NEW SYNTHESIS OF AMINOPROPYLBENZENES AND 1,2,3,4-TETRAHYDROAZOCINES FROM N-SUBSTITUTED TETRAHYDRONICOTINAMIDES WITH ACETYLENIC ESTERS

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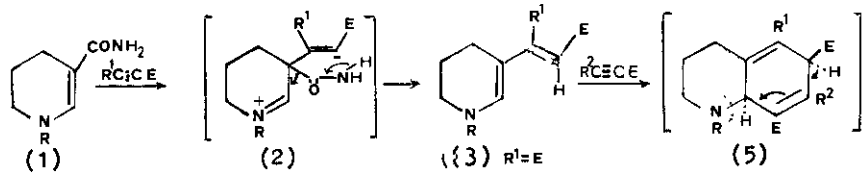
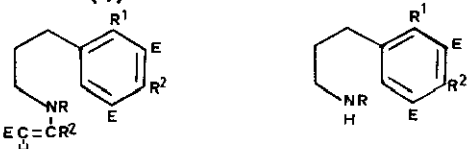
ABSTRACT - Some N-substituted tetrahydronicotinamides (1) and dimethyl acetylenedicarboxylate (DMAD) gave the dienamines (3) through a known type of carboxamide elimination. However, these compounds further undergo cycloaddition to DMAD and via the intermediate (5) formed the aminopropylbenzenes (7–9) by a trans-elimination. In contrast (1b) with methyl propiolate, along with small amounts of dienamine (4) and aminopropylbenzene (10), gave in 40% yield the tetrahydroazocine (12), thus providing a new route to this class of heterocycles.

Reactions of various N-substituted 1,2-, 1,4-, and 1,6-dihydropyridines with DMAD have been extensively investigated and yield 1,2-dihydroazocines,[1], cyclobuta-[b]-[2] and -[c]-pyridines and benzene derivatives [3] according to the particular pyridine derivative employed. The dihydropyridines can behave as dienes, or enamines. We now wish to report the results obtained on treating 1- substituted 1,4,5,6-tetrahydronicotinamides (1a–c) with DMAD and (1b) with methyl propiolate.



(1) (2) (3) R¹=E (4) R¹=H (5)

a, R=Me
b R=CH_2Ph
c, R=Ph
E=CO_2Me



(7) $R^1=R^2=E$, Z isomer (6) $R^1=R^2=E$
(8) $R^1=R^2=E$, E " "
(9) $R^1=E$, $R^2=H$, E isomer
(10) $R^1=R^2=H$, E

The different types of products formed enabled us to suggest the scheme above for their formation.

The amides (1a–c) in dry acetonitrile were treated with one mole of DMAD for 24 h at room temperature and the products separated by chromatography over deactivated alumina or silica gel. The adducts (3a–c) were formed through a known type of carboxamide elimination [2] and were obtained as yellow crystalline solids. All were assumed to be *Z* isomers owing to the high δ value of the vinyl side-chain protons (δ, 5.20, 5.25 and 5.40 respectively) in accordance with what reported by other authors.[2,4] The 2-H resonances (δ, 6.40, 6.42 and 6.86 respectively) fall at higher field than those of (1a–c).

These compounds now undergo cycloaddition, which could be concerted or otherwise, forming (5) which then aromatises by <u>trans</u>-elimination as shown, yielding (6), thus indicating that during their formation a novel ring-opening was subsequent to intramolecular protonation.

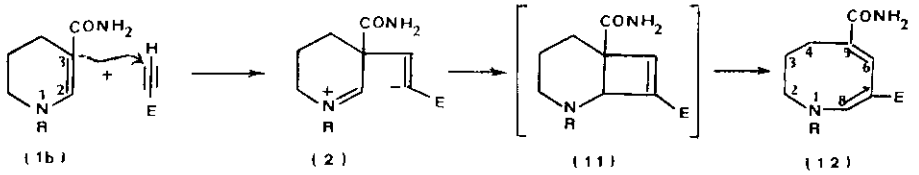
(6a) was an oil and characterised as picrate, (6c) was obtained as pure oil while (6b) could not be isolated or characterised.

(6a–c) rapidly undergo Michael-type additions to DMAD, yielding (7a–c) which are the main compounds formed. Their stereochemistry follows from the resonance positions of the side-chain vinyl protons [5] (δ, 4.55, 4.60 and 4.62 respectively). Only in the case of (1a) did DMAD yield a detectable amount of fumarate (8a) (side-chain H, δ, 5.40).

Treatment of (3a) with methyl propiolate gave only (9a) via a similar route.

One interesting result is illustrated by the reaction of 1-benzyl-1,2,3,4-tetrahydronicotinamide (1b) with methyl propiolate in refluxing acetonitrile. Although most <u>N</u>-substituted 1,2-dihydropyridines seem not to react with this ester under the conditions examined,[1] in this case we have found that the reaction affords the methyl 5-carboxamido-1,2,3,4-tetrahydro-1-benzylazocine-7-carboxylate (12) in 40% yield, along with 18% of (4b) and 7% of (10b).

The formation of the tetrahydroazocine (12) is noteworthy as methyl propiolate after suffering Michael-type additions to heterocycles almost invariably[6] abstracts a proton from another molecule of itself prior to further reactions occuring.



The formation of (4b) and (10b), which is similar to what occurs with DMAD, indicates that this type of reaction takes place through the intermediate (5) to an extent of at least 25%. The cyclisation of (2) to the hypothetical (11) followed by ring opening to the azocine (12) is similar to corresponding reactions of 1,2-dihydropyridines[1] and 1,4-dihydroquinolines[7] with DMAD, while addition of methyl propiolate to 1-acetyl-3-piperidinoindole[8] does occur through a similar cyclisation to give an azepine.

(4b) was a crystalline compound while (10b) appears as a pale yellow thick oil solidifying at +7-10°. Their structures were identified by the ^{1}H nmr and uv spectra which were similar to those of the previous described compounds. In both cases they show to be *E* isomers for the high value of the coupling constant[5] (J, 15.2 and 13.2 respectively) of the resulting AB system due to the olefinic protons of the side-chain.

The structure of the azocine (12) [pale yellow prisms, m.p. 192-194°, from MetOH; m/e M^+, 300 (35%), 91 (100%)] follows from the great similarity of its uv and ^{1}H nmr spectrum with what of other tetrahydroazocines.[1]

The achievement of (12) is the first case observed of 1-substituted 1,4-dihydronicotinamide suffering electrophilic attack at C-3 by an activated acetylene and not subsequently undergoing carboxamide elimination, and gives a new synthesis of 1,2,3,4-tetrahydroazocine-5-carboxamide derivatives.

All new compounds gave carbon, hydrogen and nitrogen analysis within normal limits; ^{1}H [and for (7a) also the ^{13}C] nmr and uv spectra are consistent with the structures proposed.

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