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SUBSTITUTION AT THE α-POSITION OF AMINES. ALPHA CYANOAMINES AS LATENT ALPHA AMINOCARBANIONS

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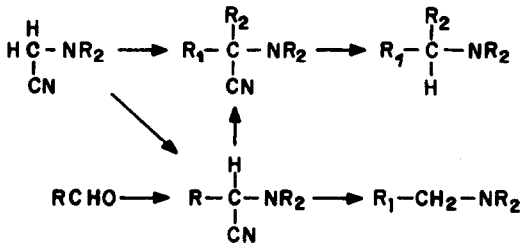
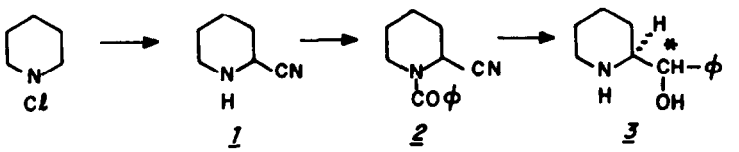
We have recently reported that the α-cyano derivatives of tertiary amines can be alkylated easily with electrophilic carbon.[1] The focus of that report was the use of the α-aminonitrile functionality as a latent carbonyl anion ("acylcarbanion equivalent") in the synthesis of aldehydes and ketones. It is apparent that since cyano groups next to a basic nitrogen can be replaced by hydrogen by simple reduction with sodium borohydride[2], the sequence is also a general route to the introduction of α-substituents in a tertiary amine, as shown below. The route is, in many cases, much more convenient and general than a variety of other schemes proposed to effect α-substitution of amines.[3] It also solves the



problem of regiospecificity, the net result being the replacement of cyano by the required electrophile. Since all the products of alkylation of α-amino nitriles with carbon electrophiles like alkyl halides, α,β-unsaturated carbonyl compounds[4] and epoxides which we have described previously can thus be transformed into the tertiary amines, we will not dwell further on these reactions. We will focus instead on the use of α-cyanoamines as a general route to the biologically important class of ethanolamine derivatives. These are obtained *via* condensation of aldehydes or unhindered ketones with α-cyanamines and, as we will see, the process can be used as a general route to secondary and tertiary aminoalcohols. It is noteworthy that these aminoalcohols are produced with a high degree of stereoselectivity when diasteromeric mixtures are possible.

We now illustrate the sequence of steps which lead to the introduction of a carbinol function alpha to the amino nitrogen of cyclic amines by the syntheis of erythro α-phenyl-2-piperidylmethanol from piperidine.

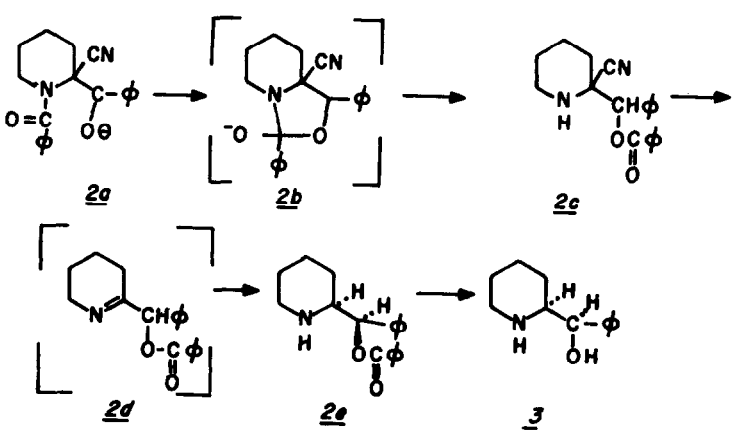
The conversion of cyclic secondary amines to their 2-cyano derivatives by addition of hydrogen cyanide to the imine derived from the N-chloroamine is well known. In the particular case of 2-cyanopiperidine (1)[5], benzoylation (methylene chloride-30% postassium carbonate, one equiv benzoyl chloride; 15 min) gave the benzamide 2,mp 79.5-82.2° (82% yield after recrystallization from ether) The cyanobenzamide 2 was converted stereoselectively, in 70% overall yield, to the phenylcarbinol 3 (ratio of erythro to threo = 85/15) by the following process, which was followed for all similar transformations: Dropwise addition of cyanobenzamide 2 (2.1 mmole in 10 ml THF) to a solution of 1.1. equiv of



1 2 3

lithium N,N-diisopropylamide in 30 ml of THF at -78°C was followed by addition of 1.2 equiv of benzaldehyde. The solution was allowed to warm to 0°C and, after 1 hr, an excess of sodium borohydride in methanol was added. Work up after 4-12 hr gave the phenylcarbinol 3. The erythro/threo ratio was established by comparison with authentic samples of the two isomers.[6] The NMR of the starred hydrogen in carbinol 3 is particularly characteristic, showing resonance at δ 4.55 (d, J = 5.5Hz) for the threo isomer and 4.30 (d, J = 8 Hz) for the threo isomer. The oxazolidines from 3 and benzaldehyde[7] showed even greater separation of signals for the same hydrogen: erythro derivative: δ 5.1, J = 8 Hz; threo: δ 4.5, J = 6 Hz.

The sequence of events in the transformation of 2 to 3 was shown to be as depicted below. Convincing spectral evidence was obtained for 2a, 2c and 2e.



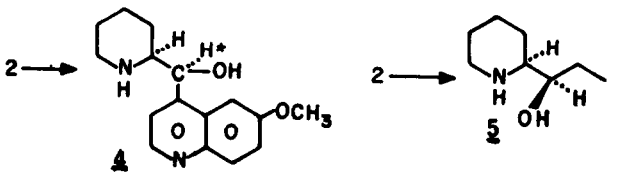
2a 2b 2c

2d 2e 3

Each one could be isolated by interrupting the reaction at appropriate points. It will be appreciated that the simplicity of the synthetic process depends on the kinetic formation of the O-benzoyl derivative 2c in which the basic nitrogen permits rapid equilibration with the imine 2d which is trapped by hydride ion. The final liberation of alcohol 3 from its benzoate is the result of methanolysis after the hydride reduction (short reduction times give 2e).

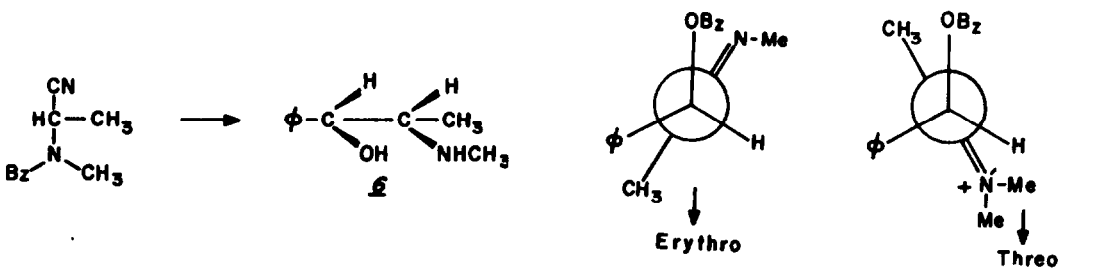
By the same process, reaction of 2 as above, with an equimolar amount of 6-methoxy-4-quinolinecarboxaldehyde led stereoselectively, in 76% yield, to a 5 ∿ 6:1 mixture of erythro and threo aminoalcohols 4.[8] The starred carbinol hydrogen had its resonance at δ 5.5, J = 3.2 Hz (erythro) and 5.1, J = 6.0 (threo).

The same route to aminoalcohols can be used with aliphatic aldehydes: The usual sequence of condensation and borohydride reduction, starting with propionaldehyde, led, in 77% yield, to crude ± conhydrine, erythro α-ethyl 2-piperidinemethanol (5), obtained essentially pure after recrystallization from ether (mp 96-7°; lit.[9] mp 99-100°).



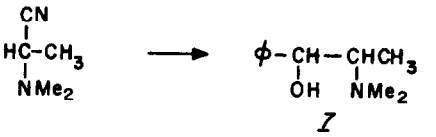
The method is even more convenient for the synthesis of acyclic amino alcohols since acyclic α-aminonitriles are so easily available from aldehydes. The secondary aminoalcohols thus obtained are again largely the erythro compounds. We illustrate this with a synthesis of ephedrine: The N-benzoyl derivative of 2-N-methylaminopropionitrile[10] was submitted to the usual reaction sequence to produce, in 75% yield, a mixture of ± ephedrine (6) (erythro) and ± ψ-ephedrine (threo) in which the former predominated by a factor of 3.3 to 1.

A reversal of stereochemistry was encountered in the application of the process to tertiary rather than secondary aminoalcohols. Since the stereochemistry of the final aminoalcohol is determined by the transition state for hydride transfer to an imine intermediate, the results may reflect net attraction between the imine and benzoate functions in a secondary amine, in contrast to dipole



repulsion with the imonium salt intermediate derived from a tertiary amine. In any event, the usual sequence applied to benzaldehyde and 2-N,N-dimethylaminopropionitrile gave (93% yield) 7 in which the threo isomer (N-methyl-ψ-ephedrine)[11] predominated over the erythro by more than five to one.

One final reaction illustrates the versatility of intermediates such as 2c: If the initial reaction is quenched with methanol, and acetic acid rather than sodium borohydride is added isomerization and hydrolysis of 2d take place to give (95% yield) the known[12] 2-benzoylpiperidine.[13]



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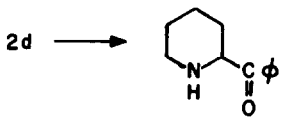

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