

4-Iodo- and 4-Cyanopyrrole-2-carboxaldehydes

Philip E. Sonnet

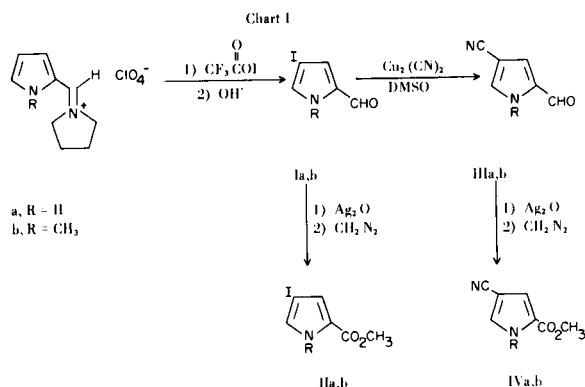
Agricultural Environmental Quality Institute, Agricultural Research Center,
Agricultural Research Service, USDA, Beltsville, Maryland 20705

Received September 20, 1972

Recently we reported the synthesis of 4-iodo-2-pyrrole-carboxaldehyde (Ia) (1). We also found that various 4-substituted-2-pyrrolecarboxaldehydes and carboxylic acid methyl esters elicited a trail-following response from the Texas leaf-cutting ant, *Atta texana* (Buckley) (2). An improved preparation of the iodoaldehyde was therefore sought which would allow examination of the iodoaldehyde and its corresponding methyl carboxylate. In addition, the iodide might serve as the source of other transformation products suitable for screening.

Treatment of 1-(pyrrol-2-ylmethylene)pyrrolidinium perchlorate and the *N*-methyl analog with trifluoroacetyl hypiodite in nitromethane-1,2-dichloroethane followed by hydrolysis of the iodinated salts gave the 4-iodo derivatives (I) in 55% yield, essentially free of the 5-iodoaldehyde and the 4,5-diiodoaldehyde. Similar treatment of the morpholinium perchlorate of 2-pyrrolecarboxaldehyde, a compound that appears to be less reactive in electrophilic substitution, provided the 4-iodoaldehyde in 59% yield. The aldehydes were oxidized to the acids with silver oxide and then esterified with diazomethane to the methyl carboxylates, II. Direct iodination of methyl 2-pyrrolecarboxylate with trifluoroacetyl hypiodite gave primarily the 4,5-diiodoester.

Although reduction of iodinated pyrroles by copper in acetic acid is generally quite successful (3), the reduction of Ia gave 2-pyrrolecarboxaldehyde in only 35% yield. The reduction of Ib and its pyrrolidinium iodide was more difficult, and glc evidence for conversion to 1-methyl-2-pyrrolecarboxaldehyde was obtained only after refluxing Ib in quinoline with copper. Accordingly, we expected other reactions catalyzed by copper to be only marginally successful. Indeed the several attempted Ullmann-type condensations failed (4) (*e.g.*, self-condensation in DMF and condensation with *m*-dinitrobenzene in quinoline with cuprous oxide). However, the iodine could be replaced in synthetically useful yields by cyanide by using cuprous cyanide in DMSO (IIIa, 42%; IIIb, 62%). The cyanoaldehydes were converted to the methyl carboxylates, (IV) in the usual manner. The replacement reaction was much slower and impractical for the more readily available 4-bromo-2-pyrrolecarboxaldehyde. Replacement of iodine with methoxy and thiocyanato groups by the usual procedures (5) also failed. Reaction of Ib with lithium-dimethyl-copper produced a mixture from which the aldehyde group was absent, and nmr evidence (a doublet at 1.47 ppm, $J \sim 7$ Hz) suggested a methyl carbinol.



EXPERIMENTAL

Gas chromatographic analyses were carried out with an Aerograph Model A-700 instrument employing principally an SE-30 column (3.05 m X 0.32 cm 5% on acid-washed Chromosorb W) at 150-200°. Infrared data were obtained with nujol mulls with a Perkin-Elmer Model 137 Infracord Spectrophotometer. Nuclear magnetic resonance spectra were recorded with a Varian T-60 instrument and shifts are reported in ppm relative to TMS. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. The mention of a proprietary product in this paper does not constitute an endorsement of this product by the U. S. Department of Agriculture.

Iodination of the Ternary Iminium Salts of the Aldehydes.

Typically, 0.035 mole of iodine was dissolved in a mixture of 35 ml. each of nitromethane (dried over molecular sieves) and dichloroethane, and the mixture was stirred vigorously for 30 minutes chilled to 0°, and treated with 0.036 mole of silver trifluoroacetate (6). The pyrrolidinium salt (1) was added 10 minutes later, and the resulting mixture was stirred at ambient temperature overnight. The quality of the ternary iminium salt was quite important, and only relatively color-free starting materials gave good yields of iodinated products. The reaction mixture was concentrated, and the product was crystallized from benzene. The solid product was then hydrolyzed by suspending and stirring it into a solution of 3 g. of sodium hydroxide in 60 ml. each of methanol and water (15 minutes). The mixture was brought to neutrality with hydrochloric acid, diluted with water, and extracted with ether. The extract was washed, dried (magnesium sulfate), and concentrated. The crude product was recrystallized from benzene-petroleum ether to give Ia (55%), m.p. 118-120°; lit. 118-120° (1), and Ib (55%), m.p. 64-67° (hexane); ν 6.0 μ ; nmr (carbon tetrachloride) 3.93 (s, 3, NCH₃), 6.87 (bs, 2, H3, H5), 9.48 (bs, 1, CHO).

Anal. Calcd. for C_6H_6INO : C, 30.66; H, 2.57; I, 54.00; N, 5.96. Found: C, 30.37; H, 2.53; I, 54.19; N, 6.04.

Preparation of the Nitriles, IIIa-b.

Cuprous cyanide, (260 mg., 2.5 equiv) and 1.0 mmole of the iodoaldehyde Ia or b were stirred vigorously in 2 ml. of DMSO under nitrogen and then heated at 140-150° for 5 hours. The crude product was obtained by cooling the mixture, diluting it with water and ether, suction-filtering through celite, and finally separating the phases. The aqueous layer was washed several times with ether and the combined ether extract was washed with water, dried (magnesium sulfate), and concentrated. Further purification was effected by recrystallization from benzene (IIIa) or isooctane (IIIb) to give IIIa, 42%, m.p. 177-177.5°; ir 4.5, 6.05 μ ; nmr (DMSO- d_6) 7.57 (d, 1, H3), 8.08 (bs, 1, H5), 9.73 (bs, 1, CHO), $J_{3,5} \sim 1.5$ Hz, and IIIb (62%), m.p. 116-120°; ir 4.5, 5.95 μ ; nmr (deuteriochloroform) 4.07 (s, 3, NCH₃), 7.28 (d, 1, H3), 8.08 (m, 1, H5), 9.78 (d, 1, CHO), $J_{3,5} \sim 1.5$ Hz.

Anal. Calcd. for $C_6H_4N_2O$: C, 60.00; H, 3.36; N, 23.33. Found: C, 59.98; H, 3.36; N, 23.19.

Anal. Calcd. for $C_7H_6N_2O$: C, 62.67; H, 4.51; N, 20.89. Found: C, 62.69; H, 4.60; N, 21.05.

Preparation of the Esters, IIa,b, and IVa,b from the Aldehydes.

The procedure for silver oxide oxidation was essentially as described previously (7). The crude acid was treated with excess diazomethane in ether and the resulting solution was allowed to evaporate. The resulting crude ester was recrystallized from isooctane. Compound IIa, (42%), m.p. 87-89°; ir 3.1, 6.05 μ ; nmr (deuteriochloroform) 3.87 (s, 3, OCH₃), 7.00 (bs, 2, aryl H's).

Anal. Calcd. for $C_6H_6INO_2$: C, 28.71; H, 2.41; I, 50.55; N, 5.58. Found: C, 28.64; H, 2.38; I, 50.32; N, 5.71.

Compound IIb was obtained in 46% yield, m.p. 62-64° (*i*-octane); ir 6.0 μ .

Anal. Calcd. for $C_7H_8INO_2$: C, 31.72; H, 3.04; I, 47.89; N, 5.29. Found: C, 31.53; H, 3.24; I, 47.61; N, 5.28.

Compound IVa was obtained in 74% yield, m.p. 168-169° (benzene); lit. m.p. 169° (8) ir, 3.1, 4.5, 5.95 μ ; nmr (DMSO- d_6) 3.87 (s, 3, OCH₃), 7.23 (m, 1, H3), 7.85 (m, 1, H5).

Compound IVb was obtained in 68% yield, m.p. 116-119° (*i*-octane); ir 4.5, 5.95 μ , nmr (deuteriochloroform) 3.88 (s, 3, NCH₃), 3.98 (s, 3, OCH₃), 7.20 (d, 1, H3), 7.28 (bs, 1, H5), assignment of NCH₃ based on broadening probably due to long range coupling.

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.40; H, 4.72; N, 17.14.

REFERENCES

- (1) P. E. Sonnet, *J. Org. Chem.*, **37**, 925 (1972).
- (2) P. E. Sonnet and J. C. Moser, in press.
- (3) A. Treibs and H. G. Kolm, *Ann. Chem.*, **614**, 176 (1958).
- (4a) C. Bjorklund and M. Nilsson, *Tetrahedron Letters*, 675 (1966). (b) M. Nilsson and O. Wennerstrom, *ibid.*, 3307 (1968).
- (5) R. G. R. Bacon and H. A. O. Hill, *J. Chem. Soc.*, 1097, 1108 (1964).
- (6) A. L. Henne and W. G. Finnegan, *J. Am. Chem. Soc.*, **72**, 3086 (1950).
- (7) P. E. Sonnet, *J. Org. Chem.*, **36**, 1005 (1971).
- (8) H. J. Anderson and S. F. Lee, *Can. J. Chem.*, **43**, 409 (1965).