SYNTHESES OF PIPERIDINE AND GRANATANINE DOUBLY ISOTOPICALLY SUBSTITUTED WITH CARBON-13

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SUMMARY

Syntheses of (2,3-$^{13}C_2$)piperidine and (1,2-$^{13}C_2$)granatanine via (1,2-$^{13}C_2$)-glutaric acid have been achieved using a benzene ring as a potential carboxyl group.

Keywords: Piperidine, glutaric acid, granatanine, carbon-13.

As part of a study of conformational equilibria in amines using the dependence of one bond carbon-carbon coupling constants ($^1J_{CC}$) on torsion angles about N-C bonds[1] we required a number of cyclic amines with adjacent carbon atoms isotopically substituted with ^{13}C. Key compounds were (2,3-$^{13}C_2$)-piperidine and (1,2-$^{13}C_2$)granatanine (9-azabicyclo-[3,3,1]-nonane) and their derivatives, all of which were derived from (1,2-$^{13}C_2$)glutaric acid (**6**). The synthesis of the latter proved to be less straightforward than anticipated. The successful route depended upon an uncommon use of a phenyl substituent as a potential carboxyl group in (1,2-$^{13}C_2$)glutaric acid. The synthesis of (2,3-$^{13}C_2$)piperidine (**8**) is outlined in Scheme 1:

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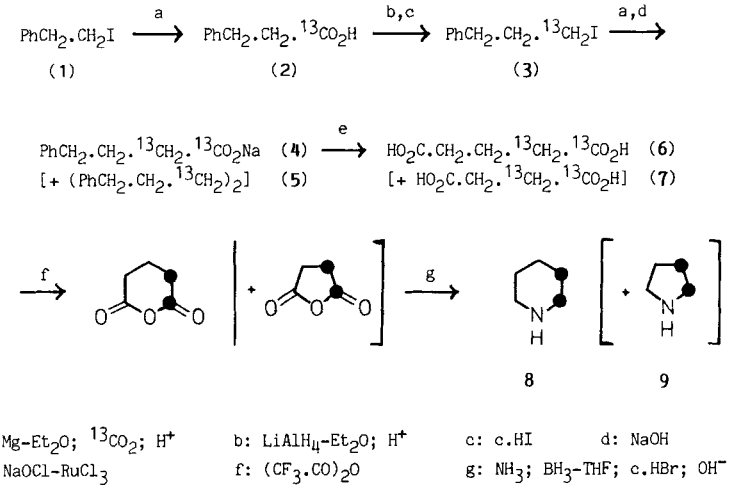
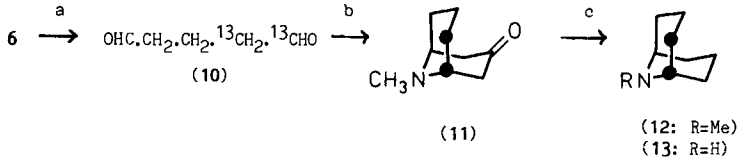


Scheme 1 (filled circles indicate isotopic substitution at ring carbon atoms)

A curious feature of the reactions in Scheme 1 is that the formation of the Grignard reagent from 1-iodo-3-phenylpropane (**2**) gave about 30% of 1,6-diphenylhexane (**5**) whereas 1-iodo-2-phenylethane (**1**) gave no significant amount of 1,4-diphenylbutane. The ruthenium catalysed oxidation[2] of **4** gave some succinic acid (**7**, ~15%) showing that some oxidation of the side chain occurs, a side reaction that does not seem to have been observed before. The amount of succinic acid may be reduced to <2% by repeatedly crystallising the crude glutaric acid from benzene but the recovery of glutaric acid is only about 60%. For our purposes, however, the presence of succinic acid was not harmful in the synthesis of (2,3-$^{13}C_2$)piperidine (**8**). As might be expected, (1,2-$^{13}C_2$)succinic acid imitated (1,2-$^{13}C_2$)glutaric acid in this synthesis so that (2,3-$^{13}C_2$)piperidine (**8**) and its derivatives[1] were accompanied by ~15 mol% of (2,3-$^{13}C_2$)pyrrolidine (**9**) and its derivatives (identified by a comparison of the chemical shifts observed in the mixtures with chemical shifts measured using authentic unlabelled samples) and this allowed additional coupling constants to be measured. Purified (1,2-$^{13}C_2$)glutaric acid was used in the synthesis of the bicyclic amines **12** and **13**.

More obvious routes to (1,2-$^{13}C_2$)glutaric acid than that given in Scheme 1 were considered. Alkylation (with either allyl or but-3-en-1-yl halides) of lithiated esters or salts of acetic acid[3] was rejected because the yields tend to be low with derivatives of acetic acid compared with higher acids and an excess of the acid derivative is commonly used. A synthesis analogous to that in Scheme 1 but based on Grignard reagents derived from 4-bromobut-1-ene and from 5-bromo-(5-^{13}C)pent-1-ene was thwarted by mediocre yields in several steps.



a: $(COCl)_2/Et_3N$; $Cu(Ph_3P)_2BH_4/Ph_3P$ b: Robinson-Schopf synthesis[4,5]
c: Huang-Minlon[9] reduction (to **12**); PhSeH at 150°

Scheme 2

The preparation of the bicyclic amines (Scheme 2) relied on the long known biomimetic synthesis of pseudopelletierine (9-methyl-9-azabicyclo[3,3,1]nonan-3-one) (**11**) from glutardialdehyde (pentane-1,5-dial; **10**).[4,5] It was not found to be possible to oxidise pentan-1,5-diol to the dialdehyde using a variety of selective oxidising agents. We therefore turned to the partial reduction of glutaroyl chloride. Glutaric acid was converted into its acid chloride by oxalyl chloride and triethylamine. This combination of reagents has not been reported before but is similar to thionyl chloride and pyridine.[6] It has the advantage of not producing byproducts that were found to reduce yields in the chemical reduction using the Fleet reagent[7] as well as preventing catalytic hydrogenation[8] completely. The yields of isotopicaly normal glutardialdehyde, as a solution in water, were estimated by conversion to the 2,4-dinitrophenylhydrazone. The yields in the preparation of pseudopelletierine (**11**) were found to be considerably better using the dialdehyde formed by chemical reduction, than by hydrogenation, apparently because of small amounts of dimethylaniline from the latter. The crude crystalline (2,3-$^{13}C_2$)pseudopelletierine isolated after step c in Scheme 2 was not purified because recrystallisation leads to losses and reduces the overall yields of **12** (by reduction[9]) and **13** (by demethylation[10] of **12**). It is worth noting that the amines **12** and **13** were dried by sublimation from excess BaO at low pressure and had m.p.s considerably higher and sharper than those previously published. Similar increases in the m.p.s of saturated amines dried with barium oxide have been noted in this laboratory. High field carbon n.m.r. studies of isotopically labelled **12** and **13** showed that each contained 1-2% of the other and no more than about 1% of isotopically substituted impurities which may be derivatives of tropane (no positive identification was made). We have not determined whether the trace of **13** present in **12** was formed by demethylation during the Huang-Minlon reduction of pseudopelletierine or originated in traces of ammonium chloride in the methylammmonium chloride, which was purified by crystallisation, used in the synthesis.

EXPERIMENTAL

Reactions were developed using isotopically normal compounds and products, all of which have been reported in the literature, were purified and characterised in standard ways. Except for **12** and **13** isotopically substituted compounds were not fully purified, although the properties of the target compounds showed that good chemical purity as well as specificity in labelling had been achieved, but were characterised spectroscopically by comparison with the isotopically normal species at the same stage of puification.

Carboxylations:- Grignard reagents (~.5-1M) were prepared from the halide (**1** or **3**) and Mg in equivalent amounts in ether in a simple vacuum line. $^{13}CO_2$ was prepared by heating $Ba^{13}CO_3$ (90 at% ^{13}C) with an excess of lead(II) chloride at 10^{-3} mm (yield taken to be quantitative) and condensed directly onto Grignard reagents at -196°. The mixtures were allowed to melt and carboxylation of the Grignard reagent took place at -20 to -30° during 1-2 hours. The mixture was allowed to warm to room temperature and acidified. The ethereal layer was washed with water and titrated with 1M sodium hydroxide to a phenolphthalein endpoint. The resulting solution of the sodium salt was evaporated to dryness for storage. When required the free acid was obtained by acidification of the sodium salt and isolated by extraction with ether. The salts of the isotopically substituted acids were characterised by their ^1H and ^{13}C n.m.r. spectra. The yields of the sodium salts of the acids were 85% (**2** from **1**) and 60% (**4** from **3**).

1-Iodo-3-phenyl(1-^{13}C)propane. 3-Phenyl(1-^{13}C)propanoic acid (14.0 g) was reduced (2 h) with lithium aluminium hydride (4 g) in boiling ether (100 ml). The mixture, cooled in an ice bath, was treated with sulphuric acid (2M, 100 ml) and the resulting ethereal solution of 3-phenyl(1-^{13}C)propanol was washed, dried and concentrated to remove ether. The crude product (12.5 g) was boiled under reflux (2 h) with hydriodic acid (d. 1.94, 125 ml), cooled, diluted with water, and extracted with pentane (3 x 20 ml). The extracts were washed with 2% KOH, filtered through a short column of alumina, dried, and distilled to give 1-iodo-3-phenyl(1-^{13}C)propane, b.p. ~40°/0.001 mm (19.7 g, 87%).

(1,2-$^{13}C_2$)Glutaric acid. Sodium hypochlorite (1.47M, 218 ml) was added to sodium 4-phenyl(1,2-$^{13}C_2$)butanoate (4.32 g, 23 mmol) and ruthenium(III) chloride (0.023 g) in water (312 ml). After 40 hr. the pH was adjusted to 2 and the solution was flushed with nitrogen for 1 hr. Sodium hydroxide (2 g) and hydrogen peroxide (33%, 40 ml) were added and after 1 day the mixture was acidified with hydrochloric acid (5M) to pH=1 and the water was removed by

distillation followed by drying in a vacuum desiccator. The residual solids were ground to a fine powder and extracted with dry ether (200 ml) in a Soxhlet extractor (5 hr.), the extraction being twice interrupted to allow the solid matter to be reground. Evaporation of the ether left (1,2-$^{13}C_2$)glutaric acid (2.575 g, 83%) containing approximately 15% of (1,2-$^{13}C_2$)succinic acid.

(2,3-$^{13}C_2$)Piperidine. (1,2-$^{13}C_2$)Glutaric acid (not purified; 1.206 g, 9 mmol) was treated for 45 min. with trifluoracetic anhydride (10 ml), the excess of the latter was evaporated, and the solid residue was dissolved in dichloromethane (30 ml) and poured into liquid ammonia (50 ml). The solvents were evaporated and the residue in hydrochloric acid (2M, 60 ml) was washed with ether and water was evaporated (at 20 mm). The residue was stirred with brine (10 ml) and water was removed. This was repeated to give a product friable enough to be ground and extracted with ether in a Soxhlet extractor to give the crude (1,2-$^{13}C_2$)glutaric acid monoamide (1.022 g, 85%). The latter (1.0 g) in tetrahydrofuran (65 ml) containing diborane (50 mmol) was boiled under reflux (5 hr.), more diborane (15 ml of a 1M solution in tetrahydrofuran) was added and boiling continued (10 hr.). Excess diborane was destroyed with methanol. After the addition of hydrobromic acid (48%; 1.2 ml) the solvents were removed under reduced pressure, more hydrobromic acid (48%; 10 ml) was added and the mixture was briefly boiled. The mixture was diluted with water, made strongly alkaline with potassium hydroxide and distilled in steam. The distillate was neutralised with hydrochloric acid (1M; 3.7 ml) and water was removed by distillation under reduced pressure followed by addition of methanol (ca. 5 ml, twice), which was removed by distillation leaving (2,3-$^{13}C_2$)piperidinium chloride (0.51 g, 48%) containing 15% of (2,3-$^{13}C_2$)pyrrolidinium chloride.

N-Methyl(1,2-$^{13}C_2$)granatanine [9-Methyl-9-azabicyclo(1,2-$^{13}C_2$)[3,3,1]-nonane]. (1,2-$^{13}C_2$)Glutaric acid (1.34 g, 10 mmol) was warmed with oxalyl chloride (4 ml) and 2 drops of triethylamine until effervescence ceased and then was boiled under reflux (2.5 hr.) before the excess oxalyl chloride was removed in vacuo. The crude (1,2-$^{13}C_2$)glutaroyl chloride in acetone (10 ml) was added (10 min) to a stirred slurry of bis(triphenylphosphine)copper(I) tetrahydroborate[7] (13.26 g, 22 mmol) and triphenylphosphine (11.53 g, 44 mmol) in acetone (40 ml). The mixture was stirred at room temperature (2 hr.) and filtered, the filter cake being washed with water (50 ml) and the combined filtrate and washings was refiltered. Acetone was removed at <20° under reduced pressure leaving a solution of (1,2-$^{13}C_2$)glutardialdehyde in water (35 ml). The yield of glutardialdehyde was estimated as 60% (by isolation of the 2,4-dinitrophenylhydrazone) in experiments with isotopically normal glutaric acid.

Methylammonium chloride (recrystallised from ethanol; 1 g, 14.8 mmol), 1,3-acetonedicarboxylic acid (freshly crystallised from ethyl acetate; 1.66 g, 11.4 mmol), disodium hydrogen phosphate (0.71 g, 5 mmol) and sodium hydroxide (0.144 g, 3.6 mmol) were added to the aqueous solution of (1,2-$^{13}C_2$)glutardialdehyde and the resulting solution was stirred under nitrogen (20 h). Hydrochloric acid (d. 1.18; 0.67 ml) was added and solution was stirred at 70-80° until evolution of CO_2 ceased (1 h), made alkaline with sodium hydroxide (1.5 g) and immediately extracted with dichloromethane (5 x 30 ml). The combined extracts were shaken successively with sodium sulphate and neutral alumina, filtered and the solvent was removed under reduced pressure to give crude crystalline (1,2-$^{13}C_2$)pseudopelletierine (0.45 g, 65%). The latter, if it is to be kept, may be purified[5] but this decreases the overall yields of **12** and **13**.

The pseudopelletierine was immediately treated with hydrazine hydrate (1.5 ml) and diethylene glycol (12 ml). The mixture was boiled under reflux (10 min), cooled, and treated with potassium hydroxide (1.5 g) and more hydrazine hydrate (0.7 ml) before being slowly distilled until the stillhead temperature reached 200°. The distillate was extracted with pentane (2 x 50 ml), each extract being washed with water (3 ml), and the combined pentane extracts were titrated with hydrochloric acid (methyl orange endpoint) to give an aqueous solution of N-methyl(1,2-$^{13}C_2$)granatanine hydrochloride (2 mmol, 20% from (1,2-$^{13}C_2$)glutaric acid). The amine was liberated by an excess of sodium hydroxide, purified by steam distillation, and reconverted once more into the hydrochloride, from which it was isolated by treatment with concentrated potassium hydroxide solution followed by sublimation (0.001 mm) from an excess of barium oxide. The sample purified in this way had a m.p. 52-52.5° (lit.[11] 49-50°). Carbon n.m.r. (see discussion) indicated traces (1-2%) of (1,2-$^{13}C_2$)granatanine and another doubly isotopically labelled compound that may have been N-methyltropane.

(1,2-$^{13}C_2$)Granatanine [9-azabicyclo(1,2-$^{13}C_2$)[3,3,1]nonane]. N-Methyl(1,2-$^{13}C_2$)granatanine (0.127 g, 0.90 mmol) and benzene selenol (0.2 ml) were sealed in a tube under nitrogen and heated at 150° (48 h). After cooling the tube was opened and the contents were extracted several times with ether and water. After acidification (to pH=1) the aqueous layer was distilled in steam to remove non-basic volatile material and the (1,2-$^{13}C_2$)granatanine was isolated and purified by the methods used for **12** (above) and then had m.p. 73-73.5° (lit.[12] 50-60°). Carbon n.m.r. indicated that the demethylation was 98-99% complete.

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References

1) J.C.J. Barna and M.J.T. Robinson, to be submitted for publication.

2) S. Wolfe, S.K. Hasan, and J.R. Campbell, J. Chem. Soc. Chem. Comm.: 1420 (1970).

3) D. Ivanov, G. Vassilev, and I. Panayotov, Synthesis: 83 (1975).

4) R.C. Menzies and R. Robinson, J. Chem. Soc. **125**: 2163 (1924).

5) A.C. Cope, H.L. Dryden, and C.F. Howell, Organic Syntheses Coll. Vol. IV, ed. N. Rabjohn, Wiley, New York, p. 816 (1963).

6) J. Cason and E.J. Reist, J. Org. Chem. 1958: **23**, 1492 (1958).

7) G.W.J. Fleet and P.J.C. Harding, Tetrahedron Letters: 975 (1979).

8) H.B. White, L.L. Sulya, and C.E. Cain, J. Lipid Research **8**: 158 (1967).

9) See, eg, L.J. Durham, D.J. McLeod, and J. Cason, Organic Syntheses Coll. Vol. IV, ed. N. Rabjohn, Wiley, New York, p. 510 (1963).

10. H.J. Reich and M.L. Cohen, J. Org. Chem. **44**: 3148 (1979).

11. G. Ciamician and P. Silber, Ber. **26**: 2738 (1893).

12. G. Ciamician and P. Silber, Ber. **27**: 2850 (1894).