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Synthesis and Synergistic Activity of Oxime Ethers Containing a Benzo-1,3-dioxole Group

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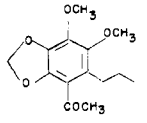
A large number of *O*-alkyl, *O*-alkenyl, and *O*-propargyl oxime ethers having a benzo-1,3-dioxole group as a common feature have been synthesized from piperonal, dillaldehyde, and acetyldihydrodillapiole as potential pyrethrum synergists. Their factors of synergism, R_m values, and structure-activity relationships are being reported. Piperonal oxime *n*-pentyl ether (XXXI) shows remarkably high activity.

Insecticide synergists play an important role in efficient and economic formulations of pesticides. Several new pyrethrum synergists have been earlier synthesized in this laboratory by chemical modification of dillapiole (Tomar et al., 1979a; b) and dihydrodillapiole and furapiole (Mukerjee et al., 1982). Synergistic activity of all these compounds has been mainly attributed to the presence of a benzo-1,3-dioxole group. Since oxime ethers have also been reported to possess synergistic insecticidal activity with pyrethroids (Hennessy, 1969), we now report the synthesis, synergistic properties, and structure-activity relationships of a large number of *O*-alkyl oxime ethers having a benzo-1,3-dioxole group as a common feature from three structurally similar carbonyl compounds, namely, piperonal (I), dillaldehyde (II), and acetyldihydrodillapiole (III).



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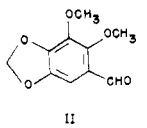

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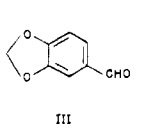

III

MATERIALS AND METHODS

Acetyldihydrodillapiole (I; Mukerjee et al., 1982) and Dillaldehyde (II; Tomar et al., 1979b) needed for this work were synthesized by literature procedures. All melting points are uncorrected. All liquid compounds were purified by column chromatography over activated silica gel followed by short-path distillation whereever possible under reduced pressure (bath temperature 150 °C). The position of all the oxime ethers on TLC plates was visualized by spraying with 2,4-dinitrophenylhydrazine reagent or H_2SO_4 spray followed by heating. NMR spectra were recorded in CCl_4 or $CDCl_3$ on a Varian EM-360 60-MHz spectrometer by using Me_4Si as the internal reference. Chemical shifts are given in δ values.

Synthesis of Test Chemicals. *Acetyldihydrodillapiole Oxime (IV).* Acetyldihydrodillapiole (I) (22.4 g), hydroxylamine hydrochloride (10.5 g), and sodium carbonate (20 g) were refluxed in ethanol for 5 h. After completion of reaction (TLC), the bulk of solvent was removed by distillation, were (500 mL) added, and mixture cooled in an ice bath. The product so separated was crystallized from ethanol as white crystals: mp 99 °C; NMR ($CDCl_3$) δ 0.9 (3 H, t, $-CH_2CH_3$), 1.5 (2 H, m, $-CH_2CH_2CH_3$), 2.2 (3 H, s, $-N{=}CCH_3$), 2.55 (2 H, t, $ArCH_2-$), 3.8 (3 H, s, $-OCH_3$), 4.0 (3 H, s, $-OCH_3$), 5.85 (2 H, s, $-OCH_2O-$). Anal. Calcd for $C_{14}H_{19}O_5N$: C, 59.9; H, 6.8. Found: C, 59.5; H, 7.1.

Dillaldehyde Oxime (XV). Dillaldehyde (II) (21 g) and hydroxylamine hydrochloride (10.5 g) were refluxed in ethanol (500 mL) containing sodium carbonate for 5 h. After working up as above, the product was crystallized from ethanol as white crystals: mp 95 °C; NMR ($CDCl_3$) δ 3.9 (3 H, s, $-OCH_3$), 4.1 (3 H, s, $-OCH_3$), 5.95 (2 H, s, $-OCH_2O-$), 6.9 (1 H, s, aromatic), 8.1 (1 H, s, $-CH{=}N-$). Anal. Calcd for $C_{10}H_{11}O_5N$: C, 53.3; H, 4.9. Found: C, 53.6; H, 5.1.

Piperonal Oxime (XXVI). Piperonal (III) (12.4 g) and hydroxylamine hydrochloride (5.25 g) were refluxed in ethanol (500 mL) in the presence of sodium carbonate for 5 h. After working up as usual, the product was crystallized from ethanol as white crystals: mp 105 °C; NMR ($CDCl_3$) δ 5.95 (2 H, s, $-OCH_2O-$), 6.75 (3 H, m, aromatic), 7.85 (1 H, s, $-CH{=}N-$). Anal. Calcd for $C_8H_7O_3N$: C, 58.2; H, 4.2. Found: C, 58.4; H, 4.5.

General Procedure for the Synthesis of Oxime Ethers. A solution of the appropriate oxime (IV, XV, or XXVI) (0.1 mol) in dry acetone containing potassium carbonate was refluxed with alkyl halides, alkenyl halides, and propargyl bromide for 3-5 h. After completion of the reaction (TLC), solvent was distilled off and water (500

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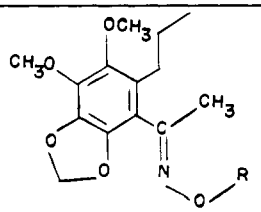
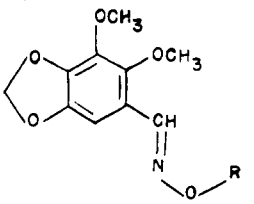
Table I. Factors of Synergism and R_m Values of Various Acetyldihydrodillapiole Oxime Ethers



sample no.	R	mp, °C	factor of synergism	R_m value
IV	H	99		
V	CH_3	L[a]	2.24	−0.42
VI	C_2H_5	L	2.14	−0.23
VII	C_3H_7	L	1.91	−0.10
VIII	C_4H_9	L	1.62	+0.08
IX	C_5H_{11}	L	1.40	+0.23
X	C_6H_{13}	L	1.78	+0.45
XI		L	1.69	+0.19
XII		104	2.0	+0.07
XIII		L	2.34	+0.09
XIV		101	2.10	+0.07

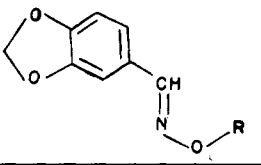
[a] L = viscous liquids. Chromatographically pure. Attempted distillation under vacuum caused decomposition at high temperature.

Table II. Factors of Synergism and R_m Values of Various Dillaldehyde Oxime Ethers



sample no.	R	mp/bp, °C	factor of synergism	R_m value
XV	H	95		
XVI	CH_3	130 (0.5 mmHg)	3.02	+0.06
XVII	C_2H_5	138 (0.5 mmHg)	2.95	+0.35
XVIII	C_3H_7	142 (0.5 mmHg)	3.5	+0.52
XIX	C_4H_9	148 (0.5 mmHg)	4.26	+0.75
XX	C_5H_{11}	155 (0.5 mmHg)	4.15	+1.0
XXI	C_6H_{13}	160 (0.5 mmHg)	4.07	+1.19
XXII		139 (0.5 mmHg)	1.82	+0.52
XXIII		89	3.24	+0.02
XXIV		150 (0.5 mmHg)	2.04	+0.55
XXV		91	2.75	+0.02

Table III. Factors of Synergism and R_m Values of Various Piperonyl Oxime Ethers



sample no.	R	mp/bp, °C	factor of synergism	R_m value
XXVI	H	104		
XXVII	CH_3	105 (0.5 mmHg)	2.08	−0.27
XXVIII	C_2H_5	110 (0.5 mmHg)	2.23	−0.12
XXIX	C_3H_7	112 (0.5 mmHg)	3.23	−0.08
XXX	C_4H_9	116 (0.5 mmHg)	4.46	+0.03
XXXI	C_5H_{11}	125 (0.5 mmHg)	6.16	+0.19
XXXII	C_6H_{13}	128 (0.5 mmHg)	4.07	+0.37
XXXIII		100 (0.5 mmHg)	3.16	+0.20
XXIV		55	3.80	+0.25
XXXV		120 (0.5 mmHg)	3.52	+0.30
XXXVI		69	2.82	−0.69

mL) added. The aqueous layer was then extracted with methylene chloride, the extract was washed and dried, and solvent was removed. The product was purified by column chromatography over silica gel to furnish oxime ethers as colorless viscous liquids or colorless solids. Cyanoethyl ethers obtained by Michael addition of the oximes with acrylonitrile in the presence of potassium carbonate were, however, obtained as white crystals. In NMR oxime ethers derived from piperonal and dillaldehyde oximes exhibit two characteristic peaks at around δ 4.1 (1 H, —CH=NOCH_2R) and 7.8 (1 H, —CH=N—), whereas oxime ethers derived from acetyldihydrodillapiole exhibit a characteristic singlet peak at around δ 2.15 [3 H, —C(CH_3)=N—]. NMR spectral and elemental analysis data of these compounds fully agreed with their structures (see paragraph at end of paper regarding supplementary material).

Formulation and Bioassay. Purified pyrethrum extract (20%) was used for making a stock solution (4%) in benzene for biological screening. The synergistic activity of all the test compounds was assessed as pyrethrum-based emulsions at an insecticide to synergist ratio of 1:5 (w/w). Benzene solvent (10%) and Tween-80 emulsifer (0.2%) were maintained throughout in the spray emulsions. Two to 3-week-old red flour beetles (*Tribolium castaneum* Herbst.) reared on wheat flour (free from pesticides) were used as test insects. The tests were conducted in three replications of 15 insects each as reported earlier by Mukerjee et al. (1973). The data were subjected to probit analysis (Finney, 1971), and factors of synergism were calculated as ratios of LC_{50} of pyrethrum alone to LC_{50} of pyrethrum in combination with various test synergists (Chadwick, 1963). Piperonyl butoxide was used as a reference synergist.

Lipophilicity of the Test Synergists. The lipophilicity of the test compounds was determined from their R_f values on reverse-phase TLC and then by calculating the R_m values by using the equation $R_m = \log (1/R_f - 1)$ (Boyce and Millborrow, 1965). Silica gel plates after activation for 2 h at 100 °C were coated with paraffin (10% paraffin in hexane). The coated plates were spotted with the test compound and developed in acetone–water (60:40) for ethers derived from acetyldihydrodillapiole oxime or dillaldehyde oxime and acetone–water (70:25) for ethers derived from piperonal oxime. R_f values were measured and R_m values were calculated from them.

RESULTS AND DISCUSSION

In all about 30 different oxime ethers belonging to three different series as listed in Tables I, II, and III were used for evaluation of their synergistic properties.

None of these test chemicals showed any significant insecticidal effect up to 1% level against the test insect *Tribolium castaneum*, but all of them showed different degree of synergism toward pyrethrum against the same test insect. The factors of synergism, and their R_m values are given in Tables I–III. It will be seen from Table I that in the case of *O*-alkyl oximes of acetyldihydrodillapiole (V–X), the lipophilicity increases linearly with an increase in the number of carbon atoms in the side chain, but there is a gradual fall in their synergistic activity (Figure 1). This behavior is unusual but has been observed earlier in

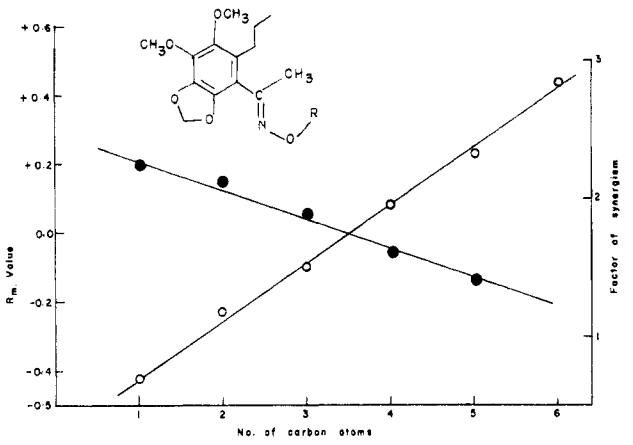


Figure 1. Relationship between R_m values, factor of synergism, and alkyl chain length for various alkyl ethers of acetyldihydrodillapiole oxime: (○) R_m values; (●) factor of synergism.

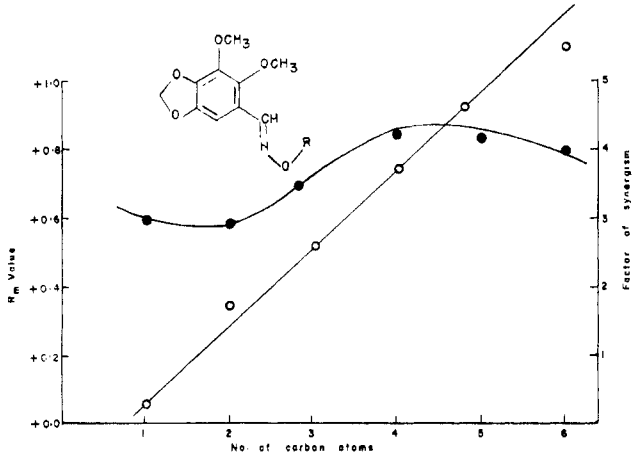


Figure 2. Relationship between R_m values, factor of synergism, and alkyl chain length for various alkyl ethers of dillaldehyde oxime: (○) R_m values; (●) factor of synergism.

the case of acyl derivatives of furapiole (Mukerjee et al., (1982). In the case of *O*-alkyl oxime ethers of dillaldehyde (Table II) and piperonal *O*-alkyl oxime ethers (Table III), the factors of synergism varied from 3.02 to 4.16 and 2.08 to 6.16, respectively, compared to 2.3 of the standard reference synergist piperonyl butoxide under the same conditions. A perusal of the data of these compounds revealed that as the lipophilicity increases, synergistic activity also increases with increasing chain length up to four or five carbon atoms and then decreases (Figures 2 and 3). This behavior has also been observed in most other cases examined earlier. Introduction of a double bond in the side chain as in XI, XXII, and XXXIII) resulted in decreased synergistic activity. This could be marginally increased by inclusion of a triple bond in the side chain. Thus, the allyl and the γ,γ-dimethyl allyl oxime ethers were less active than the corresponding propyl oxime ethers. These results further indicate that inclusion of cyanoethyl moiety in all the three series reduces the activity marginally. The cyanoethyl ethers (XIV, XXV, XXXVI) have nearly the same activity as the corresponding simple methyl ethers. Among the oxime ethers of piperonal oxime and dillaldehyde oxime, the optimum structural requirement seems to be a side chain of four to

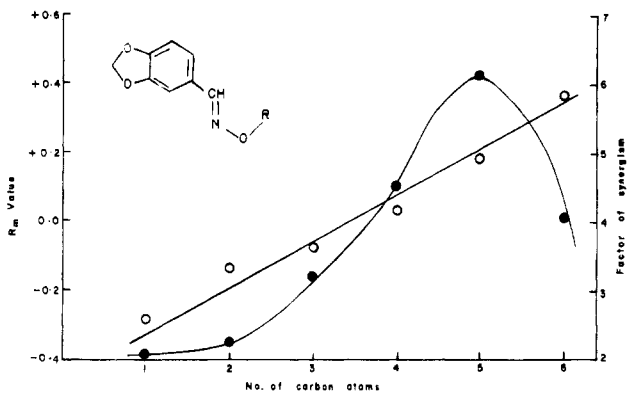


Figure 3. Relationship between R_m values, factor of synergism, and alkyl chain length of various alkyl ethers of piperonal oxime: (○) R_m values; (●) factor of synergism.

five carbon atoms, whereas in case of acetyldihydrodillapiole oxime ethers the simple methyl ether has an optimum activity. The results show another interesting observation different from those observed in the earlier series in that the simpler oxime ethers are more active than those with increased substitution in the aromatic ring. Thus, ether derivatives of piperonal oxime not only exhibit comparatively better synergistic activity than those of dillaldehyde oxime and acetyldihydrodillapiole oxime but are also more economical. Piperonal *O*-pentyl oxime ether, which showed the highest synergistic efficacy (synergism factor 6.16), therefore deserves further attention for evaluation as a future pyrethrum synergist.

Registry No. I, 76576-60-8; II, 23731-65-9; III, 120-57-0; IV, 94619-93-9; V, 94619-94-0; VI, 94619-95-1; VII, 94619-96-2; VIII, 94619-97-3; IX, 94619-98-4; X, 94619-99-5; XI, 94620-00-5; XII, 94620-01-6; XIII, 94620-02-7; XIV, 94620-03-8; XV, 94620-04-9; XVI, 94620-05-0; XVII, 94620-06-1; XVIII, 94620-07-2; XIX, 94620-08-3; XX, 94620-09-4; XXI, 94620-10-7; XXII, 94620-11-8; XXIII, 94620-12-9; XXIV, 94620-13-0; XXV, 94620-14-1; XXVI, 2089-36-3; XXVII, 33740-04-4; XXVIII, 90922-48-8; XXIX, 94620-15-2; XXX, 91641-60-0; XXXI, 94620-16-3; XXXII, 94620-17-4; XXXIII, 94620-18-5; XXXIV, 94620-19-6; XXXV, 94620-20-9; XXXVI, 75407-73-7.

Supplementary Material Available: NMR spectral and elemental analysis data of oxime ethers (7 pages). Ordering information is available on any current masthead page.

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