A Novel Cyclization Reaction of Acetylene Derivatives[1]

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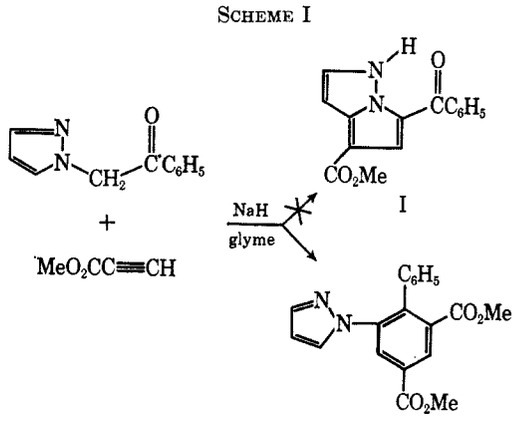
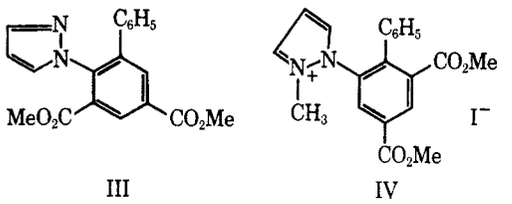
The reaction of acetylene derivatives with α-methylene carbonyl compounds in the presence of base has been shown to yield a substituted aromatic ring. This reaction is general and of potential synthetic utility, particularly for di- and terphenyl derivatives.

The formation of aromatic rings by the reaction of acetylene derivatives with 1,3-dienes followed by a thermal elimination has been studied extensively.[3] Similarly, the reaction of acetylene derivatives with 1,3-dipolar compounds to form aromatic heterocycles has been thoroughly investigated.[4,5] In the course of our studies on the reaction of acetylene derivatives with ylides,[6] we investigated the reaction of methyl propiolate with 1-phenacylpyrazole. By analogy to the behavior of ylides derived from 1-phenacylimidazole, we had anticipated the formation of the diazapentalene derivative I. Instead, the product isolated was the isophthalate derivative II (Scheme I). The formation of an aromatic ring by the reaction of acetylene derivatives with α-methylene carbonyl compounds in the presence of base is a novel reaction,[7] and the present report describes a study of the scope and generality of the reaction.

SCHEME I

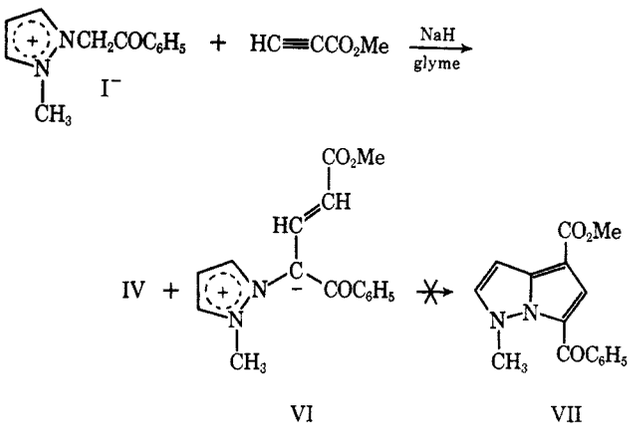


The assignment of structure II is based on its composition, spectra, and subsequent transformations. The incorporation of two molecules of methyl propiolate was evident both from elemental analysis and the molecular weight derived from its mass spectrum. The presence of the intact pyrazole ring was obvious from nmr data, which also revealed the presence of two new benzene ring protons, appearing as doublets at τ 1.49 and 1.59 (J = 1.8 Hz). The methoxyl protons appeared as singlets at τ 6.07 and 6.45, while the ir spectrum exhibited a single carbonyl band at 1725 cm^{-1}. Although all of these data are in accord with structure II and an obvious interpretation for its formation can be provided, the possibility of the alternate structure III could not be dismissed out of hand. Therefore, the product was treated with methyl iodide to obtain the corresponding pyrazolium methiodide IV. The methoxyl protons of the pyrazolium methiodide IV appear at τ 6.00 and 6.38. The fact that the transformation of the pyrazole to its pyrazolium methiodide had little effect on the chemical shifts of the ester methoxyls and no effect on their chemical-shift difference (0.38 ppm) is again in accord with structure II but inconsistent with structure III.



It is of interest that, when 1-methyl-2-phenacylpyrazolium iodide (V) was treated with methyl propiolate in the presence of base, IV was again obtained, identical in all respects with the previous preparation. However, in this case the yield of IV was poor and the major product was the ylide VI (Scheme II). It is somewhat surprising that none of the corresponding ring-closed diazapentalene VII could be detected. Furthermore, attempts to convert VI into the diazapentalene VII were unsuccessful.

SCHEME II



To explore the generality of this method for synthesizing aromatic rings the reaction was investigated with several phenacyl derivatives. The reaction of phenylacetaldehyde (VIII) with methyl propiolate

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(2) Abstracted from the Doctoral Dissertation of J. E. Nottke, University of Oregon, 1969; du Pont Teaching Fellow, 1967–1968.

(3) K. Alder and H. F. Rickert, *Ann.*, **524**, 180 (1936).

(4) R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 565 (1963).

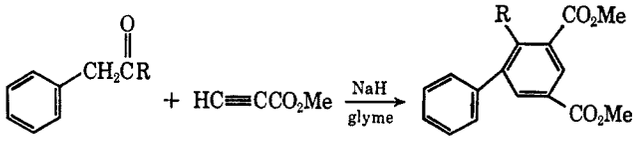
(5) A. Galbraith, T. Small, R. A. Barnes, and V. Boekelheide, *J. Amer. Chem. Soc.*, **83**, 453 (1961).

(6) V. Boekelheide and N. A. Fedoruk, *ibid.*, **90**, 3830 (1968).

(7) R. M. Acheson and W. R. Tully [*J. Chem. Soc.*, 1623 (1968)] have described the reaction of a pyruvate ester with dimethyl acetylenedicarboxylate to give a benzenepentacarboxylate ester. We thank Professor Acheson for his kindness in acknowledging our prior interest in this reaction. Actually, the prime observations in our study were made in 1964.

gave dimethyl 5-phenylisophthalate (X) in 47% yield. Similarly, the reaction of deoxybenzoin (IX) with methyl propiolate gave dimethyl 4,5-diphenylisophthalate (XI) in 58% yield. (See Scheme III.) In one experiment with deoxybenzoin, dimethyl acetylenedicarboxylate was used in place of methyl propiolate and the corresponding tetramethyl 1,2-diphenylbenzene-3,4,5,6-tetracarboxylate was formed but in only 11% yield.

SCHEME III



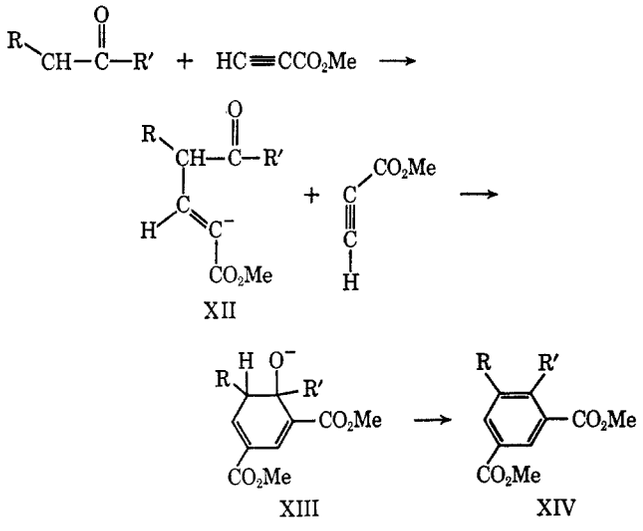
VIII, R = H
IX, R = C_6H_5

X, R = H
XI, R = C_6H_5

Finally, as an example of an aliphatic ketone, ethyl acetoacetate with methyl propiolate gave dimethyl 4-carbethoxy-2-methylisophthalate in 17% yield. Its structure was established by hydrolysis to the known 2-methyltrimesic acid.[8]

An obvious interpretation of the course of these reactions of α-methylene compounds with methyl propiolate is shown in Scheme IV. The step by which the

SCHEME IV



first intermediate XII adds a second molecule of methyl propiolate bears a formal resemblance to the reactions studied by Huisgen and his colleagues which have been termed 1,4-dipolar addition reactions.[9,10] The formation of XIII and its subsequent aromatization also bears analogy to the formation of pyrroles by the reaction of acetylene derivatives with α-amino ketones as studied by George.[11,12] Whether aromatization of XIII occurs directly by loss of hydroxide ion or is a subsequent step occurring after acidification has not been established. The reaction does provide a convenient synthesis of diphenyl and terphenyl derivatives with specific substitution.

(8) G. Dedichen, *Chem. Ber.*, **39**, 1831 (1906).
(9) R. Huisgen and K. Herbig, *Ann.*, **688**, 98 (1965).
(10) R. Huisgen, M. Morikawa, K. Herbig, and E. Brunn, *Chem. Ber.*, **100**, 1094 (1967).
(11) S. K, Khetan J. G. Hiriyakkanavar, and M. V. George, *Tetrahedron*, **24**, 1567 (1968).
(12) S. K. Khetan and M. V. George, *ibid.*, **25**, 527 (1969).

Experimental Section[13]

Dimethyl 4-Phenyl-5-(1′-pyrazolyl)isophthalate (II).—The following procedure was used in all of the additions of acetylene derivatives to α-methylene carbonyl compounds and is described in detail only for this first example. To a rapidly stirred solution of 9.3 g (0.050 mol) of 1-phenacylpyrazole[14] in 60 ml of glyme (1,2-dimethoxyethane) at 0°, there was added 1.30 g (0.054 mol) of sodium hydride. After 20 min, approximately the theoretical quantity of hydrogen had evolved and no further gas evolution was observed. A solution of 11.0 g (0.13 mol) of methyl propiolate in 25 ml of glyme was added over a 5-min period to the canary-yellow reaction mixture at 0°. After the resulting dark red solution had been stirred at room temperature for 4 hr, it was poured into 200 ml of ice–water, rapidly neutralized with 10% hydrochloric acid, and extracted with three 100-ml portions of chloroform. The combined extracts were dried and then concentrated under reduced pressure leaving a dark red oil. This was taken up in a 30% benzene in hexane mixture and chromatographed over silica gel. After elution of the fast moving impurities, the eluent was changed to a 60% benzene in hexane mixture. The main yellow eluate fraction was then collected, concentrated, and recrystallized from hexane to give 6.7 g (40%) of colorless prisms: mp 75–76°; uv, λ_{max}^{EtOH} 296 mμ (ϵ 2470) and 225 (22,400); ir, λ_{max}^{KBr} 5.80 μ (ester C=O); nmr (CD-Cl_3), a pair of doublets centered at τ 1.57 and 1.64 (2 H, J = 1.9 Hz), a pair of doublets centered at 2.49 (1 H, J_{AB} = 0.5 Hz, J_{AC} = 1.9 Hz), a multiplet from 2.6 to 3.0 (5 H), a pair of doublets centered at 3.06 (1 H, J_{AB} = 0.5 Hz, J_{BC} = 2.7 Hz), a pair of doublets centered at 3.93 (1 H, J_{AC} = 1.9 Hz, J_{BC} = 2.7 Hz), a singlet at 6.07 (3 H), and a singlet at 6.45 (3 H); mass spectrum, parent molecular ion at m/e 336.

Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.80; N, 8.33. Found: C, 67.87; H, 4.79; N, 8.47.

Dimethyl 5-(2′-Methyl-1′-pyrazoliumyl)-4-phenylisophthalate Iodide (IV).—A solution of 9.6 g of dimethyl 4-phenyl-5-(1′-pyrazolyl)isophthalate (II) and 22.0 g of methyl iodide in 100 ml of acetonitrile was boiled under reflux in a nitrogen atmosphere for 14 hr. The solution was then concentrated to a volume of 30 ml, and anhydrous ether was added causing the separation of 10.2 g of a yellow solid. Recrystallization of this from a methanol–ether mixture gave yellow needles: mp 198–199°; uv, λ_{max}^{EtOH} 263 mμ (ϵ 6300); ir, λ_{max}^{KBr} 5.81 μ (ester carbonyl); nmr (DMSO-d_6), two doublets at τ 1.19 and 1.27 (2 H, J = 1.5 Hz), two doublets at 2.22 and 2.37 (2 H, J = 2.7 Hz), a multiplet from 2.5 to 2.8 (5 H), a triplet at 3.08 (1 H, J = 2.7 Hz), a singlet at 6.00 (3 H), a singlet at 6.15 (3 H), and a singlet at 6.38 (3 H).

Anal. Calcd for $C_{20}H_{19}N_2O_4I$: C, 50.26; H, 4.00; N, 5.86. Found: C, 50.87; H, 4.08; N, 5.75.

1-Methyl-2-phenacylpyrazolium Iodide (V).—A solution of 10.0 g of 1-phenacylpyrazole and 10.0 g of methyl iodide in 50 ml of acetonitrile was heated under nitrogen at 60° for 35 hr. Addition of 50 ml of anhydrous ether caused the separation of 15.0 g of light orange crystals. This material appeared unstable in solution or when exposed to air but was stable as a crystalline solid. Recrystallization from warm ethanol gave white rhomboid plates: mp 184–185° dec; uv, λ_{max}^{EtOH} 330 mμ (ϵ 395), 282 (2260), 245 (19,200), and 221 (24,000); ir, λ_{max}^{KBr} 5.93 μ; nmr (DMSO-d_6), a doublet at τ 1.22 (1 H, J = 2.7 Hz), a doublet at 1.37 (1 H, J = 2.6 Hz), a multiplet from 1.8 to 2.4 (5 H), a triplet at 2.96 (1 H, J = 2.7 Hz), a singlet at 3.32 (2 H), and a singlet at 5.82 (3 H).

Anal. Calcd for $C_{12}H_{13}N_2OI$: C, 43.92; H, 3.99; N, 8.54; I, 38.67. Found: C, 44.03; H, 3.89; N, 8.50; I, 38.91.

Reaction of V with Methyl Propiolate.—This was carried out as described for the preparation of II using 6.56 g (0.020 mol) of

(13) Microanalyses were by Micro-Tech Laboratories and A. Bernhardt Mikroanalytisches Laboratorium. The uv and visible spectra were determined with a Cary 15 spectrometer, ir spectra with a Beckman IR-5A spectrometer, nmr spectra with a Varian A-60 or HA-100 spectrometer using tetramethylsilane as an internal standard, and mass spectra with a C.E.C. 110–21 mass spectrometer. We thank the National Science Foundation for funds permitting the purchase of the Varian A-60 and the C.E.C. 110–21 spectrometers as well as the Joy liquid nitrogen apparatus.
(14) T. W. G. Solomons, F. W. Fowler, and J. Calderazzo, *J. Amer. Chem. Soc.*, **87**, 528 (1965).

1-methyl-2-phenacylpyrazolium iodide (V). Addition of acetone to the residual oil from concentration of the chloroform extracts gave 2.0 g of pale orange crystals, mp 145–146°. The mother liquor was then chromatographed over silica gel using first benzene and then chloroform as eluent. This gave an additional small amount of the same orange crystals. The eluent was then changed to an 8% methanol in chloroform mixture yielding an eluate fraction containing 210 mg (3%) of yellow needles, mp 198–199°, identical in all respects with the sample of IV isolated previously.

The combined fractions of orange crystals (mp 145–146°) were recrystallized from an ethanol–ether mixture to give 2.0 g (35%) of pale orange needles: mp 145–146° dec; uv, λ_{max}^{EtOH} 344 mμ (ε 29,100), 274 (5200), 228 (14,000), and 220 (14,500); ir, λ_{max}^{KBr} 5.96 μ; nmr (DMSO-d_6), a doublet at τ 1.33 (1 H, J = 2.6 Hz), a doublet at 1.55 (1 H, J = 2.8 Hz), a doublet at 2.29 (1 H, J = 14.7 Hz), a broad singlet at 2.47 (5 H), a triplet at 3.04 (1 H, J = 2.8 Hz), a doublet at 5.97 (1 H, J = 14.7 Hz), a singlet at 6.13 (3 H), and a singlet at 6.53 (3 H). This has been assigned structure VI.

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.51; H, 5.71; N, 10.09.

Dimethyl 5-Phenylisophthalate (X).—The addition of 10.1 g of methyl propiolate to 6.0 g (0.050 mol) of phenylacetaldehyde was carried out as described for the preparation of II. Elution of the silica gel column with hexane gave a pale yellow oil. This crystallized from a carbon tetrachloride mixture to give 6.3 g (46%) of fine white needles: mp 116.0–116.5°; uv, λ_{max}^{EtOH} 301 mμ (ε 2490), 257 (13,900), and 231 (31,000); ir, $\lambda_{max}^{CHCl_3}$ 5.82 μ (ester C=O); nmr ($CDCl_3$), a triplet at τ 1.10 (1 H, J = 1.6 Hz), a doublet at 1.32 (2 H, J = 1.6 Hz), a multiplet at 3.1–3.5 (5 H), and a singlet at 5.99 (6 H); mass spectrum, parent molecular ion at m/e 270.

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.93; H, 5.58.

5-Phenylisophthalic Acid.—To a solution of 388 mg of dimethyl 5-phenylisophthalate in 10 ml of methanol at 50° there was added 350 mg of solid potassium hydroxide with stirring. When the solution became clear, 10 ml of water was added at a rate slow enough to prevent precipitation. The solution was then heated allowing methanol to distil off. After the solution had been cooled and filtered, it was acidified with 5% hydrochloric acid. The finely divided crystalline precipitate was collected and recrystallized from hot water to give 360 mg (100%) of white crystals: mp 344–345°; uv, λ_{max}^{EtOH} 299 mμ (ε 1310), 254 (15,000), and 231 (32,000); ir, λ_{max}^{KBr} 5.89 μ; nmr (DMSO), a triplet at τ 1.43 (1 H, J = 1.5 Hz), a doublet at 1.54 (2 H, J = 1.5 Hz), and a multiplet at 2.1–2.6 (5 H).

Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.74; H, 4.38.

Dimethyl 4,5-Diphenylisophthalate (XI).—The addition of 10.0 g of methyl propiolate to 9.8 g (0.050 mol) of deoxybenzoin was carried out as described for the preparation of II. Elution of the silica gel column with a 50% benzene–hexane mixture caused the separation of an eluate fraction of 14.2 g of a pale yellow oil. Crystallization of this from an ether–hexane mixture gave 10.1 g (58%) of colorless prisms: mp 93–94°; uv, λ_{max}^{EtOH} 300 mμ (ε 2980) and 239 (20,500); ir, $\lambda_{max}^{CCl_4}$ 5.80 μ (ester C=O); nmr ($CDCl_3$), a doublet at τ 1.45 (1 H, J = 1.8 Hz), a doublet at 1.69 (1 H, J = 1.8 Hz), a multiplet from 2.6 to 3.0 (10 H), a singlet at 6.00 (3 H), and a singlet at 6.38 (3 H).

Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, 76.32; H, 4.91.

4,5-Diphenylisophthalic Acid.—To a solution of 1.2 g of dimethyl 4,5-diphenylisophthalate (XI) in 15 ml of methanol at 60° there was added 400 mg of solid potassium hydroxide. Then 20 ml of water was added dropwise over a 10-min period, and the clear solution was acidified with 10% aqueous hydrochloric acid. The resulting precipitate was collected by filtration and recrystallized from a methanol–water mixture to give 1.02 g (90%) of white needles: mp 285°; uv, λ_{max}^{EtOH} 296 mμ (ε 2870) and 231 (23,800); ir, λ_{max}^{KBr} 5.90 μ; nmr (acetone), a doublet at τ 1.52 (1 H, J = 1.9 Hz), a doublet at 1.83 (1 H, J = 1.9 Hz), and a broad singlet at 2.85 (10 H).

Anal. Calcd for $C_{20}H_{14}O_4$: C, 75.46; H, 4.43. Found: C, 75.66; H, 4.51.

Tetramethyl 1,2-Diphenyl-3,4,5,6-tetracarboxylate.—The addition of 12.0 g (0.085 mol) of dimethyl acetylenedicarboxylate to 8.0 g (0.041 mol) of deoxybenzoin was carried out as described for the preparation of II except that 60 ml of dimethylformamide was substituted for the glyme. The combined chloroform extracts were concentrated and the residue was chromatographed over alumina (Woelm, Activity III) using carbon tetrachloride for elution. The main eluate fraction was concentrated and the resulting solid was recrystallized from a carbon tetrachloride–hexane mixture to give 1.9 g (11%) of colorless prisms: mp 224°; uv, $\lambda_{max}^{CHCl_3}$ 297 mμ (ε 3600) and 244 (19,500); ir, λ_{max}^{KBr} 5.80 μ; nmr ($CDCl_3$), a multiplet from τ 2.8 to 3.1 (10 H), a singlet at 6.12 (6 H), and a singlet at 6.54 (6 H); mass spectrum, parent molecular ion at m/e 462.

Anal. Calcd for $C_{26}H_{22}O_8$: C, 67.53; H, 4.80. Found: C, 67.53; H, 5.08.

2-Methyltrimesic Acid.—The addition of 10.0 g (0.12 mol) of methyl propiolate to 6.5 g (0.050 mol) of ethyl acetoacetate was carried out as described for the preparation of II. Elution of the silica gel column with hexane gave first an eluate fraction containing 3.1 g of ethyl acetoacetate and then a fraction containing 1.1 g (17%, based on unrecovered ethyl acetoacetate) of dimethyl 5-carbethoxy-4-methylisophthalate. To remove contamination by trimethyl trimesate (a common impurity resulting from trimerization of methyl propiolate) this sample was subjected to glpc using a column of 20% SE-30 on Chromosorb W at an oven temperature of 210°. This gave white crystals: mp 52–53°; uv, λ_{max}^{EtOH} 298 mμ (ε 400), 285 (500), 235 (13,900), and 215 (42,000); ir, $\lambda_{max}^{CHCl_3}$ 5.81 μ; nmr (CCl_4), a singlet at τ 1.38 (2 H), a quartet at 5.60 (2 H, J = 7.1 Hz), a singlet at 6.05 (6 H), a singlet at 7.26 (3 H), and a triplet at 8.56 (3 H, J = 7.1 Hz).

Anal. Calcd for $C_{14}H_{16}O_6$: C, 60.00; H, 5.75. Found: C, 61.00; H, 5.27.

For proof of structure a 160-mg sample of dimethyl 5-carbethoxy-4-methylisophthalate was heated in a mixture of 10 ml of methanol and 10 ml of water containing 100 mg of potassium hydroxide. After the solution had been heated on a steam bath for 30 min, it was concentrated and diluted with 10 ml of water. Acidification with 10% aqueous hydrochloric acid gave a solid precipitate which was collected and then recrystallized from warm methanol to yield 102 mg of white crystals: mp 307° dec (lit.[8] gives 308° dec); uv, λ_{max}^{EtOH} 293 mμ (ε 370), 284 (520), 233 (12,100), and 215 (34,000); ir, λ_{max}^{KBr} 5.92 μ; nmr (D_2O), singlets at τ 1.58 (2 H), 6.78 (3 H), and 7.76 (3 H).

Anal. Calcd for $C_{14}H_{16}O \cdot CH_4O$: C, 51.57; H, 4.60. Found: C, 51.84; H, 4.33.

The fact that the crystals of 2-methyltrimesic acid contained a molecule of methanol of crystallization was supported by the following experiment. A sample of the crystals was heated at 295° under high vacuum and then dissolved in DMSO-d_6 for an nmr determination. The spectrum showed the normal singlets at τ 1.58 (2 H) and at 7.77 (3 H), but the signal at τ 6.78, presumably due to the presence of methanol, had almost disappeared.

Registry No.—II, 21990-96-5; IV, 21990-97-6; V, 21990-98-7; VI, 21990-99-8; X, 21991-00-4; XI, 21991-01-5; 5-phenylisophthalic acid, 4445-59-4; 4,5-diphenylisophthalic acid, 21991-02-6; tetramethyl 1,2-diphenyl-3,4,5,6-tetracarboxylate, 21991-03-7; dimethyl 5-carbethoxy-4-methylisophthalate, 21991-04-8.