[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

THE ACID CATALYZED CLEAVAGE OF 4-QUINAZOLYLMALONIC ESTER AND RELATED COMPOUNDS TO 4-QUINAZOLONE[1]

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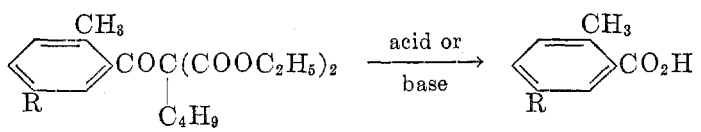
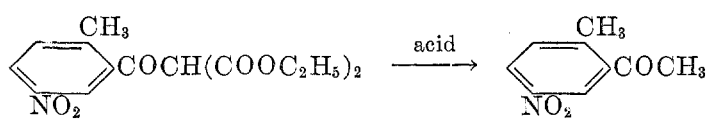
Malonic esters and their substituted derivatives undergo a well-known variety of cleavages under the influence of acidic or basic reagents. As representative of these cleavages the following examples may be cited. When a malonic ester is boiled with fairly concentrated mineral acid, it usually undergoes hydrolysis and decarboxylation to yield the corresponding acetic acid which may, in some cases, undergo further decarboxylation (1). Saponification with aqueous base generally gives the parent malonic acid. However, whereas monosubstituted malonic esters for the most part react with sodium ethoxide to give the sodium salt of the ester, under proper conditions mono- and di-substituted malonic esters undergo alcoholysis with loss of a carbethoxy group to give substituted acetic esters (2). Likewise dialkyl malonic esters give dialkyl acetic esters when treated with sodium or potassium in ether (3). One instance is reported in which a substituent other than a carbethoxy group is cleaved from a malonic ester. Under the influence of alcoholic ammonia diethyl dibenzylmalonate gives monobenzylmalonamide along with ethyl benzylmalonamate (4).

When one of the substituents in the malonic ester is an acyl group, cleavage may occur in either of two modes. Thus the following reactions have been noted



R = NO_2 or NH_2

(5)

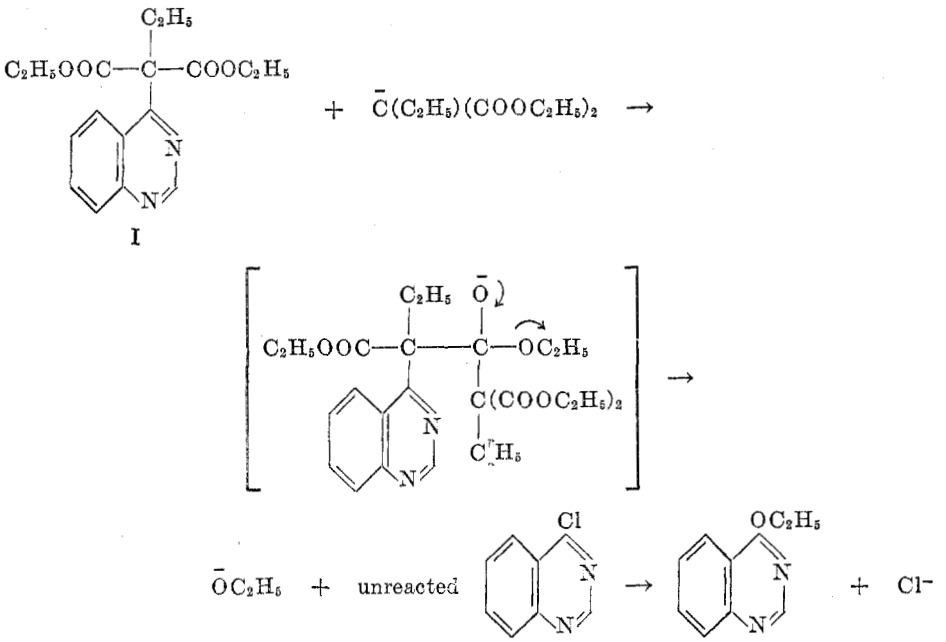


It is suggested that the course of the cleavage is determined by the presence of an enolizable hydrogen. Analogous "acid cleavages" of acyl malonic esters have also been noted (6).

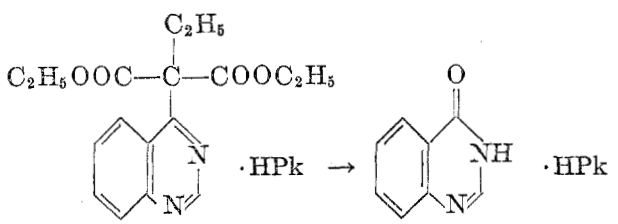
We have found that active methylene compounds of the general type of malonic ester carrying a 4-quinazolyl group as a substituent undergo cleavage in the presence of acid in a manner heretofore not observed except among the acyl derivatives of malonic ester.

[1] The material presented in this paper is taken from a dissertation presented by Irving Serlin in May 1950 in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Columbia University.

The original observation that during the preparation of diethyl ethyl-4-quinazolylmalonate from sodio diethyl ethylmalonate and 4-chloroquinazoline in absolute ether, some 13% of 4-ethoxyquinazoline was formed, suggested the following mechanism. It is assumed that the side product in this reaction was formed during the actual reaction and not during the working up of the product. A similar assumption has been made in consideration of the other reactions to be discussed.



Further, the picrate of diethyl ethyl-4-quinazolylmalonate displayed remarkable properties. Upon attempted recrystallization from 95% alcohol or when it was allowed to stand in alcoholic picric acid for long periods of time, this picrate was converted into the picrate of 4-quinazolone.

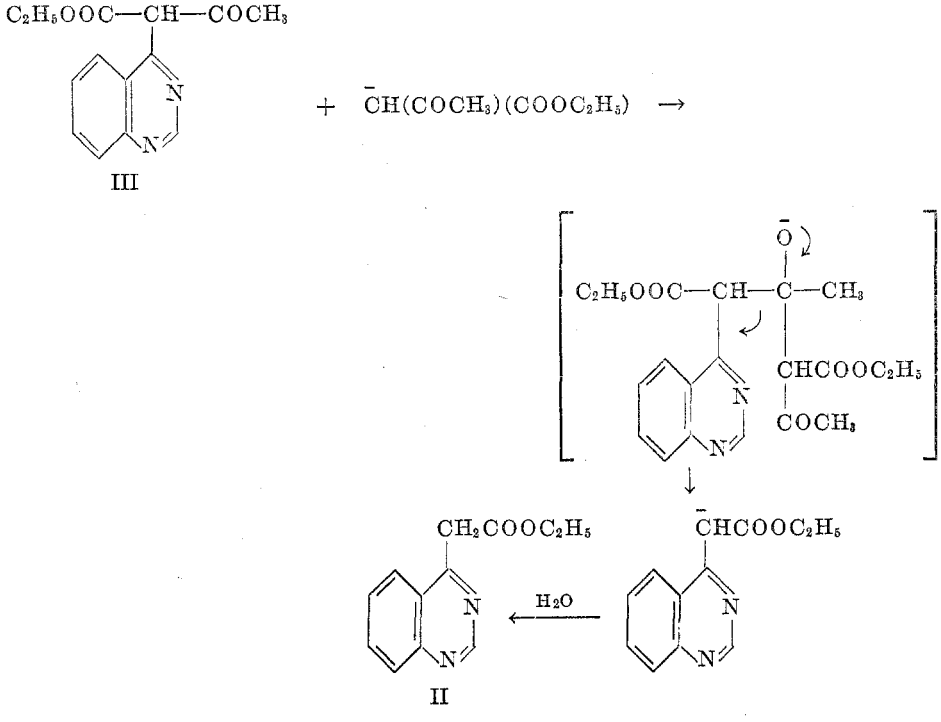


These observations prompted the preparation of a number of reactive methylene compounds carrying a 4-quinazolyl group, and a study of their behavior in acid media.

4-Chloroquinazoline readily condensed with sodio diethyl malonate to yield the 4-quinazolyl malonic ester. Likewise I was prepared from sodio diethyl

ethylmalonate. Condensation of 4-chloroquinazoline with sodio ethyl cyanoacetate proceeded easily. From 4-chloroquinazoline and sodio diethylphenylmalonate in ether solution no product was obtained but 29% of diethyl phenyl-4-quinazolyl malonate resulted when the reaction was carried out in boiling dioxane.

When the condensation of 4-chloroquinazoline with sodio ethyl acetoacetate in ether was attempted, ethyl 4-quinazolylacetate (II) was obtained in 46% yield. Since ethoxide ion was presumably not present in the reaction mixture, we believe that the formation of II is due to attack by acetoacetate ion on the primary product of the reaction with resultant acid cleavage of III in accordance with the following scheme.



A similar cleavage has been noted in the reaction of 1,3-dichloro-4,6-dinitrobenzene with sodio ethyl acetoacetate in refluxing benzene (7).

Likewise reaction of 4-chloroquinazoline with sodio ethyl phenylcyanoacetate in boiling dioxane gave a 20% yield of phenyl-4-quinazolylacetonitrile (IV). IV was amphoteric and could not be purified by the usual means. It was characterized by its picrate and picrolonate. The formation of IV can be explained on the same basis as that of II.

When 2,4-dichloroquinazoline was refluxed with sodio ethyl cyanoacetate in ether an excellent yield of a chloroquinazolylcyanoacetic ester was obtained. Since it is generally recognized that the 4-chlorine is more reactive than the

2-chlorine in quinazoline, this substance is undoubtedly ethyl 2-chloroquinazolylcyanoacetate.

The results presented in Table I show conclusively that 4-quinazolylmalonic esters and related compounds undergo a hitherto unrecognized type of cleavage under the influence of acids. As far as we are aware, no hydrolytic cleavage of

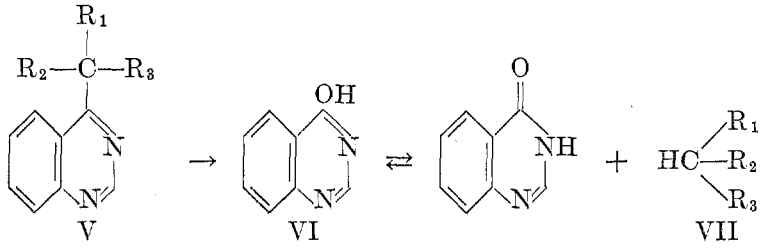
TABLE I

CLEAVAGE OF 4-QUINAZOLYL REACTIVE METHYLENE COMPOUNDS

4-QUINOZALYL DERIVATIVE	REAGENT	TIME	PRODUCTS AND YIELD
Q-CH($COOC_2H_5$)$_2$	0.3 *M* NaOEt	2 hr.	Q-$CH_2COOC_2H_5$ (82%)
Q-CH($COOC_2H_5$)$_2$	10% KOH in methanol	3 hr.	Q-CH_3 (71% crude)
Q-CH($COOC_2H_5$)$_2$	3 *N* HCl	10 min.	Q-OH (43%)
Q-C(C_6H_5)($COOC_2H_5$)$_2$	*N* HCl in 66% alcohol or acetone	10 min.	starting material
Q-C(C_6H_5)($COOC_2H_5$)$_2$	3 *N* HCl	10 min.	Q-OH (64%)
Q-C(C_2H_5)($COOC_2H_5$)$_2$	alc. HCl	20 min.	Q-OC_2H_5 (56.4%) CH(C_2H_5)($COOC_2H_5$)$_2$ (68%)
Q-C(C_2H_5)($COOC_2H_5$)$_2$	3 *N* HCl	10 min.	Q-OH (84%) CH(C_2H_5)($COOC_2H_5$)$_2$ (72%)
Q-C(C_2H_5)($COOC_2H_5$)$_2$	20% NaOH	3.5 hr.	Q-$CH_2CH_2CH_3$ (62%)
Q-CH(CN)($COOC_2H_5$)	3 *N* HCl	10 min.	starting material (73%)
Q-CH(CN)($COOC_2H_5$)	3 *N* HCl	12 hr.	Q-OH (85%)
Q-CH(CN)($COOC_2H_5$)	3 *N* HCl	4.5 hr.	Q-OH (57%)
Q-CH(C_6H_5)CN	3 *N* HCl	10 min.	starting material (100%)
Q-CH(C_6H_5)CN	3 *N* HCl	67 hr.	Q-OH (79%) $C_6H_5CH_2COOH$ (80%)
Q-CH(C_6H_5)CN	3 *N* HCl	13 hr.	Q-OH (59%) starting material (50% crude)
Q-CH(C_6H_5)CN	50% by vol. H_2SO_4	2 hr.	Q-OH (25%)
Q-$CH_2COOC_2H_5$	3 *N* HCl	10 min.	starting material (79%)
Q-$CH_2COOC_2H_5$	3 *N* HCl	2 hr.	Q-CH_3 (low yield)
Q-$CH_2COOC_2H_5$	20% NaOH	2 hr.	Q-CH_3 (63%)
2-Cl-Q-CH(CN)($COOC_2H_5$)	3 *N* HCl	20 hr.	2-OH-Q-CH(CN)($COOC_2H_5$) (85%)
2-Cl-Q-CH(CN)($COOC_2H_5$)	3 *N* HCl in 50% acetic acid	42.5 hr.	Benzoyleneurea (53%)

the type represented by V–VI with the exception of that displayed by the acyl substituted malonic esters has been reported.

It is also apparent that both aqueous and alcoholic acid accomplish the cleavage. In the latter case it must be presumed that the 4-ethoxyquinazoline is formed as the primary product of the reaction. Although the second product of the reaction (VII) was not isolated in every instance, the isolation of 4-hydroxyquinazoline (4-quinazolone) in every instance, taken together with the isolation of the



V VI VII

R_1 = H, C_2H_5, or C_6H_5 R_2 = $COOC_2H_5$
R_3 = $COOC_2H_5$, or CN

products corresponding to VII in certain cases, furnishes adequate proof for the reaction given above.

Interesting variations with respect to the nature of the substituent at the 4 position of the quinazoline nucleus manifest themselves. It is apparent that under comparable conditions (3 *N* hydrochloric acid, 10 min. boiling) a 4-quinazolylmalonic ester carrying a second substituent hydrolyzes to a greater extent than does the unsubstituted ester. However, all of the reactive methylene compounds of quinazoline were capable of cleavage in this manner, provided reaction conditions were severe enough. In particular, the 4-quinazolyl derivatives carrying a cyano group were more resistant to acid cleavage.

It therefore became of interest to investigate whether this characteristic cleavage was peculiar to the quinazoline nucleus. Two pyrimidine analogs of the type under consideration were prepared.

When sodio diethyl ethylmalonate was refluxed with 4-chloro-2,6-dimethylpyrimidine in isopropyl ether for six days no reaction occurred. However, when the same reaction was carried out in boiling dioxane for eighty-four hours, a 24.5% yield of the desired malonic ester, along with 17% of ethyl α-(2,6-dimethyl-4-pyrimidyl)butyrate was obtained. The formation of the latter compound can be explained on the same basis as that of similar compounds noted previously. From sodio ethyl cyanoacetate and 4-chloro-2,6-dimethylpyrimidine in dioxane, the pyrimidylcyanoacetate was obtained in 26% yield.

When diethyl ethyl-(2,6-dimethyl-4-pyrimidyl)malonate was boiled with 3 *N* hydrochloric acid for fourteen hours, 2,6-dimethyl-4-propylpyrimidine was obtained in 79.5% yield, along with 3% of crude 2,6-dimethyl-4-hydroxypyrimidine. The latter may have had its origin in an impurity in the original pyrimidylmalonic ester. On boiling with 3 *N* hydrochloric acid for twenty-two hours, ethyl 2,6-dimethyl-4-pyrimidylcyanoacetate gave 42% of 2,4,6-trimethylpyrimidine and no 2,6-dimethyl-4-hydroxypyrimidine.

In an attempt to prepare an analogous quinoline derivative, the readily available 4,7-dichloroquinoline was refluxed with sodio diethyl ethylmalonate in dioxane for eighty hours. From the products of the reaction, 4,7-dichloroquinoline was recovered in 69% yield and 14% of 4-ethoxy-7-chloroquinoline and 16% of ethyl α-(7-chloro-4-quinolyl)butyrate were isolated. The formation of the latter two substances can be accounted for on the same basis as those previously discussed.

From evidence presently available, it appears that the characteristic cleavage of 4-quinazolyl malonic esters and related compounds is a property traceable directly to the influence of the quinazoline nucleus, and furthermore that this reaction is characteristic of these compounds. There remain to be considered possible explanations for this behavior.

Although with information presently available it is not possible to propose a completely satisfactory mechanism for the reaction, the following considerations may be mentioned. Banks (8) has shown that reactions involving displacement of halogen from centers of low electron density in nitrogen heterocycles are acid

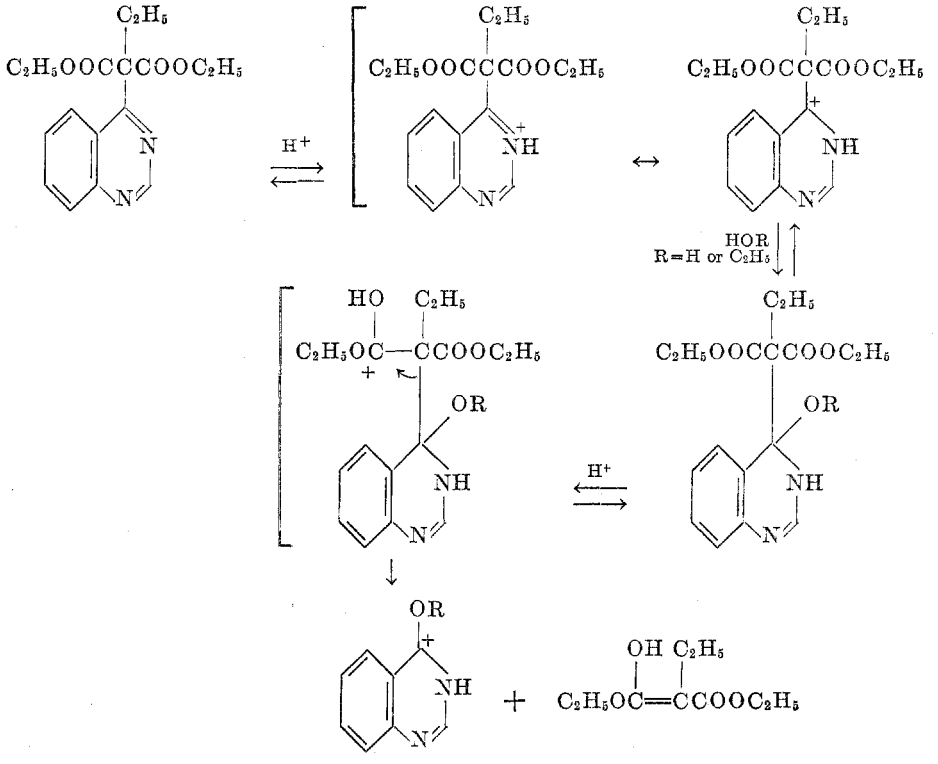


CHART I

catalyzed and Tomisek and Christensen (9) have applied this concept specifically to 4-chloroquinazoline. Based on these considerations a typical cleavage of the type under consideration may be formulated as in Chart I.

EXPERIMENTAL (10, 11)

Diethyl 4-quinazolylmalonate. This preparation is typical of the condensation of 4-chloroquinazoline with the sodio derivatives of the active methylene compounds. A 300-ml. 3-necked flask equipped with a stirrer and reflux condenser was used for the reaction.

To a suspension of sodio diethyl malonate prepared in 50 ml. of absolute ether from 0.575 g. of sodium and 4.0 g. of redistilled diethyl malonate was added all at once 4.9 g. of

powdered 4-chloroquinazoline (12). The mixture was stirred and refluxed for twenty hours. The solids were filtered off and added to 50 ml. of water. After neutralization with 3 *N* sulfuric acid, 2.2 g. of crude 4-quinazolylmalonic ester was collected. The ethereal filtrate from the solid was shaken with 3 *N* sodium hydroxide solution. Three layers separated, a dark amber oil, a yellow aqueous layer, and a yellow ethereal layer. The oil and aqueous layers were combined and neutralized with 3 *N* sulfuric acid, yielding an additional 1.1 g. of crude quinazolylmalonic ester. The total yield of crude product was 46% (based on the diethyl malonate used). The ether layer after washing with water and drying over magnesium sulfate gave 1.8 g. (37% recovery) of 4-chloroquinazoline. Diethyl 4-quinazolylmalonate forms small rosettes, m.p. 85.5–86.5°, after four recrystallizations from *n*-hexane.

Anal. Calc'd for $C_{15}H_{16}N_2O_4$: C, 62.5; H, 5.6; N, 9.7.

Found: C, 63.0, 62.5; H, 5.7, 5.8; N, 9.4.

Diethyl ethyl-4-quinazolylmalonate and 4-ethoxyquinazoline. A mixture of sodio diethyl ethylmalonate, prepared in 200 ml. of absolute ether from 38.3 g. of diethyl ethylmalonate (13) and 3.86 g. of sodium, and 27.5 g. of 4-chloroquinazoline was refluxed for fifteen hours. To the cooled colloidal suspension 100 ml. of water was added. The aqueous layer was extracted with ether, and after drying the combined ether solutions over sodium sulfate, the product was distilled under nitrogen and the following fractions were taken: I, 5.05 g., b.p. 55–100.5° (15–18 mm.); II, 3.17 g., b.p. 45–78° (0.18 mm.); III, 4.9 g. b.p. 79–90° (0.33 mm.); IV, 38.6 g. 155–168° (0.38 mm.). Fractions I and II representing 21.5% of recovered diethyl ethylmalonate were discarded.

Fraction III was a mixture of a colorless liquid and a colorless solid (it was necessary to use steam in the condenser to prevent clogging). The solid, after removal of the oil, was 4-chloroquinazoline. The liquid, b.p., 80–86° (0.35 mm.), melted at 47.8–48.5° after crystallization from dilute acetone. 4-Ethoxyquinazoline is reported as melting at 47–49°. (14).

Anal. Calc'd for $C_{10}H_{10}N_2O$: C, 68.9; H, 5.8.

Found: C, 68.9; H, 5.5.

The picrate melted at 172–173° after recrystallization from ethanol. The reported m.p. for the picrate of 4-ethoxyquinazoline is 178° (15).

Fraction IV, diethyl 4-quinazolylethylmalonate, was redistilled through a 12 inch vacuum-jacketed Vigreux column under nitrogen, and the middle fraction (24.6 g., b.p. 158–168° (0.2 mm.)) crystallized on scratching and chilling. The crystalline material, m.p. 54–62° (uncorr.), after two recrystallizations from the minimum of ether, in which it is very soluble, formed rosettes of needles, m.p. 63.5–65°.

Anal. Calc'd for $C_{17}H_{20}N_2O_4$: C, 64.5; H, 6.4; N, 8.9.

Found: C, 64.7; H, 6.4; N, 8.8.

Picrate of diethyl 4-quinazolylethylmalonate and conversion of it to 4-quinazolone picrate. When a picrate of diethyl 4-quinazolylethylmalonate was prepared in alcoholic solution, it formed bright yellow needles which melted at 108.5–110.5°.

Anal. Calc'd for $C_{23}H_{23}N_5O_{11}$: C, 50.6; H, 4.2.

Found: C, 50.7; H, 4.2.

If, however, the picrate was allowed to stand for long periods of time in excess alcoholic picric acid solution or if it was recrystallized from 95% alcohol a mixture of yellow needles and orange cubes, m.p. 110–197° (dec.) (uncorr.) resulted. When the original picrate (yellow needles) was allowed to stand in saturated alcoholic picric acid solution for two weeks and the resulting substance was recrystallized twice from 95% alcohol, yellow cubes, m.p. 203.5–204.5°, of the picrate of 4-quinazolone were obtained. Bogert and Hand (16) report the m.p. as 203.5–204.5°. The melting point of mixtures of this picrate with authentic 4-quinazolone picrate was not depressed.

The picrate of 4-quinazolone on slow cooling from its hot solution in 95% alcohol gives a mixture of orange cubes and yellow flakes. At about 190° the orange cubes appear to melt and to resolidify into yellow crystals which melt with decomposition at 203.5–204.5°.

Ethyl 4-quinazolylcyanoacetate. To a suspension of sodio ethyl cyanoacetate prepared from 1.44 g. of sodium and 7.06 g. of ethyl cyanoacetate in 100 ml. of anhydrous ether was

added 10.5 g. of 4-chloroquinazoline. After refluxing for fifteen hours, the ether was distilled to leave a thick slurry. To this was added successively 30 ml. of alcohol and 125 ml. of water. On neutralization with 3 *N* hydrochloric acid, 12.8 g. of solid separated. Recrystallization of this material from 95% alcohol gave 9.5 g. of light brown needles. After further recrystallization from 95% alcohol with decolorizing carbon, yellow-brown needles, m.p. 172–173° were obtained.

Anal. Calc'd for $C_{13}H_{11}N_3O_2$: C, 64.7; H, 4.6; N, 17.4.
Found: C, 65.0; H, 4.5; N, 17.4.

Reaction of 4-chloroquinazoline with sodio ethyl acetoacetate. Ethyl 4-quinazolylacetate. To a suspension of sodio ethyl acetoacetate prepared from 1.44 g. of sodium and 8.14 g. of ethyl acetoacetate in 100 ml. of absolute ether was added 10.5 g. of 4-chloroquinazoline. After addition of 30 ml. of absolute ether the mixture was refluxed for twenty-eight hours. After removal of most of the ether, 100 ml. of water was added giving a solution of *p*H 8. This was brought to *p*H 6 with hydrochloric acid and the heavy cream colored precipitate was filtered off. The orange filtrate was chilled and additional solid material was obtained. The combined solid was recrystallized from diluted alcohol with decolorizing carbon, yielding 6.2 g. (46%) of light yellow needles, m.p. 105° with softening below 100°. Five further crystallizations from hexane with charcoal gave very fine colorless needles, m.p. 108–109°. The substance darkened on long exposure to light.

Anal. Calc'd for $C_{12}H_{12}N_2O_2$: C, 66.6; H, 5.6; N, 13.0.
Found: C, 66.4; H, 5.3; N, 13.1.

Diethyl phenyl-4-quinazolylmalonate. To sodio diethyl phenylmalonate prepared from 18.44 g. of diethyl phenylmalonate and 1.44 g. of sodium in 200 ml. of pure dioxane (17) was added 10.54 g. of 4-chloroquinazoline. The mixture was refluxed with stirring for one hundred thirty-four hours. After chilling 3.16 g. of solid material was filtered off and the filtrate was concentrated under reduced pressure to an orange oil. This was taken up in 200 ml. of ether and about 20 mg. of flocculent solid was filtered off. The ether solution was washed with water until the washings were neutral, dried and the residue, after removal of the solvent, was distilled. The following fractions were collected: I, 13.06 g., b.p. 102–108° (0.2 mm.); II, 6.70 g., b.p. 170–180° (0.4 mm.).

Fraction I consisted of unreacted diethyl phenylmalonate (8.98 g.) and 4-chloroquinazoline (4.08 g.). Fraction II was a yellow green oily solid. After one recrystallization from 95% alcohol and four recrystallizations from ether-pentane this gave diethyl phenyl-4-quinazolylmalonate as rectangular prisms, m.p. 102–103°.

Anal. Calc'd for $C_{21}H_{20}N_2O_4$: C, 69.2; H, 5.5; N, 7.7.
Found: C, 69.3; H, 5.6; N, 7.6.

Phenyl-4-quinazolylacetonitrile. To a solution of sodio ethyl phenylcyanoacetate prepared from 1.44 g. of sodium and 13.35 g. of ethyl phenylcyanoacetate (18) in 200 ml. of pure dioxane (17) was added 10.5 g. of 4-chloroquinazoline. After refluxing for twenty-three hours, the solvent was removed under reduced pressure leaving a brown, gummy oil. This was taken up in ether and the ether solution was washed with water. When the ether solution was shaken with 3 *N* sodium hydroxide, three layers formed: a top ether layer, an intermediate thick, oily, red layer, and a bottom aqueous layer. The aqueous layer was drawn off and the remaining layers were washed with water during which the oil dissolved. After four further washes of the ether layer first with sodium hydroxide solution and then with water, the combined aqueous washes were neutralized to *p*H 7–8 with hydrochloric acid. After standing overnight, the bright yellow precipitate, m.p. 96–102° (uncorr.) was collected. This was crude phenyl-4-quinazolylacetonitrile (20% yield).

Since no satisfactory method of purification could be found, the substance was characterized as the *picrate*, prepared in 95% ethanol and recrystallized from the same solvent, m.p. 209.5–210° (dec.) in a bath preheated to 205°.

Anal. Calc'd for $C_{22}H_{14}N_6O_7$: C, 55.7; H, 3.0; N, 17.7.
Found: C, 55.9; H, 3.0; N, 17.3.

The *picrolonate* was prepared in 95% ethanol and recrystallized from the same solvent. It formed orange cubes, m.p. 229.5–230.5° (dec.) in a bath preheated to 225°.

Anal. Calc'd for $C_{26}H_{19}N_7O_5$: C, 61.3; H, 3.8; N, 19.3.

Found: C, 61.2; H, 4.0; N, 19.0.

Ethyl (2-chloro-4-quinazolyl)cyanoacetate. To a solution of sodio ethyl cyanoacetate prepared from 13.0 g. of ethyl cyanoacetate and 2.87 of sodium in 400 ml. of absolute ether was added 11.7 g. of 2,4-dichloroquinazoline (19). After refluxing for twenty-four hours, most of the ether was removed, 100 ml. of water was added to the residue and the *p*H was adjusted to 5. The cream colored precipitate (15.5 g. or 96%) was recrystallized four times from 95% ethanol with charcoal, yielding white needles, m.p. 145.5–147°.

Anal. Calc'd for $C_{13}H_{10}ClN_3O_2$: C, 56.6; H, 3.4; Cl, 12.9.

Found: C, 56.7; H, 3.7; Cl, 12.8.

Reaction of diethyl 4-quinazolylmalonate with sodium ethoxide. A solution of 8.8 g. of diethyl 4-quinazolylmalonate in sodium ethoxide (0.69 g. of sodium in 100 ml. of absolute alcohol) was refluxed for two hours and poured into 300 ml. of water containing 10 ml. of 3 *N* hydrochloric acid. From the solution (*p*H 5) a heavy pale yellow precipitate separated. The precipitate (81%) was recrystallized four times from dilute alcohol with charcoal giving thin, hair-like needles of ethyl 4-quinazolyl acetate, m.p. and mixture m.p. with a known sample, 108–109°.

Anal. Calc'd for $C_{12}H_{12}N_2O_2$: C, 66.6; H, 5.6; N, 13.0.

Found: C, 66.7; H, 5.5; N, 13.5.

The *picrate* melted at 222–225° (dec.) and did not depress the m.p. of the picrate of ethyl 4-quinazolylacetate obtained in the attempted preparation of ethyl 4-quinazolylacetoacetate.

The filtrate from the above substance was distilled until the b.p. reached 90°. To the distillate excess benzene was added and the resulting mixture was again distilled. The residue boiled at 120–122°, n_D^{21} 1.3897. Reported for diethyl carbonate, b.p. 126° (760 mm.), n_D^{20} 1.3846 (20).

4-Methylquinazoline. A. *From ethyl-4-quinazolylacetate.* When ethyl 4-quinazolylacetate was boiled for two hours with 20% sodium hydroxide solution and the cooled solution was extracted with ether, 63% of 4-methylquinazoline, m.p., 33.5–36.5°, b.p., 78° (0.15 mm.) was obtained from the ether extract. Reported m.p. 36–37° (21).

The *picrate* prepared in 95% alcohol and recrystallized from the same solvent was a mixture of light orange and green crystals, m.p. 182–183.5°. Reported m.p. 183.5° (21). The orange crystals turned green just before melting and the green crystals turned yellow on standing in 95% ethanol.

Anal. Calc'd for $C_{15}H_{11}N_5O_7$: C, 48.3; H, 3.0; N, 18.8.

Found: C, 48.3; H, 3.0; N, 18.5.

B. *From diethyl 4-quinazolylmalonate.* When this ester was boiled with 10% potassium hydroxide solution in methanol for three hours, and the resulting solution was diluted and acidified, 71% of 4-methylquinazoline, identified as above, was obtained.

4-n-Propylquinazoline. A mixture of 5 g. of diethyl ethyl-4-quinazolyl malonate was boiled with 50 ml. of 20% sodium hydroxide for three and one-half hours. The cooled solution, on which a colorless oil floated, was extracted with ether and the extract dried over sodium sulfate, yielding a milky oil which was fractionated under nitrogen giving the following fractions: I, 0.25 g., b.p. 30–80° (0.2 mm.); II, 1.37 g., b.p. 87° (0.2 mm.); III, 0.86 g., b.p., 150° (0.25 mm.); m.p., 56.5–65° (uncorr.); residue 0.10 g., m.p. 61–64° (uncorr.). Fraction III and the residue represented starting material. After correcting for recovered starting material, fraction II represented a 62% yield of 4-*n*-propylquinazoline.

The *picrate* of 4-*n*-propylquinazoline, yellow needles, melted at 166–166.5° (bath preheated to 160°) after recrystallization from 95% alcohol.

Anal. Calc'd for $C_{17}H_{15}N_5O_7$: C, 50.9; H, 3.8; N, 17.5.

Found: C, 51.3; H, 3.7; N, 17.7.

The *picrylsulfonate*, pale yellow-green plates, melted at 126–127° (bath preheated to 125°) after recrystallization from alcohol. It retained an alcohol of crystallization.

Anal. Calc'd for $C_{17}H_{16}N_5O_9S \cdot C_2H_5OH$: C, 44.6; H, 4.1; N, 13.7.

Found: C, 44.7; H, 4.2; N, 13.9.

The basic aqueous solution from the above ether extraction was neutralized with 6 *N* hydrochloric acid and extracted with ether. From the ether extract 0.02 g. of 4-quinazolone, identified by mixture m.p., was obtained. This may have been an impurity in the starting material.

Acid-catalyzed cleavage of diethyl ethyl-4-quinazolylmalonate to 4-quinazolone and diethyl ethylmalonate. This represents the typical procedure for the acid cleavage of the substances reported in Table I. In other experiments differences in the manner of working up only are given. A solution of 5 g. of the malonate was refluxed for ten minutes in 15 ml. of 3 *N* hydrochloric acid. After cooling the solution was extracted with ether. The residue from the washed and dried ether extract was fractionated yielding 2.15 g. (72%) of diethyl ethylmalonate, b.p. 103° (20 mm.), n_D^{20} 1.4143. Reported b.p., 92° (10 mm.) (22), n_D^{20} 1.4170 (23).

The *dihydrazide* prepared according to Curtius and Rechnitz (24) formed white needles from alcohol, m.p. and mixture m.p. with a known sample (25), 165.5–166.5°.

The *di-N-benzylamide* (26) showed m.p. and mixture m.p.'s 142.5–143°. Reported m.p. 137–138° (26).

The acid aqueous solution from the above ether extraction was neutralized with 3 *N* sodium hydroxide. After chilling, 4-quinazolone was filtered off. Ether extraction of the filtrate gave additional material. The total yield of 4-quinazolone, identified by m.p. and mixture m.p.'s, 214.5–215.5°, after one recrystallization from 95% ethanol and two from benzene, was 1.94 g. (84%).

The *picrate*, m.p. and mixture m.p.'s, 202–204° (dec.), was a mixture of orange and yellow crystals characteristic of the picrate of 4-quinazolone.

Acid cleavage of ethyl 4-quinazolylcyanoacetate. After refluxing for twelve hours, the acid solution was made basic and extracted with ether. Reacidification of the aqueous solution and continuous extraction with ether gave 85% of 4-quinazolone.

Acid cleavage of phenyl-4-quinazolylacetonitrile. Most of the experiments summarized in Table I followed the usual procedure.

When 0.2 g. of the acetonitrile was refluxed with 4 ml. of 3 *N* hydrochloric acid for sixty-seven hours, ether extraction of the cooled acid solution gave 80% of phenylacetic acid, m.p. and mixture m.p.'s, 75.5–77°, after one recrystallization from pentane.

Neutralization of the acid solution from the above ether extraction with sodium carbonate and continuous ether extraction for five hours gave 79% of 4-quinazolone.

Acid cleavage of ethyl 2-chloro-4-quinazolylcyanoacetate. After boiling 1 g. of the cyanoacetate in 8 ml. of 3 *N* hydrochloric acid for twenty hours, 0.79 g. (85%) of ethyl 2-hydroxy-4-quinazolylcyanoacetate separated on cooling. This formed pale yellow-green crystals, m.p. 290–291° (dec.), after two recrystallizations from alcohol.

Anal. Calc'd for $C_{13}H_{11}N_3O_3$: C, 60.7; H, 4.3; N, 16.3.

Found: C, 60.8; H, 4.1; N, 16.7.

When the cyanoacetate (1.5 g.) was boiled with a mixture of 3 *N* hydrochloric acid in 50% acetic acid (200 ml.) for forty-two and one-half hours and the solution then concentrated to one quarter of its volume, neutralization with sodium bicarbonate gave 53% of benzoyleneurea, m.p. 349–351°. Reported m.p., over 350° (27).

6,8-Dinitrobenzoyleneurea prepared from the above melted at 273–274° (dec.). Reported m.p., 274–275° (dec.) (28).

6-Nitrobenzoyleneurea prepared from the above melted at 333.5–335° (dec.). Reported m.p., 330–331° (dec.). (29).

Alcoholysis of diethyl ethyl-4-quinazolylmalonate. A solution of 2.9 g. of diethyl ethyl-4-quinazolylmalonate in 100 ml. of absolute alcohol saturated with hydrogen chloride without cooling was refluxed for twenty minutes and then poured into a mixture of ice and 100 ml. of saturated sodium bicarbonate solution. This solution was extracted with several

portions of ether, and the residue from the dried ether extract was distilled under nitrogen. The following fractions were collected: I, 0.73 g., b.p. 54° (0.25 mm.); II, 0.56 g., b.p. 84° (0.27 mm.) which solidified on cooling; III, 1.11 g. of a mixture of white solid and yellow liquid, b.p. 156° (0.3 mm.).

Fraction II was identified by mixture m.p.'s as 4-ethoxyquinazoline. The picrate, m.p. 171–174.5° (15) depending on the rate of heating, did not depress the m.p. of a known sample.

Fraction I was diethyl ethylmalonate, identified by m.p. and mixture m.p.'s (137–139°) of the di-N-benzylamide (26).

Fraction III was recovered starting material.

The yield of 4-ethoxyquinazoline was 56.5% and that of diethyl ethylmalonate was 68% based on reacted starting material.

Diethyl ethyl-(2,6-dimethyl-4-pyrimidyl)malonate. To a solution of sodio diethyl ethylmalonate prepared in 500 ml. of pure anhydrous dioxane from 32.9 g. of diethyl ethylmalonate and 3.9 g. of sodium, 25 g. of 4-chloro-2,6-dimethylpyrimidine (30) was added. After refluxing with stirring for eighty-four hours, the mixture was cooled and filtered from inorganic salts. The filtrate was concentrated at 50° (20 mm.) to a red oily residue. This was treated with 25 ml. of cold water and extracted with ether. The ether extract was washed with water, which removed most of the red color, and dried over sodium sulfate. After removal of the ether, the residue was distilled under nitrogen through a ten inch Vigreux column, the following fractions being collected: I, (20.5 g.) b.p., 25–68° (0.2 mm.) was a mixture of starting materials; (II, (6.29 g., representing a 17% yield of ethyl-α-(2,6-dimethyl-4-pyrimidyl)butyrate), b.p. 74–103° (0.3 mm.) was a pale yellow-green liquid; III, [12.25 g. representing a 24.5% yield of diethyl ethyl-(2,6-dimethyl-4-pyrimidyl)-malonate based on the sodium used], b.p. 103–110° (0.2 mm.).

Fraction II was redistilled giving a middle cut, b.p. 80° (0.14 mm.), n_D^{25} 1.4763. A *picrate* prepared from the middle cut in alcohol and recrystallized three times from water melted at 127.5–128.5°.

Anal. Calc'd for $C_{18}H_{21}N_5O_9$: C, 47.9; H, 4.7; N, 15.5.
Found: C, 48.2; H, 4.7; N, 15.5.

The *picrylsulfonate* melted at 184.5–186.5° (dec.) after three recrystallizations from alcohol-ether and one recrystallization from alcohol.

Anal. Calc'd for $C_{18}H_{21}N_5O_{11}S$: C, 41.9; H, 4.1; N, 13.6.
Found: C, 42.1; H, 4.2; N, 13.6.

Fraction III was redistilled giving a middle fraction, b.p., 107° (0.15 mm.), n_D^{25} 1.4800.

Anal. Calc'd for $C_{15}H_{22}N_2O_4$: C, 61.2; H, 7.5; N, 9.5.
Found: C, 61.4; H, 7.6; N, 9.8.

The *picrylsulfonate* prepared in alcohol formed white needles, m.p. 160.5–161.8°, after recrystallization from alcohol-ether.

Anal. Calc'd for $C_{21}H_{25}N_5O_{13}S$: C, 42.9; H, 4.3; N, 11.9.
Found: C, 43.1; H, 4.0; N, 11.6.

Ethyl 2,6-dimethyl-4-pyrimidylcyanoacetate. To a solution of sodio ethyl cyanoacetate prepared from 13.9 g. of ethyl cyanoacetate and 2.83 g. of sodium in 200 ml. of pure dioxane, 10 g. of 4-chloro-2,6-dimethylpyrimidine was added. After refluxing for twenty hours, the filtered solution was brought to *p*H 6 with hydrochloric acid. After filtering from 2.1 g. of solid material which was discarded, the filtrate was concentrated under reduced pressure and the residue was dissolved in 3 *N* sodium hydroxide and precipitated with 3 *N* hydrochloric acid. The dirty white precipitate, (3.95 g. or 26%) after drying, was recrystallized three times from *n*-heptane (1 g. per 100 ml.) and gave straw colored needles, m.p. 172.5–173°.

Anal. Calc'd for $C_{11}H_{13}N_3O_2$: C, 60.3; H, 6.0; N, 19.2.
Found: C, 60.3; 60.5; H, 5.8; 5.9; N, 19.4.

Acid hydrolysis of diethyl ethyl-(2,6-dimethyl-4-pyrimidyl)malonate. A solution of 1.97 g. of analytically pure diethyl ethyl-(2,6-dimethyl-4-pyrimidyl)malonate in 10 ml. of 3 *N* hydrochloric acid was refluxed for fourteen hours. To the cooled green solution a slight

excess of sodium bicarbonate was added. The oily layer was extracted into ether and the aqueous solution was worked up as described below. The dried ether extract was concentrated and the residue was distilled under nitrogen yielding 0.74 g. of clear colorless oil with a nicotine-like odor, b.p., 75° (10 mm.). This material, 2,6-dimethyl-4-*n*-propylpyrimidine, was characterized as the *picrate* which was prepared in alcohol and recrystallized from ether. It formed yellow plates, m.p. 85–86.5°.

Anal. Calc'd for $C_{15}H_{17}N_5O_7$: C, 47.5; H, 4.5; N, 18.5.
Found: C, 47.6; H, 4.6; N, 18.7.

The *picrylsulfonate*, prepared in alcohol and recrystallized from alcohol-ether, melted at 148–149.5°.

Anal. Calc'd for $C_{15}H_{17}N_5O_9S$: C, 40.6; H, 3.9; N, 15.8.
Found: C, 40.7; H, 3.9; N, 15.8.

Acid hydrolysis of ethyl 2,6-dimethyl-4-pyrimidylcyanoacetate. A solution of 0.5 g. of the cyanoacetate in 4 ml. of 3 *N* hydrochloric acid was refluxed for twenty-two hours. After cooling, the solution was neutralized with sodium bicarbonate to *p*H 9.1 and extracted with ether in a continuous extractor for twelve hours. From the extract, the dihydrate of 2,4,6-trimethylpyrimidine, m.p. 44.5–45.5° was obtained as a hygroscopic substance. Bowman (31) reports the substance as melting at 47–48°.

The *picrate*, prepared in alcohol and recrystallized from benzene-ether, formed yellow green needles, m.p. 145–146°. Reported 145–146° (32).

Anal. Calc'd for $C_{13}H_{13}N_5O_7$: C, 44.5; H, 3.7; N, 19.9.
Found: C, 44.5; H, 3.7; N, 19.9.

Based on an aliquot portion of the total product from which the picrate was isolated, the yield was 42%.

Reaction of 4,7-dichloroquinoline with diethyl ethylmalonate. A solution of 105 g. of 4,7-dichloroquinoline (33) and sodio diethyl ethylmalonate (prepared from 11.5 g. of sodium and 100 g. of the ester) in 500 ml. of pure dioxane was heated with stirring at 70° for fourteen hours and then at 90° for twenty-four hours. No evidence of reaction was observed. The mixture was then heated at 125° for eighty hours and the dioxane was removed under reduced pressure. The residue was treated with 200 ml. of water and extracted with ether. From the ether extract on concentration 41.1 g. of unreacted 4,7-dichloroquinoline was obtained after recrystallization from methanol. After removal of the methanol from the mother liquor obtained above, the residue was distilled through a 12-inch vacuum-jacketed Vigreux column and the following fractions were collected: I, (27.3 g.), b.p. 90–100° (10 mm.), was unreacted diethyl ethylmalonate; II, (30.8 g.), b.p. 140–150° (1.5 mm.) was 4,7-dichloroquinoline; III, (14.18 g.), b.p. 140° (0.2 mm.) was a light brown solid. After three recrystallizations from hexane it melted at 101–102.5° and gave analytical figures for 4-ethoxy-7-chloroquinoline.

Anal. Calc'd for $C_{11}H_{10}ClNO$: C, 63.6; H, 4.8; N, 6.7.
Found: C, 63.9; H, 4.7; N, 6.9.

The residue from the above distillation (38 g.) was a brown, viscous oil. It was distilled under nitrogen through a 10-inch glass-wool-lined Vigreux column, yielding more 4-ethoxy-7-chloroquinoline and a second fraction (16.0 g.), b.p. 165–175° (0.3–0.4 mm.) which consisted of a mixture of a solid and an oil. This was redistilled, and after removal of more 4-ethoxy-7-chloroquinoline, gave as a final fraction a pale light orange liquid, b.p. 146–147° (0.13–0.19 mm.). Redistillation of this gave a middle cut, b.p. 144–153° (0.15 mm.), which analyzed for impure ethyl α-(7-chloro-4-quinolyl)butyrate.

Anal. Calc'd for $C_{15}H_{16}ClNO_2$: C, 64.8; H, 5.8; N, 5.0.
Found: C, 64.2; H, 5.7; N, 4.9.

The *picrate*, prepared in alcohol and recrystallized successively from methanol, acetone-ether, and benzene, melted at 181.5–183°.

Anal. Calc'd for $C_{21}H_{19}ClN_4O_9$: C, 49.8; H, 3.8.
Found: C, 49.8; H, 3.6.

7-Chloro-4-n-propylquinoline. A solution of 2.10 g. of impure ethyl α-(7-chloro-4-

quinolyl)butyrate obtained as above was refluxed for twenty-one hours in 10 ml. of 3 *N* hydrochloric acid. After making the solution basic with sodium hydroxide, a granular precipitate separated. This was distilled three times in a molecular still at a bath-temperature 50–60° (0.2 mm.). The white needles of 4-*n*-propyl-7-chloroquinoline melted at 47.5–49.5°.

Anal. Calc'd for $C_{12}H_{12}ClN$: C, 70.1; H, 5.9; N, 6.8.
Found: C, 70.3; H, 5.9; N, 6.8.

The basic filtrate from the above compound was extracted with ether and then neutralized with hydrochloric acid. Four per cent of 4-hydroxy-7-chloroquinoline, m.p. 279–281° after recrystallization from water separated (33). This material probably had its source in 4-ethoxy-7-chloroquinoline in the starting ester.

SUMMARY

1. 4-Quinazolylmalonic ester and related compounds have been prepared and found to cleave to 4-quinazolone in acid solution.

2. Diethyl ethyl-(2,6-dimethyl-4-pyrimidyl)malonate and ethyl (2,6-dimethyl-4-pyrimidyl)cyanoacetate have been prepared. These compounds undergo hydrolysis and decarboxylation in acid.

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