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N-Carbomethoxy Aziridines

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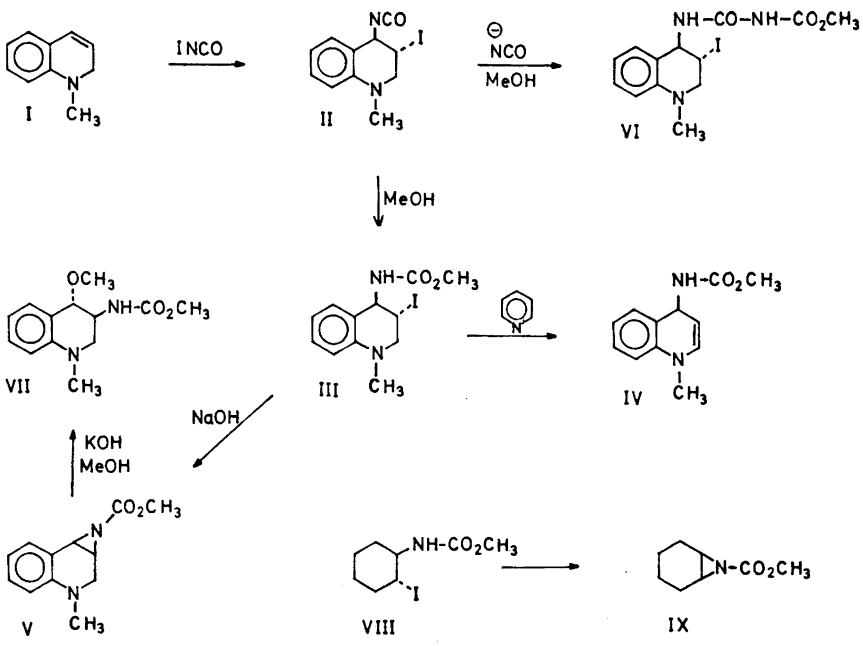
Addition of iodine isocyanate to 1-methyl-1,2-dihydroquinoline followed by treatment with methanol gave the 3-iodo-4-carbamate and a urea derivative. The reaction of methyl *N*-(*trans*-3-iodo-1-methyl-1,2,3,4-tetrahydro-4-quinolyl)carbamate with pyridine gave elimination of HI from the ring. In KOH/CH_3OH the initially formed *N*-carbomethoxy imine opened up to give as the main product methyl *N*-(*trans*-4-methoxy-1-methyl-1,2,3,4-tetrahydro-3-quinolyl)carbamate. The best conditions for transforming iodo carbamates to *N*-carbomethoxy aziridines have been found to be a two-phase system with 50 % NaOH in water as the base.

Additions of electrophilic reagents to dihydropyridines or dihydroquinolines are not often reported. This is due to the ease with which these compounds are oxidized and to the possible interference of the ringnitrogen atom. Dihalocarbene additions to alkoxy dihydroquinolines, however, are known.[1] These reactions have also been tried in more electrondeficient systems.[2] Aziridine synthesis by means of iodine isocyanate, as introduced by Hassner [3] and later utilized by Paquette,[4] was likely to succeed in these systems because of the relatively high reactivity of iodine isocyanate [5] compared to dihalocarbenes. 1-Methyl-2-phenyl-1,2-dihydroquinoline [6] which was not attacked by dibromocarbene [2] also turned out to be inert to iodine isocyanate. The less stabile 1-methyl-1,2-dihydroquinoline (I), synthesized by $LiAlH_4$ reduction of quinolinium methiodide [7] did, however, respond. Carefully controlled conditions gave the isocyanate (II) which immediately was transformed to the carbamate (III) with methanol (catalyzed by lithium methoxide). The dihydroquinoline (I) was not isolated but reacted further by iodine isocyanate addition to a dried ether solution. To prevent oxidation of the dihydroquinoline a preformed solution of iodine isocyanate was added to a dilute solution of the alkene. Treatment with methanol at room temperature gave the 3-iodo carbamate (III) rather than the isomeric 4-iodo carbamate. This follows from the reaction with pyridine at 100°C for 30 min, which gave 1-methyl-1,4-dihydroquinoline-4-methylcarbamate (IV). In deuterated pyridine the 4-methine proton of IV resonated at 5.8 τ, the 3-vinyl proton at 4.75 τ, and the 2-vinyl proton at 4.27 τ. The mass spectra showed M and $M-CH_3OH$ while



the M − 1 fragment was lacking. The *N*-carbomethoxy aziridines (V and IX) showed significant amounts of the M − 1 fragment, presumably due to α-cleavage as in *N*-aryl aziridines.[8] The addition of iodine isocyanate to alkenes is known to proceed stereospecifically *trans*.[1] The formation of IV is explained by an E2 elimination of HI from III. A 4-iodo carbamate could only have given 1-methyl-1,2-dihydroquinoline-3-methylcarbamate, which is not found. The lack of the aziridine V is according to the reported failure of ring closure of iodo carbamates in pyridine.[9] Attempts to isolate the labile compound IV only destroyed the material. The reaction could be studied, however, when performed in deuterated pyridine in the NMR tube. The NMR data are in good agreement with the known chemical shifts for dihydroquinolines.[10,11]

The overall yield of the carbamate (III) was about 20 % (3 steps). In addition an ether insoluble product was found in nearly the same yield. The solid state IR spectrum had two NH absorptions at 3280 and 3320 cm^{-1} and two CO absorptions at 1685 and 1715 cm^{-1} (compared to the carbamate (III) absorptions at 3240 and 1685 cm^{-1}). The NMR spectrum in deuteriopyridine showed two methine protons at 4.4 τ and 5.1 τ, respectively, two methylene protons at 6.5 τ, and *N*-methyl and *O*-methyl signals at 7.2 τ and 6.4 τ in addition to the lower field four aromatic protons and two NH protons. Diagnostic peaks in the mass spectrum corresponding to M, M − CH_3O and M − CH_3OCONH gave the final evidence for the urea derivative VI. The carbonyl carbon of the initially formed isocyanate (II) has been attacked by the isocyanate nucleophile producing the carbamate (VI) with methanol.

In order to synthesize the aziridine (V) several methods were examined. Refluxing III with sodium methoxide in different solvents gave only small amounts of V. Treatment with KOH in methanol, at room temperature or at reflux, gave no sign of V or any decarboxylated derivative of V. The major product was the methyl-*N*-(*trans*-4-methoxy-1-methyl-1,2,3,4-tetrahydro-3-quinolyl)carbamate (VII). The latter is characterized by the M, M−CH_3O, M−CH_3OH, and M−CH_3OCONH_2 fragments in the mass spectrum and the methine protons at about 5.9 τ, the methylene protons at 6.7 τ, the *O*-methyl protons at 6.3 τ and 6.6 τ, and the *N*-methyl protons at 7.1 τ in the NMR spectrum in $CDCl_3$. A similar product formation is reported by the KOH/MeOH treatment of methyl (*trans*-2-iodo-1-tetralin)carbamate which gave as a minor product methyl (*trans*-1-methoxy-2-tetralin)carbamate.[9] VII is thought to have arisen by *trans* ring opening of the initially formed aziridine (V).

The synthesis of V obviously required a base which did not favour eliminations and the absence of good nucleophiles. A two-phase system consisting of an organic phase (benzene) and a 50 % solution of NaOH in water filled these requirements. This is a variation of the conditions used for the generation of dihalocarbenes.[12,13] After stirring for 3 days at room temperature the aziridine was isolated in good yield. When V was treated with KOH/MeOH, VII was produced. Even in a 25 % water in methanol solution VII was the major product. The conditions for ring closure also was tried on the iodo carbamate of cyclohexene (VIII) which with KOH in methanol gave 1,2-imino-cyclohexane directly.[1] The *N*-carbomethoxy derivative (IX) now was isolated in excellent yields. The method clearly is very efficient in the synthesis of *N*-carbomethoxy aziridines free of substituted or hydrolyzed products.

EXPERIMENTAL

The NMR spectra were recorded on an Varian A-60 instrument and the high resolution mass spectra on an AEI MS-902 double focussing mass spectrometer.

Methyl N-(trans-*3-iodo-1-methyl-1,2,3,4-tetrahydro-4-quinolyl)carbamate (III).* N-(trans-*3-Iodo-1-methyl-1,2,3,4-tetrahydro-4-quinolyl)*-N′-*methyl carbamoyl-urea (VI).* To a dried ether solution (1000 ml) of I (from 0.01 mol of quinolinium methiodide and 0.01 mol $LiAlH_4$) at −78°C under nitrogen was added with stirring a freshly prepared cold solution of iodine isocyanate (from 0.01 mol of iodine and 0.02 mol of silver cyanate, filtered under nitrogen) in dry tetrahydrofuran (500 ml). After 15 min at −78°C the cooling bath was removed and the mixture stirred for another hour. Dry methanol (300 ml) and 5 drops of a 0.1 M solution of lithium methoxide in methanol were added and the solution left in the dark overnight. The solution was evaporated and the residue extracted with ether (2 × 500 ml).

From the ether solution III was recovered by washing with water (with a trace of sodium bisulfite), drying, concentrating and recrystallizing from ether; 8 g, overall yield from quinolinium methiodide 23 %, m.p. 114−116°C. (Found: C 41.90; H 4.55; N 7.81; I 36.20. Calc. for $C_{12}H_{15}IN_2O_2$: C 41.60; H 4.33; N 8.10; I 36.70.) NMR in $CDCl_3$: 7.0 τ (s, 3H, *N*-methyl),6.5 τ (m, 2H, methylene), 6.30 τ (s, 3H, *O*-methyl), 5.4 τ (*q*, 1H, 3-methine), 5.0 τ (m, 1H, 4-methine), 2.7−3.6 τ (m, 4H, aromatic). IR_{KBr}: 3240 cm^{-1} (NH), 1685 cm^{-1} (CO). MS fragmentations: M (*m/e* 346), M−CH_3OCONH, M−CH_3OCONH_2, M−I.

The in ether not soluble VI, which was filtered from the ether solution containing III, was recrystallized from pyridine/water; 7.5 g (20 % on 3 steps), m.p. 154−155°C. (Found: C 40.38; H 4.43; N 10.58; I 32.95. Calc. for $C_{13}H_{16}IN_3O_3$: C 40.10; H 4.12; N 10.80; I 32.63.) NMR in pyridine-d_5: 7.20 τ (s, 3H, *N*-methyl), 6.5 τ (m, 2H, methylene), 6.37 τ (s, 3H, *O*-

methyl), 5.10 τ (q, 1H, 3-methine), 4.40 τ (m, 1H, 4-methine), 2.5 – 3.5 τ (m, 4H, aromatic), 2.6 τ (br, 1H, NH), 1.4 τ (br, 1H, N'H). IR_{KBr}: 3320 and 3280 cm^{-1} (NH), 1715 and 1685 cm^{-1} (CO). MS fragmentations: M (*m/e* 389), M – CH_3O, M – CH_3OCONH_2, M – CH_3-OCONHCONH, M – I.

N-Methylcarbamoyl-3,4-imino-1-methyl-1,2-dihydroquinoline (V). A solution of III (1.7 g, 0.005 mol) in benzene (100 ml) was added to a 50 % solution of NaOH in water (25 ml). The mixture was stirred for 3 days in the dark, the benzene layer separated and evaporated. The residue was extracted with ether, filtered, the filtrate washed with water, dried, concentrated, hexane added, set aside, filtered and the filtrate evaporated to give a viscous light yellow oil of high purity, 0.8 g (73 %). When the oil was left in the cold it slowly crystallized, m.p. 70 – 72°. (Found: C 65.70; H 6.31; N 12.50. Calc. for $C_{12}H_{14}N_2O_2$: C 66.05; H 6.42; N 12.84.) NMR in $CDCl_3$: 7.15 τ (s, 3H, *N*-methyl), 6.9 τ (m, 2H, methylene), 6.10 τ (s, 3H, *O*-methyl), 5.6 τ (m, 1H, 3-methine), 4.43 τ (d, 1H, 4-methine), 2.5 – 3.4 τ (m, 4H, aromatic). MS fragmentations: M (*m/e* 218), M – H, M – CH_3, M – CH_3OH_2, M – CH_2CO_2.

N-Methylcarbamoyl-1,2-imino-cyclohexane (IX). The conditions used were analogous to those in the synthesis of V (starting with 0.02 mol of VIII). After having carefully evaporated the benzene layer, the residue was distilled. The constant boiling fraction at 110 – 112°C/20 mm was separated, 2.5 g (80 %). (Found: C 61.83; H 8.46; N 8.87. Calc. for $C_8H_{13}NO_2$: C 61.95; H 8.39; N 9.03.) NMR in $CDCl_3$: 8.7 τ (m, 4H, 4,5-methylene), 8.1 τ (m, 4H, 3,6-methylene), 7.3 τ (m, 2H, 1,2-methine), 6.30 τ (s, 3H, *O*-methyl). MS fragmentations: M (*m/e* 155), M – H, M – CH_3, M – C_2H_4, M – CH_2CO_2.

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