# FORMATION, SYNTHETIC UTILITY AND STRUCTURE ELUCIDATION
# OF A 2-BROMOMETHYL 1,4-DIHYDROPYRIDINE

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Abstract: The structure of the product obtained by reacting the 1,4-dihydropyridine 6 with pyridinium bromide perbromide has been confirmed by NMR spectroscopy as the 2-bromomethyl derivative 7 and its reaction with a range of nucleophiles has been studied.

As part of our structure activity relationship studies around the potent, once a day calcium antagonist amlodipine 1[1] we required a rapid entry into 1,4-dihydropyridine-3,5-dicarboxylic acid diesters in which the 2-methyl group was substituted by a range of different groups. In view of the recent publication by Sircar et al.[2], in which they report the preparation of the 2-bromomethyl derivatives 2 and their reaction with nucleophiles, we now wish to report a convenient synthetic approach to some of these derivatives.
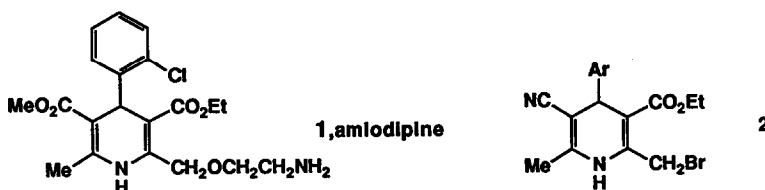
Young reported[3] that reaction of the 1,4-dihydropyridines 3 with pyridinium bromide perbromide in chloroform solution at 0°C gave an unstable brominated species which on heating at reflux for 90 minutes gave acceptable yields of the lactones 5. He proposed that the initial products, which could be detected by thin layer chromatography (TLC) but not isolated in pure form, were the 2-bromomethyl derivatives 4. We reasoned[4] that it might be possible to react 4 in situ with a range of nucleophiles thereby fulfilling our synthetic objectives.
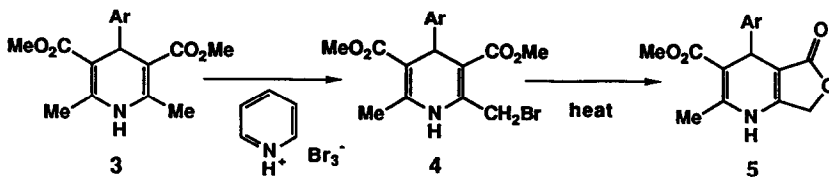

Reaction of 6[7] with 1.1 equivalents of pyridinium bromide perbromide[8] in dichloromethane at 0°C followed by rapid work-up (see Typical Procedure) afforded the crude product 7 as a yellow gum. Although 7 could be purified by rapid chromatography on silica, we were not able to obtain a crystalline sample. In all cases TLC examination of the crude reaction mixture revealed the presence of up to 10% of a close-running, less polar

<u>Table</u>: Compounds 8.

Compound	R	Base	Solvent	Yield[a] %	mp, °C
8a	-SCH₂Ph	K₂CO₃	DMF	63[b]	gum
8b	-SCH₂CH₂NH₂	K₂CO₃	DMF	13[c]	180-185
8c	CO₂Me | -SCH₂CHNH₂	K₂CO₃	DMF	48	gum
8d	-S—(pyrimidine)	K₂CO₃	THF	5	151-153
8e	-N—(imidazole)	NaH	THF	34	179-181
8f	-N—(triazole)	NaH	THF	25	162-163
8g	-O—(C₆H₄)—CN	NaH	THF	81	200-206
8h	-O—(pyridine)	NaH	THF	3	174-177
8i	-OCH₂—(pyridine)—CH₂OH	NaH	THF	11	125-127

a. Yields were not optimised. b. 4% of the bis-adduct 10 was isolated in this case.
c. Characterised as a hemifumarate salt.

9 : X = Br

10 : X = SCH₂Ph
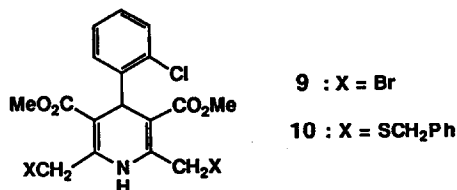
spot which is believed to be the 2,6-bis(bromomethyl)-1,4-dihydropyridine 9. We were pleased to find that 7 does indeed react with a range of nucleophiles (see Table); in general, crude 7 was taken up in THF and added directly to an ice-cooled solution of the appropriate reagent in THF or DMF. The reaction mixture was stirred until all 7 had been consumed and then worked up conventionally to give the desired products 8[9] in variable yield.
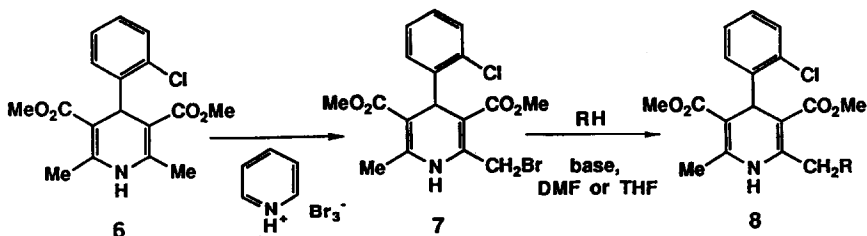
In addition to 7, two alternative structures 11 and 12 can be envisaged[3] for the brominated species. A one bond ^{13}C-^{1}H shift correlation spectrum of the crude brominated compound (Figure 1) showed clearly that the only methylene carbon (δ 27.0) is correlated to the two proton AB quartet (J = 11 Hz) at δ 4.73 in the ^{1}H NMR spectrum. These data are wholly consistent with structure 7 being correct and are inconsistent with structures 11 and 12.
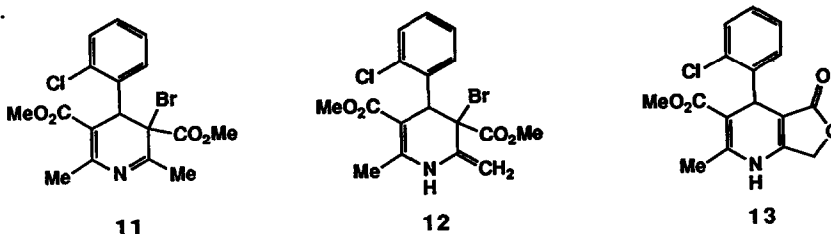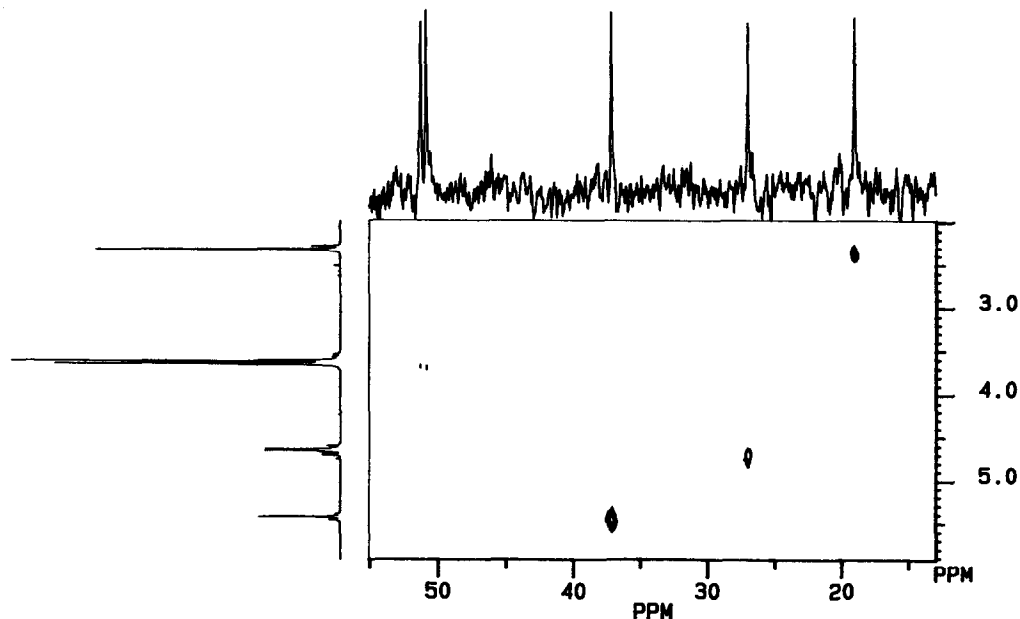

11   12   13

Figure 1: ^{13}C-^{1}H Shift Correlation Spectrum for 7.

In order to assess the stability of 7 in solution, a sample (approximately 5 mg) was kept in $CDCl_3$ (0.5 ml) at 23°C and the ^{1}H NMR spectrum recorded at various time intervals. To our surprise, under these conditions, 7 underwent decomposition only slowly with a half-life of greater than 24 hours. TLC and ^{1}H NMR spectroscopic comparisons with an authentic sample[10] confirmed that the major decomposition product was the expected lactone 13. No evidence for the intermediacy of any species was seen in the ^{1}H-NMR spectrum although substantial amounts of bromomethane were formed as evidenced by the appearance of a sharp singlet

at 2.66 ppm. This suggests that the decomposition of 7 involves attack of the ester carbonyl to displace the bromine atom and form an intermediate oxonium species which then undergoes attack by Br⁻ on the methoxy group to give 13.

In conclusion, reaction of 6 with pyridinium bromide perbromide gives a product whose structure has been shown to be 7 and which reacts with a range of nucleophiles to give 2-substituted 1,4-dihydropyridines 8.

Typical Procedure: Preparation of 8a: Solid pyridinium bromide perbromide (4.00 g, 11 mmol)[8] was added portionwise to a stirred, ice-cooled solution of 6 (3.35g, 10 mmol) in CH_2Cl_2 (80 mL) over 5 min and the mixture stirred with ice-cooling for 40 min, diluted with ice-cold CH_2Cl_2 (120 mL), washed twice with ice-cold 2M HCl and ice-water, dried over Na_2SO_4 and evaporated without external heating. The crude yellow gum was taken up in THF (20 mL) and the solution added to a mixture of benzylthiol (2.48 g, 20 mmol) and K_2CO_3 (2.76g, 20 mmol) in DMF (20 mL). The mixture was stirred with ice-cooling for 2 h and at room temperature for 3 h, by which time TLC indicated the complete disappearance of 7, and evaporated. The residue was partitioned between EtOAc and 2M HCl and the organic layer washed with water, dried over Na_2SO_4 and evaporated. The residue was purified by chromatography on SiO_2 using CH_2Cl_2 plus 0-2% EtOAc as eluant. Appropriate fractions were combined and evaporated to give 8a.

References and Notes

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4.   Since the inception of this work, the use of 4 has been reported in the patent literature by us[5] and others[6].
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