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# BRIDGEHEAD SUBSTITUTIONS. PREPARATION OF 7-CHLORO-, 7-BROMO- AND 7-METHYLSULPHINYL-GIBBERELLINS

Brian E. Cross* and Ian C. Simpson

Department of Organic Chemistry, The University, Leeds LS2 9JT

Summary: 7-Hydroxygibberellins react with nucleophiles in the presence of fluoroamine to give bridgehead substitution products.

The biological activity[1] of some fluorogibberellins[2] suggested that the preparation of other analogues would be of interest.

Treatment of methyl gibberellate (1) with fluoroamine ($ClFCH.CF_2NEt_2$) in THF in the presence of LiCl at room temperature (cf. refs. 2,3) afforded the 4β,7-dichlorogibberellin (3)[4] and the 7-(chlorobutoxy)-compound (4). The latter was presumably formed by nucleophilic attack by the solvent on the reactive intermediate, which may be the bridgehead carbonium ion. The structure and stereochemistry of compound (3) was deduced by comparison of its NMR spectrum with that of the corresponding difluoride (5).[2]

The dichloro-acid (6) was readily prepared by the reaction of gibberellic acid with fluoroamine in dimethoxyethane in the presence of LiCl. The resultant acid chlorides were decomposed with water to yield the dichlorogibberellin (6) and the ether (7).[5]

In a similar reaction benzyl gibberellate (2)[6] gave the dichloro-ester (8) (23%) and the ether (9) (24%). Hydrogenation of the former over 5% $Rh/Al_2O_3$[7] yielded the dichlorogibberellin (10) and the 7-chloro-derivative (11).

The tetrahydrogibberellic acid (12), prepared stereospecifically by reduction of gibberellic acid with diimide,[8] gave the 7-chlorogibberellin (14) (35%) and the ether (15) (27%) on treatment with fluoroamine (cf. ref. 2) and LiCl in dimethoxyethane; no 7-fluoro-derivative was detected. Replacement of the LiCl with LiBr led to the preparation of the 7-bromo-gibberellin (16),[9] but in this case some of the 7-fluoro-homologue (17) was also produced; the best sample of (16) contained ca. 8% of (17).

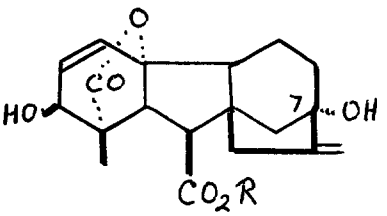
The bridgehead substitution reaction has been extended to the preparation of thio-gibberellins. Methyl tetrahydrogibberellate (13) was treated with fluoroamine and LiBr[10] in dimethylsulphide. The three products (16), (17) and (18) were difficult to separate, however, after oxidation with m-chloroperbenzoic acid the 7-methylsulphinylgibberellin (19) was isolated by PLC.

These results show that the reaction of 7-hydroxygibberellins with fluoroamine in the presence of nucleophiles provides a facile one-step method of preparing a variety of bridgehead substituted gibberellins.

In the lettuce hypocotyl bioassay the 7-chlorogibberllin (11) showed activity comparable with that of $GA_9$; it was more active than its dehydro-derivative (14) and much more active than the dichloride (10). The 7-bromogibberellin (16) was more active than the dihydro-

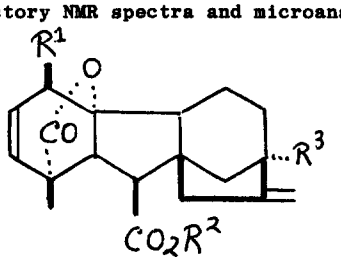
gibberellin $A_5$ (20), but less active than $GA_5$, in the Tanginbozu rice bioassay.[11]

All new compounds gave satisfactory NMR spectra and microanalyses and/or accurate masses.

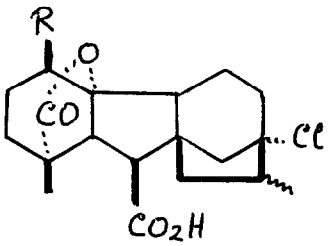


(1) R=Me

(2) R=$PhCH_2$

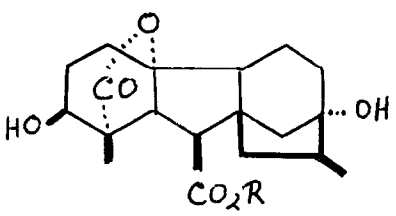


| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| (3) | Cl | Me | Cl |
| (4) | Cl | Me | $O(CH_2)_4Cl$ |
| (5) | F | Me | F |
| (6) | Cl | H | Cl |
| (7) | Cl | H | $O(CH_2)_2OMe$ |
| (8) | Cl | $PhCH_2$ | Cl |
| (9) | Cl | $PhCH_2$ | $O(CH_2)_4Cl$ |



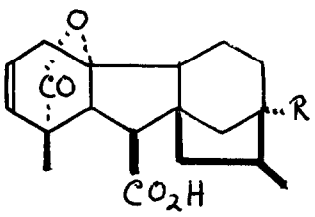
(10) R=Cl

(11) R=H



(12) R=H

(13) R=Me



| | R |
|---|---|
| (14) | Cl |
| (15) | $O(CH_2)_2OMe$ |
| (16) | Br |
| (17) | F |
| (18) | SMe |
| (19) | SO·Me |
| (20) | OH |

## REFERENCES AND NOTES


1. T.W.A. Jones, Phytochem., 15, 1825 (1976).
2. J.H. Bateson and B.E. Cross, J.C.S. Perkin I, 2409 (1974); R.E. Banks and B.E. Cross, ibid., 512 (1977).
3. E.J. Bailey, H. Fazakerley, M.E. Hill, C.E. Newall, G.H. Phillips, L. Stephenson and A. Tulley, J.C.S. Chem. Comm., 106 (1970).
4. This compound has also been prepared by Dr. J.R. Hanson.
5. Formed by the dimethoxyethane acting as a nucleophile.
6. P.J. Keay, J.S. Moffat and T.P.C. Mulholland, J. Chem. Soc., 1605 (1965).
7. G.E. Ham and W.P. Coker, J. Org. Chem., 29, 194 (1964).
8. K. Boulton and B.E. Cross, J.C.S. Perkin I, 1354 (1979); K. Mori, M. Ohki, A. Sato and M. Matsui, Tetrahedron, 28, 3739 (1972).
9. The crude bromo-compound contained some material with a terminal methylene group, which was presumably formed by radical bromination at C-8 followed by loss of HBr.
10. The thio-ether (18) was not formed in the absence of a lithium salt; the lithium may act by co-ordination with the 7-oxygen atom, thus aiding its departure.
11. We are indebted to Dr. T.W.A. Jones for the bioassays.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