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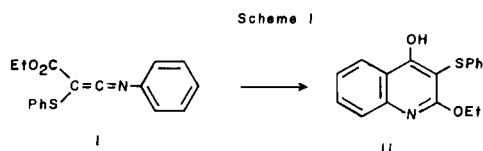
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Several ketenimines bearing ester groups were prepared and their thermal reactions gave 2-alkoxy-3-substituted-4-quinolinols VIa-e *via* presumed iminoketene intermediates. Subsequent oxidation of 2-alkoxy-3-(3-methylbut-2-enyl)-4-quinolinols VIc and VI d provided pyranoquinolines VIIIa and VIIIb.

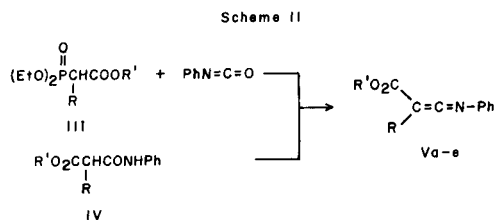
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A few examples of thermal reactions of ketenimines were known and their oligomerization gave the dimers [1], trimers [2], and quinazolines [3] arising from the cyclization across C=C or C=N bonds of cumulene groups of ketenimines. In the course of our study of functionalized heterocumulenes as the building blocks of heterocycles, we found [4] the novel cyclization of *N*-phenylcarboethoxy-(phenylthio)ketenimine (I) affording 2-ethoxy-3-phenylthio-4-quinolinol (II) (Scheme I). In this reaction the



carboethoxy group, directly bonded to the cumulene group, significantly contributed to the formation of the quinolinol. In this paper, we extended such a cyclization to the preparation of 2-alkoxy-3-substituted-4-quinolinols.

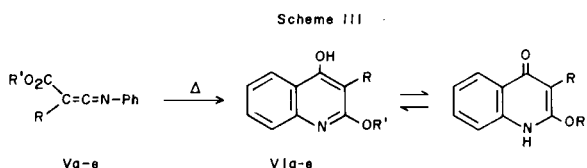
There was only one report [5], to our knowledge, related to the synthesis of ketenimines bearing ester groups. We prepared several *N*-phenylcarboalkoxy(alkyl or phenyl)-ketenimines Va-e by the Horner-Emmons reaction [6] and by the method of Bestmann *et al.* [7] (Scheme II). The Horner-Emmons reaction of phosphonates III and phenylisocyanate proceeded smoothly in the presence of sodium



hydride in benzene or tetrahydrofuran. On the other hand, the dehydration of the corresponding amides IV was carried out with triphenylphosphine, bromine, and triethylamine in dichloromethane. The ketenimines Va and Vb are known compounds [5], while Vc-e are new ones which were obtained as liquids and all exhibited characteristic absorption bands at 2030 cm^{-1} arising from C=C=N linkage in

ir spectrum. It was also found that Vc-e were too unstable to be distilled in vacuum owing to the thermal lability.

The ketenimines thus obtained were heated without solvent under reduced pressure at 150-180° for 5-30 minutes and sequential kugelrohr-distillation (Method A) gave 2-alkoxy-3-substituted-4-quinolinols VIa,b,c, and e (Scheme III). The quinolinols VIa-d were obtained when the ketenimines Va-d were heated in boiling *o*-dichlorobenzene (Method B) but lower yields were resulted in. The results were shown in Table I. It is known [8] that such



compounds exist as the quinolinol form in the crystalline state rather than quinolone form. The similar matter could be observed in our case. Namely, the ir spectrum (potassium bromide disk) showed the presence of OH groups, while in $^1\text{H-nmr}$ spectrum (deuteriochloroform and/or DMSO- d_6 as solvents) the signals of the phenolic or amide protons were vague.

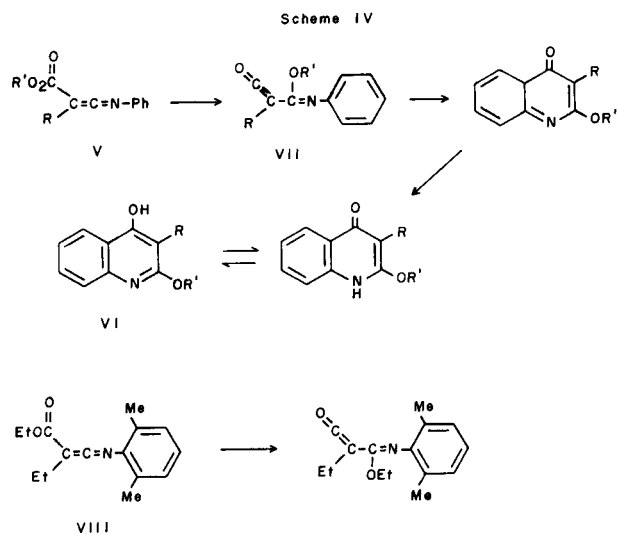
The formation of the quinolinols were thought to be ascribed to the cyclization of iminoketene intermediate VII [9], which might be generated by the initial migration of ethoxy group of the substituent, and sequential intramolecular trapping of the iminoketene by aromatic ring would derive the quinolinol (Scheme IV). However, our attempts to confirm the iminoketene intermediate were unsuccessful; *i.e.*, when *N*-(*o,o'*-dimethylphenyl) ethylcarboethoxyketenimine (VIII), that could not cyclize to quinolinol because of the substituents of aromatic ring, was heated at 250°, the absorption at 2035 cm^{-1} (ketenimine) was disappeared but the slightest absorption at 2130 cm^{-1} (iminoketene ?) was observed. This cannot declare the presence of iminoketene sufficiently.

As pointed by Grundon *et al.* [10], quinolinols VIc and VI d were convertible to pyranoquinolines IXa and IXb in 91% and 80% yields, respectively, by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in refluxing

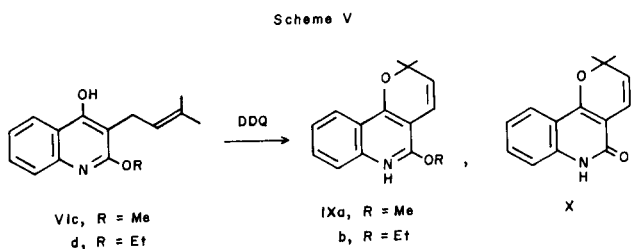
Table I
2-Alkoxy-3-substituted-4-quinolinols VIa-e

Product	R	R'	Yield (%) (Method, minutes) [a]	Mp (°C)	Empirical Formula	Elemental Analysis					
						Found			Calcd.		
						C	H	N	C	H	N
VIa	Me	Et	51 (A, 30) 31 (B)	145-146	C ₁₂ H ₁₃ NO ₂	71.22	6.61	7.01	70.91	6.45	6.89
VIb	Et	Et	22 (A, 30) 38 (B)	148-150	C ₁₃ H ₁₅ NO ₂	72.12	6.87	6.67	71.86	6.96	6.45
VIc	Me ₂ C=CHCH ₂ -	Me	29 (B)	137-138	C ₁₅ H ₁₇ NO ₂	73.75	7.16	5.67	74.05	7.04	5.76
VId	Me ₂ C=CHCH ₂ -	Et	51 (A, 15) 32 (B)	146-147	C ₁₆ H ₁₉ NO ₂	74.50	7.59	5.36	74.68	7.44	5.44
VIe	Ph	Et	81 (A, 5)	163-165	C ₁₇ H ₁₅ NO ₂	76.85	5.80	5.39	76.96	5.70	5.28

[a] Method A: Prepared by heating of V without solvent in kegelrohr at 50 mm Hg. Method B: Prepared by heating V in boiling *o*-dichlorobenzene for 1 hour.



benzene (Scheme V). The pyranoquinoline IXa was known [10] to be the precursor of flindersine X, one of the quinoline alkaloids.



EXPERIMENTAL

Melting points were determined using a Mitamura Riken melting point apparatus, and were corrected. IR spectra were recorded on a JASCO IRA-1 spectrometer. The ¹H-nmr spectra were taken on a JEOL JNNC-60 HL and mass spectra were obtained from a JEOL JMS-01SG-2 spectrometer on-line to a JEOL JEC-6 spectrum computer. Elemental Analyses were measured using a Yanagimoto CHN coder.

N-Phenylcarbethoxy-(3-methylbut-2-enyl)ketenimine (Vd) by the Horner-Emmons Reaction.

To a suspension of sodium hydride (50% in oil, 0.48 g, 10 mmoles) in benzene (10 ml) was added dropwise phosphonate III (3.0 g, 10 mmoles) in benzene (5 ml) under a nitrogen atmosphere. After the evolution of hydrogen ceased, phenylisocyanate (1.19 g, 10 mmoles) was added dropwise and the reaction mixture was heated at 30° for 15 minutes. Then the solvent was evaporated and the residue was washed with benzene-hexane. The washing was concentrated and chromatographed on silicagel to give Vd (1.44 g) in 54% yield.; ir (neat): 2030 (ν C=C=N), 1700 (ν C=O) cm^{-1} ; ¹H-nmr (carbon tetrachloride): δ 1.23 (t, 3H, CH₃CH₂O, J = 7.5 Hz), 1.65 (s, 6H, CH₃C=C), 2.85 (d, 2H, CH₂-C=C, J = 7.5 Hz), 4.12 (q, 2H, CH₃CH₂O, J = 7.5 Hz), 5.15 (brt, 1H, CH=C), 6.70-7.90 (m, 5H, aromatic protons).

The ketenimines Va, Vc and Ve were also obtained by the similar manner.

N-Phenylcarbethoxymethylketenimine Va.

This compound had ir (neat): 2030 (ν C=C=N), 1700 (ν C=O) cm^{-1} ; ¹H-nmr (carbon tetrachloride): δ 1.23 (t, 3H, CH₃CH₂O, J = 7.5 Hz), 1.83 (s, 3H, CH₃C=C), 4.15 (q, 2H, CH₃CH₂O, J = 7.5 Hz), 7.29 (s, 5H, aromatic protons).

N-Phenylcarbomethoxy-(3-methylbut-2-enyl)ketenimine Vc.

This compound had ir (neat): 2030 (ν C=C=N), 1700 (ν C=O) cm^{-1} ; ¹H-nmr (carbon tetrachloride): δ 1.63 (s, 6H, CH₃C=C), 2.85 (d, 2H, CH₂, J = 7.5 Hz), 3.65 (s, 3H, OCH₃), 5.15 (brt, 1H, CH=C), 7.25 (s, 5H, aromatic protons).

N-Phenylcarbethoxyphenylketenimine Ve.

This compound had ir (neat): 2030 (ν C=C=N), 1700 (ν C=O) cm^{-1} ; ¹H-nmr (deuteriochloroform): δ 1.23 (t, 3H, CH₃CH₂O, J = 7.5 Hz), 4.18 (q, 2H, CH₃CH₂O, J = 7.5 Hz), 7.13 (s, 10H, aromatic protons).

N-Phenylcarbethoxyethylketenimine Vb by dehydration of the Amide IVb.

To a solution of triphenylphosphine (6 mmoles) in dichloromethane (10 ml) was added dropwise bromine (6 mmoles) and sequentially amide IVb (1.18 g, 5 mmoles). After stirring for 15 minutes, triethylamine (23 mmoles) was added to the reaction mixture and the resulting solution was additionally stirred for 2 hours at room temperature. After removal of the solvent by evaporation, the residue was washed thoroughly with petroleum ether and the insoluble material was filtered off. The filtrate was concentrated to give ketenimine Vb (0.78 g) in 72% yield; ir (neat): 2030 (ν C=C=N), 1700 (ν C=O) cm^{-1} ; ¹H-nmr (carbon tetrachloride): δ 1.18 (q, 6H, CH₃CH₂O and CH₃CH₂C=C, J = 7.5 Hz), 2.25 (q, 2H, CH₃CH₂C=C, J = 7.5 Hz), 4.13 (q, 2H, CH₃CH₂O, J = 7.5 Hz), 7.28 (s,

5H, aromatic protons).

2-Ethoxy-3-(3-methylbut-2-enyl)-4-quinolinol VI d by Method A.

The ketenimine Vd (1.34 g, 5.06 mmoles) was heated at 180° and at 50 mm Hg for 15 minutes in a kugelrohr and sequential distillation at 1 mm Hg gave the quinolinol VI d (0.68 g) in 51% yield as a liquid which crystallized on standing; ir (potassium bromide): 3440 (ν OH) cm^{-1} ; ¹H-nmr (deuteriochloroform/DMSO-d₆): δ 1.38 (t, 3H, CH₃CH₂O, J = 6.75 Hz), 1.64, 1.76 (s, 6H, CH₃C=C), 3.40 (d, 2H, CH₂C=C, J = 6.75 Hz), 4.43 (q, 2H, CH₃CH₂O, J = 7.5 Hz), 5.18 (t, 1H, CHC=C, J = 7.5 Hz), 7.05-8.45 (m, 5H, aromatic protons); ms: m/e 257 (M⁺).

The similar manner employing ketenimines Va, Vb, and Ve gave the quinolinols VIa, VIb, and VIe, respectively.

2-Ethoxy-3-methyl-4-quinolinol (VIa).

This compound had ir (potassium bromide): 3400 (ν OH) cm^{-1} ; ¹H-nmr (deuteriochloroform/DMSO-d₆): δ 1.43 (t, 3H, CH₃CH₂O, J = 7.5 Hz), 2.20 (s, 3H, 3-CH₃), 4.50 (q, 2H, CH₃CH₂O, J = 7.5 Hz), 7.18-8.38 (m, 5H, aromatic protons); ms: m/e 203 (M⁺).

2-Ethoxy-3-ethyl-4-quinolinol (VIb).

This compound had ir (potassium bromide): 3400 (ν OH) cm^{-1} ; ¹H-nmr (deuteriochloroform/DMSO-d₆): δ 1.13 (t, 3H, 3-CH₃CH₂, J = 7.5 Hz), 1.40 (t, 3H, CH₃CH₂O, J = 7.5 Hz), 2.75 (q, 2H, 3-CH₃CH₂, J = 7.5 Hz), 4.45 (q, 2H, CH₃CH₂O, J = 7.5 Hz), 6.88-8.25 (m, 4H, aromatic protons), 8.60-9.60 (br, 1H, phenolic or amide proton); ms: m/e 217 (M⁺).

2-Ethoxy-3-phenyl-4-quinolinol (VIe).

This compound had ir (potassium bromide): 3440 (ν OH) cm^{-1} ; ¹H-nmr (deuteriochloroform/DMSO-d₆): δ 1.24 (t, 3H, CH₃CH₂O, J = 7.5 Hz), 4.30 (q, 2H, CH₃CH₂O, J = 7.5 Hz), 7.00-8.40 (m, 10H, aromatic protons and phenolic or amide proton); ms: m/e 265 (M⁺).

2-Methoxy-3-(3-methylbut-2-enyl)-4-quinolinol (VIc) by Method B.

The solution of the ketenimine Vc (1.5 g, 6.17 mmoles) in *o*-dichlorobenzene (10 ml) was heated under reflux for 3 hours. After removal of the solvent *in vacuo*, the residue was chromatographed on silicagel (eluent benzene-hexane) to give the quinolinol VIc (0.43 g) in 29% yield; ir (neat): 3400 (ν OH) cm^{-1} ; ¹H-nmr (deuteriochloroform): δ 1.80 (s, 6H, CH₃C=C), 2.45 (brd, 2H, CH₂C=C, J = 7.5 Hz), 4.00 (s, 3H, CH₃O), 5.25 (brt, 1H, CHC=C), 5.80-6.40 (br, 1H, amide proton), 6.90-8.10 (m, 4H, aromatic protons); ms: m/e 243 (M⁺).

5-Methoxy-2,2-dimethyl-2H-pyrano[3,2-c]quinoline (IXa).

A solution of the quinolinol VIc (0.1 g, 0.41 mmole) and DDQ (0.11 g, 0.44 mmole) in benzene (25 ml) was refluxed for 17 hours. After filtration of the reaction mixture, the filtrate was washed with 2*N* sodium hydrox-

ide solution and the organic layer was dried over anhydrous sodium sulfate. The removal of the solvent gave the pyranoquinoline IXa (0.09 g) in 91% yield as a liquid. This pyranoquinoline was known to be crystalline, but our efforts to crystallize it were unsuccessful. Gas chromatographic analysis and ¹H-nmr spectrum of this sample showed it almost pure; ¹H-nmr (deuteriochloroform): δ 1.50 (s, 6H, 2-CH₃), 4.07 (s, 3H, CH₃O), 5.50 (d, 1H, 3-vinyl H, J = 9.75 Hz), 6.60 (d, 1H, 4-vinyl H, J = 9.75 Hz), 7.10-8.10 (m, 4H, aromatic protons); ms: Calcd. for C₁₅H₁₅NO₂: 241.11131. Found: 241.11461.

Anal. Calcd. for C₁₅H₁₅NO₂: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.32; H, 6.49; N, 5.70.

In a similar manner employing the quinolinol VI d gave IXb in 80% yield; ¹H-nmr (carbon tetrachloride): δ 1.36 (t, 3H, CH₃CH₂O, J = 7.5 Hz), 1.45 (s, 6H, 2-CH₃), 4.43 (q, 2H, CH₃CH₂O, J = 7.5 Hz), 5.36 (d, 1H, 3-vinyl proton, J = 10.5 Hz), 6.56 (d, 1H, 4-vinyl H, J = 10.5 Hz), 6.90-8.10 (m, 4H, aromatic protons); ms: Calcd. for C₁₆H₁₇NO₂: 255.12595. Found: 255.12655.

Anal. Calcd. for C₁₆H₁₇NO₂: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.46; H, 6.95; N, 5.58.

REFERENCES AND NOTES

- [1] D. P. Deltsova, N. P. Gambaryan, Uy. V. Zeifman, and I. L. Knunyant, *Zh. Org. Khim.*, **8**, 856 (1972).
- [2] M. W. Barker and J. D. Rosamond, *J. Heterocyclic Chem.*, **9**, 1419 (1972).
- [3] M. N. Barker and J. D. Rosamond, *J. Heterocyclic Chem.*, **11**, 241 (1974).
- [4] J. Motoyoshiya, I. Yamamoto, and H. Gotoh, *J. Chem. Soc., Perkin Trans. I*, 2727 (1981).
- [5] G. Buono, *Tetrahedron Letters*, 5166 (1973).
- [6] W. S. Wadsworth and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).
- [7] H. J. Bestmann, J. Lienert, and L. Mott, *Ann. Chem.*, **718**, 24 (1968).
- [8] H. Gildemeister, H. Knorr, H. Mildenberger, and G. Salbeck, *Chem. Ber.*, **82**, 1656 (1982).
- [9] In the following paper the iminoketene intermediates were directly confirmed by IR spectrum under the severe conditions; H. Briebl, A. Lukosch, and C. Wentrup, *J. Org. Chem.*, **49**, 2772 (1984). The following paper described the formation of iminoketenes by chemical transformations; H. J. Gordon, J. C. Martin, and H. MacNab, *J. Chem. Soc., Chem. Commun.*, 957 (1983).
- [10] R. M. Bowman, M. F. Grundon, and K. J. James, *J. Chem. Soc., Perkin Trans. I*, 1055 (1973).