

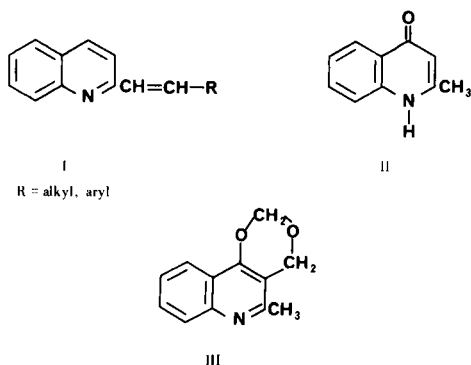
Synthesis of Some 2-Methyl-3-(2'-alkenyl)-4(1H)quinolones

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Received October 28, 1971

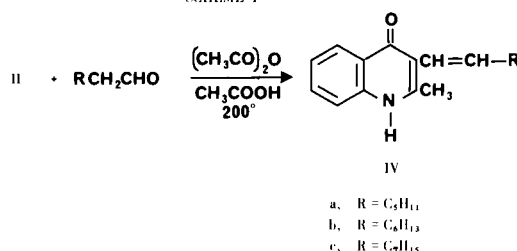
Quinaldine reacts with aliphatic and aromatic aldehydes in the presence of zinc chloride or acetic anhydride at elevated temperatures to give 2-(2'-alkenyl) and 2-styrylquinolines (I) respectively (2,3). On the other hand, it has been reported that 2-methyl-4(1H)quinolone (II) reacts with formaldehyde in the presence of sulfuric acid to give the cyclic methylene ether (III), indicating reaction at the 3-position rather than at the 2-methyl group (4).



We now wish to report that the reaction of *n*-aliphatic aldehydes with II at 200° in the presence of acetic anhydride and catalytic amounts of glacial acetic acid, leads to the formation of 2-methyl-3-(2'-alkenyl)-4(1H)quinolones (IV, Scheme 1). Heptanal, octanal and nonanal were the aldehydes used in this study. Table I shows the products obtained from this condensation reaction.

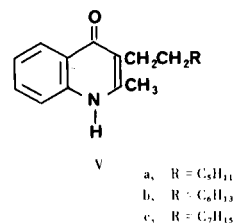
That these materials had the assigned structures and not moieties related to I or III was confirmed by elemental analysis, ultraviolet and infrared spectrophotometry and by nmr spectroscopy. In an excellent and detailed study of the ultraviolet absorption spectra of 2- and 4-quinolones, Edwig and Steck showed that 4-quinolones have 2 characteristic peaks in the near ultraviolet maximum, at wavelengths 318-330 mμ (5). This has been confirmed by other workers (6,7). Compounds IVa, IVb, and IVc showed this splitting at 314 and 334 mμ (Table II). Reported data showed that the carbonyl linkage in 4-quinolones has an infrared absorption band in the range 1647-1620 cm⁻¹ (8-10). As Table III shows, IVa, IVb and IVc have the carbonyl band at 1638 cm⁻¹. The nmr

SCHEME 1



spectrum (60 Mc) of IVb in d₅-pyridine exhibited a signal at 2.55 δ (3H, singlet) due to the 2-methyl group in the quinoline ring, thus supporting the assigned structure. All the other signals were also in complete agreement with IV.

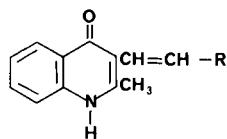
Catalytic reduction of IVa, IVb and IVc in ethyl acetate in the presence of 5% palladium on charcoal gave the corresponding dihydro derivatives V shown in Table IV. The infrared carbonyl absorption of compounds V appears at 1644 cm⁻¹, shifted to higher frequencies from the carbonyl absorption of compounds IV (see Table II). This would be expected from the disappearance of the conjugated double bond on hydrogenation.



Va was synthesized unequivocally by the Conrad-Limpach method, which involves the condensation of aniline with an appropriately substituted β-keto ester with subsequent cyclization of the 3-anilinoacetonate formed (Scheme 2) (11). Ethyl 2-*n*-heptylacetoacetate was prepared by the Knoevenagel condensation of heptaldehyde and ethyl acetoacetate followed by catalytic reduction (12). Condensation with aniline, followed by cyclization gave a material identical in all respects with Va.

2-Methyl-4(1H)quinolones have been shown to undergo the Mannich reaction at the 3-position indicating the phenolic character of the moiety (13,14). In the reaction

TABLE I



Aldehyde Used	Compound Number	Formula	M.p., °C	Yield %	C	Analysis, %			Found	
						Caled. H	N	C	H	N
Heptanal	IVa	C ₁₇ H ₂₁ NO	183-184	67 (a)	79.96	8.28	5.48	79.72	8.10	5.39
Octanal	IVb	C ₁₈ H ₂₃ NO	174-175	40 (b)	80.26	8.61	5.20	80.37	8.61	5.11
Nonanal	IVc	C ₁₉ H ₂₅ NO	168-170	27 (a)	80.52	8.89	4.94	80.42	8.66	4.81

(a) From benzene. (b) From water-ethanol.

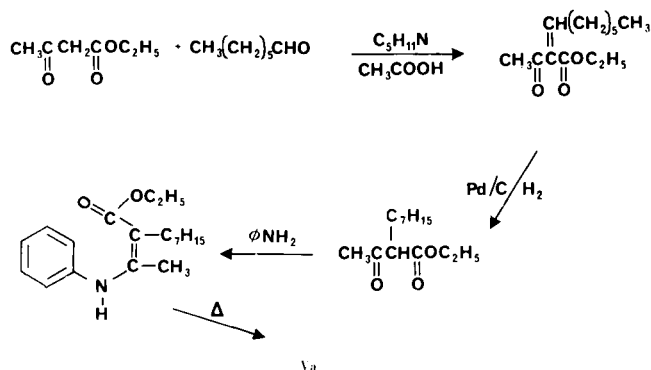
TABLE II

Ultraviolet Spectra of Some Substituted 4-Quinolones

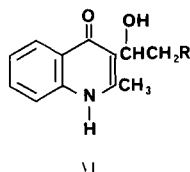
λ max (C₂H₅OH), m μ (log ϵ)

IVa	260 (4.44); 269 (4.50); 314 (4.00); 334 (3.97).
IVb	260 (4.38); 269 (4.42); 314 (3.94); 334 (3.93).
IVc	260 (4.40); 269 (4.45); 314 (3.95); 334 (3.93).
Va	240 (4.41); 247 (4.40); 322 (4.02); 336 (4.11).
Vb	240 (4.47); 247 (4.46); 322 (4.07); 336 (4.08).
Vc	240 (4.46); 247 (4.45); 322 (4.06); 336 (4.07).

SCHEME 2



of aliphatic aldehydes with II, the 3-position is similarly involved, the alcohol VI is probably formed first and dehydrates to IV under the reaction conditions.



EXPERIMENTAL

All melting points (Fisher-Johns) are uncorrected. Ir (potassium bromide pellet): Perkin-Elmer 21 spectrophotometer. Uv (ethanol solution): Beckman DK spectrophotometer with recorder. Nmr: Varian A-60 spectrometer (TMS internal standard) courtesy of Dr. Frank D. Popp, Clarkson College of Technology. Elemental analysis: Galbraith Laboratories, Knoxville, Tennessee; and Spang Microanalytical Laboratory, Ann Arbor, Michigan.

2-Methyl-3-(2'-alkenyl)-4(1H)-quinolones (IV).

General Procedure.

A mixture of 0.08 mole of the aldehyde and 0.04 mole of 2-methyl-4(1H)-quinolone (II) in a three necked flask equipped with stirrer, condenser and separatory funnel was heated to 200° in a silicone oil bath. Acetic anhydride (2.1 g.) and 6 drops of glacial acetic acid were then added and the reaction mixture kept at this temperature for 7 hours while stirring. It was then poured into 250 ml. of ice-water and allowed to stand overnight. The mixture was warmed to 60° and extracted twice with 200 ml. of benzene. The combined extracts were washed with 100 ml. of water. On cooling and partial evaporation of the benzene layer the compounds reported in Table I were obtained. Evaporation of the water layer gave unreacted II.

2-Methyl-3-Alkyl-4(1H)-quinolones by Hydrogenation of IV.

Compounds of type IV (0.004 mole) were hydrogenated in 100 ml. of ethyl acetate with 0.2 g. of 5% palladium on charcoal at 30 psi. The calculated drop in pressure was observed in 5-10 minutes. After filtering the catalyst the solvent was evaporated to give the compounds reported in Table IV.

Ethyl 2-n-Heptylideneacetoacetate.

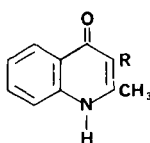
A mixture of ethyl acetoacetate (28 g., 0.22 mole) and heptaldehyde (25 g., 0.22 mole) in 50 ml. of glacial acetic acid was treated with a solution of 2 ml. of piperidine in 10 ml. of glacial acetic acid and allowed to stand at room temperature for 24 hours. After this time, the mixture was diluted with 100 ml. of water and extracted with three 200 ml. portions of benzene. The combined extracts were washed with water and dried over sodium sulfate. After removal of the solvent on the steam bath, the residue was distilled to give 24.6 g. (57%) of colorless oil, b.p. 87-91° (0.4 mm.) [lit. (12) b.p. 150-152° (14 mm.)].

TABLE III
Infrared Spectra of Some Substituted 4-Quinolones (a)

IVa	IVb	IVc	Va	Vb	Vc
3295 (w)	3425 (w)	3400 (m)	3235 (w)	3235 (w)	3235 (w)
3200 (w)	3200 (m)	3200 (m)	3030 (m)	3005 (m)	3050 (m)
3050 (w)	3008 (s)	3005 (s)	2925 (s)	2940 (s)	2900 (s)
2945 (w)	2945 (s)	2945 (s)	2850 (s)	2850 (s)	2840 (s)
2850 (w)	2850 (s)	2850 (s)	1642 (m)	1645 (m)	1644 (m)
1638 (m)	1638 (m)	1638 (m)	1610 (w)	1610 (w)	1610 (w)
1613 (m)	1614 (m)	1613 (m)	1592 (m)	1590 (m)	1591 (m)
1580 (s)	1580 (s)	1580 (s)	1555 (s)	1555 (s)	1555 (s)
1545 (s)	1548 (s)	1545 (s)	1498 (s)	1498 (s)	1497 (s)
1500 (s)	1500 (s)	1500 (s)	1438 (m)	1435 (m)	1435 (m)
1450 (s)	1440 (s)	1440 (s)	1408 (w)	1405 (w)	1405 (w)
1405 (m)	1405 (m)	1405 (m)			

(a) Bands are in cm^{-1} , w = weak, m = medium, s = strong.

TABLE IV



R	Compound Number	Formula	M.p., °C	Yield (a) %	C	Calcd. H	Analysis, %		Found H	N
							N	C		
n-Heptyl	Va	$\text{C}_{17}\text{H}_{23}\text{NO}$	233-234	100	79.33	9.01	5.44	79.36	9.04	5.43
n-Octyl	Vb	$\text{C}_{18}\text{H}_{25}\text{NO}$	228-229	100	79.65	9.28	5.16	79.60	9.21	5.14
n-Nonyl	Vc	$\text{C}_{19}\text{H}_{27}\text{NO}$	219-221	100	79.95	9.54	4.90	80.09	9.59	4.82

(a) From water-ethanol.

Ethyl 2-n-heptylacetate.

The preceding unsaturated ketoester (18 g., 0.7 mole) was hydrogenated in 70 ml. of ethyl alcohol with 0.5 g. of 5% palladium on charcoal at 45 psi. The calculated drop in pressure was observed in 25 minutes. The product was distilled to give 10.1 g. (64%) of colorless oil, b.p. 80-85° (0.4 mm.) [lit. (12) b.p. 144-146° (11 mm.)].

2-Methyl-3-n-heptyl-4(1H)quinolone (Va).

This compound was prepared from ethyl 2-n-heptylacetate and aniline by the method described by Reynolds and Hauser for the preparation of 2-methyl-4(1H)quinolone (11) but without purification of the intermediate anilinoacetonate. An overall yield of 30% was obtained, m.p. 233-234°. A mixture of the material obtained through this method with Va prepared by catalytic hydrogenation of IVa, showed no depression in melting point. The infrared and ultraviolet spectra of the two compounds were identical.

Acknowledgment.

The authors thank Dr. Frank D. Popp and Mr. Robert Piccirilli (both of Clarkson College of Technology) for helpful discussions and nmr spectrum respectively. One of us (A.C.C.) wishes to thank Dr. Donald J. Casey (American Cyanamid) and Dr. Joseph C. Carnes of this Institute for their encouragement.

REFERENCES

- (1) Rock Ledge Institute undergraduate research participant.
- (2) R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, John Wiley and Sons, Inc., New York, 1952, p. 82.
- (3) C. Kaslow and D. Stayner, *J. Am. Chem. Soc.*, **67**, 1716 (1945).
- (4) L. Monti and V. Cirelli, *Gazz. Chim. Ital.*, **66**, 42 (1936).
- (5) G. Edwig and E. Steck, *J. Am. Chem. Soc.*, **68**, 2181 (1946).

- (6) Y. Makisumi, *Chem. Pharm. Bull.* (Tokyo), **12**, 789 (1964).
- (7) I. Wells, *J. Biol. Chem.*, **196**, 331 (1952).
- (8) J. Price and J. Willis, *Aust. J. Chem.*, **12**, 589 (1959).
- (9) H. Rapoport and K. Holden, *J. Am. Chem. Soc.*, **82**, 4395 (1960).
- (10) A. Day and M. Joullie, *J. Heterocyclic Chem.*, **2**, 113 (1965).
- (11) G. Reynolds and C. Hauser, "Organic Synthesis", Col. Vol. III, John Wiley and Sons, Inc., New York, 1955, p. 593 and p. 374.
- (12) J. Stephen, I. Tonkin and J. Walker, *J. Chem. Soc.*, 1034 (1947).
- (13) C. Price and W. Jackson, *J. Am. Chem. Soc.*, **68**, 1282 (1946).
- (14) I. Nabih and M. Nasr, *Can. J. Chem.*, **34**, 1863 (1966).