Convenient Preparations of Deuterium-substituted Furan-, Thiophen-, and N-Methylpyrrole-2-carboxylic Acids, and of Tetradeuteriofuran

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Deuterium-substituted furan-, thiophen-, and N-methylpyrrole-2-carboxylic acids are conveniently prepared by heating the corresponding protio-acids with sodium deuterioxide in deuterium oxide; the 3,4,5-trideuteriofuran-2-carboxylic acid so obtained is readily converted into tetradeuteriofuran.
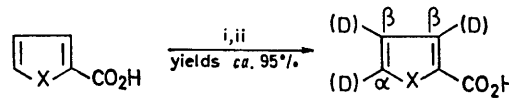
FOR spectrometric work[1] we required derivatives of simple heterocyclic systems deuteriated at various nuclear positions: to our knowledge there is little information about such compounds in the literature. Kinetic work has shown that the isotopic atoms of deuterium-labelled furan and thiophen can be removed in very strongly basic media (*e.g.* potassium t-butoxide in dimethyl sulphoxide),[2] and that the 5-hydrogen atom of 2-substituted thiophens can be exchanged by use of potassium methoxide in deuteriomethanol.[3] Recently Zoltewicz and Jacobson[4] prepared 5-deuterio-furan-2- and -thiophen-2-carboxylic acids (52 and 63% yields, respectively) by heating the protio-acids with deuterium oxide and sodium carbonate at 165 °C under pressure; when furan-2- and thiophen-2-carboxylic [2H]acids were heated at 250 °C the label was distributed between the carboxy-group and the 3- and 5-positions, but this process was accompanied by extensive decarboxylation (74% with the furoic acid). These reports suggested that base-catalysed exchange reactions might provide a general route to deuteriated heterocyclic compounds; there appeared to be less scope with acid-catalysed exchange.[5,6]

The present work stemmed from the observation, disappointing at first sight, that saponification of t-butyl 5-deuteriofuran-2-carboxylate gave a mixture of the (required) 5-deuterio-acid and the 5-protio-analogue. Partial saponification established that the hydrolysis is faster than the isotopic exchange reaction, suggesting that the latter occurs *via* the carboxylate ion. The implication, that the ring hydrogen atoms of heterocyclic 2-carboxylic acids can be exchanged by deuterium under basic conditions, is substantiated by the results shown in the Scheme.

Under the conditions specified in the Scheme, exchange occurred readily at all three nuclear positions of furan-2-carboxylic acid and fairly readily at the α-position of the thiophen acid; the β-hydrogens of the thiophen acid and the α-hydrogens of the N-methylpyrrole acid exchanged slowly, but the β-hydrogens of the latter were not replaced. N.m.r. examination

established the positions of the deuterium atoms in the products and the compositions of the mixtures obtained

SCHEME

Reagents: i, Excess of 40% NaOD in D_2O, reflux for x hours; ii, HCl aq. at 20°; iii, 40% NaOEt in EtOD, reflux; iv, 40% NaOH in H_2O, reflux; v, Na salt + $HgCl_2$; vi, $DCl–D_2O$
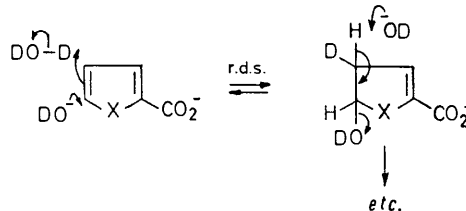
Extent (%) of deuteriation:

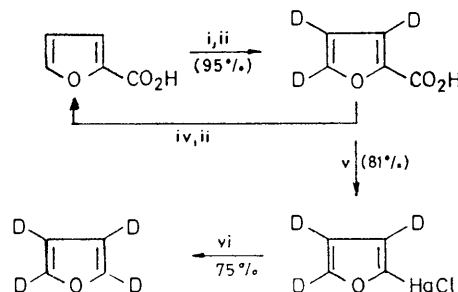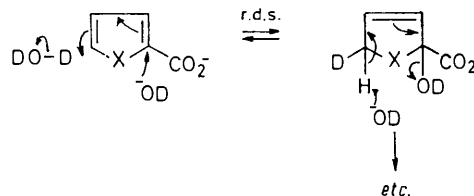| Reagents	Starting materials	x	α-position	β-position*
i, ii	(I; X = O)	2·5	94	88
		16	95	92
	(I; X = S)	2·5	90	25
		145	95	60
	(I; X = NMe)	2·5	30	0
		48	95	0
	Benzoic acid	48	(no deuteriation detected)	
iii	2-p-Bromophenylfuran	16	50 (yield 54%)	0
	Ethyl furan-2-carboxylate		(extensive decomposition)	

* Average value (see text).

Relative rates of exchange reactions: X = O, α-H > X = S, α-H ≈ X = O, β-H > X = NMe, α-H > X = S, β-H (> X = NMe, β-H).

For α- and β-deuteriation

Or, for α-deuteriation (especially with furan-2-carboxylic acid)

[1] D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J.C.S. Perkin I*, 1972, 1959.

[2] References in, 'Deuterium Labelling in Organic Chemistry,' A. F. Thomas, Meredith Corporation, New York, 1971, p. 64.

[3] N. N. Zatsepina, Yu. L. Kaminskii, and I. F. Tupitsyn, *Reakts. spos. org. Soedinenii*, 1969, **6**, 448.

[4] J. A. Zoltewicz and H. L. Jacobson, *J. Heterocyclic Chem.*, 1971, **8**, 331.

[5] E. J. Stanhuis, W. Drenth, and H. van den Berg, *Rec. Trav. chim.*, 1964, **83**, 167.

[6] F. Mönnig, H. Dreizler, and H. D. Rudolph, *Z. Naturforsch.*, 1965, **20**, 1323.

after various times; the results of elemental and mass spectral analyses, although not so precise, were in good agreement. The figures for β-deuteriation (Scheme) are the average values for positions 3 and 4. Exchange was faster at position 4 than at position 3 with furan-2-carboxylic acid, but no difference between the rates was detected with thiophen-2-carboxylic acid. Attempts to use other solvents for neutral compounds which are insoluble in the alkaline deuterium oxide have been only moderately successful (for example, ethyl furan-2-carboxylate decomposed when heated with 40% sodium ethoxide in deuterioethanol), but further investigations into this possibility are in progress.

The exchange reactions of the heterocyclic acids are reversible, and approximately first-order with respect to deuteroxide. Although there is no contrary evidence we feel that proton abstraction from the carboxylate anion is unlikely: the mechanisms (Scheme) involving nucleophilic addition appear at least as attractive as other obvious possibilities. The practical outcome is that various deuteriated heterocyclic acids can be made conveniently (apart from the dilapidation of glass flasks) and in high yield. One application, the synthesis of tetradeuteriofuran, is shown at the bottom of the Scheme.

EXPERIMENTAL

N.m.r. spectra were recorded at 60 or 100 MHz for solutions in CCl_4 or $CDCl_3$. For signals other than singlets (s) or doublets (d), the number of lines is indicated by an italicised number. The description is followed by J values, or apparent J values (in Hz) as explained in ref. 7.

The solutions used for deuterium exchange were prepared by the gradual addition of Na (freshly cut into small pieces as required; 1·8 g) to D_2O (99·8% material; 5 ml) or to EtOD (96% material; 10 ml) contained in a dry two-necked flask carefully guarded from atmospheric moisture.

Exchange of (a) Furan-2-carboxylic Acid.—A solution of the acid [τ $(CDCl_3)$ −1·96 (s, CO_2H), 2·30 (4, J 0·8 and 1·8, 5-H), 2·62 (4, J 0·8 and 3·2, 3-H), and 3·40 (4, J 1·8 and 3·2, 4-H)] (1 g) in NaOD–D_2O (8 ml) was boiled under reflux for 16 h, cooled, and acidified with 5N-HCl. The material isolated with EtOAc was sublimed at 12 mmHg to give 3,4,5-trideuteriofuran-2-carboxylic acid (975 mg), m.p. 129—130° [Found: C, 52·6; $(H_2O + D_2O)$, 33·4. $C_5HD_3O_3$ requires C, 52·2; $(H_2O + D_2O)$, 33·9%]; τ $(CDCl_3)$ −2·03 (s, CO_2H) (82·7% of total absorption), 2·30 (4, J 0·8 and 1·8, 5-H) (4·1%), 2·62 (4, J 0·8 and 3·2, 3-H) (8·3%), and 3·40 (4, J 1·8 and 3·2, 4-H) (4·9%); m/e 115 (M^+, 98%) and 98 (100). A similar experiment in which the boiling was stopped after 2·5 h gave material (952 mg), m.p. 129—130°, with τ $(CDCl_3)$ −1·28 (s, CO_2H) (76·9% of total absorption), 2·30 (4, J 0·8 and 1·8, 5-H) (4·6%), 2·62 (4, J 0·8 and 3·2, 3-H) (11·5%), and 3·40 (4, J 1·8 and 3·2, 4-H) (6·9%).

A solution of 3,4,5-trideuteriofuran-2-carboxylic acid (1 g) in NaOH (5·3 g)–H_2O (8 ml) was boiled under reflux for 20 h. Work-up as previously gave material (960 mg), m.p. 129—130°, identical (n.m.r. and mass spectra) with furan-2-carboxylic acid.

(b) Thiophen-2-carboxylic Acid.—This acid [τ $(CDCl_3)$ −2·02 (s, CO_2H), 2·14 (4, J 1·3 and 3·9, 3-H), 2·40 (4, J 1·3 and 5·1, 5-H), and 2·90 (4, J 3·9 and 5·1, 4-H)] (200 mg) was boiled with NaOD–D_2O (3 ml) for 145 h and worked up as previously to give material (184 mg), m.p. 125—127°, with τ $(CDCl_3)$ −1·98 (s, CO_2H) (54·1% of total absorption), 2·14 (complex, 3-H) (21·6%), 2·40 (complex, 5-H) (2·7%), and 2·90 (complex, 4-H) (21·6%). A similar exchange reaction, stopped after 2·5 h, gave material (174 mg) with τ $(CDCl_3)$ −1·96 (s, CO_2H) (38·5% of total absorption), 2·14 (complex, 3-H) (28·8%), 2·40 (complex, 5-H) (3·9%), and 2·90 (complex, 4-H) (28·8%).

(c) N-Methylpyrrole-2-carboxylic Acid.—This acid [τ $(CDCl_3)$ −0·78 (s, CO_2H), 2·92 (4, J 1·8 and 4·0, 3-H), 3·19 (overlapped 4, J 1·8 and 2·6, 5-H), 3·86 (4, J 2·6 and 4·0, 4-H), and 6·08 (s, CH_3)] (200 mg) treated as in (b) for 48 h, gave 5-deuterio-N-methylpyrrole-2-carboxylic acid (184 mg), m.p. 130—132° [Found: C, 56·8; N, 10·8; $(H_2O + D_2O)$, 49·5. $C_6H_6DNO_2$ requires C, 57·1; N, 11·1; $(H_2O + D_2O)$, 50·8%]; τ $(CDCl_3)$ −0·50 (s, CO_2H) (16·5% of total absorption), 2·92 (d, J 4·0, 3-H) (16·5%), 3·18 (complex, 5-H) (0·9%), 3·88 (d, J 4·0, 4-H) (16·5%), and 6·08 (s, CH_3) (49·6%); m/e 126 (M^+, 100%). A similar reaction, stopped after 2·5 h, gave material (178 mg) with τ $(CDCl_3)$ −1·40 (s, CO_2H) (14·9% of total absorption), 2·92 (complex, 3-H) (14·9%), 3·18 (complex, 5-H) (10·5%), 3·88 (complex, 4-H) (14·9%), and 6·08 (s, CH_3) (44·8%).

(d) 2-p-Bromophenylfuran.—A solution of this compound [τ (CCl_4) 2·53 (complex, phenyl and 5-H), 3·41 (4, J 0·8 and 3·3, 3-H), and 3·57 (4, J 1·8 and 3·3, 4-H)] (200 mg) in 40% NaOEt in EtOD (3 ml) was boiled under reflux for 16 h, cooled, acidified with 2N-HCl, and extracted with C_6H_6. The C_6H_6 solution was filtered through Al_2O_3 (5% de-activated; 10 g) and evaporated. Sublimation in vacuo of the residue gave material (108 mg), m.p. 80—83°, τ (CCl_4) 2·53 (complex, phenyl and 5-H) (69·2% of total absorption), 3·41 (complex, 3-H) (15·4%), and 3·57 (complex, 4-H) (15·4%).

(e) Ethyl Furan-2-carboxylate.—Treatment of this ester (200 mg) as in (d) gave a dark solution; the mixture obtained after work-up appeared to consist largely of polymerised material.

Tetradeuteriofuran.— 3,4,5-Trideuteriofuran-2-carboxylic acid (1 g) was dissolved in NaOH (0·35 g)–H_2O (4 ml) at 20 °C. Saturated $HgCl_2$ aq. (54 ml) was added; the mixture was boiled until the evolution of CO_2 ceased, and then cooled. The insoluble material (the 2-mercuri-chloride) was collected, and dried for 5 days (desiccator; conc. H_2SO_4). The dry solid was heated at 80 °C with 20% DCl in D_2O (5 ml), volatile material being collected over anhydrous K_2CO_3. Distillation at 35 °C (bath temp.) gave tetradeuteriofuran (200 mg). This compound was shown to be deuteriated to the extent of at least 94% by a comparison of its n.m.r. signals with those of a solution containing a known concentration of furan.

7 M. G. Combe, W. A. Denny, G. D. Meakins, Y. Morisawa, and E. E. Richards, J. Chem. Soc. (C), 1971, 2300.