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1. Willstätter, R. and Stoll, A. *Ann.* **416** (1918) 21.
2. Lenard, P. and Wolf, M. *Ann. Phys. und Chem.* 1888, xxxiv, 918.
3. Ahnström, G. *Acta Chem. Scand.* **15** (1961) 463.
4. Chance, B. *Arch. Biochem.* **24** (1949) 410.
5. Mann, P. J. G. *Biochem. J.* **24** (1931) 921.
6. Ettori, J. *Biochem. J.* **44** (1949) 35.

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## 3-Substituted Furans

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In connection with work on the substituent effects in heterocyclic systems, a number of 3-substituted furans was needed in order to compare the chemical shifts in their NMR-spectra with those of the corresponding thiophenes [1]. Although some 3-substituted furans occur in nature [2] most compounds of this type are only obtained with difficulty. Some compounds have been prepared by modifying the carboxyl group of 3-furancarboxylic acid [3,4], which is obtained by partial decarboxylation of polycarboxyfurans [3-5]. Recently 3-hydroxytetrahydrofuran has been used for the preparation of 3-phenylfuran [6] and new methods for the synthesis of 3-methylfuran from commercially available aliphatic compounds have been worked out [7,8]. These methods give a carbon-carbon bond in the 3-position.

In the thiophene series it has been shown that 3-thienyllithium, obtained through halogen-metal interconversion between 3-bromothiophene and *n*-butyllithium at $-70°$, is a very useful intermediate both for the formation of a new carbon-carbon bond in the 3-position and also for the introduction of other types of substituents (for review *cf.* Ref.[9]). Of the two 3-halofurans which are suitable for an analogous investigation we found that 3-iodofuran [10] could be more easily and reproducibly synthesised than 3-bromofuran [11] owing to difficulties in the reduction of 4,5-dibromo-2-furancarboxylic acid to 4-bromo-2-furancarboxylic acid. Through minor changes in the Gilman process, which consists of the pyrolysis of the mercury salt of 2-furancarboxylic acid followed by reaction of the resulting chloromercury furan with iodine, the yield of 3-iodofuran was increased from 4.0 % to 5.1 %, calculated on the weight of the 2-furancarboxylic acid used. The reactions of 3-iodofuran have been investigated very briefly by Gilman and Wright only. They found that it did not give a Grignard reagent, but that with a sodium-potassium alloy it formed a metalorganic compound, which upon carbonation gave 3-furancarboxylic acid in low yield [12]. We have now found that 3-iodofuran undergoes halogen-metal interconversion with *n*-butyllithium at $-70°$ to 3-furyllithium. Upon carbonation this compound gives 3-furancarboxylic acid in good yield, and with N,N-dimethyl formamide it reacts to give 3-furaldehyde. By contrast with 2-bromo- and 2-iodofuran [13], 3-iodofuran reacts with sodium methylate in methanol in the presence of cupric oxide, to give 3-methoxyfuran. It is not considered that the yields obtained in these preliminary experiments are the best obtainable.

Thus, although 3-iodofuran is not so readily available as 3-bromothiophene [14], its halogen metal interconversion at $-70°$ with *n*-butyllithium to form 3-furyllithium (a compound sufficiently stable at this temperature) opens up the route to many 3-substituted furans. Further investigation into its potentialities as an intermediate for such compounds is in progress.

*Experimental. 3-Furancarboxylic acid.* A solution of 8.8 g (0.045 mole) of 3-iodofuran in 25 ml of dry ether was added to a stirred solution of 47 ml of 1.20 N *n*-butyllithium at $-70°$ in the conventional four-necked, nitrogen-swept flask. After 5 min, the mixture was poured onto solid carbon dioxide covered with ether. The reaction mixture was hydrolyzed with water and the ether phase extracted with sodium carbonate solution. The 3-furancarboxylic acid was precipitated out on acidification with dilute hydrochloric acid. One recrystallization from water yielded 3.2 g (63 %) of pure 3-furancarboxylic acid, m.p. 122–123°. (Literature value:[5] m.p. 122–123°.) The characteristic peaks

of the 2-isomer were absent from its IR-spectrum.

*Methyl 3-furancarboxylate.* This was prepared by methylation with diazomethane, b.p. 72–73°/30 mm Hg, $n_D^{20} = 1.4677$ (literature values [5]: b.p. 160°, $n_D^{20} = 1.4676$).

*3-Furaldehyde.* A solution of 3-furyllithium prepared as above from 11.5 g (0.059 mole) of 3-iodofuran and 78 ml 0.90 N *n*-butyllithium was forced under a pressure of nitrogen into a stirred solution of 8 g (0.11 mole) of N,N-dimethyl formamide in 30 ml of ether. After several hours the reaction mixture was decomposed with ice-water, and the ether phase was washed with dilute hydrochloric acid and sodium bicarbonate. In order to separate the aldehyde from the *n*-butyl iodide formed, the ether layer was extracted several times with 30 % sodium bisulphite solution. The combined aqueous extracts were made alkaline and then extracted with ether. Distillation of the dried ether phase yielded 1.1 g (20 %) of 3-furaldehyde, b.p. 76°/50 mm Hg, $n_D^{20} = 1.4937$, phenylhydrazone, m.p. 148–149.5°. (Literature values[8]: b.p. 70–72°/43 mm Hg, $n_D^{20} = 1.4945$, phenylhydrazone, m.p. 149.5°.) The IR-spectrum indicated the presence of traces of furfural.

*3-Methoxyfuran.* 19.7 g (0.86 mole) of sodium were dissolved in 240 ml of anhydrous methanol; 58 g (0.299 mole) of 3-iodofuran and 29 g of cupric oxide were added. The mixture was then refluxed with vigorous stirring for 24 h. The cooled mixture was filtered, diluted with two volumes of water and extracted with ether. The combined ether phases were washed with water, dried and fractionated. 18.6 g (65 %) of 3-methoxyfuran, b.p. 112°, $n_D^{20} = 1.4488$, was obtained. (Found: C 61.19; H 6.17. Calc. for $C_5H_6O_2$ (98.1): C 61.21; H 6.16.) IR- and NMR-spectra showed it to be free from 3-iodofuran and 2-methoxyfuran.

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1. Gronowitz, S. and Hoffman, R. A. *Arkiv Kemi* **16** (1960) 539.
2. Edward, J. T. *Ann. Repts. on Progr. Chem. (Chem. Soc. London)* **51** (1954) 243.
3. Gilman, H. and Burtner, R. R. *J. Am. Chem. Soc.* **55** (1933) 2903.
4. Sherman, E. and Amstutz, E. D. *J. Am. Chem. Soc.* **72** (1950) 2195.
5. Dunlop, A. P. and Peters, F. N. *The Furans.* New York 1953, pp. 560 ff.
6. Wynberg, H. *J. Am. Chem. Soc.* **80** (1958) 364.
7. Burness, D. M. *Org. Syntheses* **39** (1959) 46.
8. Cornforth, J. W. *J. Chem. Soc.* **1958** 1310.
9. Gronowitz, S. *Arkiv Kemi* **13** (1958) 295.
10. Gilman, H. and Wright, G. F. *J. Am. Chem. Soc.* **55** (1933) 3302.
11. Shepard, A. F., Winslow, N. R. and Johnson, J. R. *J. Am. Chem. Soc.* **52** (1930) 2083.
12. Gilman, H. and Wright, G. F. *J. Am. Chem. Soc.* **55** (1933) 2893.
13. Manly, D. G. and Amstutz, E. D. *J. Org. Chem.* **21** (1956) 516.
14. Gronowitz, S. *Acta Chem. Scand.* **13** (1959) 1045.

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