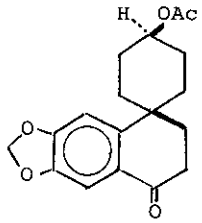
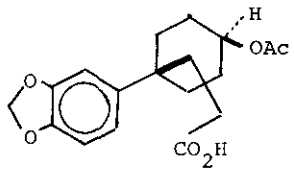


(13)



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Received, 30th July, 1979