SYNTHESIS OF 2-ETHYL-2-PHENYL-d_5-GLUTARIMIDE (GLUTETHIMIDE-d_5)

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SUMMARY

The synthesis of 2-ethyl-2-phenyl-d_5-glutarimide (glutethimide-d_5) and its mass fragmentometry is described.

KEY WORDS

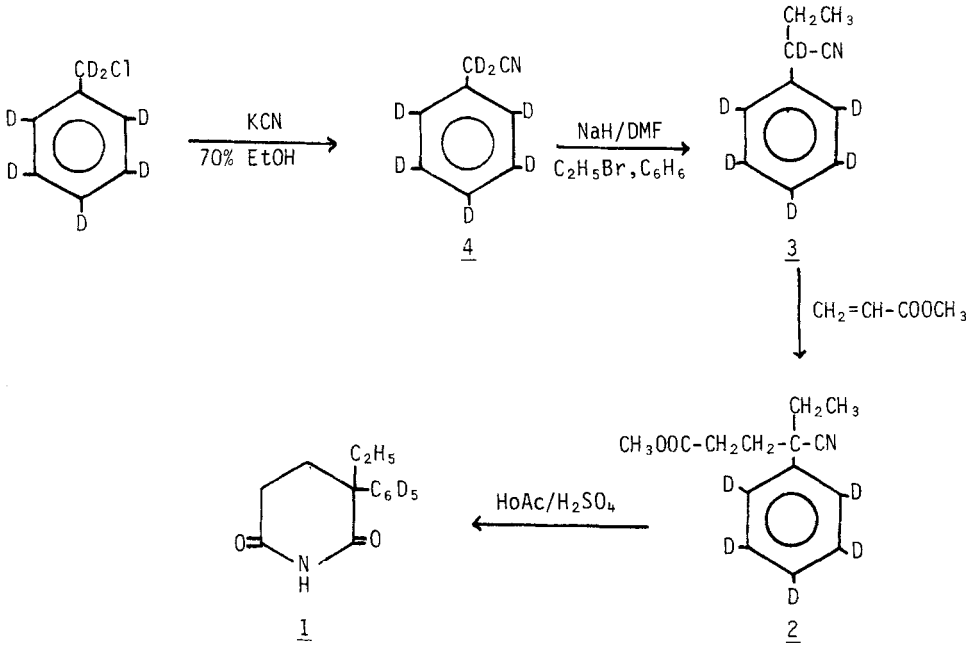
2-Ethyl-2-phenyl-d_5-glutarimide: synthesis and mass fragmentometry.
Glutethimide-d_5: synthesis and mass fragmentometry.

DISCUSSION

During an investigation aimed to develop an accurate, rapid, and quantitative method for determination of glutethimide and its metabolites in biological fluids using mass fragmentographic techniques, it was necessary to synthesize deuterated glutethimide (1) to be used as an internal standard for this analysis. The title compound 1 was prepared by direct cyclization of methyl 4-cyano-4-phenyl-d_5-hexanoate (2) in acid medium according to the method described by Paul, *et al.* [1]. Compound 2 was synthesized *via* the Michael addition of methyl acrylate to 2-phenyl-d_5-butyronitrile-2-d (3) in the presence of benzyltrimethyl-ammonium hydroxide as a catalyst.

Intermediates 4 and 3 were prepared from benzyl-d_7 chloride in high yields by substitution followed by C-alkylation with ethyl bromide in the presence of sodium hydride in dimethylformamide (See Scheme I).

The mass spectrum of the title compound (Figure 1) showed a molecular ion M^+ 222 (1.03%) and the base peak is at m/e 122. The fragmentation pattern was in support of that previously discussed by Rücker [2].



Scheme I

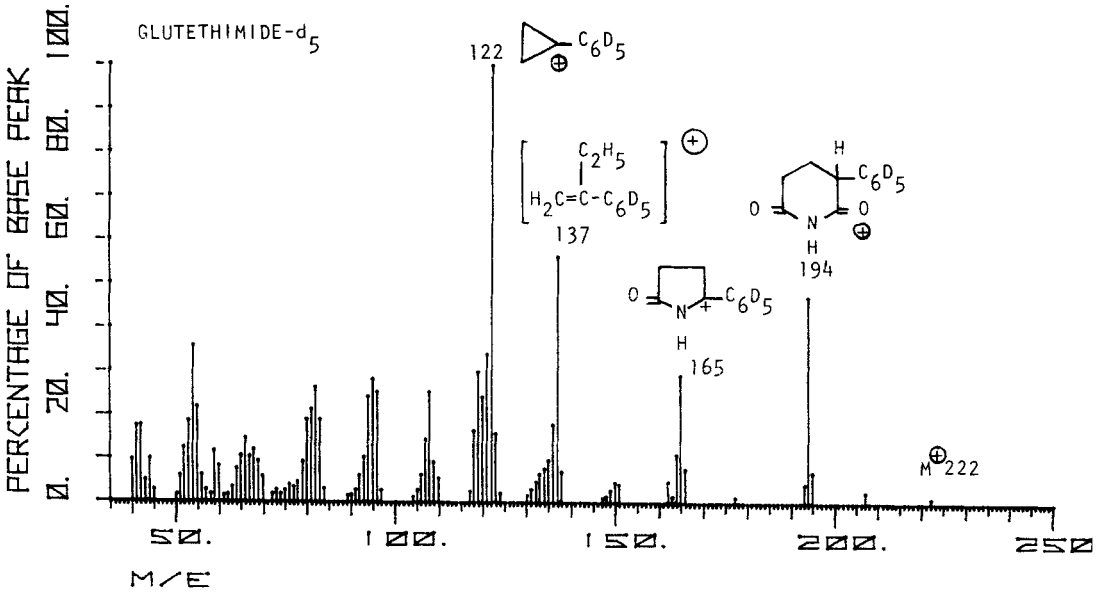


Figure 1

EXPERIMENTAL

Phenylacetonitrile-d_7 (4)--According to the method described by Bernhard, et al. [3], a mixture of 2.5 g (20 mmol) of benzyl-d_7-chloride (obtained from ICN Life Science Group, Irvine, CA with a purity of 93% atom d) and 1.5 g (23 mmol) potassium cyanide in 5 ml 70% ethanol was refluxed for 4 hr. The mixture was cooled in ice water and filtered. The filtered material was washed carefully with 10 ml of ethanol. The solvent was then distilled under reduced pressure and the remaining brown oil was distilled at 110-120° (12 mm) to give 2.15 g (91.8%) of colorless oil (reported [3] b.p. 100-120°, 10 mm).

2-Phenyl-d_5-butyronitrile-2-d (3)--A solution of 2.15 g (18 mmol) of 4 in 7 ml dimethyl formamide was cooled to -5°. A suspension of 0.46 g (19.2 mmol) sodium hydride in 5 ml of dry benzene was added dropwise. After one hr of stirring at room temperature, a solution of 2 g (18.3 mmol) ethyl bromide in 5 ml of dry benzene was added dropwise. The mixture was refluxed for 4 hr and the reaction mixture quenched with 10 ml of water and then extracted with ether (3 x 20 ml). The combined organic extracts were washed with water, dried over magnesium sulfate and the solvent evaporated under reduced pressure. The residue was distilled at 109-111° (10 mm) to yield 2.1 g (80.4%) of colorless oil (reported [3] b.p. 100-120°, 10-11 mm).

Methyl 4-Cyano-4-phenyl-d_5-hexanoate (2)--A solution of 2.1 g (14.5 mmol) of 3 and 1.25 g (14.5 mmol) of methyl acrylate in 20 ml of dioxane was maintained at 60-80° under nitrogen while 2.2 ml of benzyltrimethylammonium hydroxide (40% in methanol) was added dropwise. Upon completion of the addition, the dark solution was refluxed 19 hr. The reaction mixture was shaken twice in t-butyl alcohol to take up the base and concentrated in vacuo. Water was added and the reaction mixture was extracted in ether (3 x 20 ml). The combined ether extracts were dried over magnesium sulfate, filtered and evaporated under reduced pressure to yield a dark brown oil which was distilled at 160-180° (12 mm) to give 2.66 g (80%) of a yellow oil.

2-Ethyl-2-phenyl-d_5-glutarimide (Glutethimide-d_5) (1)--To a solution of 2.66 g (11.5 mmol) of 2 in 25 ml of glacial acetic acid, 10 ml of 85% concentrated sulfuric acid was added in portions at an initial temperature of 70°. During addition the temperature rose to 100-110°. The mixture was maintained at this temperature for 30 min, cooled and poured into ice and adjusted to pH 8.0 with 10% sodium hydroxide. The alkaline mixture was extracted with methylene chloride (3 x 25 ml). The combined methylene chloride extracts were washed with water, dried over magnesium sulfate and evaporated to yield an oily residue which solidified on standing and recrystallized from isopropyl alcohol to yield 500 mg (20%) of a colorless solid, m.p. 80-82°, mass spectrum is shown in Figure 1. The compound was chromatographically pure (a Varian Aerograph series 1400 gas chromatograph was employed) and had a retention time of 3.2 min. The column used was 3% OV-1 on Gas Chrom Q, 6 feet by ¼ inch; injector, column, and detector temperatures were 250°, 205°, and 250°, respectively. The gas flow rates were: hydrogen, 20 ml/min; air, 200 ml/min; and nitrogen as a carrier gas, 20 ml/min. The mass spectrum was determined on a Finnigan Model 1015 quadrupole instrument. The conditions at which the mass spectrum was taken were: electron energy, 70 eV; emission current, 500 μa; H.V. power supply, 3 KV; sensitivity, 10^{-7}; scan time, 1 sec.; inlet, GC.

REFERENCES

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3. K. Bernhard, M. Just, J.P. Vuillenmier, and G. Brubacher, Helv. Chim. Acta 39, 596 (1956).