SYNTHETIC STUDIES IN HEMITERPENOIDS

By

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IN FULFILMENT OF THE REQUIREMENTS
FOR THE DEGREE OF

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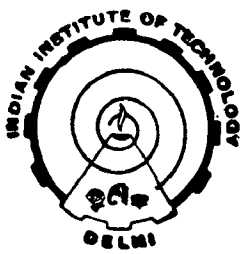

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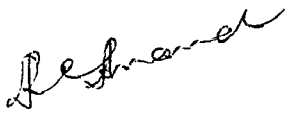
CERTIFICATE

This is to certify that the thesis entitled "Synthetic Studies in Hemiterpenoids" being submitted by Mr. Arun Kumar Sinha to the Indian Institute of Technology, Delhi, for the award of the degree of Doctor of Philosophy in Chemistry, is a record of bonafide research work carried out by him. Mr. Sinha has worked under my guidance, and supervision and has fulfilied the requirements for the submission of this thesis, which to my knowledge, has reached the requisite standard.

The results contained in this thesis have not been submitted in part or in full, to any other university or institute for the award of any degree or diploma.



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A.K. Sinha

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A B S T R A C T

The thesis embodies results of investigations towards the synthesis of following hemiterpenoids.

(a) Glycocitrine - II

(b) Acronycine

(c) Flindersine and N-Methylflindersine

A synthesis of glycocitrine-II has been accomplished regioselectively and for the first time. The key intermediate, 3-acetyl-4-chloro-2-cyanomethyl-quinoline, was prepared through two routes. The first approach utilized the substitution of thiomethyl group in ketene S,N-acetal (methyl 2-cyano-3-phenylamino-3-thiomethyl-2-propenoate) through the carbanion of ethyl acetoacetate followed by thermal cyclization of suitably positioned carbethoxy group with N-phenyl ring. The conditions for this cyclization have also been optimized. Attempts to transform 3-acetyl-2-(1'-cyano-1'-carbomethoxy-methyl)-4-quinolinol into corresponding chloro derivative were also accompanied by decarbomethoxylation to afford the aforementioned intermediate. The second pathway involves displacement of ethoxy group in 4-ethoxy-3-penten-2-one with methyl anthranilate through addition-elimination type of reaction. The resultant product undergoes base catalysed cyclization to provide 3-acetyl-2-methyl-4-quinolinol which was then converted into its corresponding 4-chloro derivative. The methyl group was finally functionalized to cyanomethyl via free radical bromination followed by sustitution by cyanide ion.

The intermediate synthesized above was then elaborated to nor-glycocitrine-II through a sequence of reactions i.e. regio-selective alkylation of cyanomethyl with prenyl bromide, alcoholyis, base catalysed cyclization and hydrolysis. The nor-glycocitrine was finally transformed into the title compound (a) through methylation of its diacetate followed by hydrolysis.

In view of potential biological activity of acronycine, it was planned to synthesize this compound through a route that can conveniently be modified for the preparation of its analogues. Nor-glycocitrine-II was chosen as the suitable intermediate because of its flexible synthetic scheme described above. This compound was transformed into acronycine through oxymercuration-demercuration followed by methylation and dehydrogenation as the reaction sequence.

Flindersine and N-methylflindersine have been synthesized through two simple and convenient routes. The first approach involves ketene S,N-acetal from carbethoxylated isobutyl methyl ketone [ethyl 3-keto-5-methyl-2-(1'-thiomethyl-1'-phenylamino-1'-methenyl)-hexanoate] followed by thermal cyclization of the carbethoxy group with N-phenyl ring to give 4-hydroxy-3-(3'-methyl-butanoyl)-2-thiomethyl-quinoline. The carbonyl group in 3-alkanoyl side chain of the 4-chloro derivative, obtained from the above 4-quinolinol, was transformed into α,β-unsaturated ketone which on subsequent hydrolysis provided 4,5-diketo-2,2-dimethyl-2,3,5,6-tetrahydro-pyrano[3,2-c]-quinoline. Reduction of the ketonic functionality of the pyran ring

and subsequent dehydration of the resulting alcohol furnished flindersine.

In an alternate route, the ketonic group of 3-alkanoyl side chain of 4-chloro-3-(3'-methyl-butanoyl)-2-thiomethyl-quinoline was converted into olefin through reduction and dehydration of the resulting alcohol as the reaction sequence. The olefinic compound was hydrolysed and the resulting product was subjected to dehydrogenative cyclization to procure flindersine.

A synthesis of N-methylflindersine was also carried out through base catalysed cyclization of 5-methyl-N-(2'- carbomethoxy-phenyl), N-methyl-2-hexenamide (prepared by acetylation of methyl anthranilate with 5-methyl-2-hexenoylchloride followed by N-methylation). The cyclized product was smoothly converted into N-methylflindersine through DDQ.

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