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INSECTICIDAL AMIDES. SYNTHESIS OF NATURAL 2(*E*),4(*E*),10(*E*)-PIPERCIDE, ITS 2(*E*), 4(*E*), 10(*Z*)-STEREOMER, AND RELATED ISOBUTYLAMIDES

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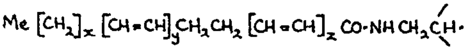
Summary: Natural [all (*E*)] pipercide and its 2(*E*),4(*E*),10(*Z*)- stereomer are synthesised, the latter having superior insecticidal potency and knock down. 10,11-Dihydro- and 10,11-dehydropipercides are also prepared.

Various natural straight-chain unsaturated isobutylamides found especially in the Compositae, Piperaceae and Rutaceae families possess insecticidal activity, generally embraced within a structure (1).[1] In (1) the acid has a chain length of 10 to 20 or more carbon atoms, z=1,2, or perhaps more double bonds having (*E*)- stereochemistry, and y=2,3 or perhaps more double bonds with (*E*)/(*Z*)- or (*Z*)/(*Z*)- geometry.[1] Usually the first double bond of

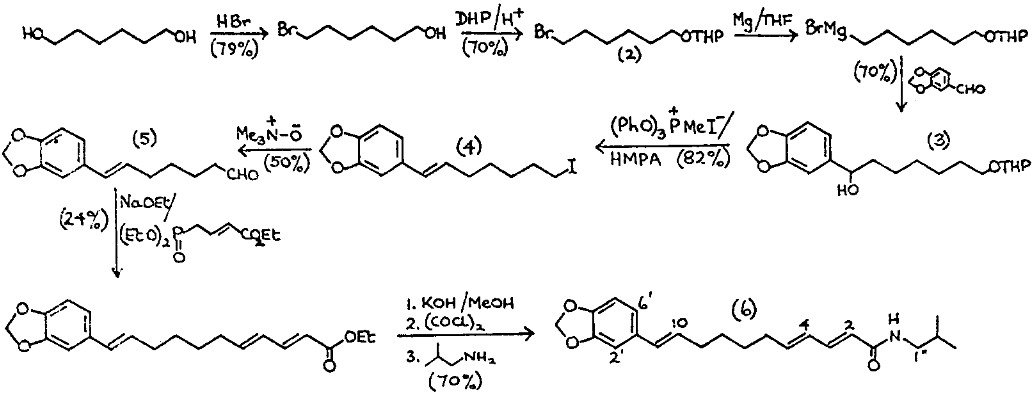


$$\mathrm{Me[CH_2]_x[CH{=}CH]_yCH_2CH_2[CH{=}CH]_zCO{\cdot}NHCH_2CH{\cdot}}$$

(1)

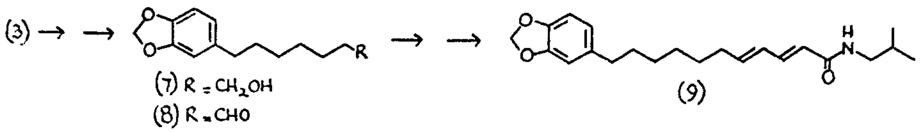
the y grouping, counting from the carboxyl end, is (*Z*)-, and there is substantial diminution in insecticidal activity if this is stereomutated to (*E*)-.[2] More recently a 2(*E*),4(*E*)- undecatrienoic isobutylamide carrying an 11-(3,4-methylenedioxyphenyl)- substituent, pipercide (6), has been isolated from *Piper nigrum* and reported to be insecticidally active against the Adzuki bean-weevil (*Callosobruchus chinensis*).[3] In the present work we have synthesised both natural pipercide and its 10(*Z*)- stereomer to compare, in the light of findings in the purely aliphatic series, their relative insecticidal potencies.

2(*E*),4(*E*),10(*E*)-Pipercide was synthesised according to Scheme 1. 1,6-Hexanediol was converted into its monobromide via a procedure employing continuous hexane extraction and then protected as the tetrahydropyranyl derivative (2).[4] Grignard formation and reaction with piperonal gave the half-protected diol (3) in 70% yield. The latter was then heated at 75°C for 1 h with methyl triphenoxyphosphonium iodide in hexamethylphosphoramide.[5] In one step this effected a virtually stereospecific dehydration to the (*E*)-olefin and transformed the pyranyloxy-group to the iodide, in high yield. The iodo-product (4) was now oxidised to the (*E*)-aldehyde (5) using anhydrous trimethylamine *N*-oxide in dry chloroform.[6] Wadsworth-Emmons reaction,[7]



Scheme 1. Synthesis of 2(E),4(E),10(E)-Pipercide

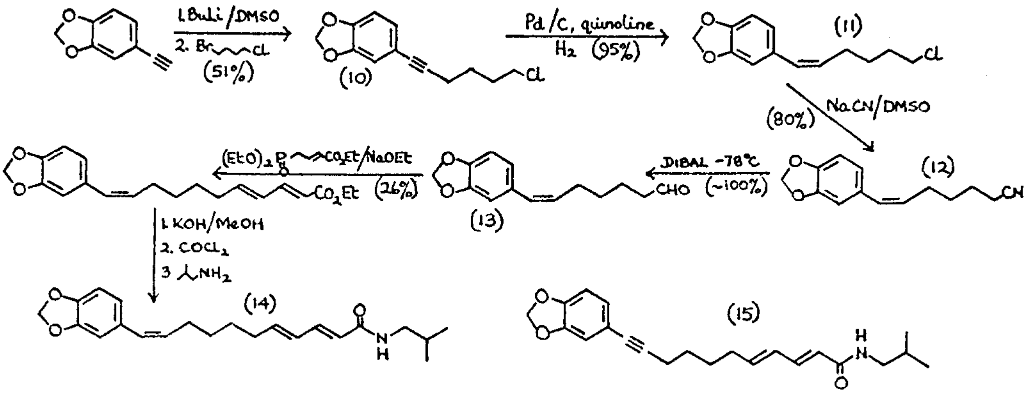
although proceeding in modest yield, formed the 2(E),4(E)-diene system in one step. Synthesis of the amide (6)[8,9] was completed by standard steps and comparison was made with natural pipercide.[10]



Synthesis of 10,11-dihydropipercide (9), which also occurs in *Piper nigrum*,[11] was effected from (3) by hydrogenolysis (Pd/C) of the benzylic hydroxyl followed by depyranylation (86% overall) to give (7). Oxidation with pyridinium chlorochromate gave the aldehyde (8) almost quantitatively, converted into dihydropipercide, m.p. 94 - 95°C, by the steps used in Scheme 1, and in similar yields. Dihydropipercide is insecticidally active and synergises the activity of pipercide.[11]

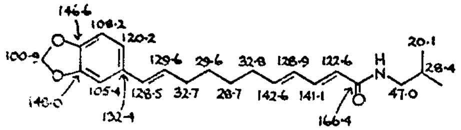
The synthesis of 2(E),4(E),10(Z)- pipercide (14) is shown in Scheme 2. 3,4-Methylenedioxyphenylacetylene[12] was lithiated in dry dimethylsulphoxide to give, on Ahmed-Strong chain extension, the acetylenic chloride (10) which was semi-hydrogenated. *cis*-Chloride (11) did not readily form a Grignard reagent and was therefore converted into the aldehyde (13) via the nitrile (12)[13] which was reduced with diisobutylaluminium hydride:[14] both steps proceeded in excellent yield. Completion of the synthesis of (14)[15] then followed similar lines to that for the (E)-(E),(E)- isomer. By proceeding directly from the acetylenic halide (11), omitting the semi-hydrogenation, 10,11-dehydropipercide m.p. 128 - 130°C (15) was also made.

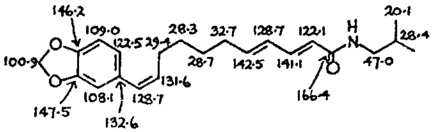
As an assurance of stereoisomeric purity the ^{13}Cmr spectra (62.9 MHz) of our synthetic 2(E),4,(E),10(E)- and 2(E),4(E),10(Z)- pipercides were determined



Scheme 2. Synthesis of 2(E), 4(E), 10(Z)-Pipercide

and assignments are as shown. There was no evidence of isomeric inhomogeneity for either (6) or (14). Chemical shifts for C-3 and C-5, being very close, were assigned by specific proton decoupling.





Evaluation of isobutylamides (6) and (14) against the common housefly (*Musca domestica*) has shown that the 2(E),4(E),10(Z)-stereomer is indeed more effective than the all-(E) both as regards kill and knockdown.^{16} Full details will be published elsewhere.

References

1. L. Crombie and A.H.A. Krasinski, Chem. and Ind., 1962, 983.
2. e.g. L. Crombie and J.D. Shah, J.Chem.Soc., 1955, 4244.
3. M. Miyakado, I. Nakayama, H. Yoshioka and N. Nakatani, Agric.Biol.Chem., 1979, 43, 1609.
4. O.L. Chapman, K.C. Mattes, R.S. Sheridan and J.A. Klun, J.Am.Chem.Soc., 1978, 100, 4878.
5. (a) R.O. Hutchins, M.G. Hutchins and C.A. Milewski, J.Org.Chem., 1972, 37, 4190; (b) S.R. Landauer and H.N. Rydon, J.Chem.Soc., 1953, 2224.
6. (a) V. Franzen, 'Organic Synthesis: Collective Volume 5'. Ed. H.E. Baumgarten, Wiley, New York, 1973, p.872; (b) W.J. Hickinbottom, 'Reactions of Organic Compounds', 3rd Ed., Longmans, London, 1957, p.420.
7. R.S. Burden and L. Crombie, J.Chem.Soc., 1969, 2477.

8. *all*-(*E*)-Pipercide had M$^+$ 355.2146, λ_{max}(EtOH): 212(log ε4.41), 261(4.63), 268i(4.59) and 304(3.78)nm, ν_{max}(KBr): 3300, 1660, 1638, 1620 cm^{-1}. The ^{1}Hmr spectrum (250 MHz, CDCl$_3$) showed resonances at δ: 0.92 (d,6H, J 6.7 Hz; 3",4"-*Me*), 1.47(m,4H; 7,8-C*H*$_2$'s), 1.81(m,1H; 2"-*H*), 2.17(m,4H; 6,9-C*H*$_2$'s), 3.16 (dt, 2H; 1"-*H*), 5.59 (broad t, 1H; N*H*), 5.76 (d, 1H, *J* 15.3 Hz; 2-*H*) 5.93 (s, 2H; ·OC*H*$_2$O, 5.60 (t, 1H; 10-*H*), 6.06 (t, 1H, 5-*H*), 6.15 (dd, 1H, *J* 15 and 9.5 Hz; 4-*H*), 6.29 (d, 1H, *J* 15.5 Hz; 11-*H*), 6.76 (s, 2H; 2' and 5'-*H*), 6.90 (s, 1H, 6'-*H*), 7.20 (dd, 1H, *J* 14.8, 10.1 Hz, 3-*H*): from cyclohexane, the sample melted at 120°C after prior softening (lit.^{3} m.p. 114 - 115°C).

9. An earlier synthesis of pipercide has been reported: M. Miyakado and H. Yoshioka, *Agric.Biol.Chem.*, 1979, 2413.

10. Dr. Miyakado has kindly supplied us with the infra-red and 60 MHz (CDCl$_3$) ^{1}Hmr spectra of natural pipercide. Our 2(*E*),4(*E*),10(*Z*), isomer (14) is clearly different, and our synthetic 2(*E*),4(*E*),10(*E*) isomer (6) bears much closer resemblance. A small sample of Dr. Miyakodo's synthetic pipercide in our hands partially melted at 75°C, the last material disappearing at 113°C. On examination at 250 MHz (CDCl$_3$) two closely spaced methylenedioxy signals were observed, δ 5.93 and 5.95. A doublet of triplets at 5.53, *J* 11.6 Hz, coupled to a doublet at 6.31, *J* 11.6 Hz signified 10(*Z*)- material whilst a doublet at 6.29, *J*, 15.6 Hz signified the 11-*H* of the 10(*E*)-olefin. Characteristic of the 2(*E*),4(*E*),10(*Z*)-isomer (see below), the multiplet at 2.31 due to the 9-C*H*$_2$, was also present. Integration indicates 55% 2(*E*),4(*E*),10(*Z*)- and 45% 2(*E*), 4(*E*), 10(*E*)- pipercides.

11. M. Miyakado, I. Nakayama and H. Yoshioka, *Agric.Biol.Chem.*, 1980, **44**, 1701.

12. W. Feuerstein and M.Heimann, *Ber.*, 1901, **34**, 1468.

13. L. Friedman and H. Schechter, *J.Org.Chem.*, 1960, **25**, 877.

14. E. Winterfeldt, *Synthesis*, 1975, 617.

15. 2(*E*), 4(*E*), 10(*Z*)-Pipercide had M$^+$ 355.2108, λ_{max}(EtOH): 209(Log ε 4.27), 261(4.45), 297 infl. (3.46), ν_{max}(KBr): 3320, 1660, 1630, 1620 cm^{-1} The ^{1}Hmr spectrum (250 MHz, CDCl$_3$) showed resonances at δ:0.91 (d, 6H , *J* 6.7 Hz; 3",4"-*Me*), 1.51 (m, 4H; 7,8-C*H*$_2$'s), 1.80 (septet, 1H; 2"*H*) 2.13 (m, 2H; 6-C*H*$_2$), 2.30 (m, 2H; 9-C*H*$_2$), 3.14 (t, 2H, 1"-H), 5.52 (dt, 1H, *J* 11.6 Hz; 10-*H*), 5.85 (d, 1H, *J* 15 Hz; 2-*H*), 5.93 (s, 2H ; ·OC*H*$_2$O·), 6.02 (t, 1H; 5-*H*), 6.06 (dd, 1H, *J* 14.5, 9.3 Hz; 4-*H*), 6.30 (d, 1H, *J* 11.6; 11-*H*), 6.78 (m, 3H; 2',5',6'-*H*), 7.34 (dd, 1H, *J* 15.0, 10.0 Hz; 3-*H*). From cyclohexane, it had m.p. 88°C after prior softening.

16. We thank Dr. M.H. Black, Wellcome Research Laboratories, Berkhamsted, for arranging the insecticidal tests.

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