N-(2-Diazo-3-oxoalkanoyl)glycine esters. I. Synthesis of 4- and 5-phenoxyl derivatives and isomerization of *N*-(2-diazo-3-oxo-3-phenylpropanoyl)glycine ethyl ester[1]

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A new preparative procedure for *N*-(diazoacetyl)glycine ethyl ester is described. The interaction of *N*-(diazoacetyl)glycine ethyl ester with four phenoxyacetyl chlorides gives the 4-phenoxyl derivatives of *N*-(2-diazo-3-oxobutanoyl)glycine ethyl ester, and with β-(*o*-methoxyphenoxy)-propionyl chloride yields *N*-[2-diazo-3-oxo-5-(*o*-methoxyphenoxy)pentanoyl]glycine ethyl ester. A general chromatographic procedure for separating *N*-(2-diazo-3-oxoalkanoyl)glycine ethyl esters from *N*-(chloroacetyl)glycine ethyl ester has been developed. Crotonyl chloride reacts with a 1 mole excess of *N*-(diazoacetyl)glycine ethyl ester to form *N*-(2-diazo-3-oxo-4-hexenoyl)glycine ethyl ester, and with a 2 mole excess to form *N*-{2-diazo-3-oxo-3-[4′-methyl-5′-(carboethoxymethyl)carbamoyl-Δ^2-pyrazolin-3′-yl]propanoyl}glycine ethyl ester, presumably by isomerization of an initially formed Δ^1-pyrazoline derivative. The interaction of benzoyl and *m*-bromobenzoyl bromide with *N*-(diazoacetyl)glycine ethyl ester results initially in yellow oily products which, on the basis of spectral data, are the expected *N*-(2-diazo-3-oxo-3-arylpropanoyl)glycine ethyl esters. During chromatographic purification and (or) attempted crystallization, there occurs an isomerization to colorless crystalline products. The analytical and molecular weight data, together with the spectral evidence, support the tentative assignment of 1,2,3-triazole structures to the isomerization products. A spontaneous reverse Dimroth rearrangement is postulated.

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INTRODUCTION

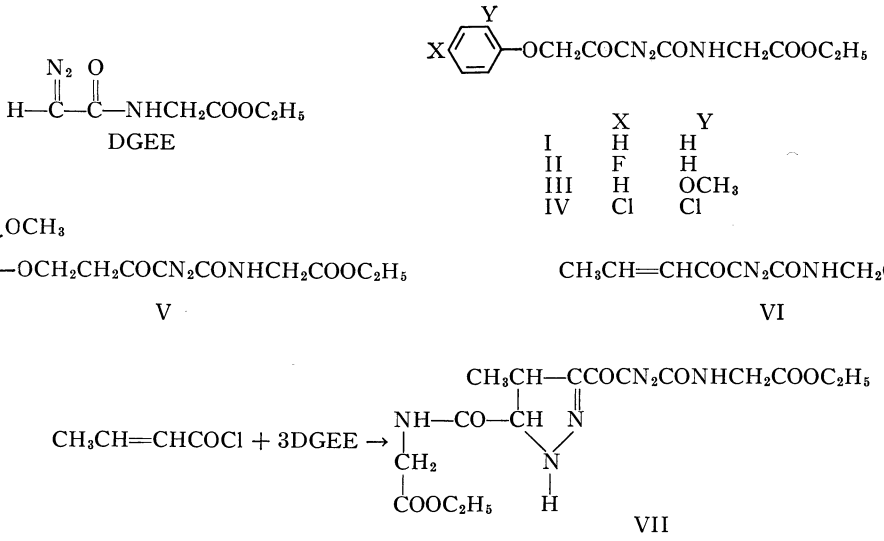
In the field of aliphatic diazo chemistry, the diazoketones obtained from the interaction of acid halides with excess diazomethane (1) are well known. Acyl- and aroyl-diazoacetic esters have been prepared in a similar manner by the interaction of acid halides with excess methyl or ethyl diazoacetate (2, 3). More recently, the reactions of methyl diazoacetate with acid halides have been reinvestigated, with emphasis on the importance of water in the reaction medium (4, 5). *N*-(Diazoacetyl)glycine ethyl ester (DGEE), first prepared by Curtius and Darapsky in 1906 (6), is structurally similar to diazomethane and diazoacetic ester in having a terminal diazo group, which would be expected to permit acylation with retention of the diazo group. Curtius and his colleagues have reported the reactions of DGEE with water, iodine, several organic and inorganic acids, and ammonia. Of these substances, only ammonia yields a product (*N*-(diazoacetyl)glycine amide) in which the diazo group is retained. The reactions of DGEE with acids and iodine to give various products, and in all cases nitrogen, are analogous to well-known transformations of other diazo compounds.

RESULTS AND DISCUSSION

DGEE has been prepared by diazotization of glycylglycine ethyl ester, and isolated directly from the reaction mixture (6). A more satisfactory method, which yields DGEE in a purer state, involves the use of methylene chloride to extract the diazo compound as rapidly as it is formed. The procedure is similar to that employed in the synthesis of ethyl diazoacetate (7).

The addition of acyl halide to excess diazo compound in ethereal solution is not applicable to the synthesis of *N*-(2-diazo-3-oxoalkanoyl)glycine esters because of the insolubility of DGEE in ether. Methylene chloride, however, is a satisfactory solvent. DGEE is moderately soluble, and water only slightly soluble, in this solvent. Any accumulation of water is undesirable, since hydrolysis of acid chlorides leads ultimately to *N*-glycolylglycine derivatives (sequel) with loss of diazo nitrogen. The

[1]Abstracted from a portion of the doctorate thesis of James William Carpenter, 1965.



course of the reaction of acyl halide with DGEE was followed by measuring the carbonyl absorption of the reaction mixture in the 1 815 – 1 770 cm^{-1} region. When this acid halide carbonyl band had disappeared, the reaction was assumed to be complete, and solvent and traces of acid halide were removed by rotary evaporation. The residue consisted mainly of the diazo compound and the ethyl ester of either *N*-chloroacetylglycine or *N*-bromoacetylglycine. The latter two substances, which result from the interaction of hydrogen halide with DGEE, are solids at room temperature and, accordingly, are more difficult to remove than the gaseous or liquid materials methyl chloride or ethyl chloroacetate, which result from the action of hydrogen chloride on diazomethane and ethyl diazoacetate, respectively. The separation of the diazo compound from the haloacetylglycine ester by both fractional crystallization and column chromatographic techniques has been investigated. With one exception, the chromatographic method has resulted in a higher yield of the *N*-(2-diazo-3-oxoalkanoyl)glycine ester.

Of several adsorbents investigated, silicic acid – cellulose was the most efficient. In many experiments gas evolution was observed when the total residue from the reaction mixture was placed on the column. However, such gas evolution results from the decomposition of unreacted or excess DGEE, not of the product *N*-(2-diazo-3-oxoalkanoyl)glycine esters, which, in the pure state, are stable on the adsorbent system. Large amounts of unreacted or excess DGEE interfered with the chromatographic purification procedures, since the evolved gas disrupted the packed column.

Phenoxyacetyl chloride and its *p*-fluoro, *o*-methoxy, and 2,4-dichloro derivatives react with a 1 mole excess of DGEE to give the *N*-[2-diazo-3-oxo-4-(phenoxy)butanoyl]-glycine ethyl ester derivatives I–IV in yields ranging from 35 to 59%. In one experiment, III was obtained in a 67% yield when purified by fractional crystallization from ether – methylene chloride. β-(*o*-Methoxyphenoxy)propionyl chloride and excess DGEE gave V in a 16% yield. In the infrared spectra, compounds I–V show diazo bands at 2 150 ± 10 cm^{-1}, and ester, amide, and keto carbonyl bands near 1 750, 1 670, and 1 630 cm^{-1}, respectively. Detailed spectral data are presented in Table I.

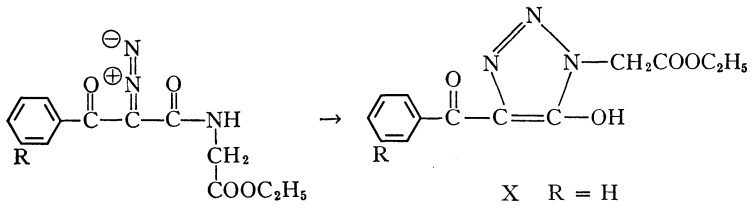
The interaction of crotonyl chloride with a 1 mole excess of DGEE gave *N*-(2-diazo-3-oxo-4-hexenoyl)glycine ethyl ester (VI) in a 27% yield. However, when DGEE in 2 mole excess was employed, a Δ^2-pyrazoline derivative (VII) was obtained,

TABLE I

Infrared absorption spectra* (cm^{-1}) of *N*-(2-diazo-3-oxoalkanoyl)glycine esters and *N*-(*O*-acylglycolyl)glycine esters

Compound	NH stretching	CN_2	Ester C=O	Amide C=O	Keto C=O	Amide NH deformation	Aromatic bands†
I	3 333	2 153	1 747	1 667	1 629	1 536	1 604, 1 597, 1 501
II	3 320	2 142	1 745	1 670	1 625	1 525	1 601, 1 500
III	3 320	2 150	1 748	1 670	1 623	1 535	1 600, 1 501
IV	3 345	2 160	1 760	1 680	1 635	1 540	1 490
V	3 312	2 140	1 750	1 670	1 630	1 535	1 595, 1 510
VI‡§	3 320	2 150	1 750	1 685 or 1 665	1 640	1 576 or 1 535	—
VII‖	3 425, 3 380, 3 335	2 160	1 750	1 690, 1 675	1 610	1 535	—
XII¶	3 350	—	1 780, 1 735	1 670	—	1 550	1 603, 1 590, 1 503
XIII	3 435	—	1 775, 1 750	1 695	—	1 528	—
DGEE	3 415	2 115	1 743	1 653	—	1 520	—

*Of CH_2Cl_2 solutions, unless otherwise indicated.
†In-plane skeletal bands, exclusive of the 1 450 cm^{-1} band.
‡Of KBr disk.
§An *N*-(2-diazo-3-oxoalkenoyl)glycine ester.
‖An *N*-[2-diazo-3-oxo-3-(Δ^2-pyrazolinyl)propanoyl]glycine ester.
¶Of Nujol mull.



VIII R = H
IX R = Br

X R = H
XI R = Br

$RCH_2COOCH_2CONHCH_2COOCH_2CH_3$

XII R = OC_6H_5
XIII R = Cl

presumably by cycloaddition of DGEE to the conjugated carbon-to-carbon double bond of crotonyl chloride to give initially a Δ^1-pyrazoline. Bond migration would give VII. The postulated structure VII was supported by combustion analysis and the infrared spectrum, which contains three distinct bands in the NH stretching region (3 347, 3 285, and 3 237 cm^{-1}). In addition, the ultraviolet absorption spectrum contains a maximum at 333 mμ, which supports the conjugated nitrogen-to-carbon double bond in the Δ^2-pyrazoline structure (8).

When benzoyl bromide and its *m*-bromo derivative react with DGEE, the initial products obtained after chromatographic purification are yellow oils. Although the degree of homogeneity of the latter is not known, the infrared spectral data support the presence therein of the aroyl diazo compounds VIII and IX. A strong band at 2 150 cm^{-1} indicates the aliphatic diazo group. Peaks at 3 335 and 3 340 cm^{-1} in the spectra of VIII and IX, respectively, probably are associated with the NH stretching mode of the amide function. It has not been possible to obtain VIII and IX in a pure state because of a transformation to colorless substances which occurs during crystallization from methylene chloride – ether, or possibly partially during chromatographic purification. Combustion analyses and molecular weight determinations indicate that the colorless crystalline solids are isomeric with VIII and IX. The infrared spectra of the colorless products contain no diazo peak, and no amide band at 3 340 or 3 335 cm^{-1}. The disappearance of both the diazo and amide groups during the isomerization is suggestive of a reverse Dimroth rearrangement (9), which would lead to the *vic*-triazoles X and XI. Although such reverse rearrangements are known, they usually require alkaline catalysis. The solution spectrum of X contains distinct bands at 1 780 and 1 610 cm^{-1}, probably associated, respectively, with ester and benzoyl carbonyl stretching modes. A weak band at 3 500 cm^{-1} may be due to OH stretching. The solid-state spectrum of X is in essential agreement, but contains an additional band in the ester carbonyl region, at 1 755 cm^{-1}. An adequate explanation of this apparent solid-state anomaly is not presently available. The solid-state spectrum of XI also shows a double carbonyl band in the ester region, but no distinct benzoyl band near 1 610 cm^{-1}.

In the nuclear magnetic resonance spectra of X and XI, the chemical shifts and peak multiplicities (10) permitted the assignment of signals near τ 8.75 and τ 5.8 to the methyl and methylene protons of the ethyl group, respectively, and the singlet near τ 4.84 to the methylene protons alpha to the carbonyl group. The multiplets near τ 2.0 are aromatic signals and, since the peaks integrate for six and five protons in the spectra of X and XI, respectively, also contain a signal ascribable to some other proton, possibly in an OH or NH group. Thus, the nuclear magnetic resonance spectra are consistent with

structures X and XI, but also with certain tautomeric structures.

Repeated attempts were made to prepare *N*-(2-diazo-3-oxobutanoyl)glycine ethyl ester through the interaction of acetyl chloride or bromide with DGEE in ethyl acetate, methylene chloride, tetrahydrofuran, propylene chloride, and 1,1,2,2-tetrachloroethane. Although a reaction occurred between acetyl bromide and DGEE in ethyl acetate, as evidenced by the formation of *N*-(bromoacetyl)glycine ethyl ester, the other product was not obtained in a pure state. The hydrogen bromide required for the interaction with DGEE could result from either the direct reaction of acetyl bromide with DGEE or the hydrolysis of acetyl bromide.

Phenoxyacetyl chloride and DGEE in methylene chloride gave *N*-[2-diazo-3-oxo-4-(phenoxy)butanoyl]glycine ethyl ester (I) in a 31% yield, and *N*-[*O*-(phenoxyacetyl)-glycolyl]glycine ethyl ester (XII). Water originally present in the methylene chloride, or subsequently incorporated from the atmosphere, could effect the hydrolysis of phenoxyacetyl chloride. Reaction of the liberated acid with DGEE would give XII. Such a process is similar to the reactions of carboxylic acids with diazomethane (11) and diazoacetic esters (4). An independent synthesis from DGEE and phenoxyacetic acid also gave XII. In the reaction of chloroacetyl chloride with DGEE, *N*-[*O*-(chloroacetyl)glycolyl]glycine ethyl ester (XIII), the product expected from the interaction of chloroacetic acid with DGEE, was obtained.

EXPERIMENTAL

All melting points are uncorrected, and were determined by the capillary tube method. Elemental analyses and molecular weight determinations were performed by A. Bernhardt, Mülheim (Ruhr), Germany. Infrared spectra were obtained with a Perkin–Elmer model 237 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A60 spectrometer (60 mc.p.s.), with tetramethylsilane as an internal standard. Mallinckrodt chromatographic-grade silicic acid ($SiO_2 \cdot xH_2O$) and Whatman cellulose Chromedia CF-1 were used in all chromatographic purification procedures. In general, reactant acid chlorides were distilled *in vacuo* just before use.

Glycylglycine Ethyl Ester Hydrochloride

This substance was prepared from diketopiperazine (Aldrich Chemical Company glycine anhydride) in an 87% yield by the literature method (12).

DGEE

To a stirred solution of glycylglycine ethyl ester hydrochloride (30.0 g) in 60 ml of 2 *F* sodium acetate trihydrate solution was added a sodium nitrite solution (15.0 g of sodium nitrite in 30 ml of water) at 5°. After 800 ml of methylene chloride and 6 ml of glacial acetic acid were added, the reaction mixture was stirred for 5 h. The methylene chloride layer was washed with 300 ml of 5% $NaHCO_3$ (or until neutral), concentrated to 100 ml, and cooled to yield 17.6 g (67.7%) of yellowish-green crystals, m.p. 105–107° (lit. (6) m.p. 107°). Nuclear magnetic resonance peaks ($CDCl_3$) were found at τ 8.70 (3 H, triplet, *J* 6.5 c.p.s.), τ 5.99–5.59 (4 H, multiplet), τ 4.94 (1 H, singlet, CHN_2), and τ 3.67–3.25 (1 H, singlet, NH).

N-[2-Diazo-3-oxo-4-(phenoxy)butanoyl]glycine Ethyl Ester (I)

A 4.76 g quantity (0.0278 mole) of phenoxyacetyl chloride was dissolved in 25 ml of methylene chloride and added dropwise to a solution of 10.000 g of DGEE (0.0585 mole) in 125 ml of methylene chloride. The reaction was carried out in a three-necked, round-bottomed flask fitted with a water-cooled condenser, dropping funnel, and glass stopper, calcium chloride drying tubes being used at both exits to provide protection from atmospheric moisture. Stirring was provided by a bar magnet and magnetic stirrer. After 24 h, the reaction mixture was washed with 5% sodium bicarbonate (methylene chloride layer retained). The bicarbonate phase was back-extracted with methylene chloride, and the combined methylene chloride layers were dried over anhydrous sodium sulfate in a separatory funnel for 5 min. The mixture was filtered through a cotton plug in the stem, the filtrate was concentrated by rotary evaporation, and the residue was dissolved in the minimal quantity of methylene chloride. The resulting solution was subjected to elution chromatography on 330 g of silicic acid – cellulose (5:1 by weight).

The chromatographic column was packed in the following order: glass wool, sand, adsorbent, and again sand. The adsorbent was introduced into the column (88 cm long, 39 mm inside diameter, 41 mm outside diameter) as a slurry in benzene. The column was eluted with 1.7 l of CH_2Cl_2 to give a malodorous oil (discarded). Further elution with 1 l of CH_2Cl_2 – ethyl acetate (49:1 by volume) and 1 l of CH_2Cl_2 – ethyl acetate (19:1 by volume) gave 5.5221 g of a white solid, which was recrystallized from CH_2Cl_2 – ethyl ether to give 3.4103 g (40.2%) of I, m.p. 106.5–108°. Nuclear magnetic resonance peaks ($CDCl_3$) were found at τ 8.73 (3 H, triplet, *J* 7 c.p.s.), τ 6.08–5.62 (4 H, quintet; *J* 6, 8, 8, and 7 c.p.s.), τ 5.27 (4 H, doublet, *J* 3.5 c.p.s.), τ 3.50–3.17 (1 H, singlet), and τ 3.17–2.50 (5 H, multiplet).

Anal. Calcd. for $C_{14}H_{15}N_3O_5$: C, 55.08; H, 4.95; N, 13.77. Found: C, 55.18; H, 5.16; N, 14.05.

N-[2-Diazo-3-oxo-4-(p-fluorophenoxy)butanoyl]-glycine Ethyl Ester (II)

p-Fluorophenoxyacetyl chloride (5.25 g) in 25 ml of CH_2Cl_2 was added dropwise to 10.000 g of DGEE in 125 ml of CH_2Cl_2; the reaction time was 26.5 h. The general procedure was the same as that in the preceding section. Elution first with 2 l of CH_2Cl_2 gave a yellow, ether-soluble oil (discarded), and then with 2 l of CH_2Cl_2–EtOAc (49:1 by volume) gave 4.1582 g of a crystalline solid, partially soluble in ether. Recrystallization from ether–CH_2Cl_2 gave colorless II (3.4565 g, 38.4%), m.p. 104–107°. Nuclear magnetic resonance peaks were found at τ 7.05 (3 H, triplet, J 7 c.p.s.), τ 6.00–5.50 (4 H, multiplet), τ 5.20 (2 H, singlet), τ 3.25–2.42 (4 H, multiplet), and τ 1.50–1.08 (1 H, singlet).

Anal. Calcd. for $C_{14}H_{14}FN_3O_5$: C, 52.01; H, 4.36; F, 5.88; N, 13.00. Found: C, 52.78; H, 4.34; F, 6.60; N, 13.52.

N-[2-Diazo-3-oxo-4-(o-methoxyphenoxy)butanoyl]-glycine Ethyl Ester (III)

o-Methoxyphenoxyacetyl chloride (4.00 g) in 25 ml of CH_2Cl_2 was added dropwise to 7.1716 g of DGEE in 100 ml of CH_2Cl_2; the reaction period was 20 h. The general procedure was the same as that used for I. Elution with 750 ml of CH_2Cl_2 and 1 l of CH_2Cl_2–EtOAc (49:1 by volume) gave a yellow oil (not characterized). Further development with 1 l of CH_2Cl_2–EtOAc (49:1 by volume) and 2.5 l of CH_2Cl_2–EtOAc (24:1 by volume) gave 6.6091 g of a crystalline solid, partially soluble in ether. Recrystallization from ether–CH_2Cl_2 gave colorless III (3.8505 g, 58.8%), m.p. 114–116°. Nuclear magnetic resonance peaks ($CDCl_3$) were found at τ 8.87 (3 H, triplet, J 7.3 c.p.s.), τ 6.12 (3 H, singlet), τ 6.0–5.5 (4 H, multiplet), τ 5.19 (2 H, singlet), τ 3.17–2.84 (4 H, multiplet), and τ 1.42–0.92 (1 H, singlet).

Anal. Calcd. for $C_{15}H_{17}N_3O_6$: C, 53.73; H, 5.11; N, 12.53. Found: C, 53.93; H, 5.07; N, 12.37.

N-[2-Diazo-3-oxo-4-(2',4'-dichlorophenoxy)butanoyl]-glycine Ethyl Ester (IV)

2,4-Dichlorophenoxyacetyl chloride (1.9044 g) in 25 ml of CH_2Cl_2 was added dropwise to 2.7226 g of DGEE in 25 ml of CH_2Cl_2; the reaction time was 21.66 h. The general procedure was the same as that used for I. Elution with 700 ml of benzene gave a malodorous red oil (discarded). Further development with 580 ml of benzene and 1 l of benzene–CH_2Cl_2 (49:1 by volume) gave 3.4813 g of a solid, partially soluble in ether. Recrystallization from ether–CH_2Cl_2 gave colorless IV (1.0529 g, 35.4%), m.p. 98–100°. Nuclear magnetic resonance peaks ($CDCl_3$) were found at τ 8.73 (3 H, triplet, J 7.0 c.p.s.), τ 6.00–5.60 (4 H, multiplet), τ 5.22 (2 H, singlet), τ 3.32–2.60 (3 H, multiplet), and τ 1.59–1.23 (1 H, broad singlet).

Anal. Calcd. for $C_{12}H_{13}Cl_2N_3O_5$: C, 44.94; H, 3.50; N, 11.23. Found: C, 45.10; H, 2.75; N, 10.61.

N-[2-Diazo-3-oxo-5-(o-methoxyphenoxy)pentanoyl]-glycine Ethyl Ester (V)

β-(*o*-Methoxyphenoxy)propionyl chloride (1.3800 g) in 15 ml of CH_2Cl_2 was added dropwise to 2.5308 g of DGEE in 30 ml of CH_2Cl_2 (cf. the section on *N*-[2-diazo-3-oxo-4-(phenoxy)butanoyl]glycine ethyl ester). After 165 h, 5 g of silicic acid – cellulose (5:1 by weight) was added to the reaction mixture. After the reaction mixture was stirred for 7 h, no gas evolution was observed. The entire contents of the reaction mixture were deposited on a chromatographic column containing 175 g of silicic acid – cellulose adsorbent (5:1 by weight). Elution with 1 l of CH_2Cl_2, 1 l of CH_2Cl_2–EtOAc (49:1 by volume), 500 ml of CH_2Cl_2–EtOAc (24:1 by volume), and 500 ml of CH_2Cl_2–EtOAc (23:2 by volume) gave 245, 274, 75, and 296.5 mg, respectively, of solids and oils (completely soluble in ether and discarded). The title compound (0.7925 g), partially soluble in ether, was obtained by further elution with 500 ml of CH_2Cl_2–EtOAc (4:1 by volume) and 250 ml of CH_2Cl_2–EtOAc (1:1 by volume). Recrystallization from ether–CH_2Cl_2 gave V as light-yellow needles (0.3601 g, 16.0%), m.p. 105–106°. Nuclear magnetic resonance peaks ($CDCl_3$) were found at τ 8.72 (3 H, triplet, J 7 c.p.s.), τ 6.96 (2 H, triplet, J 6 c.p.s.), τ 6.14 (3 H, singlet), τ 6.0–5.4 (6 H, multiplet), τ 3.03 (4 H, singlet), and τ 1.50–1.09 (1 H, singlet).

Anal. Calcd. for $C_{16}H_{19}N_3O_6$: C, 55.01; H, 5.48; N, 12.03. Found: C, 55.41; H, 5.52; N, 12.07.

N-(2-Diazo-3-oxo-4-hexenoyl)glycine Ethyl Ester (VI)

Crotonyl chloride (2.038 g) in 60 ml of CH_2Cl_2 was added dropwise to 7.000 g of DGEE in 90 ml of CH_2Cl_2; the reaction period was 72 h. The general procedure was the same as that for *N*-[2-diazo-3-oxo-4-(phenoxy)butanoyl]glycine ethyl ester. Elution with 700 ml of CH_2Cl_2 and then with 1.4 l of CH_2Cl_2–EtOAc (1:1 by volume) gave 4.0042 g of *N*-(chloroacetyl)glycine ethyl ester. Further development with 700 ml of EtOAc gave 1.2465 g (26.7%) of VI. Recrystallization from methanol–CH_2Cl_2 gave colorless VI, m.p. 199° (partial decomposition at 197°).

Anal. Calcd. for $C_{10}H_{13}N_3O_4$: C, 50.21; H, 5.48; N, 17.56. Found: C, 49.89; H, 5.57; N, 17.48.

N-{2-Diazo-3-oxo-3-[4'-methyl-5'-(carboethoxymethyl)-carbamoyl-Δ^2-pyrazolin-3'-yl]propanoyl}-glycine Ethyl Ester (VII)

Crotonyl chloride (1.426 g) in 60 ml of CH_2Cl_2 was added dropwise to 7.0000 g of DGEE in 90 ml of CH_2Cl_2; the reaction time was 58 h. (For the general procedure, see the section on *N*-[2-diazo-3-oxo-4-(phenoxy)butanoyl]glycine ethyl ester.) Elution with 1 l of CH_2Cl_2–EtOAc (4:1 by volume) and 1.8 l of CH_2Cl_2–EtOAc (1:1 by volume) gave *N*-(chloroacetyl)glycine ethyl ester, m.p. 58–60°. Further elution with pure ethyl acetate gave 1.4191 g (25.3%) of VII, m.p. 183° after recrystallization from CH_2Cl_2–ether.

Anal. Calcd. for $C_{16}H_{22}N_6O_7$: C, 46.83; H, 5.40; N, 20.48. Found: C, 46.48; H, 5.17; N, 20.38.

Reaction of Benzoyl Bromide with DGEE; Isolation of Isomerization Product (X) of Oil Presumed to be N-[2-Diazo-3-oxo-3-(phenyl)propanoyl]-glycine Ethyl Ester (VIII)

Benzoyl bromide (3.78 g) in 50 ml of CH_2Cl_2 was added dropwise to 7.0000 g of DGEE in 90 ml of CH_2Cl_2; the reaction period was 91 h. (For the

general procedure, see the section on *N*-[2-diazo-3-oxo-4-(phenoxy)butanoyl]glycine ethyl ester.) Elution with 510 ml of CH_2Cl_2–EtOAc (9:1 by volume) and 225 ml of CH_2Cl_2–EtOAc (4:1 by volume) gave 4.192 g of a light-yellow oil (strong infrared absorption at 2 150 cm^{-1}). Solution in ether–CH_2Cl_2 (2:1 by volume) and cooling gave colorless needles (2.7397 g), m.p. 113°. Nuclear magnetic resonance peaks ($CDCl_3$) were found at τ 8.76 (3 H, triplet, J 7 c.p.s.), τ 5.71 (2 H, quartet, J 7.5 c.p.s.), τ 4.85 (2 H, singlet), and τ 2.57–1.80 (6 H, multiplet).

Anal. Calcd. for $C_{13}H_{13}N_3O_4$: C, 56.73; H, 4.76; N, 15.27; mol. wt. 275. Found: C, 56.71; H, 4.69; N, 15.14; mol. wt. (Rast) 279.

The filtrate from the isomerization product isolation was concentrated to a yellow oil. Infrared bands (CH_2Cl_2) were found at 3 510, 3 440, 3 335, 2 150, 1 770, 1 720, 1 685, 1 635, and 1 620 cm^{-1}, and nuclear magnetic resonance peaks ($CDCl_3$) at τ 1.28–0.90 (broad triplet).

Reaction of m-Bromobenzoyl Bromide with DGEE; Isolation of Isomerization Product (XI) of Oil Presumed to be N-[2-Diazo-3-oxo-3-(m-bromophenyl)propanoyl]glycine Ethyl Ester (IX)

m-Bromobenzoyl bromide (3.70 g) in 50 ml of CH_2Cl_2 was added dropwise to 5.0000 g of DGEE in 70 ml of CH_2Cl_2; the reaction time was 76 h. (For the general procedure, see the section on *N*-[2-diazo-3-oxo-4-(phenoxy)butanoyl]glycine ethyl ester.) Elution with 2.0 l of CH_2Cl_2 gave a malodorous oil (discarded). Further elution with 1 l of CH_2Cl_2–EtOAc (49:1 by volume) gave 2.5827 g of a yellow oil (partially soluble in ether), which was dissolved in ether–CH_2Cl_2 and cooled. A white crystalline solid (0.9419 g), m.p. 94–96°, separated. Recrystallization from ether gave 0.6236 g of XI as colorless needles, m.p. 99°. The infrared spectrum (KBr) contained absorption bands at 3 475, 1 760, 1 740, and 1 555 cm^{-1}. Nuclear magnetic resonance peaks ($CDCl_3$) were found at τ 8.73 (3 H, triplet, J 7.3 c.p.s.), τ 5.90–5.54 (2 H, quartet, J 7.0 c.p.s.), τ 4.83 (2 H, singlet), and τ 2.68–1.70 (5 H, multiplet).

Anal. Calcd. for $C_{13}H_{12}BrN_3O_4$: C, 44.09; H, 3.42; Br, 22.56; N, 11.87; mol. wt. 354. Found: C, 44.36; H, 3.36; Br, 22.53; N, 11.71; mol. wt. (Rast) 387.

Reaction of Acetyl Bromide with DGEE in Ethyl Acetate; Isolation of N-(Bromoacetyl)glycine Ethyl Ester

Acetyl bromide (12.4 g) in 13 ml of ethyl acetate was added dropwise to 34.3 g of DGEE in 87 ml of the same solvent at 71° over 85 min. The mixture was refluxed for 17 min at 77°, and then cooled in an ice bath. A yellowish-white precipitate (16.9 g, 74.8%), m.p. 64–67°, separated. Recrystallization from anhydrous methanol gave *N*-(bromoacetyl)-glycine ethyl ester, m.p. 77.5°, as colorless needles. Infrared bands (KBr) were found at 1 738 (ester C=O) and 1 645 cm^{-1} (amide C=O); in CH_2Cl_2 solution, bands appeared at 1 745 (ester C=O) and 1 680 cm^{-1} (amide C=O).

Anal. Calcd. for $C_6H_{10}BrNO_3$: C, 32.16; H, 4.50; Br, 35.67; N, 6.25. Found: C, 32.55; H, 4.63; Br, 35.52; N, 6.05.

Isolation of N-[O-(Phenoxyacetyl)glycolyl]glycine Ethyl Ester (XII) as a By-product in the Preparation of N-[2-Diazo-3-oxo-4-(phenoxy)-butanoyl]glycine Ethyl Ester

Phenoxyacetyl chloride (3.12 g) in 20 ml of CH_2Cl_2 was added dropwise to 7.81 g of DGEE in 80 ml of CH_2Cl_2, with vigorous stirring, over 40 min. After 9 h, the mixture was concentrated by rotary evaporation at 100 mm and ice-bath temperature; a dry yellow residue resulted, which was subjected to Soxhlet extraction with 800 ml of pentane. The pentane extract yielded 2.37 g (72%) of *N*-(chloroacetyl)glycine ethyl ester, m.p. 60–62°. The residue was then extracted with 800 ml of ether. Concentration of the extract yielded 1.73 g (31.0%) of *N*-[2-diazo-3-oxo-4-(phenoxy)butanoyl]glycine ethyl ester, m.p. 104–106°, identified by mixture melting point and infrared spectrum. Further concentration yielded *N*-[*O*-(phenoxyacetyl)glycolyl]glycine ethyl ester, m.p. 78–79.2°. Nuclear magnetic resonance peaks ($CDCl_3$) were present at τ 8.73 (3 H, triplet, J 7 c.p.s.), τ 6.08–5.62 (4 H, quintet; J 6, 8, 8, and 7 c.p.s.), τ 5.27 (4 H, doublet, J 3.5 c.p.s.), τ 3.50–3.17 (1 H, singlet), and τ 3.17–2.50 (5 H, multiplet).

Anal. Calcd. for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.62; H, 5.92; N, 5.02.

Reaction of Phenoxyacetic Acid with DGEE

Phenoxyacetic acid (0.890 g) in 20 ml of methylene chloride was added dropwise to 1.00 g of DGEE in 10 ml of the same solvent. After 65 h, concentration by rotary evaporation gave a yellow oil. Cooling of an ethereal solution of the latter resulted in 1.47 g (85.5%) of colorless XII, m.p. 76°. Recrystallization from ether–methanol gave XII, m.p. 78°; its infrared and nuclear magnetic resonance spectra were identical with those in the preceding section.

Anal. Calcd. for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.96; H, 5.75; N, 4.81.

Attempted Synthesis of N-(2-Diazo-3-oxo-4-chlorobutanoyl)glycine Ethyl Ester; Isolation of N-[O-(chloroacetyl)glycolyl]glycine Ethyl Ester (XIII)

Chloroacetyl chloride (1.32 g) in 10 ml of CH_2Cl_2 was added dropwise to 4.0 g of DGEE in 40 ml of the same solvent at room temperature over 32 min. After 4.5 h, concentration by rotary evaporation gave an oil, which was extracted with 50 ml of 5% $NaHCO_3$ (vigorous gas evolution). The bicarbonate solution was extracted with methylene chloride, which, upon solvent removal, yielded a residual oil. Solution of the latter in ether and cooling gave colorless XIII, m.p. 69–70°. Nuclear magnetic resonance peaks ($CDCl_3$) were found at τ 8.70 (3 H, triplet, J 7 c.p.s.), τ 6.0–5.5 (6 H, multiplet), τ 5.22 (2 H, singlet), and τ 3.08–2.67 (1 H, singlet).

Anal. Calcd. for $C_8H_{12}ClNO_5$: C, 40.43; H, 5.09; Cl, 14.92; N, 5.89. Found: C, 40.40; H, 5.61; Cl, 14.77; N, 5.74.

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