A REGIOSELECTIVE AND FLEXIBLE SYNTHESIS OF ACRONYCINE

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Abstract--A regioselective synthesis of acronycine has been described through a methodology which can conveniently be modified for the preparation of its analogues.

Acronycine, a 2,2-dimethylpyranoacridone alkaloid, was isolated from 

Baurella simplicifolia (syn. Acronycia baueri)\(^1\) and Vepris amphody.\(^2\) It has been assigned structure (I) on the basis of degradative and spectroscopic studies.\(^3\) In view of its potential biological activity,\(^4\) a lot of synthetic\(^5\) investigations have been carried out towards acronycine and its analogues.\(^6\) Most of the synthesis reported give a mixture of angular and linear isomers in different proportions.\(^5\)

In the present communication, we wish to record a regioselective synthesis of the title compound through an approach which opens pathway for the preparation of its analogues.

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\begin{align*}
(\text{I}) \quad & R_1 = \text{CH}_3 \\
(\text{II}) \quad & R_1 = \text{H} \\
C_6H_5\text{NH}(\text{SCH}_2)C=\text{C}(&\text{CN})\text{COOCH}_3 & \quad \text{\text(V)} \quad R = \text{OH}; \quad R_1 = \text{COOCH}_3; \quad R_2 = \text{CN} \\
(\text{III}) \quad & \text{(CH} (\text{COOCH}_3)\text{COOC}_2\text{H}_5) \\
(\text{IV}) \quad & \text{N} \\
C_6H_5\text{NH}C(\text{CN})\text{COOCH}_3 & \quad \text{(VI)} \quad R = \text{OH}; \quad R_1 = \text{H}; \quad R_2 = \text{CN} \\
(\text{VII}) \quad & R = \text{Cl}; \quad R_1 = \text{H}; \quad R_2 = \text{CN} \\
(\text{VIII}) \quad & R = \text{Cl}; \quad R_1 = \text{CH}_2\text{CH}=\text{C}(&\text{CH}_3)\text{2}; \quad R_2 = \text{CN} \\
(\text{IX}) \quad & R = \text{Cl}; \quad R_1 = \text{CH}_2\text{CH}=\text{C}(&\text{CH}_3)\text{2}; \quad R_2 = \text{COOCH}_3
\end{align*}
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Ketene-S,N-acetal (III) was prepared by reaction of the carbanion of ethyl cyanoacetate with phenyl isothiocyanate using sodium methoxide in methanol followed by addition of methyl iodide in 84% yield, mp 76-78°C; $\nu_{\max}$ 3290, 2255, 1710, 1616 cm$^{-1}$; $\delta$(CDCl$_3$) 2.40(3H, s), 3.98(3H, s), 4.16(1H, br), 7.20-7.60 (5H, m), indicating thereby complete methanolysis of the ethyl ester under the reaction conditions. Substitution of thiomethyl group in III was carried out by refluxing it for 24h with the carbanion of ethyl acetoacetate obtained through sodium isopropoxide in isopropanol to afford IV as a white crystalline compound in 71% yield, mp 91-93°C. $\nu_{\max}$ 3100, 2214, 1748, 1715-1700, 1672, 1648 cm$^{-1}$. $\delta$(CDCl$_3$) 1.68(3H, t, $J=7$ Hz), 2.20(3H, s), 3.90(3H, s), 4.24(2H, q, $J=7$ Hz), 4.82(1H, br), 7.10(2H, m), 7.50(3H, m), 11.80(1H, br). In order to effect the cyclization of the compound (IV), it was refluxed in $\alpha$-dichlorobenzene to a give mixture of compounds (V), (VI) as white solid, and the starting compound (IV). It was found that the proportion of this mixture is dependent upon refluxing time and when the duration was limited to 2 h, the cyclized product (V) was obtained predominantly in 55% yield, mp 138-140°C. $\nu_{\max}$ 3250, 2215, 1750-1731, 1675, 1634, 1605 cm$^{-1}$. $\delta$(CDCl$_3$) 2.80(3H, s), 4.05(3H, s), 4.90(1H, s), 7.80(4H, m), 13.80(1H, s). Ms: m/z 284(M$^+$, 100%), 253(25%), 224(75%), 209(10%), 77(57%). The hydroxyl group in V was transformed into corresponding chloro group by treatment with phosphoryl chloride on steam bath only in 20% yield. Prolonged reaction time also did not improve the yield. However, when the reaction was carried out at 120-125°C for 5 h, no starting compound was detected and the only compound isolated was found to be devoid of carbomethoxy group in ir but had characteristic bands at 2250, 1680, 1659, 1608 cm$^{-1}$. $\delta$(CDCl$_3$) 2.60(3H, s), 3.70(2H, s), 7.70(4H, m). On the basis of this data and elemental analysis the possible structure could be VII i.e. decarbomethoxylation also takes place under the reaction conditions. Alkylation of the cyanomethylene in VII with 1-bromo-3-methyl-2-butene was executed in dimethylformamide using anhydrous potassium carbonate as the base through stirring at room temperature for 30 h. The desired alkylated product VIII was secured in 48% yield after chromatography over silica gel using benzene:ethyl acetate (2:1) as eluent, mp 178-181°C. $\nu_{\max}$ 2200, 1685 cm$^{-1}$. $\delta$[(CD$_3$)$_2$CO] 1.70 and 1.74(each 3H, 2xs), 2.10(poorly resolved t), 2.80(3H, s), 4.20(1H, t, $J=7$ Hz), 5.40(1H, m), 7.70(4H, m). Alcoholysis of the nitrile was accomplished by stirring it overnight in methanol saturated with hydrogen chloride followed by refluxing for 3 h to give corresponding ester (IX) as a white crystalline...
compound in 70% yield. \( \nu_{\text{max}} \) 1730, 1680 cm\(^{-1}\). \( \delta(\text{CD}_3\text{CO}) \) 1.70 and 1.78 (each 3H, 2xs). 2.05(2H, poorly resolved t), 2.70(3H, s), 4.02(3H, s), 4.30(1H, t, \( J=7 \) Hz), 5.45(1H, m), 7.65(4H, m). Cyclization of the keto ester (IX) was done by refluxing it for 3 h with sodium hydride in tetrahydrofuran to provide a thick reddish oil which was heated at 100°C for 3 h with phenol and the resulting product after work up was refluxed with hydrochloric acid in methanol for 15 h. The crude compound was purified by column chromatography on silica gel using n-hexane: benzene (1:5) as a eluent, to obtain 4-(3'-methyl-2'-butenyl)-1,3-dihydroxy-9-acridone (X) in 47% yield, mp 242-246°C. \( \nu_{\text{max}} \) 3424-3392, 1660 cm\(^{-1}\). \( \delta(\text{CDCl}_3) \) 1.69 and 1.84 (each 3H, 2xs), 3.59(2H, d, \( J=6 \) Hz), 5.16(1H, unresolved t), 6.48(1H, s), 7.40-7.90(3H, m), 8.40(1H, d, \( J=8 \) Hz), 10.20(1H, s), 13.80(1H, s).

Acridone (XI) was refluxed with 2,3-dichloro-5,6-dicyano-1,4-benzquinone in toluene for 14 h to have bis-nor-acronyicine (II), mp 238-239°C. \( \nu_{\text{max}} \) 3254, 1647, 1617, 1607 cm\(^{-1}\). \( \delta(\text{CDCl}_3) \) 1.50(6H, s), 5.50(1H, d, \( J=10 \) Hz), 6.25(1H, s), 6.50(1H, d, \( J=10 \) Hz), 7.8-8.05(3H, m), 8.35(1H, d, \( J=9 \) Hz), 10.34(1H, br), 12.88(1H, s).

Methylation of the acridone (II) was carried out by stirring it at 60°C for 18 h with methyl iodide in dimethylformamide using sodium hydride as the base to give acronyicine in 85% yield, mp 173-175°C. (lit. \(^3\) mp 176°C). IR, UV and nmr spectral data were in good agreement with the values reported for the natural product. \(^3\)

REFERENCES

7. Satisfactory C,H,N analytical data were obtained for compounds I to X.

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