TABLE I

ISOQUINOLINE REISSERT COMPOUNDS

Substituent	M.P.[b]	Yield, % Method A[c]	Yield, % Method B[d]	Calcd., % C	Calcd., % H	Calcd., % N	Found, %[a] C	Found, %[a] H	Found, %[a] N	Yield, % Benzaldehyde[e]
H	125–126[f]	69	72							95
4-Amino-[g]	158[h]	20				11.08			11.12	90
4-Bromo-	173	38	0	60.20	3.27		60.45	3.46		90
5-Hydroxy-[i]	198	68				7.37			7.38	90
5-Nitro-	148	10	0	66.88	3.63	13.77	66.95	3.65	13.82	12
8-Nitro-	181	9		66.88	3.63	13.77	66.77	3.54	13.68	9
3-Methyl-5-cyano-	175[h]	45		76.24	4.38		76.53	4.40		97
3-Methyl-5-nitro-	159[h]	83		67.70	4.10	13.16	67.68	4.23	13.39	63
3-Methyl-8-nitro-	134[j]	28		67.70	4.10	13.16	67.74	4.06	13.29	85
5-Carbomethoxy-	121[h]	29		71.69	4.43		71.81	4.58		98

[a] Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Drs. Weiler and Strauss, Oxford, England. [b] Melting points are uncorrected. Recrystallized from 95% ethanol unless stated. [c] Methylene chloride–water method, see Experimental. [d] Aqueous method, see Experimental. [e] From acid-catalyzed hydrolysis, isolated as the 2,4-dinitrophenylhydrazone, see ref. 10. [f] Reported m.p. 124–126°, ref. 6. [g] Isolated as the benzoylamino derivative. [h] Recrystallized from 80% ethanol. [i] Isolated as the benzoate derivative. [j] Recrystallized from 75% isopropyl alcohol.

EXPERIMENTAL

Reagents. Reagent grade benzoyl chloride, methylene chloride, and potassium cyanide were used. The isoquinolines were obtained commercially or prepared by standard literature procedures.

Aqueous method of Reissert compound formation. This method was carried out as described in the previous paper of this series. The results are listed in Table I.

Methylene chloride-water method of Reissert compound formation. This method was carried out as described in the two previous papers of this series. The results are listed in Table I.

Reaction of 1-azapyrene. Reaction of 1-azapyrene, benzoyl chloride, and potassium cyanide by the methylene chloride–water method gave a 54% yield of solid, m.p. 212–213° (from 95% ethanol).

Anal. Calcd. for $C_{23}H_{14}N_2O$: C, 82.62; H, 4.22; N, 8.38. Found: C, 82.37; H, 4.23; N, 8.14.

Acid-catalyzed hydrolysis of this compound as described below gave a 95% yield of benzaldehyde-2,4-dinitrophenylhydrazone.

Reaction of 2-azafluoranthene. Reaction of 2-azafluoranthene, benzoyl chloride, and potassium cyanide by the methylene chloride–water method gave a 23% yield of solid, m.p. 158–159° (from 95% ethanol).

Anal. Calcd. for $C_{23}H_{14}N_2O$: C, 82.62; H, 4.22; N, 8.38. Found: C, 82.71; 82.84; H, 4.36, 4.48; N, 8.38, 8.55.

Acid-catalyzed hydrolysis of Reissert compounds. This was carried out with concentrated hydrochloric acid and 2,4-dinitrophenylhydrazine as previously described.[1,10]

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The Formation of the N—N Bond in Pyrazolines

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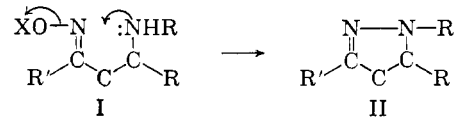
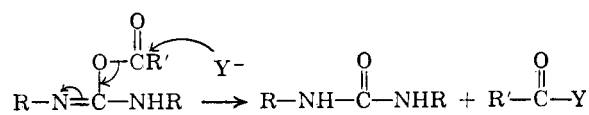
Syntheses of pyrazolines[1,2] generally require that the N—N bond be formed prior to cyclization. In fact, cyclization reactions of organic compounds involving the formation of an N—N bond are scarcely known. The examples reported[3] for the preparation of triazoles or tetrazoles are usually not applicable to the synthesis of pyrazolines.

While in search for a method of N—N bond closure in the formation of pyrazolines, we felt that a reaction of type (1) might be feasible under special conditions. The case where OX represents a good leaving group, *i.e.*, acylate or tosylate, would appear desirable but the presence of an amino group in oxime I (X = H) precludes the use of acylating agents in the formation of I (OX = acylate).



I II (1)

During the last few years *N,N'*-dicyclohexylcarbodiimide has been used successfully in dehydrative cyclizations of amino acids to lactams[4] and of hydroxy acids to lactones.[5] The mechanism presumably involves[6] the addition of the acid to *N,N'*-dicyclohexylcarbodiimide to give an intermediate *O*-substituted isourea from which urea can be displaced by a nucleophile. We felt that perhaps *N,N'*-



(1) R. C. Elderfield, *Heterocyclic Compounds*, Vol. 5, J. Wiley & Sons, Inc., New York, 1957, pp. 48–89.

(2) E. H. Rodd, *Chemistry of Carbon Compounds*, Vol. IV A, Elsevier Publishing Co., Amsterdam, 1957, pp. 261–263.

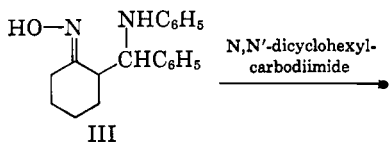
(3) Ref. 2, pp. 440–443, 481–483.

(4) J. C. Sheehan and K. R. Henery-Logan, *J. Am. Chem. Soc.*, **79**, 1262 (1957).

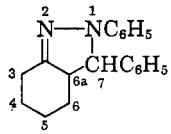
(5) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 20 (1958).

(6) H. G. Khorana, *Chem. Revs.*, **53**, 145 (1953).

dicyclohexylcarbodiimide in an analogous reaction using amino oximes[7] would be useful in bringing about cyclization to pyrazolines. This proved to be the case in the examples reported here. The method involves heating β-amino oximes in tetrahydrofuran or, better in acetonitrile with *N,N'*-dicyclohexylcarbodiimide.



III



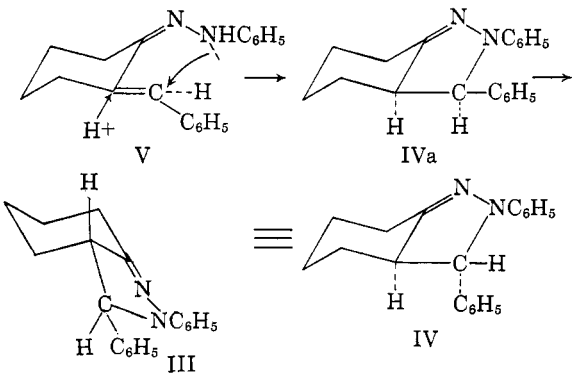
+ dicyclohexylurea (2)

IV

The starting amino oximes can often be prepared *via* a Mannich condensation. Thus, 2-(α-anilinobenzyl)cyclohexanone oxime (III) was prepared by condensation of cyclohexanone with benzaldehyde and aniline[8] and subsequent formation of the oxime. Compound I (R, R' = C_6H_5; X = H) was obtained by oximation of the aniline addition product of benzalacetophenone.[9,10]

When the amino oxime III was heated with *N,N'*-dicyclohexylcarbodiimide in acetonitrile, a 42% yield of pure pyrazoline IV is obtained after chromatography. The use of tetrahydrofuran instead of acetonitrile under identical conditions resulted in only a 20% yield of IV. In accordance with equation (1) the reaction should still be applicable if, in formula I, OX represented phosphite. It was therefore not surprising to find that the cyclization of III to IV could also be accomplished by means of phosphorus pentachloride in refluxing chloroform, the yield of pyrazoline being 22%.

The structure of pyrazoline IV was established by independent synthesis. Cyclization of the phenylhydrazone of 2-benzalcyclohexanone in hot acetic acid gave in 17% yield the pyrazoline IV, identical with material obtained in the *N,N'*-dicyclohexylcarbodiimide reaction. When the cyclization of 2-benzalcyclohexanone phenylhydrazone was carried out in ethanol in the presence of hydrochloric acid, it was possible by careful work-up to isolate a pyrazoline IVa isomeric with IV. IVa, like IV, gave a positive Knorr[11] and bromine[12] test for a pyrazoline; its infrared spectrum showed absence of NH absorption and, in fact, differed from that of IV



only in the fingerprint region. Mixed with IV it caused a melting point depression of 15°. It was converted by heating with acid into pyrazoline IV.

The foregoing lead us to believe that IV and IVa possess the *trans* and *cis* structures shown below. This assignment is strengthened by theoretical considerations that ring closure of the phenylhydrazone V, if proceeding by *trans* addition to the double bond, should lead to the *cis* isomer IVa. The stereochemistry of the double bond in V is indicated by the fact that in the parent 2-benzalcyclohexanone the phenyl group is *trans* to the carbonyl.[13] NMR data on the two isomers corroborate the configurational assignments made above. Each of the isomers (IV and IVa) shows a doublet for the splitting of the benzylic hydrogen by the neighboring hydrogen at the ring junction. In the *trans* isomer IV the benzylic hydrogen at C-7 is more shielded than in the *cis* isomer IVa. Models show that the eclipsed conformation of the C-7 phenyl with respect to the ring CH_2 group in IVa disallows this phenyl group to orient itself in such a way that the π electrons could cause shielding of the hydrogen at C-7. For the *trans* isomer IV one observes a smaller chemical shift[14] (to 5.67 τ) than for the *cis* isomer IVa (to 4.98 τ). In the latter the hydrogen at C-7 is deshielded being in the plane of the aromatic ring.

The method of cyclization with *N,N'*-dicyclohexylcarbodiimide was also applied to the preparation of 1,3,5-triphenyl-Δ²-pyrazoline (II) (R, R' = C_6H_5), albeit in only 5% yield. The product obtained according to equation (1) had an identical infrared spectrum and melting point as material isolated from the reaction of benzalacetophenone with phenylhydrazine.[15] Polyphosphoric acid did not bring about cyclization of I to II.

The low yield in the conversion of I (R, R' = C_6H_5; X = H) to II (R, R' = C_6H_5) could be due to a requirement in the cyclization for the *trans* stereoisomer of the oxime (as illustrated by I).

(7) Added in proof: It has recently been demonstrated [(E. Schmidt and W. Carl, *Ann.*, **639**, 24 (1961)] that oximes can react with carbodiimides to form *O*-substituted isoureas.

(8) F. Pirrone, *Gazz. chim. ital.*, **66**, 429 (1936).

(9) J. Tambor and F. Wildi, *Ber.*, **31**, 352 (1898).

(10) N. H. Cromwell, Q. T. Wiles, and O. C. Schroeder, *J. Am. Chem. Soc.*, **64**, 2432 (1942).

(11) L. Knorr, *Ber.*, **26**, 100 (1893).

(12) L. C. Raiford and W. J. Peterson, *J. Org. Chem.*, **1**, 544 (1937).

(13) From ultraviolet absorption data and conversion to a *cis* isomer, A. Hassner and T. C. Mead, unpublished results.

(14) For analogous examples in a substituted cyclopentane see L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon Press, New York, 1959, p. 18, 126.

(15) L. Knorr and H. Laubmann, *Ber.*, **21**, 1210 (1888).

Oxime I (R, R′ = C_6H_5; X = H) is expected to be largely a *syn* isomer (OH *syn* to alkyl), as is the case for most acetophenone type oximes. In fact, when crude rather than purified oxime I (R, R′ = C_6H_5; X = H) was employed in the cyclization reaction the yield of pyrazoline was increased to 15%. The crude oxime presumably contains a larger amount of the desired stereoisomeric form of the oxime.

From behavior in Beckmann rearrangements it was expected that in oximes of the acetone rather than of the acetophenone type the desired *anti* configuration of the oxime (as in I) would predominate. When we applied the cyclization reaction to I (R = C_6H_5; R′ = CH_3; X = H), the oxime of 4-anilino-4-phenyl-2-butanone, we were able to isolate a 33% yield of pyrazoline II (R = C_6H_5; R′ = CH_3), identical with material prepared by an independent route.

The method is not very applicable to aromatic aldoximes since benzaldoxime itself as well as its *o*-amino derivative were dehydrated in part to nitriles.

EXPERIMENTAL[16]

1,3,5-Triphenyl-Δ²-pyrazoline (II) (R, R′ = C_6H_5) a. *By N,N′-dicyclohexylcarbodiimide cyclization of pure β-anilino-β-phenylpropiophenone oxime.* To a solution of 316 mg. (1 mmole) of recrystallized β-anilino-β-phenyl-propiophenone oxime[9,10,15,17,18] [m.p. 131–132°; infrared: 3400 cm.$^{-1}$ (NH, OH), 1640 cm.$^{-1}$ (C=N)] in 6 ml. of dry acetonitrile there was added 254 mg. (1.25 mmoles) of *N,N′*-dicyclohexylcarbodiimide. The mixture was protected from moisture by a calcium chloride drying tube and refluxed for 45 hr., during which time a precipitate of *N,N′*-dicyclohexylurea was formed. Following the addition of glacial acetic acid to convert unreacted *N,N′*-dicyclohexylcarbodiimide to the urea, the latter was removed by filtration and the mother liquor evaporated in vacuum. The resulting oil was chromatographed on Merck aluminum oxide. The petroleum ether (b.p. 40–60°) benzene fractions gave 15 mg. (5%) of 1,3,5-triphenyl-Δ²-pyrazoline, recrystallized from ethanol, which gave an identical infrared spectrum, (1668 cm.$^{-1}$), melting point (136–137°)[15] and Knorr test[11] as the product from the reaction of benzalacetophenone phenylhydrazone.[15]

b. By N,N′-dicyclohexylcarbodiimide cyclization of crude β-anilino-β-phenylpropiophenone oxime. Repeating the *N,N′*-dicyclohexylcarbodiimide cyclization with crude oxime (m.p. 114–121°), by allowing the mixture to stand at room temperature for 11 days, gave a 16% yield of 1,3,5-triphenyl-Δ²-pyrazoline after chromatography. The yield of the pyrazoline was substantially the same (14%) if the reaction of the crude oxime was carried out by heating in acetonitrile under reflux. Polyphosphoric acid was ineffective in this cyclization.

1,5-Diphenyl-3-methyl-Δ²-pyrazoline (II) (R = C_6H_5, R′ = CH_3). *By N,N′-dicyclohexylcarbodiimide cyclization of 4-anilino-4-phenyl-2-butanone oxime.* Heating of a solution of 325 mg. (1.28 mmoles) of 4-anilino-4-phenyl-2-butanone oxime [m.p. 94–96°, infrared: 3380 cm.$^{-1}$, 3200 cm.$^{-1}$ (OH,NH), 1650 cm.$^{-1}$ (C=N), prepared by the sodium acetate method from 4-anilino-4-phenyl-2-butanone[19] in 73% yield] and 308 mg. (1.5 mmoles) of *N,N′*-dicyclohexylcarbodiimide in 10 ml. of dry acetonitrile under reflux gave, after treating with glacial acetic acid, evaporation, and chromatography, 78 mg. (33%) of 1,5-diphenyl-3-methyl-Δ²-pyrazoline, m.p. 115–115.5° infrared: 1648 cm.$^{-1}$, identical by infrared and melting point to material prepared by cyclization of benzalacetone phenylhydrazone.[20]

6α,7-trans-Cyclohexano-(1,2-c)1,7-diphenyl-Δ²-pyrazoline (IV). a. *By N,N′-dicyclohexylcarbodiimide cyclization of 2-(α-anilinobenzyl)cyclohexanone oxime* (III). 6α,7-*trans*-Cyclohexano(1,2-*c*)1,7-diphenyl-Δ²-pyrazoline was prepared by heating under reflux for 45 hr. 294 mg. (1 mmole) of III [m.p. 152°, infrared: 3390 cm.$^{-1}$, 3200 cm.$^{-1}$ broad (OH,NH), 1660 cm.$^{-1}$ (C=N); lit.[8] m.p. 154–155°] and 254 mg. (1.23 mmoles) of *N,N′*-dicyclohexylcarbodiimide in 7 ml. dry acetonitrile. After the usual work-up there was obtained 114 mg. (42%) of pyrazoline IV. Using tetrahydrofuran as a solvent under identical conditions a 20% yield of IV was obtained. This pyrazoline gave an intense purple Knorr test[11] and an immediate blue-green color on exposure to bromine vapors.[12] The analytical sample, from methanol, had a m.p. of 138.5–140.5°. λ_{max} (methanol): 278 mμ (13,800).

Anal. Calcd. for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.33; H, 7.32; N, 10.11.

Infrared showed no NH absorption either in potassium bromide or in solution ($Cl_2C{=}CCl_2$, CS_2). NMR (tetramethylsilane as standard): τ (p.p.m.) 5.52, 5.67.

b. *By phosphorus pentachloride cyclization of 2-(α-anilinobenzyl)cyclohexanone oxime* (III). To 100 mg. of III (0.34 mmole) in 6 ml. of freshly distilled chloroform was added portionwise 150 mg. (0.72 mmole) of phosphorus pentachloride. The mixture was heated for 25 hr. under reflux, cooled, and washed with 2 ml. of water and 5 ml. of 10% sodium carbonate. The dried chloroform layer was evaporated, and the resulting oil was chromatographed on Merck aluminum oxide to give 21 mg. (22%) (eluted with petroleum ether–benzene) of pyrazoline IV, identical with the material obtained in the *N,N′*-dicyclohexylcarbodiimide cyclization.

c. *From 2-benzalcyclohexanone phenylhydrazone* (V). A solution of 264 mg. (0.96 mmole) of V (m.p. 77–80°, infrared: 3380 cm.$^{-1}$, 1540 cm.$^{-1}$, obtained from 2-benzalcyclohexanone[21] in 70% yield, stable for only 1–2 days in the refrigerator) in glacial acetic acid was heated under reflux for 3.5 hr., then evaporated in vacuum. The resulting oil was chromatographed and a 17% yield of pyrazoline IV was obtained. This pyrazoline was identical in all respects to material obtained in the *N,N′*-dicyclohexylcarbodiimide cyclization.

6α,7-cis-Cyclohexano-(1,2-c)-1,7-diphenyl-Δ²-pyrazoline (IVa). A solution of 350 mg. of 2-benzalcyclohexanone phenylhydrazone (V) in 20 ml. ethanol containing 3 drops of concd. hydrochloric acid was heated on a steam bath. Aliquots were taken and tested for the presence of pyrazoline by the Knorr method.[11] At the first positive test, about 5 min. after heating, the reaction mixture was immediately evaporated in vacuum at 60° to one third of the original volume. The precipitate was collected by filtration and washed with cold ethanol. Evaporation of the filtrate afforded more solid to give a total of 66 mg. (19%) of pyrazoline IVa. The pyrazoline gave an intense purple Knorr test[11] and an immediate blue-green color when exposed to bromine vapors.[12] The analytical sample, from

(16) All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analysis by Pascher Laboratories, Bonn, Germany. Infrared spectra were run in potassium bromide on a Beckman IR-5 spectrophotometer.

(17) C. Mayer, *Bull. soc. chim. France*, [3], **33**, 158 (1905).

(18) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, 3rd ed., J. Wiley & Sons, Inc., New York, 1948, p. 202.

(19) E. Macovski and A. Silberg, *J. prakt. Chem.*, **137**, 131 (1933).

(20) K. Auwers and H. Voss, *Ber.*, **42**, 4411 (1909).

(21) W. S. Emerson, G. H. Birrum, and R. I. Longley, Jr., *J. Am. Chem. Soc.*, **75**, 1312 (1953).

methanol, melted at 137–139°. Mixed m.p. with IV 123–129°; λ_{max} (methanol): 284 mμ (12,600).

Anal. Calcd. for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.33; H, 7.22; N, 10.35.

Infrared showed no NH absorption either in potassium bromide or in solution ($Cl_2C{=}CCl_2$, CS_2). NMR (tetramethylsilane standard): τ (p.p.m.) 4.77, 4.98.

Attempts at preparation of IVa from 2-benzalcyclohexanone phenylhydrazone in ethanol–hydrochloric acid using longer heating times gave a mixture of pyrazolines IVa and IV.

Isomerization of IVa *to* IV. When pyrazoline IVa was heated in glacial acetic acid under reflux for 4 hr. and the product was chromatographed, pyrazoline IV was isolated in 30% yield. The two pyrazolines were not isomerized by chromatography over aluminum oxide, each isomer being recovered unchanged.

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Diels-Alder Reactions of 1-Carbomethoxypyrroles and Dimethyl Acetylenedicarboxylate

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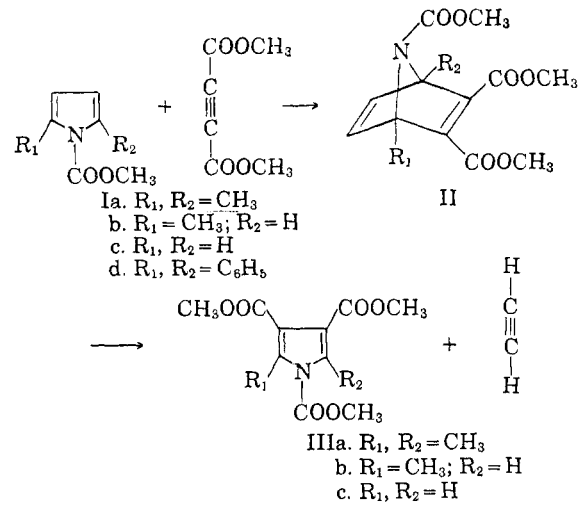
As part of a research program directed toward the study of electron deficient nitrogen compounds it appeared desirable to synthesize derivatives of 7-azabicyclo[2.2.1]hepta-2,5-diene (II). A possible entry into this ring system seemed to be given by the Diels-Alder reaction of a suitably substituted pyrrole with dimethyl acetylenedicarboxylate. Two examples of normal additions of dienophiles to pyrroles have been reported in the recent literature. The addition of benzyne to 1-methylpyrrole[1] and the reaction of acetylenedicarboxylic acid with 1-benzylpyrrole[2] both give moderately stable, normal Diels-Alder adducts in poor yields. All other examples of attempted diene syntheses involving pyrroles led to α-substitution products,[3] although initial normal addition followed by rearrangement cannot be excluded as a possible mechanism for these reactions.

It was hoped that carbomethoxy substitution on nitrogen would decrease the aromatic character of the pyrrole and would tend to stabilize the adduct sufficiently to allow normal Diels-Alder addition to occur in preparative yields. Furthermore, alkyl substituents on both the 2 and 5 positions should minimize the possibility of an α-substitution reaction. When equimolar quantities of methyl 2,5-dimethylpyrrole-1-carboxylate (Ia) and dimethylacetylenedicarboxylate were heated to 160° a crystalline product was isolated from the reaction mixture which was identified as trimethyl 2,5-dimethylpyrrole-1,3,4-tricarboxylate (IIIa) by spectral and chemical evidence. The NMR spectrum revealed the presence of two equivalent allylic methyl groups (7.75 τ) and two equivalent (6.35 τ) and one different (6.15 τ) methoxy groups. Base-catalyzed hydrolysis led to 2,5-dimethylpyrrole-3,4-dicarboxylic acid, which was characterized as its diethyl ester. In a subsequent run the gas which began to escape from the reaction mixture at 140° was identified as acetylene.



The formation of IIIa seems to be explained best by assuming the transient formation of the normal adduct II which undergoes a reverse Diels-Alder reaction to give the observed product.[4] Attempts to obtain the initial adduct at temperatures below 140° resulted in the recovery of starting material.

The scope of this reaction has been extended to include the formation of trimethyl 2-methylpyrrole-1,3,4-tricarboxylate (IIIb) and trimethylpyrrole 1,3,4-tricarboxylate (IIIc) from methyl 2-methylpyrrole-1-carboxylate (Ib) and methyl pyrrole-1-carboxylate (Ic), respectively, and dimethyl acetylenedicarboxylate.[5] The latter two cases demonstrate that α-alkyl substitution is not a necessary factor in determining the mode of decomposition of the Diels-Alder adduct.

The attempted reaction of methyl 2,5-diphenylpyrrole-1-carboxylate (Id) with dimethyl acetylenedicarboxylate resulted in recovery of starting material. Similarly, attempted use of maleic anhy-

(1) G. Wittig, *Ang. Chem.*, 69, 245 (1957).

(2) L. Mandell and W. A. Blanchard, *J. Am. Chem. Soc.*, 79, 6198 (1957).

(3) O. Diels and K. Alder, *Ann.*, 498, 1 (1932).

(4) A similar reverse reaction is the thermal decomposition of 1-methyl-2,3-dicarboethoxycyclohexene-2 oxide-1,4 to ethylene and 2-methyl-3,4-dicarboethoxyfuran, K. Alder and H. F. Rickert, *Ber.*, 70, 1354 (1937).

(5) While this work was in progress R. M. Acheson and J. M. Vernon [*J. Chem. Soc.*, 457 (1961)] reported the formation of trimethyl pyrrole-1,3,4-tricarboxylate by the same method.