Reaction of Cyclic Acid Anhydrides with Ethyl Cyanoacetate

EDWARD E. SMISSMAN▲, MICHAEL WACHTER, CHARLES BARFKNECHT, and R. BRUCE GABBARD

Abstract □ The reactions of cyclic carboxyanhydrides and substituted cyclic carboxyanhydrides with ethyl sodiocyanoacetic ester were studied. The resulting dicarboxylic acid esters failed to undergo Dieckmann cyclization.

Keyphrases □ Cyclic acid anhydrides—reaction with ethyl sodiocyanoacetate, absence of Dieckmann cyclization □ Sodiocyanoacetic acid ethyl ester—reaction with cyclic acid anhydrides, absence of Dieckmann cyclization □ Ring formation reactions, potential cyclic acid anhydrides and ethyl sodiocyanoacetate, absence of Dieckmann cyclization

In a previous paper, the preparation of an A-D ring analog of the tetracycline molecule, I, was discussed (1). A review of the chemistry of the tetracyclines (2) and of the substituents necessary for the desired biological activity based on numerous structure–activity relationship studies (3) was published.

With this general information in view, the possibility of cyclizing a properly constituted alicyclic molecule, II, to obtain the polysubstituted ring A, III, of tetracycline as an intermediate in the A-D ring synthesis (1) (Scheme I) and for biological testing was investigated.

DISCUSSION

The acylation of ethyl sodiocyanoacetate with cyclic carboxyanhydrides to give half-esters of α-cyano-β-ketodicarboxylic acids was reported (4). This procedure was modified to give the diester rather than the half-ester in the acylation of ethyl sodiocyanoacetate with glutaric or succinic anhydrides.

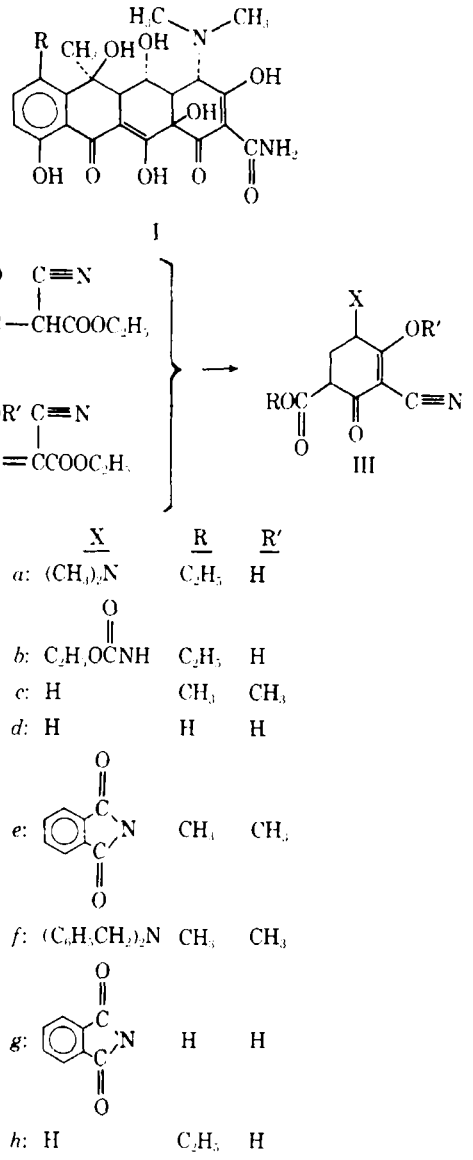
To utilize this method to prepare diethyl 2-cyano-3-hydroxy-4-*N*,*N*-dimethylamino-2-heptenedioate, II*a*, the previously unreported *N*,*N*-dimethylglutamic anhydride was required. *N*,*N*-Dimethylglutamic acid, IV*a*, was prepared by a modification of the method of Bowman and Stroud (5), which involved the reductive condensation of glutamic acid with formaldehyde under hydrogen. All attempts to convert IV*a* to the anhydride, V*a*, by known procedures failed.

N-Carbethoxyglutamic acid, IV*b*, was prepared by the method of Aberhalden and Kautzsch (6) and was cyclized by refluxing in acetic anhydride to give the corresponding anhydride, V*b*. On treatment of V*b* with ethyl sodiocyanoacetate, diethyl 2-cyano-3-hydroxy-4-*N*-carbethoxyamino-2-heptenedioate, II*b*, was produced. The assignment of the *N*-carbethoxyamino group to the 4-position was based on an analogous reaction by Bergman and Zervas (7). They reported the treatment of *N*-carbobenzoxyglutamic anhydride, V*c*, with ammonia to give *N*-carbobenzoxyisoglutamine, VI, which was then decarbobenzoxylated to isoglutamine. By analogy, the product of V*b* with sodiocyanoacetate would be expected to yield II*b* rather than the isomeric diethyl 2-cyano-3-hydroxy-6-*N*-carbethoxyamino-2-heptenedioate, VII*a*.

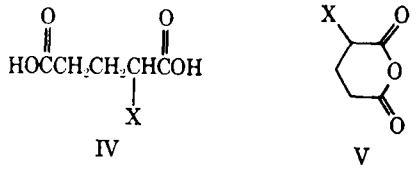
Attempts to cyclize II*b* utilizing sodium ethoxide and potassium *tert*-butoxide to produce the desired cyclohexanedione failed.

It was assumed that the preparation of III failed where R′ = H because the molecule II forms the anion VIII*a* or IX in preference to VIII. Formation of the desired cyclic compound is not possible when the enolic oxygen bears the negative charge as in IX (Scheme II). To circumvent this possibility, the enolic hydroxyl was protected as the enol methyl ether, II*c*, by treatment with diazomethane. It was assumed that VIII and VIII*a* would be in facile equilibrium. The assignment of the location of the ethyl and methyl ester groups in II*c* was undertaken by NMR studies. Ethyl acetate shows a triplet centered at δ1.25 and a quartet at δ4.12 for the ethyl function, while ethyl cyanoacetate shows peaks at δ1.32 and 4.27. The ethyl group in the latter is being deshielded by the electronegative groups in the acid portion of the molecule. The ethyl absorption in II*c* is at δ1.42 and 4.47. Since the ethyl group is deshielded, it is assigned to the 1-carboxyl function.

N-Phthalylglutamic anhydride, V*d*, proved to be a more convenient intermediate for the preparation of an amino-substituted pimelate. The reaction of V*d* with ethyl sodiocyanoacetate in xylene, followed by esterification of the resulting acids with diazomethane, gave two crystalline compounds. These compounds were shown to be the *cis*- and *trans*-isomers of VII*b* by the spectral data. Mass



Scheme I



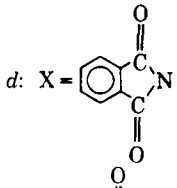
IV

V

a: X = $(CH_3)_2N$

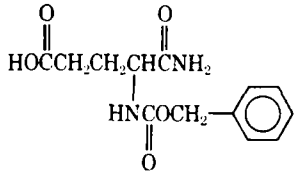
b: X = C_2H_5OCNH (O)

c: X = $C_6H_5CH_2OCNH$ (O)

d: X = 

e: X = F_3CCNH (O)

f: X = $(C_6H_5CH_2)_2N$



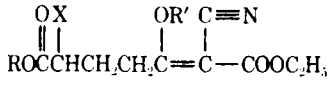
VI

spectroscopy was conclusive in establishing that they were the 6-*N*-phthalyl geometric isomers. Both *cis*- and *trans*-VII*b* gave identical fragmentation patterns, with a base peak of *m/e* 219. This peak arises from a McLafferty-type rearrangement (Scheme III) The 4-*N*-phthalyl isomer, II*e*, cannot give rise to a peak of *m/e* 219 by a similar rearrangement or fragmentation.

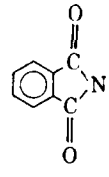
Attempts at the Dieckmann condensation of VII*b* failed.

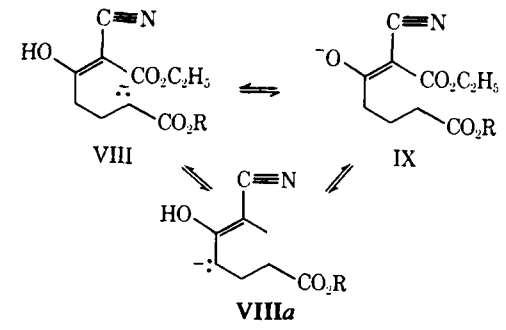
Since the 4-phthalimido compound, II*e*, could not be obtained, other systems were explored to secure an open-chain precursor of the tetracycline A ring with a nitrogen function at C-4. *N*-Trifluoroacetylglutamic anhydride, V*e*, was viewed as a potential precursor with a labile *N*-protecting group. The reaction of V*e* with ethyl sodiocyanoacetate, followed by esterification with diazomethane, yielded 2-trifluoroacetamidopentanedioate, IV*e*, as the only isolable product.

Despite previous failures in attempts to prepare *N,N*-dimethylglutamic anhydride, V*a*, it was thought that increasing the basicity of the nitrogen in such a system would lead to the desired 4-*N*-substituted heptenedioate. *N,N*-Dibenzylglutamic acid, IV*f*, contains a more basic nitrogen than the phthalyl or trifluoroacetyl



VII

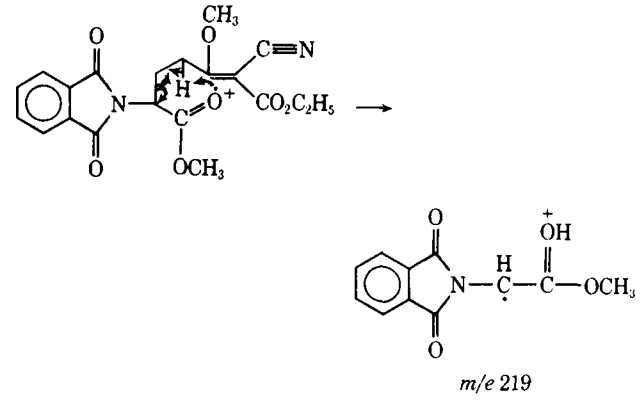
	X	R	R′
a:	C_2H_5OCNH (O)	C_2H_5	H
b:		CH_3	CH_3
c:	$(C_6H_5CH_2)_2N$	CH_3	CH_3



VIII IX

VIII*a*

Scheme II



m/e 219

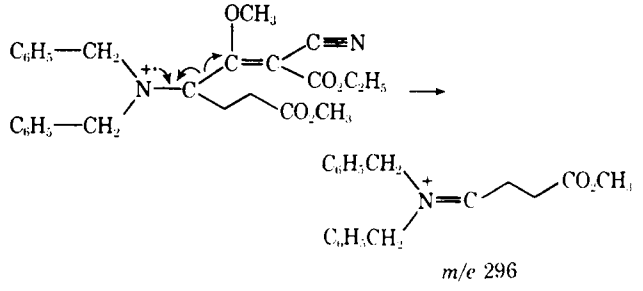
Scheme III

derivatives and was prepared by a modification of a reported procedure (8). Compound IV*f* was converted to the corresponding anhydride, V*f*, by heating with acetic anhydride.

Anhydrous potassium carbonate has been found effective as a reagent in the acylation of cyanoacetic esters with simple anhydrides (9). Use of these conditions for the reaction with V*f* and esterification of the products with diazomethane produced a mixture of heptenedioate esters. Column chromatography of this mixture gave an oil, which was identified as ethyl methyl 2-cyano-3-methoxy-4-*N,N*-dibenzylamino-2-heptenedioate, II*f*. The structure was assigned primarily from the mass spectrum along with the NMR and IR spectra. The mass spectrum of II*f* showed a base peak of *m/e* 296 below 100°. This represents a simple fragmentation of the C—C bond adjacent to the nitrogen typical of tertiary amines. The 4-*N,N*-dibenzyl isomer, II*f*, can give rise to this fragmentation, whereas the 6-*N,N*-dibenzyl isomer, VII*c*, cannot (Scheme IV).

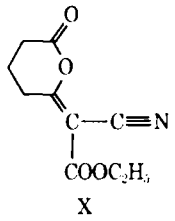
The use of sodium hydride gave superior yields of II*f* as compared to the method utilizing potassium carbonate. This procedure gave adequate quantities of II*f* to allow numerous attempts at the Dieckmann cyclization under various conditions. Potassium *tert*-butoxide in benzene, triethylamine in benzene, sodium hydride in benzene, and sodium hydride in dimethylformamide all proved to be unsuccessful in the cyclization.

Since the cyclization failed, it was decided to attempt an isomerization of the substituted enol lactone, X. The half-ester ethyl hydrogen 2-cyano-3-hydroxy-2-hepteneoate, II*d*, was treated with acetic anhydride to give a neutral compound in quantitative yield.

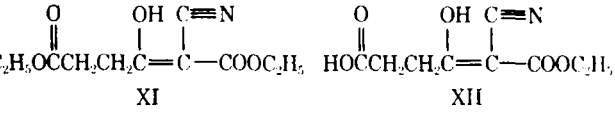


m/e 296

Scheme IV



X



XI XII

The enol lactones of the α-cyano-β-keto acids have not been reported previously. The compound was slowly soluble in sodium bicarbonate with effervescence; it gave a gradually deepening red color on reaction with ferric chloride solution within 20 min.; a strong band at 5.60 μ was present in the IR, indicating a vinyl ester structure. Thus, Compound X was established as the enol lactone rather than a cyclohexanedione. Compound X could not be isomerized to a 2,6-cyclohexanedione with sodium ethoxide (10) or boron trifluoride (11) or by thermal rearrangement.

Succinic anhydride was allowed to react with an equivalent amount of ethyl sodiocyanoacetate in the presence of ethanol to produce diethyl 2-cyano-3-hydroxy-2-hexenedioate, XI. This compound was partially hydrolyzed with hydrochloric acid to yield ethyl hydrogen 2-cyano-3-hydroxy-2-hexenedioate, XII, which was identical to the compound previously reported (4, 12).

EXPERIMENTAL[1]

Diethyl 2-Cyano-3-hydroxy-2-hexenedioate, XI A sodium dispersion was added under nitrogen to dry xylene (250 ml.) and absolute ethanol (12 ml.) until the stirred suspension was gray. The color was discharged by the addition of 1–2 ml. of ethanol. Ethyl cyanoacetate (22.5 g., 0.20 mole) was added all at once, resulting in a thick milky suspension. Succinic anhydride (20.0 g., 0.20 mole) was added immediately, and the thick emulsion became a yellowish turbid suspension. The mixture was stirred for 4 hr., after which it was shaken with 100 ml. water. The xylene layer was separated and the aqueous layer was extracted with ether (2 × 100 ml.). The xylene and ether extracts were combined and the solvent was removed to give an oily residue. The residue was distilled under reduced pressure. A fraction, b.p. 150–156°/0.1 mm., solidified on standing and was recrystallized (petroleum ether, b.p. 60–68°) to give 10 g. (21%) of a colorless crystalline material, m.p. 52.5–53.0° [lit. (4) m.p. 51°].

Ethyl Hydrogen 2-Cyano-3-hydroxy-2-heptenedioate, IId—The previous procedure was modified by heating the reaction vessel to 100° after 20 g. (0.20 mole) of ethyl cyanoacetate had been added to the sodium dispersion. A forceful current of nitrogen was introduced to entrain the ethanol vapors; when the ethanol had been removed, the heating was discontinued and 21 g. (0.10 mole) of glutaric anhydride was added. The procedure following the addition of glutaric anhydride was the same as previously described. Twenty-four grams (57%) of ethyl hydrogen 2-cyano-3-hydroxy-2-hepteneoate, IId, was obtained [lit. (4) m.p. 136°].

Anal.—Calc. for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.17. Found: C, 52.91, 52.95; H, 5.85, 5.95; N, 5.98.

If this modification was not followed, 20% of the half-ester and 14% of a colorless oil, diethyl 2-cyano-3-hydroxy-2-heptenedioate, IIh, were obtained. The latter formed a green crystalline chelate with cupric acetate, m.p. 120–121°.

Anal.—Calc. for $C_{21}H_{32}CuN_2O_{10}$: C, 50.20; H, 5.30; N, 4.95. Found: C, 50.49; H, 5.48; N, 4.75.

Ethyl 2-Pentanolidenecyanoacetate, X—Ethyl hydrogen 2-cyano-3-hydroxy-2-hepteneoate, IId (10 g., 0.05 mole), was refluxed in acetic anhydride (25 ml., 0.25 mole) until solution was effected. The excess acetic anhydride and the acetic acid were distilled *in vacuo*. The solid residue was crystallized from benzene–petroleum ether (b.p. 60–68°). Ethyl 2-pentanolidenecyanoacetate, X (10 g., 100%) was obtained as colorless plates, m.p. 104–106°.

Anal.—Calc. for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 56.98; H, 4.97; N, 6.54.

***N*-Carbethoxyglutamic Acid, IVb** The method of Aberhalden and Kautzsch (6) was followed. A colorless oil (22 g., 50%), soluble in water, was obtained from 29.4 g. (0.20 mole) glutamic acid and 21.7 g. (0.20 mole) ethyl chloroformate.

***N*-Carbethoxyglutamic Anhydride, Vb**—*N*-Carbethoxyglutamic acid (22.0 g., 0.10 mole) was refluxed with 50 ml. (0.50 mole) acetic anhydride for 1 hr. The excess acetic anhydride and acetic acid were removed *in vacuo*. *N*-Carbethoxyglutamic anhydride (20 g., 100%) was obtained as a pale-yellow oil.

Diethyl 2-Cyano-3-hydroxy-4-*N*-carbethoxyamino-2-heptenedioate, IIb—The procedure for the preparation of diethyl 2-cyano-3-hydroxy-2-heptenedioate, IIh, was followed. *N*-Carbethoxyglutamic anhydride (20 g., 0.10 mole) and 11.3 g. (0.10 mole) ethyl cyanoacetate were used and yielded 14 g. of a liquid acidic toward sodium bicarbonate. This material was distilled *in vacuo*. Diethyl 2-cyano-3-hydroxy-4-*N*-carbethoxyamino-2-heptenedioate, IIb (2.5 g., 7%), was obtained as a colorless liquid, b.p. 98°/6 mm.; n_D^{25} 1.454. The distillation flask contained a considerable amount of carbonaceous material.

Anal.—Calc. for $C_{15}H_{22}N_2O_7$: C, 52.62; H, 6.47; N, 8.18. Found: C, 52.96; H, 6.28, 6.24; N, 8.10, 8.15.

***N*-Phthalylglutamic Anhydride, Vd** The procedure was essentially that of King and Kidd (13). A suspension of L-glutamic acid (16.8 g., 0.113 mole) and phthalic anhydride (16.8 g., 0.113 mole) in 60 ml. of dry pyridine was refluxed for 2 hr. The solution was cooled, filtered, and evaporated under reduced pressure. Acetic anhydride (45 ml.) was added, the solution was heated at reflux for 3 min. and then cooled, and the solvent was partially removed. Crystallization began upon evaporation of the acetic anhydride and was completed upon the addition of 300 ml. of ether. After filtering and washing with ether, 21.5 g. of a white solid, m.p. 194–199°, 70% yield, was obtained. Two recrystallizations from ethyl acetate afford Vd, m.p. 200–204° [lit. (13) m.p. 195–200°].

Ethyl Hydrogen 2-Cyano-3-hydroxy-6-*N*-phthalimido-2-heptenedioate—A suspension of sodium hydride (0.632 g. of 57% NaH, 0.015 mole) was washed three times with dry dioxane, and then 125 ml. of dioxane was added to the reaction vessel. The vessel was equipped with a nitrogen inlet, and ethyl cyanoacetate (1.7 g., 0.015 mole) in 25 ml. of dioxane was added dropwise with stirring over 10 min. The mixture was heated at reflux for 2 hr. and a milky suspension formed. *N*-Phthalylglutamic anhydride, Vd (3.89 g., 0.015 mole), was added as a solid and the mixture was heated at reflux for 18 hr. After cooling, the dioxane was removed under reduced pressure and equal volumes of water and ether were added. A solid (0.4 g.), insoluble in either layer, was filtered. The aqueous layer was acidified with dilute hydrochloric acid and extracted three times with ether. The ethereal layer was dried (magnesium sulfate) and gave 3.8 g. of a viscous, nondistillable, yellow-orange oil. The NMR spectrum of this crude material indicated a mixture of heptenoic acids.

The insoluble material (0.4 g.) was dissolved in 25 ml. of ether–methanol (9:1) and esterified with diazomethane to give 411 mg. of a yellow oil, which was shown to be dimethyl 2-*N*-phthalimidopentanedioate: IR (chloroform): 1780–1720 cm.$^{-1}$, no C≡N stretch; NMR ($CDCl_3$): δ 2.3–2.7 (m, 4, CH_2CH_2), 3.63 (s, 3, OCH_3), 3.75 (s, 3, OCH_3), 4.93 (broad t, 1, methine H), and 7.84 (broad s, 4, aromatic H); mass spectroscopy: *m/e* 305 (parent peak) and 186 (base peak).

Ethyl Methyl 2-Cyano-3-methoxy-6-phthalimido-2-heptenedioate, VIIb The crude heptenoic acids (3.6 g.) were dissolved in 75 ml. of ether–methanol (9:1). An ethereal solution of diazomethane, generated from *N*-nitrosomethylurea, was added to this solution at 0°. Addition was continued until the effervescence ceased. The solvent was removed under reduced pressure to yield 3.7 g. of a yellow-orange nondistillable oil. TLC and NMR showed the oil to be a mixture of at least three compounds. The crude heptenedioate esters (3.0 g.) were chromatographed on 100 g. of silica gel, using chloroform as the eluting solvent. The first fraction eluted (550 mg.) was a colorless oil. Recrystallization from chloroform–hexane (1:1) gave 507 mg. of a white solid, m.p. 150–151°; IR (chloroform): 2960, 2220, 1780, 1720, 1580, 1380, 1125, and 1060 cm.$^{-1}$; NMR ($CDCl_3$): δ 1.24 (t, 3, CH_3), 2.85–3.25 (m, 2, CH_2), 3.0–

[1] Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. IR data were recorded on a Beckman IR-10 spectrophotometer. NMR data were recorded on Varian Associates A-60, A-60A, and HA 100 spectrometers using tetramethylsilane as an internal standard. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M 185 C, H, N analyzer.

3.3 (m, 2, CH_2), 3.75 (s, 3, OCH_3), 4.08 (s, 3, OCH_3), 4.1 (q, 2, CH_2CH_3), 4.98 (t, 1, methine H), and 7.86 (d, 4, aromatic H); UV (ethanol) λ_{max}: 261, 241, and 231 nm.; mass spectroscopy: *m/e* 399 (parent peak), 219 (base peak), 187 (90%), 132 (20%), and 104 (20%).

Anal.—Calc. for $C_{20}H_{20}N_2O_7$: C, 60.00; H, 5.03; N, 7.00. Found: C, 59.71; H, 4.91; N, 6.80.

A second fraction was collected which contained 750 mg. of a pale-yellow oil. Trituration of this oil with ether gave 532 mg. of a white solid, m.p. 90–91°; IR (chloroform): 2960, 2215, 1780–1720, 1575, 1380, 1210, and 1040 cm.$^{-1}$; NMR ($CDCl_3$): δ 1.27 (t, 3, CH_3), 2.4 2.95 (m, 4, CH_2CH_2), 3.76 (s, 3, OCH_3), 4.08 (s, 3, OCH_3). 4.2 (q, 2, CH_2CH_3), 4.95 (t, 1, methine H), and 7.85 (d, 4, aromatic H); UV (ethanol) λ_{max}: 261, 241, and 231 nm.; mass spectroscopy: *m/e* 399 (parent peak), 219 (base peak), 187 (90%), 132 (20%), and 104 (20%).

Anal.—Calc. for $C_{20}H_{20}N_2O_7$: C, 60.00; H, 5.03; N, 7.00. Found: C, 60.13; H, 5.17; N, 6.91.

The two isomers were obtained in the same overall yield using potassium carbonate as the base. The reaction was performed in dioxane using the same molar quantities reported in the synthesis of ethyl methyl 2-cyano-3-methoxy-4-*N,N*-dibenzyl-2-heptenedioate.

cis- and *trans*-VII*b* were also obtained using xylene as the reaction solvent. However, the yields were lower and the product composition was nearly identical by NMR.

Reaction of Ethyl Methyl 2-Cyano-3-methoxy-6-phthalimido-2-heptenedioate, VII*b*, with Sodium Hydride—Sodium hydride (25 mg. of 57% in mineral oil, 5.8×10^{-4} mole) was suspended in 10 ml. of dry benzene. Compound VII*b* (231 mg., 6.0×10^{-4} mole, m.p. 150–151°), in 10 ml. of dry *N,N*-dimethylformamide, was added dropwise to the suspension. A red-orange color, indicative of anion formation, developed within 30 min. The reaction was stirred at 25° for 22 hr. and, on workup, 210 mg. of starting material was recovered unchanged.

N*-Trifluoroacetylglutamic Anhydride, V*e—Compound V*e* was prepared by a modification of the method of Weygand and Leising (14). Trifluoroacetic anhydride (30 ml.) was added slowly to 10 g. of glutamic acid. After the resulting solution was cooled, 250 ml. of dry ether was added and a slightly exothermic reaction occurred. The solution was immediately decanted and diluted with 600 ml. of dry hexane. The mixture was cooled to 0° for 2 hr., and the crystals were filtered and washed sparingly with hexane. The resulting white needles were dried over calcium hydroxide in a vacuum desiccator. Recrystallization from chloroform gave 11.0 g. (72%) of white needles, m.p. 61–64°. Further recrystallization gave 9.1 g., m.p. 68–71° [lit. (14) m.p. 70°]; NMR ($CDCl_3$–CD_3COCD_3): δ 2.2–2.6 (m, 2, CH_2), 3.05–3.3 (m, 2, CH_2), and 5.1 (t, 1, methine H).

Attempted Synthesis of Ethyl Methyl 2-Cyano-3-methoxy-4-trifluoroacetamido-2-heptenedioate—A suspension of sodium hydride (300 mg. of 57% NaH, 0.007 mole) in 50 ml. of dioxane and 750 mg. (0.0067 mole) of ethyl cyanoacetate were allowed to react as before to form the sodio salt. After the milky suspension was cooled, 1.5 g. (0.0067 mole) of *N*-trifluoroacetylglutamic anhydride, V*e*, in 20 ml. dioxane was added slowly. The suspension was stirred at 25° for 16 hr. and treated as previously described for the *N*-phthalyl derivative.

The resulting oil was methylated with diazomethane to give 1.1 g. of a yellow oil. Chromatography on silica gel, using chloroform as the eluting solvent, gave only one isolable compound. It was shown to be dimethyl 2-*N*-trifluoroacetylpentanedioate by comparison of its IR and NMR spectra with that of the corresponding phthalimido derivative; IR (chloroform): 1725 cm.$^{-1}$, no C≡N stretch; NMR ($CDCl_3$): δ 2.2–2.6 (m, 4, CH_2CH_2), 3.7 (s, 3, OCH_3), 3.8 (s, 3, OCH_3), and 4.7 (broad t, 1, methine H).

N,N*-Dibenzylglutamic Acid, V*f—The procedure of Kanao and Sakayari (8) to prepare 1-benzyl-5-oxo-pyrrolidinecarboxylic acid was modified to obtain *N,N*-dibenzylglutamic acid. Glutamic acid (22.05 g., 0.15 mole), 16 g. sodium hydroxide in 256 ml. of 60% ethanol, and benzyl chloride (40.64 g., 0.32 mole) were stirred for 48 hr. at 25° (heating the reaction leads to decreased yields). The solution was neutralized to approximately pH 7 with cold, dilute hydrochloric acid and the ethanol was removed. The solution was extracted with ether, and an insoluble material was filtered (5.4 g.). The aqueous solution was made acid to congo red paper with hydrochloric acid and allowed to stand for 4 hr. A white solid (11.6 g.) precipitated and was filtered. The two solids were combined, stirred with hot water (85°), and filtered. The remaining solid was recrystallized from ethanol to give 6.7 g. of *N,N*-dibenzylglutamic acid, m.p. 214–217° [lit. (8) m.p. 215°].

The aqueous filtrate was cooled and 5.1 g. of 1-benzyl-5-oxo-pyrrolidinecarboxylic acid was obtained, m.p. 157–159° [lit. (8) m.p. 160°].

N,N*-Dibenzylglutamic Anhydride, V*f—Acetic anhydride (35 ml.) was added to *N,N*-dibenzylglutamic acid (6.0 g., 0.018 mole). The resulting suspension was heated to 80°, whereupon a deep-blue solution was formed. The heating was discontinued and the solution was immediately cooled. The acetic anhydride was removed under reduced pressure. Trituration of the resulting blue solid with ether gave 4.9 g. of a white solid. Recrystallization from chloroform–ether gave 4.1 g. (74%) *N,N*-dibenzylglutamic anhydride, V*f*, m.p. 110–112°; IR (KBr): 1810, 1780, 1760, 1060, 1020, 740, and 700 cm.$^{-1}$; NMR ($CDCl_3$): δ 1.9–2.3 (m, 2, CH_2), 2.5–2.9 (m, 2, CH_2), 3.7 (t, 1, methine H), 3.85 (s, 2, benzyl CH_2), 3.95 (s, 2, benzyl CH_2), and 7.4 (m, 10, aromatic H).

Ethyl Methyl 2-Cyano-3-methoxy-4-*N,N*-dibenzylamino-2-heptenedioate, II*f*—To a suspension of sodium hydride (1.75 g. of 57%, 0.04 mole) in 250 ml. of anhydrous benzene was added 4.5 g. (0.04 mole) of ethyl cyanoacetate. The suspension was cooled, 12.4 g. (0.04 mole) of *N,N*-dibenzylglutamic anhydride, V*f*, was added, and the mixture was refluxed for 16 hr. After cooling, the benzene was removed and equal volumes (250 ml.) of water and ether were added to the reaction mixture. The ether layer was separated and concentrated to give 11.3 g. of a mixture of acids. The mixture of acids was dissolved in anhydrous ether and esterified with diazomethane to give 11.4 g. of material.

Column chromatography on silica (300 g.) of 8.7 g. of the material and elution with chloroform afforded 1.1 g. of dimethyl 2-*N,N*-dibenzylaminopentanedioate; IR (chloroform): 1725 cm.$^{-1}$; NMR ($CDCl_3$): δ 1.8–2.7 (m, 5, aliphatic CH), 3.3 4.2 (2s–m, 10, OCH_3–benzylic CH_2), and 7.35 (s, 10, aromatic H); mass spectroscopy: *m/e* 355 (parent peak) and 296 (base peak).

A second material (1.7 g.) was obtained as a pale-yellow oil and proved to be the desired compound, II*f*; IR (chloroform): 2225, 1720, 1575, 1440, 1130, and 700 cm.$^{-1}$; NMR ($CDCl_3$): δ 1.27 (t, 3, CH_3), 1.65–3.2 (m, 4, CH_2CH_2), 3.35–4.4 (overlapping peaks, 13, 2-OCH_3, 2-benzyl CH_2, CH_2CH_3, methine H), and 7.33 (m, 10, aromatic H); mass spectroscopy: *m/e* 450 (parent peak), 296 (base peak at 19–88°), and 392 (base peak at 129°).

Anal.—Calc. for $C_{26}H_{30}N_2O_5$: C, 69.33; H, 6.66; N, 6.22. Found: C, 69.03; H, 6.68; N, 6.36.

REFERENCES

(1) E. F. Smissman and R. B. Gabbard, *J. Amer. Chem. Soc.*, **79**, 3203(1957).

(2) H. Muxfeldt and R. Bangert, *Fortschr. Chem. Org. Naturst.*, **21**, 80(1963).

(3) C. F. Barfknecht, Ph.D. thesis, University of Kansas, Lawrence, Kan., 1964.

(4) F. Sorm, J. Gut, and P. Kankovsky, *Collect. Czech. Chem. Commun.*, **15**, 99(1950).

(5) R. E. Bowman and H. H. Stroud, *J. Chem. Soc.*, **1950**, 1342.

(6) E. Aberhalden and K. Kautzsch, *Z. Physiol. Chem.*, **68**, 501 (1910).

(7) M. Bergman and L. Zervas, *Chem. Ber.*, **65B**, 1192(1932).

(8) S. Kanao and Y. Sakayari, *Yakugaku Zasshi*, **86**, 1105 (1966).

(9) I. Hori and H. Midorikawa, *Sci. Pap. Inst. Phys. Chem. Res. (Tokyo)*, **56**, 216(1962).

(10) S. Gabriel and A. Newman, *Chem. Ber.*, **26**, 953(1893).

(11) F. G. Young, F. C. Frostick, Jr., J. J. Sanderson, and C. R. Hauser, *J. Amer. Chem. Soc.*, **72**, 3635(1950).

(12) S. R. Best and J. F. Thorpe, *J. Chem. Soc.*, **95**, 1523(1909).

(13) F. E. King and D. Kidd, *ibid.*, **1949**, 3315.

(14) F. Weygand and E. Leising, *Chem. Ber.*, **87**, 248(1954).

ACKNOWLEDGMENTS AND ADDRESSES

Received May 3, 1973, from the *Department of Medicinal Chemistry, School of Pharmacy, University of Kansas, Lawrence, KS 66044*

Accepted for publication June 28, 1973.

Supported by Grant GM-01341 from the National Institutes of Health.

▲ To whom inquiries should be directed.