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Received March 1, 1977

A synthetic method of attaching carbon-chain substituents to the 4-position of the quinoline ring was developed. In our approach enolate anions were generated from highly acidic enols under conditions in which the 4-chloroquinoline can be *N*-acylated or *N*-protonated. Isopropylidene alkyl(4-quinolyl)malonates or 5-alkyl-5-(4-quinolyl)barbituric acids were obtained from the reaction of 4-chloroquinolines with isopropylidene alkylmalonates in acetic anhydride or with 5-alkylbarbituric acids by heating in the absence of solvent. Some of the products were hydrolyzed and decarboxylated to give the corresponding 4-alkylated quinolines.

*J. Heterocyclic Chem.*, 14, 1081 (1977)

The versatile malonic ester synthesis can be in some instances applied to aryl halides, however, this usually requires the presence of strong electron withdrawing groups on the aromatic ring. In the case of 4-halogenated quinolines the nitrogen atom is somewhat electron withdrawing but is apparently too weak of an activating group to allow for facile displacements by malonic ester anions. In 1951 Elderfield and Serlin (2) reported a less than 12 percent yield of 2-(7-chloro-4-quinolyl)butanoate upon heating 4,7-dichloroquinoline with the sodium salt of diethyl ethylmalonate in dioxane at 125 degrees for 80 hours; recovered 4,7-dichloroquinoline (68 percent) and 4-ethoxy-7-chloroquinoline (13 percent) made up the balance of the reaction mixture. During the same year Nakayama (3) reported no reaction for the ethoxy-magnesium salt of diethyl malonate in refluxing benzene

with 4-chloroquinoline (5 hours) and with 4-bromoquinoline (6 hours).

It is well known that protonation or quaternization of a pyridine or quinoline nitrogen makes the ring much more susceptible to nucleophilic attack. However, the use of highly basic malonic ester anions precludes protonation and the use of a *N*-quaternizing group would normally require the additional step of its removal after reaction.

We have developed a method, successfully employed with 4-chloropyridine (4), where enolate anions can be generated from highly acidic enols under conditions in which the 4-chloroquinoline could be *N*-acylated or *N*-protonated reversibly in the reaction solution. The isopropylidene alkyl (4-quinolyl)malonates (I) outlined in Table I were prepared by warming a concentrated solution of the isopropylidene alkylmalonate with the 4-chloroquinoline in acetic anhydride. Several 5-alkyl-5-(4-quinolyl)barbituric acids (II) outlined in Table II were prepared by heating a slurry of the 5-alkylbarbituric acid with the 4-chloroquinoline in the absence of solvent. Some of the products I and II were hydrolyzed and de-

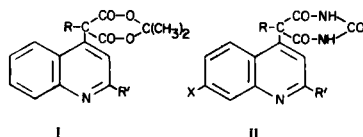


Table I

## Isopropylidene Alkyl (4-quinolyl)malonates (I)

R	R'	Yield (%)	Characterization (a)
Ethyl	H	50	m.p. 143-144° (heptane). <i>Anal.</i> Calcd. for C <sub>17</sub> H <sub>17</sub> NO <sub>4</sub> : C, 68.21; H, 5.73; N, 4.68. Found: C, 68.17; H, 5.73; N, 4.68.
Ethyl	Methyl	38	m.p. 199-200° (heptane-toluene). <i>Anal.</i> Calcd. for C <sub>18</sub> H <sub>19</sub> NO <sub>4</sub> : C, 68.99; H, 6.11; N, 4.47. Found: C, 69.08; H, 6.15; N, 4.52.
Allyl (b)	H	47	m.p. 154-155° (petroleum ether). <i>Anal.</i> Calcd. for C <sub>18</sub> H <sub>17</sub> NO <sub>4</sub> : C, 69.44; H, 5.51; N, 4.50. Found: C, 69.42; H, 5.52; N, 4.51.
Allyl (b)	Methyl	51	m.p. 154-156° (petroleum ether). <i>Anal.</i> Calcd. for C <sub>19</sub> H <sub>19</sub> NO <sub>4</sub> : C, 70.14; H, 5.88; N, 4.31. Found: C, 69.98; H, 5.85; N, 4.31.
Benzyl	H	44	m.p. 212-213° (heptane-toluene). <i>Anal.</i> Calcd. for C <sub>22</sub> H <sub>19</sub> NO <sub>4</sub> : C, 73.11; H, 5.30; N, 3.87. Found: C, 73.03; H, 5.34; N, 3.89.

(a) Examination by ir (Nujol) showed the same carbonyl absorption pattern (1740 vs, 1780 s) for all compounds. (b) Examination by pmr showed no rearrangement of the double bond; the same complex olefinic hydrogen pattern that is obtained with diethyl allylmalonate was observed.

Table II  
5-Substituted-5-(4-quinolyl)barbituric Acids (II)

R	R'	X	Yield (%)	Temperature (a)	Characterization (b)
Ethyl	H	H	52	130	m.p. 265-266°, softens at 175° and resolidifies (H <sub>2</sub> O). <i>Anal.</i> Calcd. for C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> ·H <sub>2</sub> O: C, 59.79; H, 5.02; N, 13.95. Found: C, 59.80; H, 5.04; N, 13.95.
Ethyl	H	Cl	62	170	m.p. 183-185° (H <sub>2</sub> O). <i>Anal.</i> Calcd. for C <sub>15</sub> H <sub>12</sub> ClN <sub>3</sub> O <sub>3</sub> : C, 56.70; H, 3.81; N, 13.23. Found: C, 56.61; H, 3.84; N, 13.21.
Benzyl	H	H	61	150	m.p. 292-293° (EtOH). <i>Anal.</i> Calcd. for C <sub>20</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub> ·C <sub>2</sub> H <sub>5</sub> OH (c): C, 67.50; H, 5.41; N, 10.74. Found: C, 67.59; H, 5.44; N, 10.76.
Ethyl	Methyl	H	66	(d)	m.p. 276-277°, softens at 161 and resolidifies (EtOH-H <sub>2</sub> O). <i>Anal.</i> Calcd. for C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub> ·H <sub>2</sub> O: C, 60.94; H, 5.44; N, 13.33. Found: C, 60.95; H, 5.43; N, 13.36.

(a) Temperature at which the slurry changed to a rigid gum. (b) Examination by ir (Nujol) showed the same carbonyl absorption pattern (1700 vs, 1740 s, 1760 m) for all compounds. (c) Examination by pmr showed the presence of one mole equivalent of ethanol, the characteristic peaks were superimposable upon added ethanol. (d) 4-Chloroquinaldine did not react by the fusion method; this compound was prepared under conditions used for the preparation of the malonates.

Table III  
Products of Hydrolysis and Decarboxylation

Product	Characterization	Starting Material	Yield (%)
4-Propylquinoline	Picrate m.p. 201-203° (EtOH). Lit. m.p. 204° (5).	5-Ethyl-5-(4-quinolyl)-barbituric acid	70
		Isopropylidene ethyl (4-quinolyl)malonate	81
4-Propylquinaldine	pmr identical to that reported (6).	5-Ethyl-5-(4-quinaldyl)-barbituric acid	96
		Isopropylidene ethyl (4-quinaldyl)malonate	86
4-Propyl-7-chloroquinoline	m.p. 44-45° (H <sub>2</sub> O). Lit. m.p. 47.5-49.5° (sublimed) (2).	5-Ethyl-5-[4-(7-chloroquinolyl)]barbituric acid	77
4-Phenethylquinoline	m.p. 102-103° (hexane). Lit. m.p. 103-104° (petroleum ether) (7)	5-Benzyl-5-(4-quinolyl)-barbituric acid	83
		Isopropylidene benzyl (4-quinolyl)malonate	78

carboxylated to the corresponding 4-alkylated quinolines (Table III).

#### EXPERIMENTAL

Melting points were determined in an oil bath apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, Georgia. The 5-substituted barbituric acids were prepared by the sodium methoxide catalyzed condensation of substituted diethyl malonates with urea (8). The substituted isopropylidene malonates were prepared as previously described (9) by dissolving the alkylmalonic acid in acetic anhydride-acetone solution, adding a few drops of sulfuric acid and allowing the solution to stand at room temperature for one or two days.

#### Isopropylidene Alkylmalonate.

The solution prepared as described above was diluted with

crushed ice. The crystals of product were filtered out and washed with water. Recrystallization from petroleum ether gave a 50% yield of crystals, m.p. 71-72.

*Anal.* Calcd. for C<sub>9</sub>H<sub>12</sub>O<sub>4</sub>: C, 58.68; H, 6.57. Found: C, 58.66; H, 6.61.

#### Isopropylidene Alkyl(4-quinolyl)malonates I.

A slurry of 2 millimoles of the 4-chloroquinoline, 2 millimoles of the isopropylidene alkylmalonate and 0.40 g. of acetic anhydride was warmed in a test tube fitted with a calcium chloride drying tube on an oil bath heated at 55° for 48 hours with stirring. Proper temperature control is necessary as slightly higher temperatures decompose the reagent ester. Also, the reaction fails under more dilute conditions. The product was isolated by cooling the reaction mixture, adding about 5 g. of crushed ice, 5 ml. of water, 5 ml. of hexane (to dissolve the unreacted 4-chloroquinoline) and then adding sodium bicarbonate to bring the pH to 7-8. The crystalline product was then filtered out and washed with water.

#### 5-Substituted-5-(4-quinolyl)barbituric Acids II.

A slurry of one millimole of the 5-substituted barbituric acid and one millimole of the 4-chloroquinoline was stirred in a test tube oil bath. The temperature was slowly increased to 130° over a period of 10 to 15 minutes. Upon increasing the temperature further, a rapid reaction apparently occurred somewhere between 130 and 170° since the thin slurry solidified. After heating at this temperature for an additional 10 minutes, the solid was cooled and triturated with 5 ml. of aqueous sodium bicarbonate solution and 5 ml. of hexane. The solid product was then filtered out and washed with water.

4-Chloroquinoline did not react by this fusion method, however, 5-ethyl-5-(4-quinolyl)barbituric acid was prepared in acetic anhydride media utilizing the conditions employed for the preparation of the isopropylidene alkyl (4-quinolyl)malonates given above.

#### Hydrolysis and Decarboxylation of Isopropylidene Alkyl(4-quinolyl)malonates to 4-Alkylated Quinolines.

A suspension of 300 mg. of the compound in 4 ml. of water was made slightly acidic with hydrochloric acid until the crystals almost all dissolved. The solution was then refluxed for 24 hours, cooled, and made strongly basic with sodium hydroxide, whereupon the product separated.

#### Hydrolysis and Decarboxylation of 5-Substituted-5-(4-quinolyl)barbituric Acids to 4-Alkylated Quinolines.

The compound, 300 mg., was dissolved in a solution of 200 mg. of sodium hydroxide in 4 ml. of water and refluxed overnight. The

solution was then made slightly acidic (pH 4-5) with hydrochloric acid and again refluxed overnight. The product separated after the solution was cooled and made strongly basic with sodium hydroxide.

#### Acknowledgment.

We are grateful to the Scientific Research Society of North America (Sigma XI) for a Grant-in-Aid of Research, and to Professor Gordon G. Evans of Tufts University for his encouragement.

#### REFERENCES AND NOTES

- (1) Author to whom correspondence should be directed.
- (2) R. C. Elderfield and I. Serlin, *J. Org. Chem.*, **16**, 1669 (1951).
- (3) I. Nakayama, *J. Pharm. Soc. Japan*, **71**, 1391 (1951).
- (4) F. X. Smith and G. G. Evans, *J. Heterocyclic Chem.*, **13**, 1025 (1976).
- (5) "Beilsteins Handbuch der Organischen Chemie", **20**, 412 (1935).
- (6) F. Minisci, R. Bernardi, F. Bertini, R. Galli, and M. Perchinummo, *Tetrahedron*, **27**, 3575 (1971).
- (7) M. Avramoff and Y. Sprinzak, *J. Am. Chem. Soc.*, **78**, 4090 (1956).
- (8) W. Pfeleiderer and E. Nubel, *Ann. Chem.*, **631**, 168 (1960).
- (9) B. Eistert and F. Geiss, *Chem. Ber.*, **94**, 929 (1961).