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SHORT COMMUNICATION

FLUOROCYCLOHEXANES PART XIV [1] 1-H-DECAFLUOROCYCLOHEXYLAMINE

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SUMMARY

1-H-Decafluorocyclohexylamine (V) has been prepared from decafluorocyclohexene (I). (I) gave the corresponding epoxide (II) by reaction with alkaline hydrogen peroxide, reaction of (II) with fluoride ion in sulpholane yielded decafluorocyclohexanone (III). This then gave decafluorocyclohexylidene imine (IV), lithium aluminium hydride reduction affording the desired 1-H-decafluorocyclohexylamine (V).

INTRODUCTION

In a programme on the development of new anti-cancer agents, we are synthesising a range of fluorine-containing derivatives of drugs in current clinical use. In these analogues, fluorine-containing moieties are introduced at strategic positions, to exert influence on reactive sites, metabolic pathways, etc. Part of this work requires new fluorine-containing primary amines as intermediates.

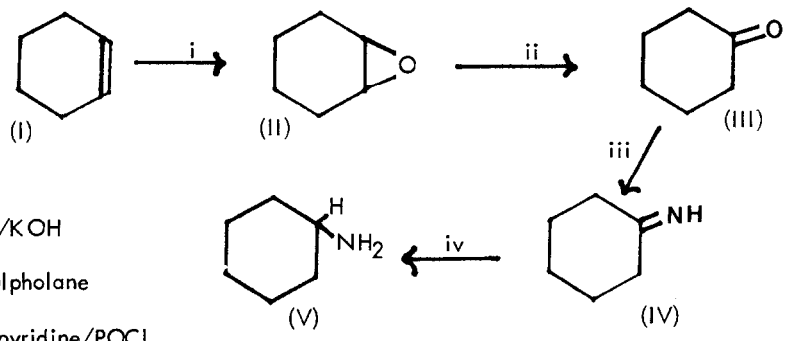
The groups $-CF_2-NH_2$ and $>CF-NH_2$ are unstable, though CF_3NH_2 in salt form has just been reported [2]. Structures of the type $(Rf)_3CNH_2$ are quite stable, and are exemplified by nonafluoro-tert-butyl amine [3], and undecafluorobicyclo[2,2,1]heptyl amine [4] (both made from acids via modified Curtius reactions), and by amines derived from oligomers of tetrafluoroethylene [5] (made by direct addition of ammonia). Amines of the type $RfCH_2NH_2$ have long been known; nucleophilic replacement by ammonia is difficult [6] and they are best made by reduction of cyanides [7] or of acid amides [8]. Related primary amines with one perfluoroalkyl group have been made by reduction of

acid amides [9] and by reaction of amino-acids with sulphur tetrafluoride in anhydrous hydrogen fluoride [10].

Few amines of the general type $(R_f)_2CHNH_2$ have been reported, though $(CF_3)_2CHNH_2$ has been made by reduction of hexafluoroisopropylidene imine [11]. We needed a cyclic example of this category, 1-H-decafluorocyclohexylamine $[CF_2]_5>CHNH_2$, as a drug analogue precursor. Amines of this type have not so far been reported.

RESULTS AND DISCUSSION

The route chosen was from decafluorocyclohexene (I) via decafluorocyclohexanone (III). This ketone (III) was first made in this Department [12] from (I) via



i H_2O_2/KOH

ii $F^{\ominus}$/sulpholane

iii NH_3/pyridine/$POCl_3$

iv $LiAlH_4$

ALL UNMARKED BONDS JOINED TO FLUORINE

alkoxy-derivatives, but this route was rather laborious, and we preferred now to develop the alternative approach of Moore and Milian [13]. Cyclo-alkene (I) was smoothly converted to its epoxide (II) using alkaline hydrogen peroxide essentially as described [13]. Rearrangement of (II) to ketone (III) was originally done by heated metal fluorides, but we found that better yields were obtained with potassium fluoride in dry sulpholane. The method of Krespan and Middleton [11], reaction with liquid ammonia and phosphorus oxychloride in pyridine, converted ketone (III) to decafluorocyclohexylidene imine (IV), though in our case it was necessary to distil the product through a short fractionating column to free it from phosphorus oxychloride. Imine (IV) was reduced with lithium aluminium hydride in diglyme to the desired 1-H-decafluorocyclohexylamine (V) [14].

Though this is the first cyclic amine of its type to be reported, we believe the preparative method should be general for many amines of this class.

EXPERIMENTAL

NMR Spectroscopy

All spectra were recorded on a Perkin Elmer R12B instrument; ^{1}H spectra at 60 MHz using TMS as internal reference, and ^{19}F spectra at 56.4 MHz using $CFCl_3$ as internal reference.

Mass spectra

These were measured on an A.E.I. MS9 instrument.

Epoxidation of decafluorocyclohexene

To a stirred mixture of decafluorocyclohexene (400 g), methanol (380 cm^3) and hydrogen peroxide (267 cm^3; 100 vol), maintained at -15°C, was added dropwise a 20% solution (992 cm^3) of potassium hydroxide in methanol. When the addition was complete ($3\frac{1}{2}$ hrs) the mixture was allowed to warm to room temperature and the lower layer separated, washed with water and dried ($MgSO_4$). Fractional distillation of the fluorocarbon layer, using a Fischer spaltrohr column gave decafluorocyclohexene epoxide (190.2 g) b.p. 54°C (cited [13] 53-55°).

Preparation of decafluorocyclohexanone from decafluorocyclohexene epoxide

A magnetically stirred mixture of decafluorocyclohexene epoxide (176 g), sulpholane (200 cm^3) and dry potassium fluoride (20 g) was heated under reflux on an oil bath maintained between 140° and 185° for $5\frac{1}{2}$ hrs. The resulting mixture was distilled to give a colourless distillate (170 g) b.p. 53 - 110° fractional distillation of which, using a 15 cm column packed with Dixon gauze rings, gave decafluorocyclohexanone (139 g) b.p. 54° (cited [12] 54°).

Preparation of decafluorocyclohexylidenimine from decafluorocyclohexanone

Dry pyridine (500 cm^3) was placed in a 3-necked 1 litre flask equipped with dropping funnel, stirrer and drikold condenser, and cooled to between -35 and -40°C. Addition of decafluorocyclohexanone (139 g) to the stirred pyridine resulted in the formation of a white precipitate. Stirring was maintained and liquid ammonia (12 cm^3) was distilled into the flask. When all the ammonia had been added the mixture was allowed to warm to room temperature and phosphorus oxychloride (73.8 g) was added dropwise with gentle heating. The mixture darkened and a marked rise in temperature was observed. Stirring was continued and the mixture heated between 90 - 100°C for 1 hr. Distillation of the mixture, using a 15 cm column packed with Dixon gauze rings, afforded a fraction b.p. 85 - 93°C which solidified on standing. The volatile, waxy solid was decafluorocyclohexylidenimine (nc) (103g) m.p. 41-42°C (Found: C, 25.8; H, 0.5; F, 68.2; N, 5.3. $C_6HF_{10}N$ requires C, 26.0; H, 0.4; F, 68.6; N, 5.0%), ν_{max} 3300 cm^{-1} (NH), m/e 277 ($C_6HF_{10}N$), its ^1H NMR spectrum consisted of a broad band (=NH) at 12.2δ and its ^{19}F NMR spectrum showed complex multiplets centred at 121.8, 123.5, 133.2 and 134.3 ppm in the relative intensity ratio of 1:1:1:2 respectively,

Preparation of 1-H-decafluorocyclohexylamine from decafluorocyclohexylidenimine

To a stirred suspension of lithium aluminium hydride (0.38 g) in dry diglyme (6 cm^3), cooled to 0°C, was added a solution of decafluorocyclohexylidenimine (2.77 g) in dry diglyme (6 cm^3). When the addition was complete the reaction mixture was allowed to warm to room temperature and stirred for a further 2hr. After the cautious addition of wet diglyme, followed by excess water, the resultant mixture was distilled in vacuo (0.1 mm). The distillate afforded a lower fluorocarbon layer (1.94 g) a portion (0.81 g) of which on separation by semi-preparative GLC (silicone gum SE30/Universal B; 80°C; N_2 61/h) gave (i) decafluorocyclohexylidenimine (0.1 g) with a correct IR spectrum; (ii) 1-H-decafluorocyclohexylamine (nc) (0.32 g) m.p. 43 - 44° (sealed tube) (Found: C, 25.5; H, 1.0; F, 68.6; N, 4.7. $C_6H_3F_{10}N$ requires C, 25.8; H, 1.1; F, 68.1; N, 5.0%), ν_{max} 3470 and 3395 cm^{-1} (NH_2), m/e 279 ($C_6H_3F_{10}N$), its ^1H NMR spectrum consisted of two broad bands at 1.75δ and 3.72δ in the intensity ratio of 2:1 respectively, complex signals in the ^{19}F NMR spectrum occurred between 120 and 150 ppm; (iii) diglyme (0.2 g) identified by GLC retention time.

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