Short Communication

The *Piperaceae* Amides II*: Synthesis of Pipercide, A New Insecticidal Amide from *Piper nigrum* L.

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We previously reported the isolation and structure determination of a new insecticidal amide, pipercide $C_{22}H_{29}NO_3$, occurring in *Piper nigrum* L. and its remarkable toxicity against the adzuki bean weevil (*Callosobruchus chinensis* L.).[1] The proposed structure for pipercide was deduced mainly on the basis of spectral data to be (2*E*,4*E*,10*E*)-*N*-isobutyl-11-(3,4-methylenedioxyphenyl)-2, 4, 10-undecatrienamide (**1**).

The major constituents of *Piperaceae* plants, piperine (**2**) and pellitorine (**3**) have been synthesized by Normant *et al.*[2] and Jacobson *et al.*,[3] respectively. As a more closely related compound to pipercide, Joshi *et al.*[4] isolated piperstachine from *Piper trichostachyon* C. DC. and deduced its structure to be (2*E*,8*E*, 10*E*)-*N*-isobutyl-11-(3, 4-methylenedioxyphenyl)-2,8,10-undecatrienamide (**4**). Later, Viswanathan *et al.*[5] synthesized the compound (**4**) and its 2*E*,4*E*,6*E*-isomer (**5**) and confirmed the proposed structure for piperstachine to be as reported (**4**) (see Fig. 1). In this communication we wish to report the synthesis of the amide of the proposed structure (**1**) and the identity with pipercide.

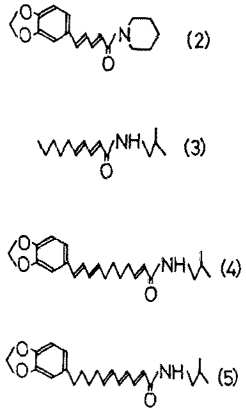

Fig. 1.

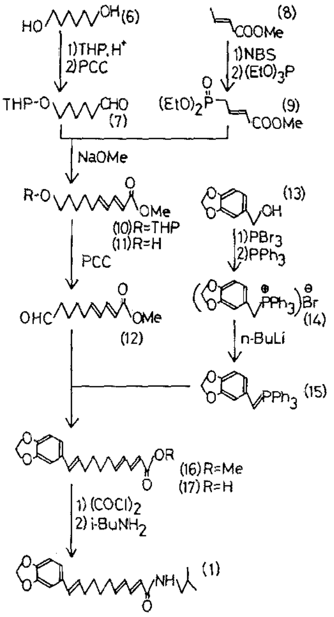

Fig. 2. Synthetic Schema of Pipercide (**1**).

The present synthesis is based on a piperonyl $+C_6+C_4$ principle employing piperonyl alcohol (**13**), 1,6-hexanediol (**6**) and methyl crotonate (**8**) which are readily available as starting materials (see Fig. 2). Firstly, the preparation of the C_6 construction unit: In the usual manner[6] 6-(tetrahydro-2′-pyranyloxy)-1-hexanol was prepared from 1,6-hexanediol (**6**), which was oxidized with pyridinium chlorochromate[7] affording the corresponding aldehyde (**7**) with a 95% yield. In order to obtain the C_4 construction unit, methyl crotonate (**8**) was brominated with NBS to give methyl 4-bromocrotonate[8] (92% yield), which was converted with triethyl phosphite to diethyl 3-methoxycarbonyl-2-propenylphos-

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phonate (**9**) (77% yield) according to the method of Davis *et al.*[9]

The 2,4-dienoate (**10**)[*1] was prepared by condensation of the aldehyde (**7**) with the phosphonate (**9**) in the presence of sodium methoxide, whose configurations were predominantly *trans* at C–2 and exclusively *trans* at C–4.[9,10,11] The protecting group of the 2,4-dienoate (**10**) was removed by *p*-TsOH in MeOH to give (2*E*,4*E*)-methyl 10-hydroxy-2,4-decadienoate (**11**),[*2] which was oxidized with pyridinium chlorochromate[7] to (2*E*,4*E*)-methyl 10-oxo-2,4-decadienoate (**12**).

In order to obtain the piperonyl construction unit, piperonyl alcohol (**13**) was brominated with PBr_3 to give piperonyl bromide with a quantitative yield, which was converted with triphenylphosphine to 3,4-methylenedioxybenzyltriphenylphosphonium bromide (**14**) (93% yield) according to the method of Grewe *et al.*[12] The phosphonium bromide(**14**) in benzene was converted with an equimolar amount of *n*-BuLi (in *n*-hexane sol.) to the Witting reagent (**15**),[13] which was coupled *in situ* with an equimolar amount of (2*E*,4*E*)-methyl 10-oxo-2,4-decadienoate (**12**) to give the condensation product (**16**) with a 70% yield. The ratio of the (*E*)-isomer to the (*Z*)-isomer at the C_{10} double bond was about 8 : 2 as determined by GLC and NMR. The *E* and *Z* ester mixture (**16**) was hydrolyzed (KOH–MeOH) to give the acid (**17**). The crude acid was recrystallized twice from benzene to give (2*E*,4*E*,10*E*)-11-(3,4-methylenedioxyphenyl)-2,4,10-undecatrienoic acid (**17**)[*3] as fine needles (60% yield), which was chlorinated with oxalyl chloride. The resultant acid chloride was finally condensed with isobutylamine yielding (2*E*, 4*E*, 10*E*)-*N*-isobutyl-11-(3, 4-methylenedioxyphenyl)-2, 4, 10-undecatrienamide (**1**).[*4] The synthetic product was identical in all respects (mixed mp., NMR, IR, MS and UV) with natural pipercide. Evaluation of detailed insecticidal properties of pipercide and co-occurring compounds is now in progress and will be reported elsewhere.

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[*1] We tried Wittig reaction of the aldehyde (**7**) with (*E*)-3-methoxycarbonylallyltriphenylphosphonium bromide to obtain the 2,4-dienoate (**10**). A phosphonium salt was prepared from triphenylphosphine and methyl 4-bromocrotonate in benzene according to the method described by Buchta *et al.*[14] (mp, 178.5～179.5°C, lit. 179～180°C). However, the Wittig reaction whose procedure was in accordance with Buchta's description,[14] gave methyl 8-(tetrahydro-2′-pyranyloxy)-2-ethenyl-2-octenoate instead of the desired product, the 2,4-dienoate (**10**), as a result of an allylic phosphonium salt rearrangement. Similar γ-rearrangements have already been described by Font *et al.*[15] and E. J. Corey *et al.*[16]

[*2] $n_D^{21.5°}$ 1.5113, NMR: $\delta_{TMS}^{CDCl_3}$ 1.45 (s, 6H), 2.15 (br.m, 2H), 3.08 (s, 1H, disappeared on D_2O addition), 3.49 (t, 2H, $J=6.0$ Hz), 3.68 (s, 3H), 5.68 (d, 1H, $J=15.5$ Hz), 6.00～6.23 (m, 2H), 6.95～7.43 (m, 1H), IR: ν_{max}^{film} 3400, 1710, 1635 cm^{-1}, MS: (*m*/*e*) 198 (rel. int., 7.0) M^+, 113 (26), 111 (43), 107 (32), 91 (21), 81 (55), 79 (100, base peak), 67 (37), 59 (31), 55 (28), 53 (28).

[*3] mp, 136～137°C, NMR: $\delta_{TMS}^{CDCl_3\text{-}DMSO\text{-}d_6}$ 1.47 (br.s, 4H), 2.18 (br.m, 4H), 5.59～6.23 (br.m, 5H), 5.92 (s, 2H), 6.73 (s, 2H), 6.87 (s, 1H), 6.98～7.50 (br.m, 1H), 11.53 (br.s, 1H, disappeared on D_2O addition), IR: ν_{max}^{nujol} 1680, 1660, 1625, 1600 cm^{-1}, MS: (*m*/*e*) 300 (rel. int., 60) M^+, 192 (32), 187 (29), 173 (36), 148 (34), 135 (100, base peak), 131 (82), 103 (60), 77 (32), UV: λ_{max}^{EtOH} 212 nm (log ε 4.37), 260 (4.62), 270 (4.54), 305 (3.81), UV absorption at 270 and 305 nm reveals the presence of the 10-*E* double bond, see ref. (1b).

[*4] mp, 114～115°C, NMR: $\delta_{TMS}^{CDCl_3}$ 0.92 (d, 6H, $J=6.5$ Hz), 1.44 (m, 4H), 1.60～2.00 (m, 1H), 2.12 (m, 4H), 3.12 (t, 2H, $J=6.5$ Hz), 5.60～6.20 (br.m, 6H, 1H disappeared on D_2O addition), 5.90 (s, 2H), 6.72 (s, 2H), 6.86 (s, 1H), 6.94～7.42 (br.m, 1H), IR: ν_{max}^{nujol} 3280, 1650, 1620, 1603 cm^{-1}, MS: (*m*/*e*) 355 (rel. int., 28) M^+, 220 (38), 161 (30), 135 (100, base peak), 131 (68), 103 (47), UV: λ_{max}^{EtOH} 209 nm (log ε 4.34), 261 (4.68), 268 (4.63), 304 (3.80).

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