TABLE II

REACTION OF KETENE WITH PHENIDONES I, II, AND III

Reactant	Product	M.P. or B.P.	Crystallization Solvent	Formula		Analysis C	Analysis H	Analysis N	Infrared Absorption Bands, μ
I	IV[a]	b.p. 125–131°/40 μ m.p. 72–73°	Ethyl acetate–petroleum ether	$C_{11}H_{12}N_2O_2$	Calcd.	64.7	5.9		5.63, 5.80
					Found	64.7	6.2		
I	V	m.p. 84–85°	Benzene–petroleum ether	$C_{11}H_{12}N_2O_2$	Calcd.	64.7	5.9	13.7	5.72
					Found	64.5	5.9	14.0	
II	IV[b]	b.p. 121–126°/30 μ	—	$C_{12}H_{14}N_2O_2$	Calcd.	66.0	6.5	12.8	5.73, 5.90
					Found	66.2	6.6	13.1	
II	V	m.p. 65°	Ethyl acetate–petroleum ether	$C_{12}H_{14}N_2O_2$	Calcd.	66.0	6.5	12.8	5.68
					Found	66.1	6.4	12.9	
III[d]	IV[c]	b.p. 132–136°/100 μ m.p. 91–93°	Petroleum ether	$C_{13}H_{16}N_2O_2$	Calcd.	67.2	6.9	12.1	5.75, 5.85
					Found	67.4	6.9	11.8	

[a] Prepared in 73.5% yield from I and acetic anhydride. [b] Prepared in 56% yield from II and acetic anhydride. [c] Prepared in 50% yield from III and acetic anhydride. [d] The infrared spectrum of the oil obtained from III and ketene prior to distillation had the three characteristic carbonyl absorptions at 5.65 μ, 5.75 μ, and 5.85 μ, indicating that the enol acetate was formed but rearranges to the *N*-acetate during the distillations.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.7; H, 5.9; N, 13.7. Found: C, 64.5; H, 5.9; N, 14.0.

The infrared absorption spectrum of the material showed a single carbonyl absorption at 5.72 μ, indicating that the material is the O-acetyl derivative.

The mother liquor was evaporated to leave an oil, b.p. 125–131°/40 μ, 12.35 g., 24.6%. This oil could then be crystallized from ethyl acetate-petroleum ether (b.p. 65–75°), m.p. 72–73°.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.7; H, 5.9. Found: C, 64.7; H, 6.2. The infrared spectrum of this material showed two carbonyl absorptions, one at 5.63 μ and one at 5.80 μ, indicating that the material is the *N*-acetyl derivative.

The reactions of ketene with II and III were carried out as above and the products are described in Table II.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MIAMI]

The Preparation of 3-Methyl-6- and -7-carboxy-2-quinoxalones

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3-Methyl-6-carboxyquinoxalone-2 and 3-methyl-7-carboxyquinoxalone-2, their esters, and dihydro derivatives have been prepared by unequivocal procedures. The ambiguous condensation of 3,4-diaminobenzoic acid with pyruvic acid was demonstrated to give only 3-methyl-7-carboxyquinoxalone-2, whereas the ambiguous condensation of ethyl 3,4-diaminobenzoate with ethyl pyruvate gave equal portions of 3-methyl-6-carbethoxyquinoxalone-2 and 3-methyl-7-carbethoxyquinoxalone-2.

Zehra[1] condensed 3,4-diaminobenzoic acid with pyruvic acid, obtaining a product reported as one compound—either 3-methyl-6- *or* 7-carboxyquinoxalone-2. We wish to report the syntheses by unequivocal methods of both 3-methyl-6- and 7-carboxyquinoxalone-2, as well as a study of the products obtained from the equivocal condensation reported by Zehra.

N-(2-Nitro-4-carboxyphenyl)-*dl*-α-alanine, the precursor for the preparation of 3-methyl-7-carboxyquinoxalone-2, was synthesized in virtually quantitative yield by condensing *dl*-α-alanine with 3-nitro-4-bromobenzoic acid, by modifications of the procedures of Micheel *et al.*[2] and of Holley and Holley,[3] who condensed *dl*-α-alanine with ethyl 3-nitro-4-fluorobenzoate. *N*-(2-Nitro-4-carboxyphenyl)-*dl*-α-alanine was reduced in alcohol over palladium chloride on charcoal, but better in aqueous sodium bicarbonate solution over Raney nickel catalyst. In the latter procedure the initial reduction product was probably the disodium salt

(1) A. Zehra, *Ber.*, 23, 3629 (1890).

(2) F. Micheel, K. Weichbrodt, and J. Plenikowski, *Ann.*, 581, 242 (1953).

(3) R. Holley and A. Holley, *J. Am. Chem. Soc.*, 74, 1110 (1952).

of *N*-(2-amino-4-carboxyphenyl)-*dl*-α-alanine, for the reduction solution was very sensitive to air oxidation, turning purple immediately upon exposure to air; but when the reduction solution was filtered into acid solution without exposure to air, cyclization occurred and a precipitate of 3-methyl-3,4-dihydro-7-carboxyquinoxalone-2 formed immediately. This dihydro derivative could be redissolved in base to give a colorless solution perfectly stable in air. Indeed, unlike many 3,4-dihydro-2-quinoxalones reported previously in the literature as being easily oxidized either with air or dilute hydrogen peroxide solution, the 3-methyl-3,4-dihydro-7-carboxyquinoxalone-2 required vigorous oxidation in concentrated, basic hydrogen peroxide solution for transformation into 3-methyl-7-carboxyquinoxalone-2.

A simpler, more productive route to 3-methyl-7-carboxyquinoxalone-2 consisted of treating ethyl *p*-aminobenzoate with *dl*-α-bromopropionic acid to give *N*-(4-carbethoxyphenyl)-*dl*-α-alanine, which was nitrated under carefully controlled conditions to *N*-(2-nitro-4-carbethoxyphenyl)-*dl*-α-alanine. The ester could be hydrolyzed in acid solution to *N*-(2-nitro-4-carboxyphenyl)-*dl*-α-alanine, or reduced directly in alcohol over palladium-charcoal catalyst to 3-methyl-3,4-dihydro-7-carbethoxyquinoxalone-2. This dihydro quinoxalone was easily oxidized in low yield in neutral hydrogen peroxide solution to 3-methyl-7-carbethoxyquinoxalone-2.

N-(2-Nitro-5-carboxyphenyl)-*dl*-α-alanine was successfully prepared by condensing *dl*-α-alanine with 3-bromo-4-nitrobenzoic acid in concentrated, aqueous sodium bicarbonate solution.

Claus and Scheulein[4] reported the preparation of 3-bromo-4-nitrobenzoic acid from 3-bromo-4-nitrobenzonitrile. Unfortunately, a detailed procedure for the transformation of 3-bromo-4-nitroaniline into 3-bromo-4-nitrobenzonitrile was not given; considerable research resulted in a process that gave only a 22% yield in this transformation, hence a more productive route to 3-bromo-4-nitrobenzoic acid was sought.

4-Nitro-3-toluidine was transformed into 3-bromo-4-nitrotoluene *via* the diazonium bromide, utilizing cu*pric* bromide[5] as the catalyst for this reaction, rather than the usual cu*prous* bromide. The 3-bromo-4-nitrotoluene was oxidized to 3-bromo-4-nitrobenzoic acid with potassium permanganate in aqueous suspensions buffered with carbon dioxide or magnesium ion.

The preparations of *N*-(2-nitro-5-carboxyphenyl)-*dl*-α-alanine, 3-methyl-6-carboxyquinoxalone-2, and related compounds were similar to those of the position isomers discussed above.

Synthesis of 3-methyl-6-carboxyquinoxalone-2 was successful, however, only after several unsuccessful routes had been attempted. Some of these routes resulted in the synthesis of several new compounds. Ethyl 3-amino-4-acetamidobenzoate and 3-amino-4-acetamidobenzoic acid were condensed with ethyl *dl*-α-bromopropionate in an attempt to follow a successful reaction sequence used by Marks and Schultz[6] for the synthesis of 3,6-dimethylquinoxalone-2. Instead of the desired intermediate, *N*-(2-acetamido-5-carboxy-*or*-5-carbethoxyphenyl)-*dl*-α-alanine, 2-methyl-5-carboxy-*or*-5-carbethoxybenzimidazole was obtained.

The decomposition points of both 3-methyl-6- and 7-carboxy-2-quinoxalones were very high (*ca.* 330°); the exact temperature of decomposition depended, within a 5° to 10° range, upon the temperature at which the sample was placed in the melting point block, as well as the rate of heating. Ultraviolet absorption spectra, therefore, were utilized for identification of the free carboxylic acids and mixtures of the acids. The esters, however, possessed melting points (*ca.* 200°) that were readily determined and duplicated. A melting point curve of mixtures of known composition of 3-methyl-6- and 7-carbethoxy-2-quinoxalones indicated that no eutectic was formed between the two compounds.

When 3,4-diaminobenzoic acid was condensed with pyruvic acid according to the procedure of Zehra, only 3-methyl-7-carboxyquinoxalone-2 was found in both the crude and purified reaction products. However, condensation of ethyl 3,4-diaminobenzoate with ethyl pyruvate gave a reaction product that contained about equal parts of the two position isomers. By taking advantage of the fact that 3-methyl-7-carbethoxyquinoxalone-2 was relatively insoluble in hot benzene, in contrast to the other isomer, a pure sample of each isomer was separated from the reaction product.

EXPERIMENTAL

N-(2-Nitro-4-carboxyphenyl)-dl-α-alanine. Method A. A mixture of 24.6 g. (0.1 mole) of 3-nitro-4-bromobenzoic acid,[7] 26.8 g. (0.3 mole) of *dl*-α-alanine, 33.6 g. of sodium bicarbonate, and 50 ml. of water was heated at 95° ± 5° for 48 hr. The solution was cooled, diluted with 200 ml. of water, acidified with 60 ml. of concd. hydrochloric acid, and filtered. The filter cake was dissolved in 300 ml. of water and 20 ml. of concd. ammonium hydroxide, treated with charcoal and filter-aid, then filtered into a boiling solution of 30 ml. of concd. hydrochloric acid in 1200 ml. of water. Yellow prisms of analytically pure *N*-(2-nitro-4-carboxyphenyl)-*dl*-α-alanine, 23.3 g. (91.8%), m.p. 245–245.5°, were obtained.

Anal. Calcd for $C_{10}H_{10}N_2O_6$: N, 11.0. Found: N, 11.0.

Diethyl ester of N-(2-nitro-4-carboxyphenyl)-dl-α-alanine. This compound was prepared in 82% yield by refluxing *N*-(2-nitro-4-carboxyphenyl)-*dl*-α-alanine for 4 hr. in ethanol (1 g./20 ml.) and sulfuric acid (0.5 ml./20 ml. of alcohol); yellow crystals, m.p. 92.5–93°, from ethanol-water (2:1).

(4) A. Claus and W. Scheulein, *J. prakt. Chem.*, **43**(2), 202 (1891).

(5) H. Hodgson, *Chem. Revs.*, **40**, 262 (1947).

(6) B. Marks and H. Schultz, *J. Am. Chem. Soc.*, **73**, 1368 (1951).

(7) H. Hübner and J. Raveill, *Ann.*, **222**, 177 (1883).

Anal. Calcd. for $C_{14}H_{18}O_6N_2$: N, 9.03. Found: N, 9.03.

N-(4-Carbethoxyphenyl)-dl-α-alanine. A mixture of 16.5 g. (0.1 mole) of ethyl *p*-aminobenzoate and 15.3 g. (0.1 mole) of *dl*-α-bromopropionic acid was heated in a steam bath for 1.5 hr. The cold reaction mixture was crushed, rinsed with three 30-ml. portions of 1*N* hydrochloric acid, and recrystallized from hot water to yield 10.3 g. (43.6%) of white platelets, m.p. 133–135°. Blackburn and Schultz,[8] who prepared the compound by a somewhat different procedure, reported m.p. 133–135°.

N-(2-Nitro-4-carbethoxyphenyl)-dl-α-alanine. Method B. In a three-necked flask equipped with stirrer, thermometer, and cooling bath was placed 35 ml. of concd. nitric acid (sp. gr. 1.42). The acid was cooled to 4°, and with stirring 10.3 g. (0.043 mole) of *N*-(4-carbethoxyphenyl)-*dl*-α-alanine was added portionwise over 10 min., holding the temperature at 4°. The cooling bath was removed and the temperature of the reaction solution allowed to rise to 26°, then maintained between 23–26° with an ice bath. After 5 min. a yellow precipitate formed; after 10 more min. the reaction was poured over ice, filtered, rinsed with hot water, and dried to give 9.5 g. of yellow powder, m.p. 144–147°. The crude product was recrystallized from toluene to give 5.9 g. (49%) of yellow crystals of *N*-(2-nitro-4-carbethoxyphenyl)-*dl*-α-alanine, m.p. 151–152°. Micheel *et al.*[2] reported m.p. of 152°.

This ester was hydrolyzed in boiling 20% hydrochloric acid (1 g./20 ml.)to give 88.5% yield of yellow prisms, m.p. 244–245°; no depression was observed during mixture melting point determination with *N*-(2-nitro-4-carboxyphenyl)-*dl*-α-alanine prepared as already described.

3-Methyl-7-carboxy-3,4-dihydroquinoxalone-2. Into a 500-ml. Parr reduction bottle was placed 2.54 g. (0.01 mole) of *N*-(2-nitro-4-carboxyphenyl)-*dl*-α-alanine, 1.68 g. of sodium bicarbonate, 25 ml. of water, and 2 g. of Raney nickel catalyst.[9] The solution was reduced at 60 p.s.i. and 50° for 1 hr.; the colorless solution was filtered directly into 10 ml. of water containing 2 ml. of concd. hydrochloric acid. A white precipitate weighing 1.9 g. (92.3%), m.p. 287–290°, was obtained.

The product was purified for analysis by recrystallizing it from 95% ethanol (1 g./10 ml.) to give 1.2 g. (58.4%) of white crystals, m.p. 291–293°.

Absorption maxima, mμ, and molar absorptivity (ε × 10^3), 95% ethanol: 220 (22.1); 237.5, inf. (17.8); 255 (17.5); 315 (12.1); 0.1*N* sodium hydroxide: 235–240, plat. (24.2); 303 (7.65); 0.1*N* hydrochloric acid: 220 (25.4); 253 (20.7); 315 (12.3).

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.3; H, 4.89; N, 13.6. Found: C, 58.5; H, 4.99; N, 13.8.

3-Methyl-7-carboxyquinoxalone-2. A solution of 618 mg. (0.003 mole) of 3-methyl-7-carboxy-3,4-dihydroquinoxalone-2, 6 ml. of 10% sodium hydroxide solution, and 3 ml. of 30% hydrogen peroxide was heated 1 hr. on a steam bath, then evaporated to dryness. The residue was taken up in 15 ml. of water and poured into a solution of 60 ml. of boiling water and 2 ml. of concd. hydrochloric acid to give a pearly white, crystalline precipitate; 600 mg., m.p. 322–332° dec.

The crude, dry product was sublimed at 170° (1 mm.) to give 300 mg. of white solid, m.p. 328–330° dec., then recrystallized from 300 ml. of water to give 300 mg. (48.9%) of long, thin prisms, m.p. 329–332° dec.

Absorption maxima, mμ, and molar absorptivity (ε × 10^3), 95% ethanol: 220 (32.5); 266 (11.4); 283, very slight (10.4); 350 (7.77); 0.1*N* sodium hydroxide: 222.5 (25.3); 265 (15.9); 352.5 (7.95); 0.1*N* hydrochloric acid: 220 (35.2); 265 (15.0); 282.5, inf. (11.6); 345 (7.88).

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.8; H, 3.95; N, 13.7. Found: C, 58.7; H, 3.99; N, 13.6.

Reduction of 100 mg. of 3-methyl-7-carboxyquinoxalone-2 with Raney nickel catalyst at 25° in 5 ml. of water containing 100 mg. of sodium bicarbonate gave 75 mg. of 3-methyl-3,4-dihydro-7-carboxyquinoxalone-2, m.p. 289–291°; mixture melting point with an analytical sample of the dihydro compound showed no change.

3-Methyl-7-carbethoxyquinoxalone-2. Method A. A solution of 2.8 g. (0.01 mole) of *N*-(2-nitro-4-carbethoxyphenyl)-*dl*-α-alanine, 0.2 g. of 5% palladium chloride on charcoal,[10] and 30 ml. of absolute ethanol was reduced at 100°, 60 p.s.i. for 2 hr. After filtration and evaporation of the solution to dryness, the residue was heated on a steam bath for 15 min. with 10 ml. of water and 3.5 ml. of 30% hydrogen peroxide, then again evaporated to dryness. Sublimation of the residue at 150° (1 mm.) gave 0.4 g. of white powder, m.p. 175°–185°. The sublimate was recrystallized from toluene to give 125 mg. (5.4%) of white needles, m.p. 199–200°.

Absorption maxima, mμ, and molar absorptivity (ε × 10^3), 95% ethanol: 220 (31.3); 270 (12.4); 282.5, inf. (10.9); 350 (6.97).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: N, 12.1 Found: N, 12.0.

A sample of the ester was saponified by boiling in 10% sodium hydroxide solution; the 3-methyl-7-carboxyquinoxalone-2 isolated had m.p. 328–330° dec; no depression of a mixture melting point with an analytical sample of 3-methyl-7-carboxyquinoxalone-2.

3-Methyl-7-carbethoxyquinoxalone-2. Method B. A solution of 150 mg. of 3-methyl-7-carboxyquinoxalone-2, 20 ml. of absolute ethanol, and 0.5 ml. of sulfuric acid was refluxed 4 hr., drowned in ice water, and filtered to give 50 mg. of product, m.p. 180°–191°. The crude product was recrystallized from toluene to give 5 mg. (3.3%) of white needles, m.p. 199–200°. No depression of a mixture melting point was observed with material prepared by Method A.

Ethyl 3-amino-4-acetamidobenzoate. A solution of 9 g. (0.036 mole) of ethyl 3-nitro-4-acetamidobenzoate (prepared as reported[11] for the preparation of 3-nitro-4-acetamidobenzoic acid), 1 g. of Raney nickel catalyst, and 60 ml. of absolute ethanol was reduced at 25° and 60 p.s.i. for 2 hr. The solution was filtered, evaporated to dryness on a steam bath, and recrystallized from water to give 3.8 g. (48%) of white platelets, m.p. 142–143°.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: N, 12.6. Found: N, 12.7.

Condensation of ethyl 3-amino-4-acetamidobenzoate with ethyl *dl*-α-bromopropionate in ethanol solution gave a 20% yield of 2-methyl-5-carbethoxybenzimidazole, m.p. 180°. Einhorn and Uhlfelder[12] reported m.p. of 2-methyl-5-carbethoxybenzimidazole to be 180°.

In a similar fashion 3-nitro-4-acetamidobenzoic acid[13] was reduced over palladium-charcoal catalyst in ethanol. After removing the catalyst from the solution, ethyl *dl*-α-bromopropionate was added and the solution refluxed 4 hr. A 10% yield of the hydrate of 2-methyl-5-carboxybenzimidazole, m.p. 312–314.5°, was obtained. Kaiser[13] reported m.p. of 301–302° for this compound.

Anal. Calcd. for $C_9H_8N_2O_2 \cdot H_2O$: N, 14.4. Found: N, 14.4.

The 3-methyl-5-carboxybenzimidazole was transformed into 3-methyl-5-carbethoxybenzimidazole, m.p. 180°. No depression of a mixture melting point was observed when this ester was mixed with 3-methyl-5-carbethoxybenzimidazole prepared by direct condensation between ethyl 3-amino-4-acetamidobenzoate and ethyl *dl*-α-bromopropionate.

Ethyl 3-aminobenzoate. A solution of 39 g. (0.2 mole) of ethyl *m*-nitrobenzoate[14] in 150 ml. of 95% ethanol was re-

(8) W. Blackburn and H. Schultz, *J. Am. Chem. Soc.*, **73**, 5507 (1951).

(9) R. Mozingo, *Org. Syntheses*, Coll. Vol. III, 181 (1955).

(10) R. Mozingo, *Org. Syntheses*, Coll. Vol. III, 685 (1955).

(11) E. Borel and H. Deuel, *Helv. Chim. Acta*, **36**, 806 (1953).

(12) A. Einhorn and E. Uhlfelder, *Ann.*, **371**, 165 (1909).

(13) A. Kaiser, *Ber.*, **18**, 2944 (1885).

duced over 5 g. of Raney nickel catalyst for 3 hr. at 80 p.s.i. and 55°. The solution was distilled to give 30.7 g. (93%) of colorless liquid, b.p. 294–295° (760 mm.), 160–161° (5 mm.); η_D^{22} 1.5600; d_4^{22} 1.1248. Bamberger and Elger,[15] who executed the same reduction at 12–16 atm., reported b.p. 294°.

N-(3-Carbethoxyphenyl)-dl-α-alanine. Ethyl *m*-aminobenzoate and *dl*-α-bromopropionic acid were mixed and heated 4 hr. at 120°. The condensation product, obtained in 28% yield as already described above for *N*-(4-carbethoxyphenyl)-*dl*-α-alanine, was a white, crystalline compound, m.p. 115–117°, from benzene (1 g./10 ml.).

Anal. Calcd. for $C_{12}H_{15}NO_4$: N, 5.91. Found: N, 6.13.

When *N*-(3-carbethoxyphenyl)-*dl*-α-alanine was treated with nitric acid under a variety of conditions, only tars were obtained.

3-Bromo-4-nitrobenzonitrile. A magma of 4.34 g. (0.02 mole) of 3-bromo-4-nitroaniline[16] and 3.5 ml. of concd. hydrochloric acid was added to 100 ml. of water in a Waring blendor. A solution of 1.4 g. of sodium nitrite in 8 ml. of water was added over a period of 8 min. After 10 min. of stirring, 0.6 g. of unchanged amine was filtered from the aqueous solution of diazonium salt.

A solution of cuprous cyanide was prepared (HOOD) by adding 5 g. of copper (II) sulfate pentahydrate and 5.6 g. of potassium cyanide to 50 ml. of water. After heating the cyanide solution to 90°, the filtrate of diazonium salt was added over 15 min.; the reaction mixture was then boiled for 5 min.

The mixture was filtered hot, and the solid residue extracted with ten 100-ml. portions of boiling water. The combined filtrates were cooled and filtered. The precipitate was extracted with two 5-ml. portions of hot carbon tetrachloride, and the combined extracts evaporated to 2 ml. of solution. Upon cooling the solution, 1.0 g. (21.8%) of cream colored needles, m.p. 104–105° was deposited. Claus and Scheulein[4] reported m.p. 104° for 3-bromo-4-nitrobenzonitrile, although they cited no specific directions for its preparation.

3-Bromo-4-nitrobenzoic acid. Method A. 3-Bromo-4-nitrobenzonitrile was hydrolzed to the carboxylic acid in 61% yield, according to the specific directions of Claus and Scheulein[4]; m.p. 199–201°, light yellow micro crystals, from ethanol (3 ml./g.)-water (6 ml./g.); reported,[4] m.p. 197°.

3-Bromo-4-nitrotoluene. In a 1-l., three necked flask equipped with stirrer, thermometer, and dropping funnel was placed 45.6 g. (0.3 mole) of 3-amino-4-nitrotoluene[17] and 180 g. of glacial acetic acid. With stirring and cooling to 50–60°, 294 g. of concd. sulfuric acid was added to the solution, after which the dark red sirup was stirred and cooled to 0°.

A solution of 27.6 g. of sodium nitrite in 54 ml. of water was added dropwise at 0–5° over 1 hr. to the stirred solution of amine salt. Stirring at 0° was contained for 30 min.

The diazonium salt solution was added portionwise to a stirred, cooled (10°) solution of 450 ml. of water, 144 g. of potassium bromide, and 67 g. of cupric bromide in a 4-l. breaker. A black mush resulted which dissolved when 40 ml. of ice water was added to the reaction mixture. Stirring was continued at 0° for 15 min., then the solution was heated at 75° for 4 hr.; gas evolution (HOOD, some bromine and/or nitrogen dioxide fumes) became vigorous at 50°.

After 12 hr. at 25°, 1500 ml. of water was added to the solution, precipitating a dark brown oil. The water was decanted; the oil dissolved in 150 ml. of ethyl ether; and the ether solution washed with water, 5% sodium hydroxide solution, and again with water. After drying the solution over calcium chloride, it was distilled to give 53 g. (81.6%) of yellow solid, b.p. 135–140° (5 mm.); m.p. 35–36°. Elson *et al.*[18] reported m.p. 36.2° for 3-bromo-4-nitrotoluene.

3-Bromo-4-nitrobenzoic acid. Method B. In a 3-l. round-bottom flask equipped with stirrer, condenser, and heating mantle was placed 1500 ml. of water, 36.2 g. of anhydrous magnesium sulfate, 43.2 g. (0.2 mole) of 3-bromo-4-nitrotoluene, and 31.6 g. of potassium permanganate. The reaction mixture was stirred and heated at gentle reflux for 5 hr.; two more 31.6-g. portions of potassium permanganate were added at hourly intervals. When the purple color of the permanganate ion disappeared (5 hr.), 15 g. of filter-aid was added to the mixture, stirring was ceased, and the mixture cooled at 10° in ice and water.

The mixture was filtered; unchanged starting material, 13 g. (0.06 mole), was recovered as a large, solid, insoluble button. The filter cake was copiously rinsed with water, and the combined filtrates were refiltered. The addition of 30 ml. of concd. hydrochloric acid to the filtrates precipitated 15.8 g. (32.2%) of white, microcrystalline 3-bromo-4-nitrobenzoic acid, m.p. 200–202°. The carboxylic acid was recrystallized from ethanol (3 ml./g.)-water (6 ml./g.) in 96% yield with no change of melting point. Over-all yield based on starting material recovered, 44.3%.

A mixture melting point with material prepared by Method A gave no depression of the melting point.

Oxidation of 3-bromo-4-nitrotoluene with permanganate buffered with a stream of carbon dioxide gas gave 38% over-all yield of carboxylic acid; nonbuffered solutions gave no yield of product and no starting material; oxidation with permanganate in sulfuric acid–water solution gave 7% yield of carboxylic acid, 90% recovery of starting material.

3-Chloro-4-nitrobenzoic acid, m.p. 184–185°, was also prepared in 28% over-all yield by the magnesium ion buffered permanganate oxidation of 3-chloro-4-nitrotoluene.[18] Claus and Kurz,[19] reported m.p. 185–186° for 3-chloro-4-nitrobenzoic acid.

N-(2-Nitro-5-carboxyphenyl)-dl-α-alanine. This material was prepared by the condensation of 3-bromo-4-nitrobenzoic acid with *dl*-α-alanine by the same method used for the preparation of *N*-(2-nitro-4-carboxyphenyl)-*dl*-α-alanine. The crude product, m.p. 227–229°, required an extra recrystallization from water (1 g./750 ml.) to give 37.4% yield of dark orange platelets, m.p. 236–237°.

Anal. Calcd. for $C_{10}H_{10}N_2O_6$: N, 11.0. Found: N, 11.3.

3-Chloro-4-nitrobenzoic acid did not react with *dl*-α-alanine under the above conditions.

Diethyl ester of N-(2-nitro-5-carboxyphenyl)-dl-α-alanine. This compound was prepared in 85% yield by the direct esterification of *N*-(2-nitro-5-carboxyphenyl)-*dl*-α-alanine by the procedure used for the preparation of the other isomer. Orange platelets, m.p. 58–59°, from ethanol-water (2:1).

Anal. Calcd. for $C_{14}H_{18}N_2O_6$: N, 9.03. Found: N, 9.11.

3-Methyl-3,4-dihydro-6-carboxyquinoxalone-2 hydrate. This material was prepared in 13.4% yield from *N*-(2-nitro-5-carboxyphenyl)-*dl*-α-alanine in the same manner as was its position isomer; the product was recrystallized from water (200 ml./g.) to give a yellow, crystalline hydrate, m.p. 261–262°, if placed in the bath above 230°. If placed in the melting point bath below 230°, the product never melted, but gradually shrunk to a dark resin at temperatures from 255–270°.

Absorption maxima, mμ, and molar absorptivity ($\epsilon \times 10^3$), 95% ethanol: 210, inf. (19.1); 240 (36.8); 275, inf. (7.2); 325 (6.4); 0.1*N* sodium hydroxide: 233 (27.2); 280 (8.3); 330 (7.7); 0.1*N* hydrochloric acid: 240 (27.8); 275, inf. (10.6); 328 (6.2).

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Anal. Calcd. for $C_{10}H_{10}N_2O_3 \cdot H_2O$: C, 53.6; H, 5.40; N, 12.5. Found: C, 53.4; H, 5.27; N, 12.7.

3-Methyl-6-carboxyquinoxalone-2 hydrate. 3-Methyl-3,4-dihydro-6-carboxyquinoxalone-2 hydrate was oxidized and purified in 35.9% yield in a similar fashion to that already described for its position isomer, except that the oxidation solution of the 6-isomer required vigorous heating with a direct flame. The 3-methyl-6-carboxyquinoxalone-2 was recrystallized from ethanol (30 mg./ml.) or from water (1 mg./ml.) as a crystalline hydrate, m.p. 334–336°, dec., to give products with the same analytical values and the same ultraviolet absorption spectra.

Absorption maxima, mμ, and molar absorptivity ($\epsilon \times 10^3$), 95% ethanol: 255 (34.4); 335 (7.95); 0.1*N* sodium hydroxide: 255 (26.0); 345 (8.36); 0.1*N* hydrochloric acid: 255 (33.7); 335 (8.40).

Anal. Calcd. for $C_{10}H_8N_2O_3 \cdot H_2O$: C, 54.1; H, 4.54; N, 12.6. Found: C, 53.9; H, 4.61; N, 12.6.

Reduction of 75 mg. of 3-methyl-6-carboxyquinoxalone-2 with Raney nickel catalyst at 65° (the substance was not reduced at 25°) and 60 p.s.i. in 5 ml. of water containing 100 mg. of sodium bicarbonate gave 50 mg. of yellow, crystalline 3-methyl-3,4-dihydro-6-carboxyquinoxalone-2 hydrate, m.p. 257–259°, mixture melting point with an analytical sample of the compound, no change.

3-Methyl-6-carbethoxyquinoxalone-2. This material was prepared in 6.7% yield by direct esterification (Method B) of 3-methyl-6-carboxyquinoxalone-2; and in 40% yield from the diethyl ester of *N*-(2-nitro-5-carboxyphenyl)-*dl*-α-alanine, by the procedure (Method A) given above for the preparation of the isomeric ester. The product was purified for analysis by recrystallizing it from benzene (25 mg./ml.), colorless prisms, m.p. 229–230°.

Absorption maxima, mμ, and molar absorptivity ($\epsilon \times 10^3$), 95% ethanol: 222 (13.3); 255 (35.9); 336 (8.0).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: N, 12.1 Found: N, 12.0.

Saponification of a sample of the ester gave 3-methyl-6-carboxyquinoxalone-2, m.p. 334–336°; there was no depression of a mixture melting point with an analytical sample of 3-methyl-6-carboxyquinoxalone-2.

3-Methyl-6- and/or 7-carboxyquinoxalone-2; equivocal procedure of Zehra.[1] A solution of 5 g. (0.0275 mole) of 3-nitro-4-aminobenzoic acid[20] in 50 ml. of 95% ethanol was catalytically reduced over palladium-charcoal catalyst; the solution was filtered without exposure to air into a water solution of 1.2 equivalents of pyruvic acid to give 1.2 g. (21.8%) of 3-methyl-7-carboxyquinoxalone, m.p. 328–330° dec. Sublimation at 180° (1 mm.) and recrystallization from ethanol of a sample of material gave m.p. 330–332° dec. Zehra[1] reported that his product did not melt below 330°. The ultraviolet absorption spectra of both crude and purified samples were identical with that of the analytical sample of 3-methyl-7-carboxyquinoxalone-2 prepared by unequivocal procedures.

When ethyl 3,4-diaminobenzoate was prepared from ethyl 3-nitro-4-aminobenzoate[12] and condensed with pyruvic acid in the same general fashion described above, 55.5% yield of 3-methyl-7-carbethoxyquinoxalone-2, m.p. 194–197°, was obtained. One recrystallization of the crude product from benzene gave m.p. 200–201°. A mixture melting point of this substance with an analytical sample of 3-methyl-7-carbethoxyquinoxalone-2, gave no depression of the melting point; ultraviolet absorption spectra of both crude (m.p. 194–197°) and purified (m.p. 200–201°) esters were identical with that of the analytical sample prepared by unequivocal procedures.

But when ethyl 3,4-diaminobenzoate was condensed with ethyl pyruvate in absolute ethanol solution by procedures similar to those described above, a 100% yield of mixed esters melting at 173–185° was obtained. Examination of the ultraviolet absorption spectrum of this product indicated approximately equal portions of the two isomers were present in the crude reaction mixture.

By recrystallizing (with frequent treatment with charcoal) the crude product repeatedly from toluene, 17% of pure 3-methyl-7-carbethoxyquinoxalone-2 was obtained. The residue gave a like amount of pure 3-methyl-6-carbethoxyquinoxalone-2 when recrystallized repeatedly (again with frequent charcoal treatment) from benzene. Melting point, mixture melting point with analytical sample, and ultraviolet absorption spectrum of each ambiguous product proved the identity of the material.

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Diuretics. IV. 6-Chloro-3-substituted 7-Sulfamoyl-1,2,4-benzothiadiazine 1,1-Dioxides

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Trifluoroacetic acid anhydrides of carboxylic acids were allowed to react with 6-amino-4-chlorobenzene-1,3-disulfonamide to yield 6-carbamyl-4-chlorobenzene-1,3-disulfonamides. These latter compounds were cyclized in base to 6-chloro-3-substituted 7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxides. Titrations of the 3-substituted 1,2,4-benzothiadiazine 1,1-dioxides indicated the influence of the 3-substituent on the ionization potential of the proton in the 2-position. Definite correlations are observed between diuretic activity and the nature of the 3-substituent.

Since the discovery of the diuretic activity of 6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide (I. R = H)[1] more active compounds have been prepared by modifying this interesting structure.[2–6] Ameliorable changes have been 1, saturation of the 3,4-double bond and 2, introduction of appropriate substituents in the 3-position. Derivatives of the 3,4-dihydro compound II are gen-

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