[CONTRIBUTION NO. 514 FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

SUBSTITUTED QUINOLINEACETIC ACIDS[1]

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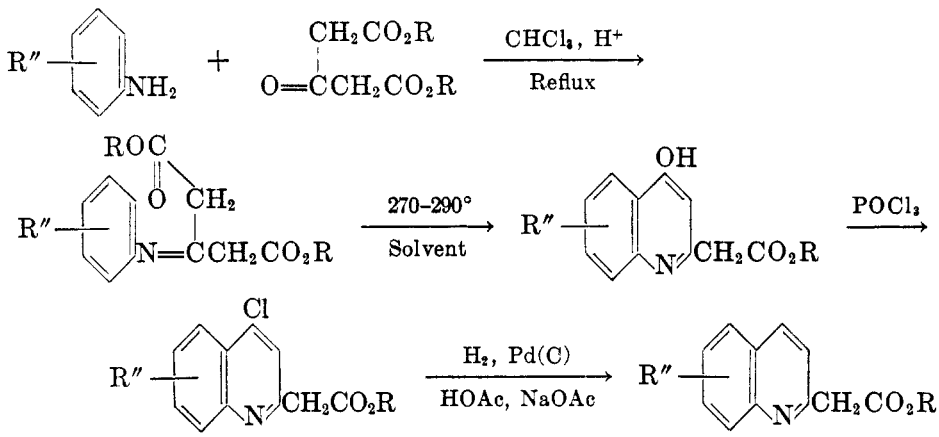
Received January 15, 1951

Ethyl 2-quinolineacetate has been prepared (1) by conversion of ethyl 2-quinolinepyruvate to the oxime, hydrolysis of the oxime to the α-oximino carboxylic acid, and decarboxylation to 2-quinolineacetonitrile. The nitrile was then converted to the desired ester. Ziegler and Zeiser (2) reported an unsuccessful attempt at the preparation of 2-quinolineacetic acid from quinaldyllithium and carbon dioxide. At about the same time, Bergstrom (3) also reported a similar attempt starting with quinaldylpotassium. Hauser and Weiss (4), however, succeeded in the carbethoxylation of quinaldine using potassium amide as the condensing agent. Ethyl 3-carbethoxy-2-quinolineacetate has been prepared (5) by the condensation of *o*-aminobenzaldehyde and ethyl acetonedicarboxylate.

The purpose of this work was to study the feasibility of the synthesis of 2-quinolineacetic acid esters through the use of the Conrad-Limpach reaction. Of the quinolineacetic acid esters reported in this paper, only ethyl 2-quinolineacetate has been reported previously (1, 4). The reactions involved in the syntheses are illustrated by the following series of equations.



R″ = H—, 4-CH_3—, 4-CH_3O—, 4-C_6H_5CO—, 3-Cl.
R = CH_3—, C_2H_5—. (See Table I)

The condensation between the aromatic amine and ethyl or methyl acetonedicarboxylate was most successful at the temperature of refluxing chloroform. Ring closure of the γ-carbalkoxy-β-arylaminocrotonic esters could not be accom-

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plished in quantity and required a short-time heat treatment in order to obtain the best yield of purer 4-hydroxy-2-quinolineacetic esters. A temperature higher than that attainable with boiling phenyl ether was necessary but either mineral oil alone or a mixture of mineral oil and phenyl ether did not give satisfactory results at the higher temperature. However, "Arochlor" and also a mixture of equal amounts of *n*-butyl phthalate and mineral oil gave satisfactory results at about 275°. The time factor was quite critical; periods longer than 15–30 seconds at this temperature gave a rather impure material. Except in the case of methyl β-(*p*-benzoylanilino)-γ-carbomethoxycrotonate, ring closure of the methyl ester gave no better yield than did the ethyl ester. Ring closure of ethyl β-carbethoxy-γ-(*p*-chloroanilino)crotonate should give a mixture of two isomers but the presence of a second substance could not be proven; it was assumed that the substance obtained was the 7-chloro compound. Saponification of the 4-hydroxyquinolineacetates was carried out either at room temperature or slightly above but in the case of the 6-methoxy- and the 7-chloro-4-hydroxyquinolineacetic ester only the decarboxylated substance, *i.e.* the corresponding quinaldine, could be isolated. The instability of the 2-pyridineacetic acids has been discussed previously (6, 7).

Conversion of the 4-hydroxy-2-quinolineacetic esters to the corresponding 4-chloro compounds could not be accomplished with the customary ease. Under the usual reaction conditions, only intractable, highly colored, nonsaponifiable oils were obtained. If, however, the 4-hydroxy compound and phosphoryl chloride were heated together for a short time in purified Diethyl Carbitol, reasonable yields were obtained following the procedure described in the experimental part. These substances could not be distilled without considerable decomposition even at 0.5 mm. Catalytic reduction of the 4-chloro-2-quinolineacetates proceeded satisfactorily, using palladized charcoal catalyst.

Typical procedures are described in the experimental part. The results are summarized in Table I.

EXPERIMENTAL

Ethyl β-anilino-γ-carbethoxycrotonate. Ethyl acetonedicarboxylate (8) (30 g., 0.15 mole), 13.8 g. (0.15 mole) of aniline, 100 ml. of chloroform, and two drops of hydrochloric acid were refluxed until no further quantity of water collected in a water separator. Most of the chloroform was removed by distillation and the remainder removed in a vacuum. The oily residue was dissolved in 150 ml. of hot ligroin and the solution filtered. After the cold filtrate remained in a salt-ice bath for 1–2 hours, the yield of snow-white fine crystalline solid was 36.6 g. (89%), m.p. 69–70°.

Anal. Calc'd for $C_{15}H_{19}NO_4$: N, 5.03. Found: N, 4.96.

Following the same procedure, *p*-toluidine and *p*-anisidine gave ethyl β-(*p*-toluidino)-γ-carbethoxycrotonate (m.p. 50–51°, 88%) and ethyl β-(*p*-anisidino)-γ-carbethoxycrotonate (m.p. 59.5–60.5°, 80%), respectively. *m*-Chloroaniline and *p*-aminobenzophenone gave β-arylamino-γ-carbethoxycrotonates which were noncrystallizable oils.

Ethyl 4-hydroxy-2-quinolineacetate. To 100 ml. of a 50–50 mixture of mineral oil and *n*-butyl phthalate heated to 270–275° was added 2 g. of ethyl β-anilino-γ-carbethoxycrotonate; the solution was stirred for 15 seconds and then poured immediately into a shallow aluminum cup immersed in an ice-water bath. The solution was stirred until crystallization began and the cup was removed and allowed to cool to room temperature. The com-

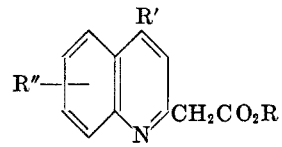
bined material from 25 runs was diluted with 1.5 liters of ligroin, filtered, and recrystallized from a mixture of 250 ml. ethyl alcohol, 150 ml. of ligroin, and 25 ml. of benzene. The yield of light yellow solid was 27.6 g. (66%), m.p. 202–204°.

Anal. Calc'd for $C_{13}H_{13}NO_3$: N, 6.06. Found: N, 6.22.

4-Hydroxy-2-quinolineacetic acid. Ethyl 4-hydroxy-2-quinolineacetate (3 g.) was allowed to stand with a cold, 10% potassium hydroxide solution for seven hours, then was filtered, ice was added, and the solution was neutralized with hydrochloric acid. The yield of solid was 2.46 g. (86%); m.p. 100–101° d., resolidifies and m.p. 224–225°.

TABLE I

SUBSTITUTED 2—QUINOLINEACETIC ACIDS AND ESTERS



R"	R'	R	M.P., °C.	YIELD, %	FORMULA	ANALYSIS N	
						Calc'd	Found
6-CH_3	OH	C_2H_5	210–212	75[b,f]	$C_{14}H_{15}NO_3$	5.72	5.79
7-Cl	OH	C_2H_5	235.5–238	62[b,f]	$C_{13}H_{12}ClNO_3$	5.28	5.63
6-CH_3O	OH	C_2H_5	181–184	50[c,g]	$C_{14}H_{15}NO_4$	5.37	5.38
6-C_6H_5CO	OH	CH_3	216–217	50[d,f]	$C_{19}H_{15}NO_4$	4.37	4.32
6-CH_3	OH	H	115 (dec.)		$C_{12}H_{11}NO_3$	6.45	6.36
6-C_6H_5CO	OH	H	83 (dec.)		$C_{18}H_{13}NO_4$	4.56	4.35
7-Cl	Cl	C_2H_5	65.5–66	69	$C_{13}H_{11}Cl_2NO_2$	4.93	5.00
6-CH_3O	Cl	C_2H_5	64–65	79	$C_{14}H_{14}ClNO_3$	5.02	5.15
6-C_6H_5CO	Cl	CH_3	117–118	43	$C_{19}H_{14}ClNO_3$	4.13	4.14
H	H	C_2H_5	[a]	37[e]			
7-Cl	H	C_2H_5	67–69	23	$C_{13}H_{12}ClNO_2$	5.62	5.84
6-CH_3O	H	C_2H_5	45.5–46	66	$C_{14}H_{15}NO_3$	5.72	5.76
6-C_6H_5CO	H	CH_3	98–100	64	$C_{19}H_{15}NO_3$	4.59	4.58

[a] B.p. 147–150° at 5 mm.; see ref. (4). [b] Recrystallized from abs. ethyl alcohol. [c] Recrystallized from abs. ethyl alcohol-benzene-ligroin (1:1:2). [d] Recrystallized from either 95% ethyl alcohol or acetone. [e] Yield based on ethyl 4-hydroxy-2-quinolineacetate; the intermediate 4-chloro compound was an oil which could not be distilled without extensive decomposition. [f] Ring closure in Arochlor, 290°. [g] Ring closure in mineral oil-*n*-butyl phthalate, 275°.

Anal. Calc'd for $C_{11}H_9NO_3$: N, 6.90. Found: N, 7.04.

A sample of the decarboxylated substance did not depress the melting point of authentic 4-hydroxyquinaldine.

Ethyl 4-chloro-6-methyl-2-quinolineacetate. A 50–50 solution (21 ml.) of phosphoryl chloride in Diethyl Carbitol was added to 3 g. of ethyl 4-hydroxy-6-methyl-2-quinolineacetate. The contents of the flask were mixed well and warmed on a steam-bath until the internal temperature was 80–85°, then the flask was cooled in ice-water and the contents poured with vigorous stirring onto 150 g. of cracked ice and 45 ml. of concentrated ammonium hydroxide. After pulverizing the solid, it was dissolved in ether and washed first with dilute ammonia solution and then with water. After removal of the ether, the substance was crystallized from dilute alcohol as slightly pink needles; yield, 2.2 g. (66%); m.p. 69–69.5°.

Anal. Calc'd for $C_{14}H_{14}ClNO_2$: N, 5.32. Found: N, 5.5.

Ethyl 6-methyl-2-quinolineacetate. Ethyl 4-chloro-6-methyl-2-quinolineacetate (5 g.) was reduced according to the standard procedure (9) using a palladized charcoal catalyst prepared according to the method of Hartung (10). The yield of the ester was 2 g. (46%), m.p. 49.2–50.5°.

Anal. Calc'd for $C_{14}H_{15}NO_2$: N, 6.13. Found: N, 5.95.

SUMMARY

The synthesis of substituted 2-quinolineacetic esters by the Conrad-Limpach reaction has been studied. Aniline, *p*-toluidine, *p*-anisidine, *m*-chloroaniline, and *p*-aminobenzophenone were condensed with acetonedicarboxylic esters to give the corresponding γ-carbalkoxy-β-arylaminocrotonate which on ring closure gave, respectively, the esters of 4-hydroxy-, 6-methyl-4-hydroxy-, 6-methoxy-4-hydroxy-, 7-chloro-4-hydroxy-, and 6-benzoyl-4-hydroxy-2-quinolineacetic acid. These were converted to the corresponding 4-chloro derivatives and the halogen atom was removed by catalytic reduction.

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REFERENCES

(1) BORSCHE AND MANTEUFEL, *Ann.*, **526**, 22 (1936).
(2) ZIEGLER AND ZEISER, *Ann.*, **485**, 174 (1931).
(3) BERGSTROM, *J. Am. Chem. Soc.*, **53**, 3027 (1931).
(4) HAUSER AND WEISS, *J. Am. Chem. Soc.*, **71**, 2023 (1949).
(5) BOBRANSKI AND SUCCHARDA, *Chem. Zentr.*, I, 2092 (1928).
(6) DOERING AND PASTERNAK, *J. Am. Chem. Soc.*, **72**, 143 (1950).
(7) ELDERFIELD, *Heterocyclic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1950, Vol. I, p. 595.
(8) GILMAN AND BLATT, *Org. Syntheses*, Coll. Vol. I, 2nd edition, 237 (1941).
(9) ADKINS, *Org. Syntheses*, **26**, 48 (1946).
(10) HARTUNG AND IWAMOTO, *J. Org. Chem.*, **9**, 514 (1944).