[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

vic-DICARBOXYLIC ACID DERIVATIVES OF PYRAZOLE, ISOXAZOLE, AND PYRIMIDINE

R. G. JONES AND C. W. WHITEHEAD

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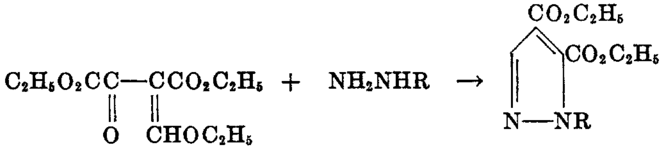
The purpose of this paper is to describe the preparation and properties of some *vicinal*-dicarboxylic acid derivatives of pyrazole, isoxazole, and pyrimidine. These new compounds were used for the synthesis of a number of condensed heterocyclic ring systems to be described later.

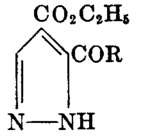
A common intermediate, ethyl ethoxymethyleneoxalacetate (I), was employed for most of these preparations. The reaction of I with one equivalent of hydrazine or hydrazine dihydrochloride gave diethyl 4,5-pyrazoledicarboxylate (II) in good yield. In like manner, I reacted with phenylhydrazine to yield diethyl 1-phenyl-4,5-pyrazoledicarboxylate (III).



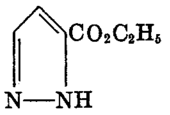
I

II R = H
III R = C_6H_5

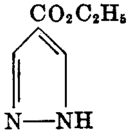
When II was heated with dilute hydrochloric acid, one of the ester groups was readily hydrolyzed to give 4-carbethoxy-5-pyrazolecarboxylic acid (IV). Long heating with acid or base was required to hydrolyze both ester groups of II. Reaction of II with alcoholic ammonia at room temperature, or at 100° under pressure for several hours, gave only a monoamide, ethyl 3-carbamyl-4-pyrazolecarboxylate (V).



IV R = OH
V R = NH_2



VI

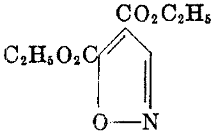


VII

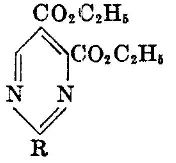
The reason for believing that hydrolysis and ammonolysis of II gave IV and V instead of the alternative 5-carbethoxy compounds was based on analogy with reactions of the monocarbethoxy compounds VI and VII. Ethyl 5-pyrazolecarboxylate (VI) was much more easily hydrolyzed and ammonolyzed than the isomer VII. Assignment of structure III to the 1-phenyldicarbethoxypyrazole followed from the observation that III did not react with alcoholic ammonia but was recovered unchanged even after several months at room temperature. This fact is best explained by steric hindrances of the 5-carbethoxy group by the phenyl.

Diethyl 4,5-isoxazoledicarboxylate (VIII) was prepared readily by reaction of I with hydroxylamine. The condensation of I with guanidine gave diethyl 2-amino-4,5-pyrimidine dicarboxylate (IX) in moderate yield. With urea, however, I reacted to form the ureaide (X). No pure product was isolated from the reaction of I with thiourea.

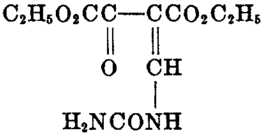
Another and more convenient method for the preparation of X consisted of heating together diethyl oxalacetate, ethyl orthoformate, and urea in alcohol. This is an extension of a recently described general procedure for the preparation of ureidomethylene derivatives (1). Although compound X was relatively quite stable and did not undergo cyclization when treated with sodium ethoxide or hydrochloric acid, it did lose water to form the desired diethyl 2-hydroxy-4,5-pyrimidinedicarboxylate (XI) in 75% yield when it was carefully heated at or near the melting point (about 170°). Some darkening took place, and the product had a brown or tan color. An alternative and milder procedure was to heat under reflux a suspension of X in xylene. By this method an 88% yield of XI was obtained.



VIII



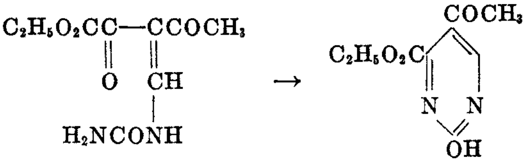
IX R = NH_2
XI R = OH



$$\underset{\substack{\| \\ O}}{C_2H_5O_2CC}-\underset{\substack{\| \\ CH \\ | \\ H_2NCONH}}{CCO_2C_2H_5}$$

X

Ethyl ureidomethyleneacetylpyruvate (XII) was readily prepared by treating ethyl ethoxymethyleneacetylpyruvate with urea or better by heating ethyl acetylpyruvate, ethyl orthoformate, and urea in alcohol. When XII was heated in xylene, water was eliminated, and a new compound, presumably ethyl 5-acetyl-2-hydroxy-4-pyrimidinecarboxylate (XIII), was obtained in 43% yield.



XII XIII

EXPERIMENTAL

Diethyl 3,4-pyrazoledicarboxylate (II). A solution of 48.6 g. (0.2 mole) of ethyl ethoxymethyleneoxalacetate (2) in 100 ml. of absolute ethanol was cooled in an ice-bath, and with stirring, 11 g. (0.22 mole) of hydrazine hydrate was added dropwise. The temperature was kept at 10–20° during the addition. At first a voluminous precipitate formed but by the time all the hydrazine had been added, the precipitate had dissolved leaving a clear brown solution. This was evaporated under reduced pressure by heating on the steam-bath. The residual liquid together with a little white solid was mixed with 300 ml. of ether and filtered to remove the precipitate (4 g.). The filtrate was evaporated, and the product was distilled under reduced pressure to give 35 g. (82.5% yield) of diethyl 3,4-pyrazoledicarboxylate as a colorless liquid, b.p. 160–165° (0.5 mm.); 180–185° (2 mm.). It crystallized after standing. A sample recrystallized from benzene-petroleum ether mixture melted at 69–70°.

Anal. Calc'd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20.
Found: C, 50.86; H, 5.72; N, 13.40.

To a solution of 11.5 g. (0.11 mole) of hydrazine dihydrochloride in 50 ml. of water was added 25 ml. of ethanol and then, with stirring, 24.3 g. (0.1 mole) of ethyl ethoxymethyleneoxalacetate was added. Heat was evolved, and the temperature went up to 75°. The solution was evaporated under reduced pressure to remove most of the alcohol, and 12 g. of solid sodium carbonate was added. The mixture was extracted with ether, and the solution was dried, evaporated and the ester distilled. The yield of diethyl 3,4-pyrazoledicarboxylate by this method ranged from 67 to 81%. When the acid solution was heated or allowed to stand too long before neutralization some hydrolysis of the ester took place (see below).

4-Carbethoxy-3-pyrazolecarboxylic acid (IV). To a solution of 11 g. (0.11 mole) of hydrazine dihydrochloride in 50 ml. of water and 50 ml. of ethanol was added 24.3 g. (0.1 mole) of ethyl ethoxymethyleneoxalacetate. After the exothermic reaction, the mixture was heated on the steam-bath. At first a clear solution was formed, then, after about 15 minutes, a white crystalline precipitate began to separate. After heating for three hours the mixture was cooled, and the solid was collected, washed with water and air dried. The yield was 15 g. (82%). It was readily soluble in dilute base and was reprecipitated with acid. A sample recrystallized from absolute ethanol melted at 263° (dec.).

Anal. Calc'd for $C_7H_8N_2O_4$: C, 45.75; H, 4.35; N, 15.22.
Found: C, 45.79; H, 4.01; N, 15.51.

3,4-Pyrazoledicarboxylic acid. A solution of 1 g. of diethyl 3,4-pyrazoledicarboxylate in 25 ml. of 6 *N* hydrochloric acid was heated on the steam-bath for four hours. During this time a finely divided crystalline precipitate separated. The solid was recrystallized from water and was obtained as an almost jelly-like curdy mass. It was dried by heating under reduced pressure; m.p. above 300°.

Anal. Calc'd for $C_5H_4N_2O_4$: N, 17.95. Found: N, 17.93.

When the diester was saponified with sodium hydroxide and the solution was acidified with hydrochloric acid, a clear gel could be obtained which melted when heated and resolidified when cooled.

Diethyl 1-phenyl-4,5-pyrazoledicarboxylate (III). This compound was prepared from ethyl ethoxymethyleneoxalacetate and either phenylhydrazine or phenylhydrazine hydrochloride by procedures similar to those described above for the preparation of diethyl 3,4-pyrazoledicarboxylate. By either method the yields were 82-84%. The compound was a viscous liquid; b.p. 168–173° (0.7 mm.); n_D^{25} 1.5390.

Anal. Calc'd for $C_{15}H_{16}N_2O_4$: N, 9.72. Found: N, 9.99.

1-Phenyl-4,5-pyrazoledicarboxylic acid. The diethyl ester was saponified with sodium hydroxide in alcohol-water solution. Acidification gave the acid as a crystalline precipitate. It was recrystallized from an ethyl acetate-petroleum ether mixture and was obtained as colorless platelets; m.p. 214–215°.

Anal. Calc'd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47; N, 12.05.
Found: C, 56.63; H, 3.29; N, 11.88.

1-Phenyl-4,5-diacetoxymethylpyrazole. A solution of 42 g. (0.146 mole) of diethyl 1-phenyl-4,5-pyrazoledicarboxylate in 100 ml. of dry ether was added dropwise with stirring to 6.5 g. of lithium aluminum hydride in 400 ml. of dry ether. The reaction was worked up in the usual way (3) to give a viscous sirup that would not crystallize. This was acetylated with excess acetic anhydride to give the diacetoxy compound as a pale yellow liquid, b.p. 170–173° (0.1 mm.).

Anal. Calc'd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72.
Found: C, 62.39; H, 5.46; N, 9.75.

Ethyl 3-carbamyl-4-pyrazolecarboxylate (V). A solution of 42.5 g. (0.2 mole) of diethyl 3,4-pyrazoledicarboxylate in 500 ml. of absolute ethanol saturated with ammonia was allowed to stand at room temperature for four days. During this time a mass of crystalline precipitate separated. This was collected, washed with a little absolute ethanol, and air-dried. The yield was 31 g. (85%). A sample recrystallized from absolute ethanol melted at 248–250°.

Anal. Calc'd for $C_7H_9N_3O_3$: C, 45.90; H, 4.92; N, 22.95.
Found: C, 45.88; H, 4.92; N, 22.71.

When diethyl 1-phenyl-4,5-pyrazoledicarboxylate in absolute ethanol solution saturated with ammonia was allowed to stand for several months, no appreciable reaction took place. The unchanged ester was recovered in 73% yield.

Triethyl 1-phenyl-3,4,5-pyrazoletricarboxylate. A mixture of 14.5 g. (0.1 mole) of phenylhydrazine hydrochloride, 100 ml. of water, 50 ml. of ethanol, and 31.6 g. (0.1 mole) of triethyl α-ethoxy-γ-ketoaconitate (4) was heated for 15 minutes on the steam-bath. It was evaporated under reduced pressure to a volume of about 100 ml., 100 ml. of water was added, and the mixture was extracted with three 100-ml. portions of ether. The insoluble solid, 1.7 g. (presumably 1-phenyl-4,5-dicarbethoxy-3-pyrazolecarboxylic acid) was removed by filtration. The ether solution was evaporated to a volume of about 150 ml., 150 ml. of petroleum ether was added, and the whole was heated to boiling. Another 2.1 g. of insoluble product was removed by filtration. To the filtrate was added another 150 ml. of petroleum ether. After standing in the ice box for 24 hours, 19 g. (53% yield) of the triethyl ester was obtained as a crystalline solid. A sample recrystallized from petroleum ether melted at 74–74.5°.

Anal. Calc'd for $C_{18}H_{20}N_2O_6$: C, 59.98; H, 5.60; N, 7.78.
Found: C, 60.17; H, 5.57; N, 7.74.

The tricarboxylic acid obtained by saponification of the ester melted at 213–214°.

Diethyl 4,5-isoxazoledicarboxylate (VIII). To a solution of 8 g. (0.11 mole) of hydroxylamine hydrochloride in 50 ml. of water was added 50 ml. of ethanol followed by 24.4 g. (0.10 mole) of ethyl ethoxymethyleneoxalacetate (2). After stirring, a clear solution was formed. To it was added in portions 9 g. (0.11 mole) of sodium bicarbonate. When the foaming had subsided, the mixture was warmed under reduced pressure to remove alcohol. Water, 50 ml., was added to dissolve precipitated salt, and the mixture was extracted with 100 ml. of ether. The ether solution was dried, evaporated, and the residual liquid was distilled under reduced pressure to yield 14 g. (66%) of colorless liquid; b.p. 110–115° (1 mm.), 98–100° (0.5 mm.); n_D^{25} 1.4588; d_{25}^{25} 1.186. A mid-fraction was taken for analysis.

Anal. Calc'd for $C_9H_{11}NO_5$: C, 50.70; H, 5.20; N, 6.57.
Found: C, 50.58; H, 5.45; N, 6.81.

Diethyl 2-amino-4,5-pyrimidinedicarboxylate (IX). To a solution made by dissolving 14 g. (0.61 g.-atom) of sodium in 300 ml. of absolute ethanol was added slowly with stirring and cooling in an ice-bath a warm solution of 62 g. (0.65 mole) of guanidine hydrochloride in 300 ml. of absolute ethanol. The resulting mixture was cooled in the ice-bath and stirred while 133 g. (0.55 mole) of ethyl ethoxymethyleneoxalacetate (2) was added from a dropping-funnel during 15 minutes. A quantity of crystalline precipitate separated. After stirring for one-half hour the mixture was filtered, and the filtrate was evaporated under reduced pressure to dryness. The residue was mixed with the original precipitate, and the whole was stirred up to a paste with 250 ml. of cold water. The solid was collected, washed twice with fresh 250-ml. portions of water, and air-dried. The yield of white finely divided crystalline solid was 75 g. (57%). A sample recrystallized from water melted at 151–152°.

Anal. Calc'd for $C_{10}H_{13}N_3O_4$: C, 50.20; H, 5.48.
Found: C, 50.16; H, 5.45.

2-Amino-4,5-pyrimidinedicarboxylic acid. To a solution of 10 g. of sodium hydroxide in 100 ml. of water was added 24 g. of diethyl 2-amino-4,5-pyrimidinedicarboxylate. The mixture was heated on the steam-bath for one hour, then cooled, and the solution acidified with 25 ml. of concentrated hydrochloric acid. The finely divided white crystalline precipitate was collected, washed with water, alcohol, and ether and air-dried; yield 18 g. (98%). A sample was recrystallized from water. It remained unmelted at 300°.

Anal. Calc'd for $C_6H_5N_3O_4$: N, 22.95. Found: N, 23.17.

Diethyl ureidomethyleneoxalacetate (X). A mixture of 6 g. (0.1 mole) of urea and 24 g. (0.1 mole) of diethyl ethoxymethyleneoxalacetate (2) was heated gently with a flame until an exothermic reaction began. The mixture became homogeneous and then set to a white crystalline solid. After crushing and triturating with ether the product was air-dried, yield 24 g. (93%). A sample was recrystallized from alcohol and obtained as white needles, m.p. 171–172°.

A mixture of 30 g. (0.5 mole) of urea, 74 g. (0.5 mole) of triethyl orthoformate, and 94 g. (0.5 mole) of ethyl oxalacetate was heated on the steam-bath for about one hour. A mass of white crystalline product was formed. The crystalline solid was washed well with water, then with 100 ml. of ether and air-dried; yield 105 g. (81%). A sample was recrystallized from ethyl acetate; m.p. 171–172°.

Anal. Calc'd for $C_{10}H_{14}N_2O_6$: N, 10.84. Found: N, 10.84.

Ethyl ureidomethyleneacetylpyruvate (XII). This was prepared from urea and ethyl ethoxymethyleneacetylpyruvate (2) in the same way as described above for diethyl ureidomethyleneoxalacetate. The yield was 78%; m.p. 182–183°.

Anal. Calc'd for $C_9H_{12}N_2O_5$: N, 12.28. Found: N, 12.30.

Ethyl ureidomethyleneacetylpyruvate also was prepared in 88% yield by heating urea, ethyl acetylpyruvate, and ethyl orthoformate in alcohol in the same manner as described above for the preparation of diethyl ureidomethyleneoxalacetate; m.p. 182–183°.

Diethyl 2-hydroxy-4,5-pyrimidinedicarboxylate (XI). In a 300-ml. round bottom flask was placed 100 g. (0.39 mole) of diethyl ureidomethyleneoxalacetate. The flask was placed in an oil-bath at 175° and the contents occasionally were stirred until melted. The bath temperature then was lowered to 160° and heating was continued for 15 minutes. After cooling the dark sirup to room temperature, 150 ml. of ethyl acetate was added and the mixture was stirred and heated. The sirup crystallized and the product mostly all dissolved. The ethyl acetate solution was cooled to 0°, kept for several hours, and the product was collected and air-dried; yield 70 g. (75%) of a tan crystalline powder. A sample for analysis was recrystallized again from ethyl acetate and from water in which it was appreciably soluble, white powder, m.p. 161–162°.

Anal. Calc'd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66.
Found: C, 50.02; H, 5.10; N, 11.57.

A suspension of 60 g. of diethyl ureidomethyleneoxalacetate in 300 ml. of xylene was heated under reflux for six hours. Water, 4 ml., that was formed during the reaction was collected in a water separator. The xylene solution was cooled and 49 g. (88% yield) of diethyl-2-hydroxy-4,5-pyrimidinedicarboxylate was obtained as a crystalline solid. A sample recrystallized from water melted at 161–162°.

Anal. Calc'd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66.
Found: C, 50.12; H, 5.19; N, 11.44.

Ethyl 5-acetyl-2-hydroxy-4-pyrimidinecarboxylate (XIII). A suspension of 82 g. of ethyl ureidomethyleneacetylpyruvate in 300 ml. of xylene was heated under reflux for six hours. During this time 8.5 ml. of water was evolved, but the solid did not all go into solution. After cooling, the product was collected and recrystallized from water in which it was appreciably soluble. The yield of almost white crystalline solid was 32.5 g. (43%); m.p. 206–208°.

Anal. Calc'd for $C_9H_{10}N_2O_4$: C, 51.42; H, 4.80; N, 13.33.
Found: C, 51.72; H, 4.85; N, 13.20.

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SUMMARY

The diethyl esters of 3,4-pyrazoledicarboxylic acid, 1-phenyl-4,5-pyrazoledicarboxylic acid, 4,5-isoxazoledicarboxylic acid and 2-amino-4,5-pyrimidine-

dicarboxylic acid were prepared from ethyl ethoxymethyleneoxalacetate. Diethyl 2-hydroxy-4,5-pyrimidinedicarboxylate was obtained by heating diethyl ureidomethyleneoxalacetate, and ethyl 5-acetyl-2-hydroxy-4-pyrimidinecarboxylate was obtained by heating ethyl ureidomethyleneacetylpyruvate. The ester group in the 3-position of diethyl 3,4-pyrazoledicarboxylate was much more reactive than that in the 4-position.

INDIANAPOLIS 6, INDIANA

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