

# Reaction of Cyclic Acid Anhydrides with Ethyl Cyanoacetate

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**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  $\alpha$ -cyano- $\beta$ -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, IIa, the previously unreported *N,N*-dimethylglutamic anhydride was required. *N,N*-Dimethylglutamic acid, IVa, 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 IVa to the anhydride, Va, by known procedures failed.

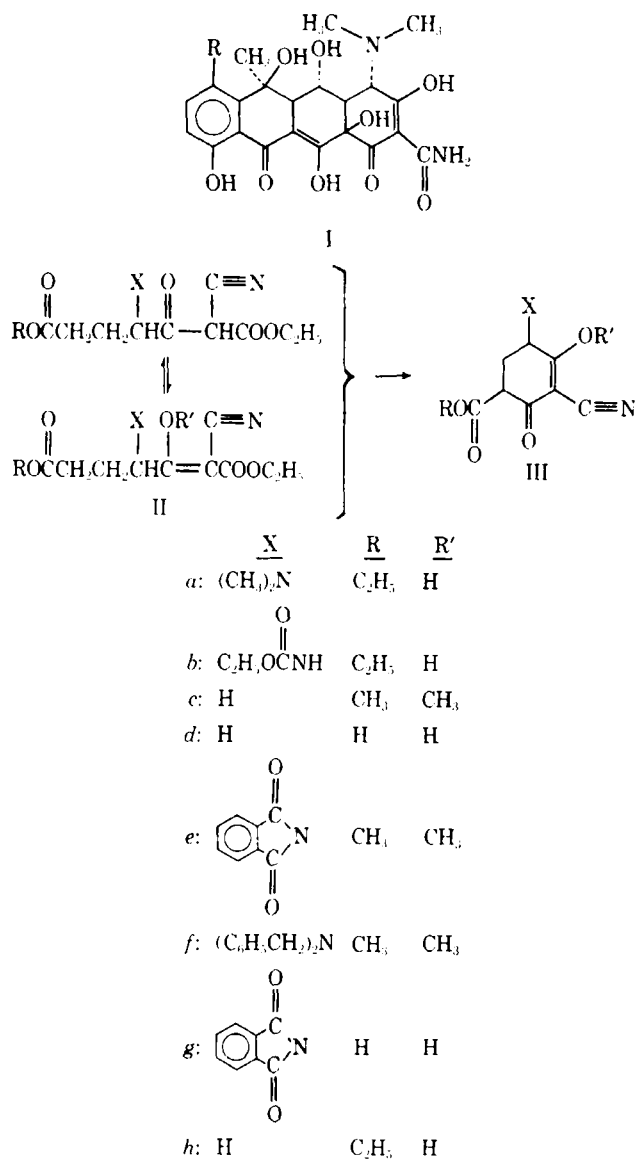
*N*-Carbomethoxyglutamic acid, IVb, was prepared by the method of Aberhalden and Kautsch (6) and was cyclized by refluxing in acetic anhydride to give the corresponding anhydride, Vb. On treatment of Vb with ethyl sodiocyanoacetate, diethyl 2-cyano-3-hydroxy-4-*N*-carbomethoxyamino-2-heptenedioate, IIb, was produced. The assignment of the *N*-carbomethoxyamino group to the 4-position was based on an analogous reaction by Bergman and Zervas (7). They reported the treatment of *N*-carbomethoxyglutamic anhydride, Vc, with ammonia to give *N*-carbomethoxyisoglutamine, VI, which was then decarbomethoxylated to isoglutamine. By analogy, the product of Vb with sodiocyanoacetate would be expected to yield IIb rather than the isomeric diethyl 2-cyano-3-hydroxy-6-*N*-carbomethoxyamino-2-heptenedioate, VIIa.

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

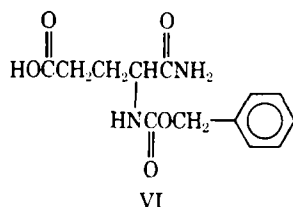
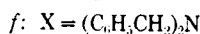
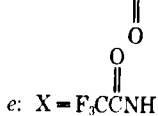
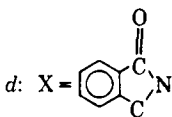
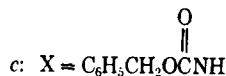
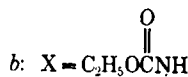
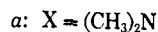
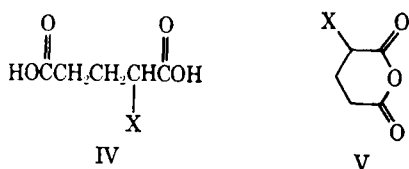
It was assumed that the preparation of III failed where R' = H because the molecule II forms the anion VIIIa or IX in preference to VIII. Formation of the desired cyclic compound is not possible when the enolic oxygen bears the negative charge as in IX (Scheme II). To circumvent this possibility, the enolic hydroxyl was protected as the enol methyl ether, IIc, by treatment with diazomethane. It was assumed that VIII and VIIIa would be in facile equilibrium. The as-

signment of the location of the ethyl and methyl ester groups in IIc was undertaken by NMR studies. Ethyl acetate shows a triplet centered at  $\delta$ 1.25 and a quartet at  $\delta$ 4.12 for the ethyl function, while ethyl cyanoacetate shows peaks at  $\delta$ 1.32 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 IIc is at  $\delta$ 1.42 and 4.47. Since the ethyl group is deshielded, it is assigned to the 1-carboxyl function.

*N*-Phthalylglutamic anhydride, Vd, proved to be a more convenient intermediate for the preparation of an amino-substituted pimelate. The reaction of Vd 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 VIIb by the spectral data. Mass



Scheme I

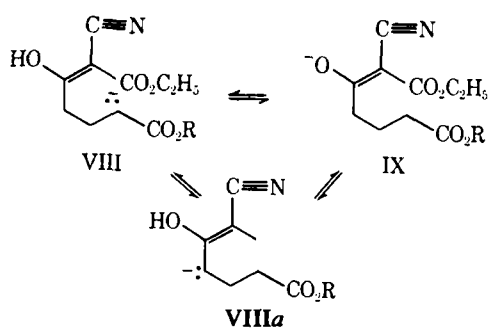
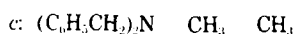
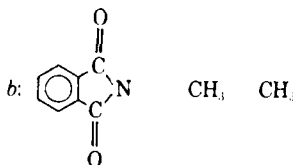
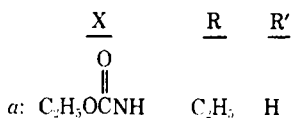
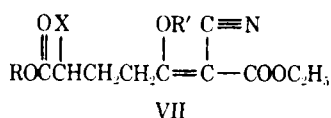


spectroscopy was conclusive in establishing that they were the 6-*N*-phthalyl geometric isomers. Both *cis*- and *trans*-VIIb gave identical fragmentation patterns, with a base peak of *m/e* 219. This peak arises from a McLafferty-type rearrangement (Scheme III). The 4-*N*-phthalyl isomer, IIe, cannot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

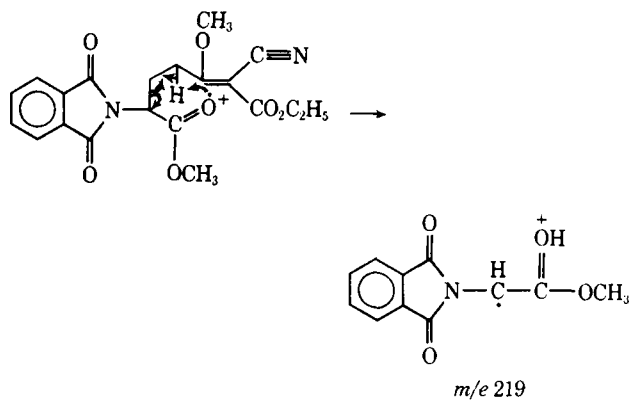
Attempts at the Dieckmann condensation of VIIb failed.

Since the 4-phthalimido compound, IIe, 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, Ve, was viewed as a potential precursor with a labile *N*-protecting group. The reaction of Ve with ethyl sodiocyanoacetate, followed by esterification with diazomethane, yielded 2-trifluoroacetamidopentanedioate, IVe, as the only isolable product.

Despite previous failures in attempts to prepare *N,N*-dimethylglutamic anhydride, Va, 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, IVf, contains a more basic nitrogen than the phthalyl or trifluoroacetyl



Scheme II



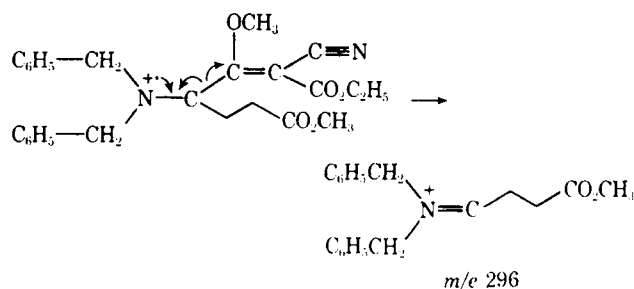
Scheme III

derivatives and was prepared by a modification of a reported procedure (8). Compound IVf was converted to the corresponding anhydride, Vf, 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 Vf 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<sub>f</sub>. The structure was assigned primarily from the mass spectrum along with the NMR and IR spectra. The mass spectrum of II<sub>f</sub> 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<sub>f</sub>, can give rise to this fragmentation, whereas the 6-*N,N*-dibenzyl isomer, VIIc, cannot (Scheme IV).

The use of sodium hydride gave superior yields of II<sub>f</sub> as compared to the method utilizing potassium carbonate. This procedure gave adequate quantities of II<sub>f</sub> 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<sub>d</sub>, was treated with acetic anhydride to give a neutral compound in quantitative yield.



Scheme IV



3.3 (m, 2, CH<sub>2</sub>), 3.75 (s, 3, OCH<sub>3</sub>), 4.08 (s, 3, OCH<sub>3</sub>), 4.1 (q, 2, CH<sub>2</sub>CH<sub>3</sub>), 4.98 (t, 1, methine H), and 7.86 (d, 4, aromatic H); UV (ethanol) λ<sub>max</sub>: 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<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O<sub>7</sub>: 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.<sup>-1</sup>; NMR (CDCl<sub>3</sub>): δ 1.27 (t, 3, CH<sub>3</sub>), 2.4–2.95 (m, 4, CH<sub>2</sub>CH<sub>2</sub>), 3.76 (s, 3, OCH<sub>3</sub>), 4.08 (s, 3, OCH<sub>3</sub>), 4.2 (q, 2, CH<sub>2</sub>CH<sub>3</sub>), 4.95 (t, 1, methine H), and 7.85 (d, 4, aromatic H); UV (ethanol) λ<sub>max</sub>: 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<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O<sub>7</sub>: 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*-VIIb 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, VIIb, with Sodium Hydride**—Sodium hydride (25 mg. of 57% in mineral oil, 5.8 × 10<sup>-4</sup> mole) was suspended in 10 ml. of dry benzene. Compound VIIb (231 mg., 6.0 × 10<sup>-4</sup> 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, Ve**—Compound Ve 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<sub>3</sub>-CD<sub>3</sub>COCD<sub>3</sub>): δ 2.2–2.6 (m, 2, CH<sub>2</sub>), 3.05–3.3 (m, 2, CH<sub>2</sub>), 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, Ve, 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*-trifluoroacetylglutamate by comparison of its IR and NMR spectra with that of the corresponding phthalimido derivative; IR (chloroform): 1725 cm.<sup>-1</sup>, no C≡N stretch; NMR (CDCl<sub>3</sub>): δ 2.2–2.6 (m, 4, CH<sub>2</sub>CH<sub>2</sub>), 3.7 (s, 3, OCH<sub>3</sub>), 3.8 (s, 3, OCH<sub>3</sub>), and 4.7 (broad t, 1, methine H).

***N,N*-Dibenzylglutamic Acid, Vf**—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, Vf**—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, Vf, m.p. 110–112°; IR (KBr): 1810, 1780, 1760, 1060, 1020, 740, and 700 cm.<sup>-1</sup>; NMR (CDCl<sub>3</sub>): δ 1.9–2.3 (m, 2, CH<sub>2</sub>), 2.5–2.9 (m, 2, CH<sub>2</sub>), 3.7 (t, 1, methine H), 3.85 (s, 2, benzyl CH<sub>2</sub>), 3.95 (s, 2, benzyl CH<sub>2</sub>), and 7.4 (m, 10, aromatic H).

**Ethyl Methyl 2-Cyano-3-methoxy-4-*N,N*-dibenzylamino-2-heptenedioate, IIj**—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, Vf, 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.<sup>-1</sup>; NMR (CDCl<sub>3</sub>): δ 1.8–2.7 (m, 5, aliphatic CH), 3.3–4.2 (2s–m, 10, OCH<sub>2</sub>-benzylic CH<sub>2</sub>), 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, IIj; IR (chloroform): 2225, 1720, 1575, 1440, 1130, and 700 cm.<sup>-1</sup>; NMR (CDCl<sub>3</sub>): δ 1.27 (t, 3, CH<sub>3</sub>), 1.65–3.2 (m, 4, CH<sub>2</sub>CH<sub>2</sub>), 3.35–4.4 (overlapping peaks, 13, 2-OCH<sub>3</sub>, 2-benzyl CH<sub>2</sub>, CH<sub>2</sub>CH<sub>3</sub>, 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<sub>26</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub>: C, 69.33; H, 6.66; N, 6.22. Found: C, 69.03; H, 6.68; N, 6.36.

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