The Stability, Decomposition, and Reactivity of a 1,2-Diazacyclopentene-3,5-dione. 4,4-Diethylpyrazoline-3,5-dione[1]

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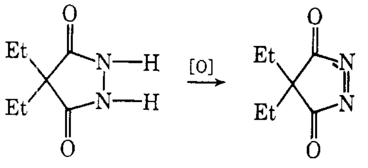
The diazacyclopentene-3,5-dione, 4,4-diethylpyrazoline-3,5-dione (**2**), was prepared by the oxidation of 4,4-diethylpyrazolidine-3,5-dione (**1**) with either nitrogen tetroxide or lead tetraacetate (LTA). Dilute solutions of **2** proved to be more stable when nitrogen tetroxide was used to oxidize **1** and could be stored for indefinite periods at −15°. On warming to room temperature, **2** decomposed readily to give products which depended on the nature of the oxidant and decomposition conditions. Oxidation of **1** with nitrogen tetroxide and decomposition gave nitrogen, 2,2,6,6-tetraethylpyrazolo[1,2-*a*]pyrazole-1,3,5,7-tetraone (**3**), 1-(diethylcarboxyacetyl)-4,4-diethylpyrazolidine-3,5-dione (**4**), and diethylmalonic acid (**5**) as products. Oxidation of **1** with LTA and decomposition gave nitrogen, **3**, lead diethylmalonate (**9**), 3-acetoxy-4,4-diethyl-2-pyrazolin-5-one (**10**), 3,5-diacetoxy-4,4-diethylpyrazole (**11**), and diacetoxy diethylmalonate (**13**) as products. The *in situ* reaction of **2** with dienes yielded a series of Diels–Alder adducts. Adducts were obtained by the reaction of **2** with 2,3-dimethyl-1,3-butadiene, isoprene, 1,4-diphenyl-1,3-butadiene, cyclopentadiene, 1,3-cyclohexadiene, α-phellandrene, 1,3-cyclooctadiene, and anthracene. Higher yields of the adducts resulted when LTA was used to oxidize **1**. The nmr and uv spectra of the adducts gave a considerable amount of information about their geometry.

The preparation of diazabicyclic systems by the reaction of electron-deficient *cis*-azo dienophiles and conjugated dienes in 1,4 cycloaddition has been reported.[2-8] These *cis*-azo dienophiles were found to be generally more reactive than *trans*-azo dienophiles.[2-8] The purpose of this investigation was to develop and study new *cis*-azo compounds which may be useful as dienophiles in 1,4-cycloaddition reactions.

Oxidation of the hydrazide, 4,4-diethylpyrazolidine-3,5-dione (**1**), was found to yield the 1,2-diazacyclopentene-3,5-dione **2**.[9]

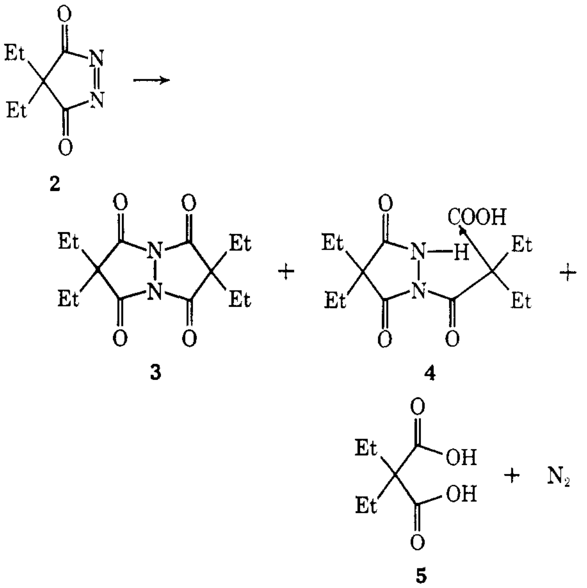


1 **2**

The presence of **2** could easily be detected by the deep color of its methylene chloride solutions. When lead tetraacetate (LTA) was used as the oxidizing agent, the solution containing **2** appeared green. When nitrogen tetroxide was used to oxidize **1**, a transient green solution formed which gave way to a deep blue solution containing **2**. Since the addition of LTA to commercial methylene chloride gave an orange solution, the blue color of **2** produced by this oxidizing agent was probably masked.[10]

At any rate, the visible spectrum of **2** was found to be independent of the oxidizing agent. In general, solutions of **2** were more stable when nitrogen tetroxide was used as an oxidant. Dilute solutions of **2** were 29% decomposed after standing at room temperature for 72 hr, as measured by the decrease of molar absorptivity when nitrogen tetroxide was used, but, when LTA was used, 50% decomposition at room temperature had taken place after 72 hr. The visible spectrum of **2** is summarized in Table I. It can be seen that little decomposition had taken place after 32 weeks.

The ultraviolet spectrum showed only end absorption. Attempts were made to obtain pure **2** by the isolation method of Stickler and Pirkle.[11] In all cases, a deep blue liquid was obtained, which, on warming to room temperature, decomposed rapidly with gas evolution. This decomposition, which gave nitrogen, 2,2,6,6-tetraethylpyrazolo[1,2-*a*]pyrazole-1,3,5,7-tetraone (**3**), 1-(diethylcarboxyacetyl)-4,4-diethylpyrazolidine-3,5-dione (**4**), and diethylmalonic acid (**5**), can be represented by eq 1.



(1)

When the decomposition of **2** was allowed to proceed in methylene chloride solution, it was noted that the solution remained strongly acidic even in the presence of excess sodium sulfate. The solution was therefore neutralized by adding sodium bicarbonate and filtered

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[1] This investigation was supported by Grant GP-7680 from the National Science Foundation.

[2] B. T. Gillis and R. Weinkam, *J. Org. Chem.*, **32**, 3321 (1967).

[3] R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *J. Chem. Soc.*, *C*, 19, 1905–1909 (1967).

[4] B. T. Gillis and J. D. Hagarty, *J. Org. Chem.*, **32**, 330 (1967).

[5] B. T. Gillis, "1,4-Cycloaddition Reactions," Academic Press Inc., New York, N. Y., 1967, Chapter 6.

[6] R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *Tetrahedron Lett.*, 615 (1962).

[7] T. J. Kealy, *J. Amer. Chem. Soc.*, **84**, 966 (1962).

[8] R. A. Clement, *J. Org. Chem.*, **25**, 1724 (1960).

[9] Sulfo derivatives of pyrazoline-3,5-dione have previously been reported; see A. M. Khaletskii and B. L. Moldover, *Materialy 1-go (Pervogo) Vseros. Sezda Farmatsevtov* (Moscow: Med.) *Sh.*, 330 (1962), *Chem. Abstr.*, **63**, 5625*f* (1965).

[10] Under anhydrous conditions, LTA oxidation of **1** also gave a blue color.

[11] J. C. Stickler and W. H. Pirkle, *J. Org. Chem.*, **31**, 3444 (1966).

Table I

Visible Spectrum of 4,4-Diethylpyrazoline-3,5-dione[a]

λ_{max}, mμ, in methylene chloride[c]	Molar absorptivity, ε			
	Initial	1 week[b]	14 weeks	32 weeks
724	37	36	32	26
680	111	109	102	82
644	154	150	127	110
621	139	136	117	94

[a] Nitrogen tetroxide was used as the oxidant of **1**. [b] The solution was stored at −15°. [c] Oxidation of **1** with LTA gave the same four peaks with comparable absorptivities.

before allowing the decomposition to proceed. Compounds **3**, **4**, **5**, and nitrogen were again obtained. Table II shows that the yields of the decomposition products were dependent on the mode of decomposition.

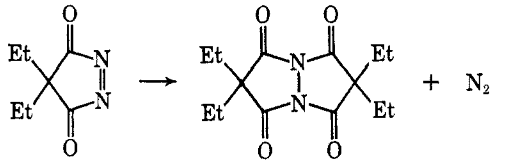
Table II

Decomposition Products of 4,4-Diethylpyrazoline-3,5-dione[a]

Product	Yield, %	
	No solvent	Neutral methylene chloride solution
3	26.8	50.0
4	41.9	29.4
5	10.3	2.1

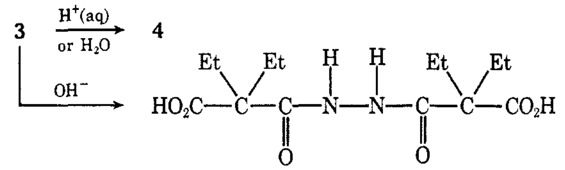
[a] Nitrogen tetroxide was used as the oxidant of **1**.

The formation of **3** can be represented simply by eq 2. Similar reactions have been reported by Kealy.[7]



2 **3** (2)

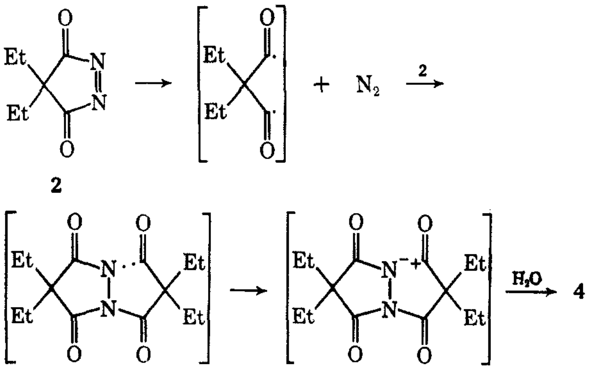
It was found that **3** reacted with acid or water to give the carboxylic acid **4**, but that it reacted with base to furnish the further opened dicarboxylic acid **6**, as shown in eq 3.



$$3 \xrightarrow[\text{or } H_2O]{H^+(aq)} 4 \qquad 3 \xrightarrow{OH^-} HO_2C\text{-}C(Et)_2\text{-}C(=O)\text{-}NH\text{-}NH\text{-}C(=O)\text{-}C(Et)_2\text{-}CO_2H$$

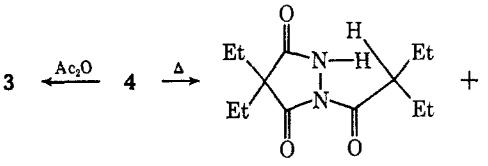
6 (3)

Since **3** was found to be indefinitely stable to atmospheric moisture, the formation of **4** by decomposition of **2** can be ascribed to sequence 4.



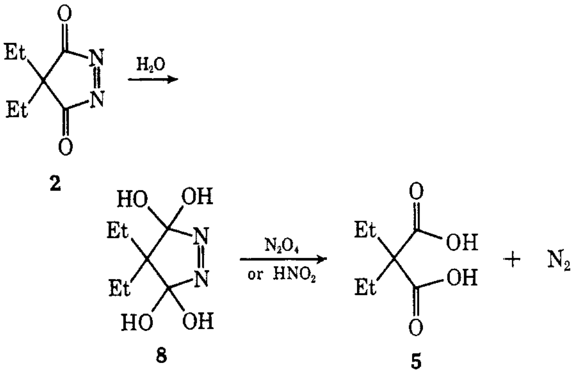
2 (4)

The acid **4** was thermally unstable and decarboxylated readily on heating under reduced pressure to give 1-(diethylacetyl)-4-4-diethylpyrazolidine-3,5-dione (**7**). Dehydration of **4** using acetic anhydride quantitatively furnished **3**. These latter two conversions of **4** are summarized by eq 5.



7 (5)

The presence of diethylmalonic acid (**5**) can be accounted for either by the presence of excess nitrogen tetroxide or by the presence of nitrous acid, as shown by eq 6.



2 **8** **5** (6)

Table II shows that, when the decomposition of **2** was carried out in neutral methylene chloride solution, only 2.1% diethylmalonic acid (**5**) was isolated. It is noteworthy to mention that, when the decomposition of **2** was allowed to proceed in methylene chloride solution without the addition of sodium bicarbonate solution, the yield of diethylmalonic acid (**5**) increased to 35%, even when only 1 equiv of nitrogen tetroxide was used. In this case, it appears that the nitrous acid formed in the oxidation of **1** is acting as a further oxidant of **2**. This latter mode of decomposition also yielded a little diethylacetic acid, which was probably formed from decarboxylation of diethylmalonic acid in the acidic media.

When LTA was used as the oxidizing agent, the decomposition of **2** gave **3**, lead diethylmalonate (**9**), 3-acetoxy-4,4-diethyl-2-pyrazolin-5-one (**10**), 3,5-diacetoxy-4,4-diethylpyrazole (**11**), and diacetoxy diethylmalonate (**13**). The products were possibly formed as shown in Scheme I.

The dianhydride **13** was characterized by its elemental analysis, infrared spectra, and nmr spectra. It reacted readily with aniline to give acetanilide and diethylmalonic acid, and it reacted slowly over a period of several days with lead acetate to give lead diethylmalonate (**9**).

The acetoxy derivatives **10** and **11** were characterized by their elemental analysis and by ultraviolet, infrared, and nmr spectra, as well as by comparison with authentic samples of **10** and **11** which were prepared from the reaction of the hydrazide **1** with acetic anhydride.

The high stability of **2** at 0°, in addition to the fact that it is readily available, made it a potentially at-

SCHEME I

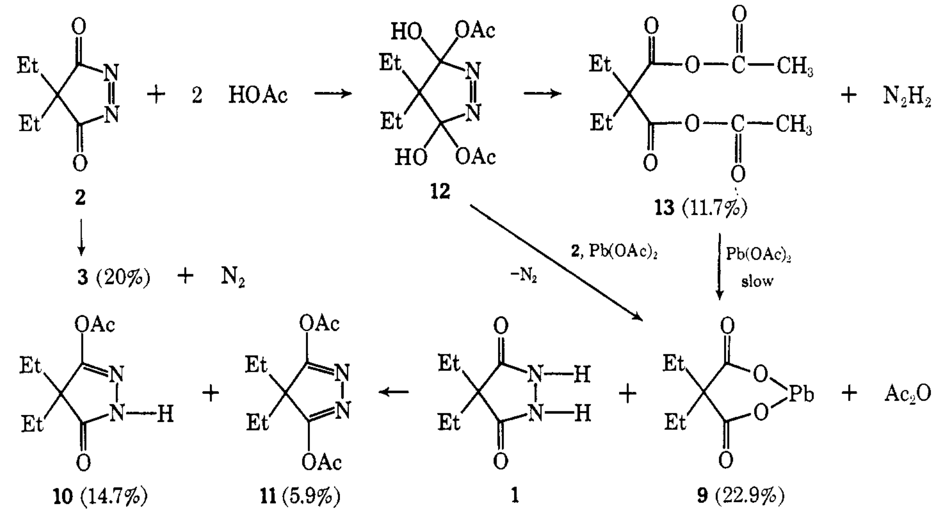
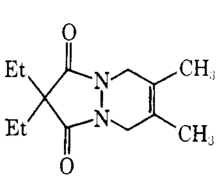


TABLE III

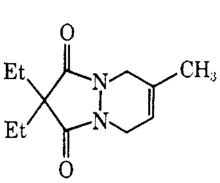
Diene	Adduct	Mp, °C (bp, mm)	Yield, %[a]	λ_{max} mμ, (solvent)	ε
2,3-Dimethylbutadiene	**14′**	107–108	94.3 (55.3)[b]	256 (cyclohexane)	2040
				257 (95% ethanol)	2250
Isoprene	**14**	58.5–60	46.6	256 (cyclohexane)	2210
				256 (95% ethanol)	2850
1,4-Diphenylbutadiene	**15**	147–148	51.9	259 (cyclohexane)	2170
				259 (95% ethanol)	2270
Cyclopentadiene	**16**	76–77	40.0	269 (cyclohexane)	3030
			(15.9)[b]	254 (95% ethanol)	4150
Cyclohexadiene	**17**	105–106	76.1	268 (cyclohexane)	3900
				256 (95% ethanol)	4520
α-Phelladrene	**18**	(141–143, 0.2)	41.4	256 (cyclohexane)	3810
				247 (95% ethanol)	4180
1,3-Cyclooctadiene	**19**	134–136	21.0	261 (cyclohexane)	3790
				257 (methanol)	2820
Anthracene	**20**	224–226	13.6	262 (methanol)	5740
Diethylmalonic acid cyclic hydrazine	**1**			253 (water)	3600

[a] LTA was used as the oxidant of **1**. [b] Nitrogen tetroxide was used as the oxidant of **1**.

tractive dienophile. When **2** was generated by LTA oxidation in the presence of a 1,3-diene, the characteristic green color of **2** was completely absent after 5 min to 3 hr or longer, depending on the reactivity of the diene towards Diel–Alder addition. The results are summarized in Table III.



14′



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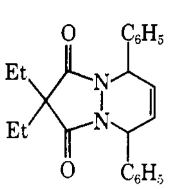

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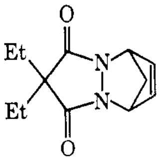

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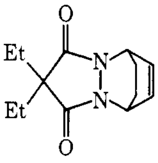

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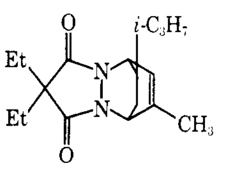

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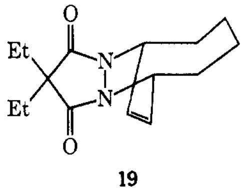

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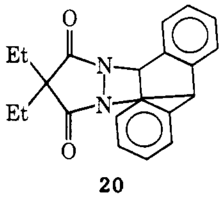

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It can be seen from the yields of compounds **14′** and **1** that far higher yields of Diels–Alder adducts resulted when LTA was used to oxidize **1**. Nitrogen tetroxide oxidations always led to large amounts of polymeric materials. Norbornadiene gave no adduct with **2**. Instead, the mixed acetates of norbornadiene (LTA oxidation) that were reported by Alder,[12] or polymeric materials (nitrogen tetroxide oxidation), were isolated.

Thus, 4,4-diethylpyrazoline-3,5-dione is one of the more reactive *cis*-azo dienophiles. It is more reactive than 5-substituted pyrazol-3-one derivatives[2] but a little less reactive than 4-phenyl-1,2,4-triazoline-3,5-dione, which gives an adduct with norbornadiene.[4,7,8]

Each of the adducts was identified by its nmr, infrared, and ultraviolet spectra as well as by elemental analysis. The main feature of their infrared spectra was a split carbonyl absorption of unequal intensity at about 5.95 and 5.80 μ with the former being more intense. The degree of rigidity of the various adducts about the N,N ring fusion was illustrated by their nmr and ultraviolet spectra. Those adducts with 1,4 substitution as a bridge showed nonequivalent C-

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[12] K. Alder, F. H. Flock, and H. Wirtz, *Chem. Ber.*, **91**, 609 (1958).

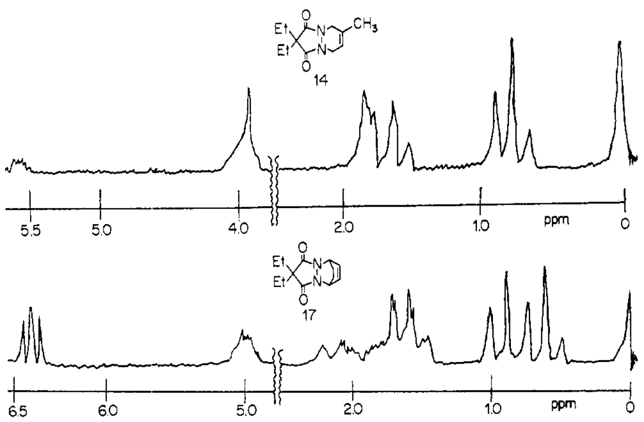
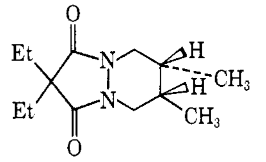


Figure 1.–Nmr spectra of adducts **14** and **17**.

methyl proton absorptions for the two ethyl groups in the nmr.

Those adducts with no bridge at the 1,4 positions showed only an average C-methyl absorption due to the free inversion about the 1,4-carbon atoms. This distinction is shown by the nmr spectra of **14** and **17**, which are illustrated in Figure 1. The nmr data is complemented by the ultraviolet data, which is tabulated in Table III. The table shows that those adducts with no 1,4 bridge exhibit no shift in wavelength with a change in the polarity of the solvent. However, those adducts with a 1,4 bridge, with the exception of **15**, which is not nearly so strained as the other 1,4-bridged adducts, show an increase in the wavelength of absorption with a decrease in solvent polarity. This bathochromic shift is probably due to an interaction between the endocyclic double bond and the nonbonded electrons on the two nitrogen atoms, even though they are shielded by the nitrogen nuclei. The table shows a correlation between the magnitude of the bathochromic shift and the rigidity of the various bridged adducts. In polar solvents, the lone pair of electrons on the two nitrogen atoms form a hydrogen bond with the solvent, and no bathochromic shift is observed. To investigate further the difference in the ultraviolet behavior between the bridged and nonbridged adducts, the endocyclic double bond of adducts **14′**, **16**, and **17** were hydrogenated to give **21**, **22**, and **23**, respectively.



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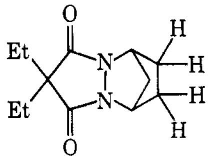

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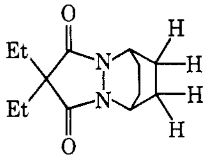

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Table IV summarizes the ultraviolet spectral data of compounds **14′**, **16**, **17**, **21**, **22**, and **23** in both cyclohexane and 95% ethanol. From the table it can be seen that in a given solvent system, the nonbridged adduct shows little or no change in wavelength on saturation of the endocyclic double bond. However, the bridged adducts show a significant increase in wavelength on saturation, with the increase being proportional to the rigidity of the adduct. It is apparent that an interaction between the endocyclic double bond and the two nitrogen atoms stabilizes the ground state of the bridged adducts. It should also be noted that the solvent effect on **21**, **22**, and **23** is proportional to the rigidity of the compound.

Table IV

Compd	$\lambda_{max}^{cyclohexane}$, mμ (ε)	$\lambda_{max}^{95\%\ ethanol}$, mμ (ε)
14′	256 (2040)	257 (2250)
21	256 (2520)	258 (2570)
17	268 (3900)	256 (4520)
23	270 (2780)	264 (3600)
16	269 (3030)	254 (4150)
22	277 (2140)	266 (2420)

The high stability and reactivity of **2** at 0°, in addition to the fact that it is readily available, make it an efficient reagent for obtaining derivatives of the pyrazolo[1,2-*a*]pyridazine ring system. An investigation of the chemistry of this ring system is currently in progress.

Experimental Section[13]

Synthesis of 4,4-Diethylpyrazolidine-3,5-dione (1).—A mixture of 86.4 g of diethyl diethylmalonate and 283 g of an 85% solution of hydrazine hydrate was heated at reflux for 8 days. The reaction mixture was distilled to dryness at atmospheric pressure. The first fraction, consisting mainly of ethanol, water, and a little hydrazine hydrate, was discarded, but the remaining distillate, consisting mainly of hydrazine hydrate plus a little unreacted ester, was saved for recycling in future preparations of **1**. The crude crystals of **1** were recrystallized from water to give 43.0 g (69%) of **1** as white crystals, mp 266–267° (lit.[14] mp 270°).

Oxidation of 1 with Nitrogen Tetroxide.—A mixture of 1.400 g (0.089 mol) of **1** and 10 g of anhydrous sodium sulfate in 100 ml of methylene chloride was oxidized with nitrogen tetroxide according to the procedure of Stickler and Pirkle.[11] A deep blue solution of 4,4-diethylpyrazoline-3,5-dione (**2**) was obtained. A 1-ml aliquot of the solution was transferred to a 100-ml volumetric flask and diluted to volume with cold methylene chloride: concn 8.9×10^{-4} *M;* visible λ_{max} (methylene chloride) 724 (ε 37), 680 (ε 111), 644 (ε 154), and 621 mμ (ε 139).

In a similar manner, 18.6 g (0.12 mol) of **1** was oxidized. The solvent was removed under reduced pressure at 0° to give **2** as a blue liquid. On warming to room temperature, the liquid decomposed with gas evolution. The decomposed mixture was dissolved in 100 ml of methylene chloride and washed twice with 100-ml portions of water. The aqueous washings were washed twice with 50-ml portions of methylene chloride, and these washings were added to the methylene chloride solution containing the non-water-soluble materials. To the aqueous solution was added 150 ml of 1 *M* lead diacetate trihydrate to precipitate 4.5 g (10.3%) of lead diethylmalonate (**9**).

The lead salt **9** was characterized as follows. A quantity of **9** weighing 6.2 g was dissolved in 90% acetic acid. Concentrated hydrochloric acid was added dropwise until no more lead chloride precipitated. The mixture was filtered and washed with water to give 3.5 g of lead chloride (56.5% lead in **9**). The acetic acid solution was distilled to dryness under reduced pressure, and the residue was sublimed three times to give pure diethylmalonic acid (**5**): mp 126–127° (lit.[15] mp 125°); nmr ($CDCl_3$) δ 2.36 (m,

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[13] Melting points are corrected. Microanalyses were performed by Dr. Alfred Bernhardt, Mulheim, Germany. Infrared spectra were taken with a Perkin-Elmer Model 137 double-beam spectrophotometer. The nmr spectra were taken with a Varian Model A-60 using either carbon tetrachloride, deuterochloroform, or deuterium oxide as a solvent and tetramethylsilane as a reference standard. The ultraviolet spectra were taken with a Cary Model 14 Spectrophotometer.

[14] H. Ruhkopf, *Chem. Ber.*, **73B**, 820 (1940).

[15] N. A. Lange, "Handbook of Chemistry," Handbook Publishers, Inc., Sandusky, Ohio, 1949, p 464.

2) 1.29 (t, 3); mol wt (potentiometric titration) 160; mp of *p*-nitrobenzyl ester, 91–91.5° (lit.[16] mp 91°).

A solution of the water-insoluble materials in 300 ml of methylene chloride was washed three times with 100-ml portions of 10% sodium bicarbonate. The bicarbonate washings were acidified with excess hydrochloric acid and back-extracted three times with methylene chloride. These latter methylene chloride extracts were dried (Na_2SO_4) and the solvent was removed to give 7.5 g (41.9%) of 1-(diethylcarboxyacetyl)-4,4-diethylpyrazolidine-3,5-dione (**4**). The crude acid was recrystallized from benzene–petroleum ether (low boiling) to give pure **4**: mp 180–181° dec; uv λ_{max} (95% ethanol) 255 mμ (ϵ 2100).

Anal. Calcd for $C_{14}H_{22}N_2O_5$: C, 56.36; H, 7.43; N, 9.39. Found: C, 56.57; H, 7.47; N, 9.40.

The methylene chloride containing the neutral component[17] was dried (Na_2SO_4) and the solvent was removed to give 4.5 g (26.8%) of 2,2,6,6-tetraethylpyrazolo[1,2-*a*]pyrazole-1,3,5,7-tetraone (**3**), which may be recrystallized from ethanol–water: mp 206–207.5°; uv λ_{max} (95% ethanol) 270 (ϵ 1000), 260 (ϵ 1100), and 233 mμ (ϵ 11,200); ir (Nujol) 1755 and 1786 cm^{-1} (ring C═O); nmr ($CDCl_3$) δ 1.96 (m, 8, CH_2C), and 0.96 (t, 12, CH_3C).

Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.98; H, 7.19; N, 9.99. Found: C, 59.87; H, 7.13; N, 10.13.

When **2** was prepared as above and allowed to decompose in its methylene chloride solution which had been neutralized with solid sodium bicarbonate, 7.4 g (50.0%) of **3**, 5.25 g (29.4%) of **4**, and 0.9 g (2.1%) of **5** was obtained. The same isolation procedure of the decomposition products as above was employed.

When the decomposition of **2** was allowed to proceed in its methylene chloride solution without neutralization, a 35% yield of diethylmalonic acid was obtained; also isolated was a little diethylacetic acid.

Sublimation of the acid **4** at 80° gave the decarboxylated product 1-(diethylacetyl)-4,4-diethylpyrazolidine-3,5-dione. Recrystallization from ethanol–water gave a pure sample of **7**: mp 113–113.5°; uv$_{max}$ (95% ethanol) 260 mμ (ϵ 3500; ir (Nujol) 3175 (N–H), 1755, and 1786 cm^{-1} (ring C═O); nmr ($CDCl_3$) δ 3.56 (m, 1, Et_2CHCO), 1.80 (m, 8, CH_2C), and 0.86 (t, 12, CH_3C).

Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.02. Found: C, 61.40; H, 8.69; N, 11.02.

Reaction of 3 with Sodium Hydroxide.—To 25 ml of 10% sodium hydroxide at 40° was added 1.0 g (0.0036 mol) of **3** with stirring. All of compound **3** had gone into solution after 10 min. Acidification with hydrochloric acid caused the precipitation of 1.1 g (100%) of the dicarboxylic acid **5**, which was recrystallized from ethanol–water: mp 236–236.5°; uv λ_{max} (95% ethanol) 233 mμ (ϵ 4900); nmr (D_2O, Na salt) δ 2.19 (m, 8, CH_2C) and 1.24 (t, 12, CH_3C).

Anal. Calcd for $C_{14}H_{24}N_2O_6$: C, 53.15; H, 7.65; N, 8.86. Found: C, 53.18; H, 7.70; N, 8.84.

Reaction of 3 with Dilute Hydrochloric Acid.—To 0.5 g (0.0018 mol) of **3** in 20 ml of 95% ethanol was added enough 3 *M* hydrochloric acid to give pH 1. The solution was allowed to stand at room temperature for 6 days. To the solution was added 50 ml of methylene chloride, after which it was washed twice with 25-ml portions of 5% sodium bicarbonate. The bicarbonate washings were acidified (HCl) and back-extracted twice with 25-ml portions of methylene chloride. The methylene chloride extracts were dried (Na_2SO_4) and the solvent was removed to give 0.35 g (66.0%) of the acid **4**, mp 176–182° dec.

Reaction of 3 with Water.—To 0.5 g (0.0018 mol) of **3** in 40 ml of 95% ethanol was added 5 ml of water, and the resulting solution was allowed to stand at room temperature for 5 days. To the solution was added 50 ml of methylene chloride, after which it was washed twice with 25-ml portions of 5% sodium bicarbonate. The bicarbonate washings were acidified (HCl) and back-extracted twice with 25-ml portions of methylene chloride. The methylene chloride extracts were dried (Na_2SO_4) and the solvent was removed to give 0.2 g (38%) of **4**, mp 179–181° dec.

Reaction of 4 with Acetic Anhydride.—To 2.1 g (0.007 mol) of the acid **4** in 50 ml of methylene chloride at room temperature was added 2.2 g of acetic anhydride with stirring. Stirring was continued for 3 days, after which the reaction mixture was filtered to remove a trace of the starting acid. The solvent was removed to give 1.9 g (97.0%) of **3**, mp 206–207.5°.

Reaction of 1 with Lead Tetraacetate.—To 18.6 g (0.12 mol) of the hydrazine **1** in 400 ml of methylene chloride was added 66 g (0.126 mol) of an 85% solution of lead tetraacetate with stirring. During the lead tetraacetate addition, a deep green color appeared. The reaction mixture was allowed to warm to room temperature, after which 2 days were required for the complete decomposition of **2** as evidenced by the absence of any green color. The reaction mixture was filtered, and the filtered solids were placed in 1 l. of water. The insoluble solids were filtered to give 10.3 g (11.9%) of the lead salt **9**.

The methylene chloride solution was washed twice with 150-ml portions of water and three times with 100 ml of 10% sodium bicarbonate. The bicarbonate washings were acidified to precipitate 3.5 g (14.7%) of **10**: mp 174–175°; uv λ_{max} (95% ethanol) 275 (ϵ 4100) and 219 mμ (ϵ 9000); ir (Nujol) 3260 (NH), 1748 (ester C═O), and 1700 cm^{-1} (amide C═O); nmr ($CDCl_3$) δ 2.52 (s, 3, CH_3CO) and 1.83 (m, 4, CH_2C).

Anal. Calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.46; H, 6.98; N, 14.27.

The methylene chloride solution was dried (Na_2SO_4) and the solvent was removed to give a solid–liquid mixture. The mixture was dissolved in 25 ml of benzene, and an excess of petroleum ether was added to precipitate 3.4 g (20.0%) of **3**, mp 206–207.5°.

The benzene was removed under reduced pressure to give 5.5 g of a liquid mixture containing 1.8 g (5.9%) of 3,5-diacetoxy-4,4-diethylpyrazole (**11**) and 3.7 g (11.7%) of diacetoxy diethylmalonate (**13**), as shown by vpc data and elemental nitrogen analysis. The presence of **11** was confirmed by comparison of its properties with that of an authentic sample of **11** whose synthesis is described below. Three distillations gave an analytical sample of the dianhydride **13**: bp 96–96.5° (0.16 mm); $n^{24.5}$D 1.4510; uv λ_{max} (95% ethanol) end absorption; nmr ($CDCl_3$) δ 2.05 (s, 6, CH_3C), 2.00 (m, 4, CH_2C), and 0.97 (m, 6, CH_3C); mol wt (vapor phase osmometry) 240.

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 5418; H, 6.38.

The dianhydride **13** was further characterized as follows. To 2 drops of **13** on a watch glass was added 4 drops of acetic anhydride. The reaction mixture was mixed and heated on the steam bath for 10 min, and on cooling it solidified. The solidified product was washed with water, and to the washings were added a few drops of 1 *M* lead diacetate trihydrate. An immediate precipitate of the lead salt **9** appeared. The water-insoluble solid was found to be identical with acetanilide. A few drops of the dianhydride **13** were placed in 5 ml of 1 *M* lead diacetate trihydrate at room temperature. Partial conversion to the lead salt **9** had taken place after 72 hr.

Reaction of 1 with Acetic Anhydride.—To 9.3 g (0.06 mol) of **1** in 50 ml of methylene chloride at room temperature was added 10 ml of acetic anhydride with stirring. Stirring was continued for 3 days, after which the reaction mixture was filtered to give 7.8 g (65.6%) of **10**, mp 173–174°. The methylene chloride and excess acetic anhydride were removed by distillation. The residue was distilled to give 2.5 g (17.4%) of **11**, bp 88–98° (0.1 mm). Redistillation gave an analytical sample of **11** which solidified on standing: bp 86–88° (0.12 mm); mp 54–54.5°; uv λ_{max} (95% ethanol) 217 mμ (ϵ 9500); nmr ($CDCl_3$) δ 2.58 (s, 6, CH_3CO), 1.88 (m, 4, CH_2C), and 0.86 (t, 6, CH_3C). The solid **11** can be recrystallized from ethanol–water.

Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.34; H, 6.41; N, 11.65.

General Procedure for the Diels–Alder Reactions (LTA Oxidation).—To a mixture of 0.04 mol of **1** and 0.04 mol of the 1,3-diene in 200 ml of methylene chloride at 0° was added 22.0 g (0.042 mol) of an 85% solution of LTA with stirring. Stirring was continued at 0° until the characteristic green color had faded. The reaction mixture was filtered and washed with 100 ml of water and two 100-ml portions of 10% sodium bicarbonate solution. The methylene chloride solution was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude Diels–Alder adduct. Purification was accomplished by recrystallization, sublimation, or distillation.

1,4-Dihydro-2,3-dimethyl-7,7-diethylpyrazolo[1,2-*a*]pyridazine-6,8(7H)-dione (14′).—From a mixture of 0.12 mol each of 2,3-dimethyl-1,3-butadiene, **1**, and LTA was obtained 26.7 g (94.3%) of **13** after removal of the solvent and drying. Recrystallization

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[16] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1964, p 313.

[17] Also obtained with the neutral component was a little bis(2-ethylhexyl)phthalate, which was identified by comparison of its ir and nmr spectra with that of an authentic sample. It was possibly leached out of the plasticized tubing employed in the oxidation of **1** by nitrogen tetroxide.

from water gave an analytical sample of 14′: mp 107–108°; nmr (CCl$_4$) δ 3.86 (s, 4, bridgehead CH$_2$), 1.71 (m, 4, CH$_2$C), 1.78 (s, 6, CH$_3$), and 0.78 (t, 6, CH$_3$C).

Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 65.93; H, 8.33; N, 12.02.

1,4-Dihydro-2-methyl-7,7-diethylpyrazolo[1,2-*a*]pyridazine-6,-8(7H)-dione (14).—From a mixture of 0.09 mol of isoprene and 0.06 mol each of 1 and LTA was obtained 8.4 g of a viscous liquid. Distillation gave a fraction, bp 110–125° (0.2 mm), yield 6.2 g (46.6%), of 14 which solidified on standing. Repeated sublimations gave 14 as white crystals: mp 58.5–60°; nmr (CCl$_4$) δ 5.58 (s, 1, vinylic H), 3.93 (s, 4 bridgehead CH$_2$), 1.71 (m, 4, CH$_2$C), 1.86 (s, 3, allylic CH$_3$C), and 0.79 (t, 6, CH$_3$C).

Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.70; H, 8.14; N, 12.48.

1,4-Dihydro-1,4-diphenyl-7,7-diethylpyrazolo[1,2-*a*]pyridazine-6,8(7H)-dione (15).—From a mixture of 0.02 mol each of 1,4-diphenyl-1,3-butadiene, 1, and LTA was obtained 15 as a crude solid which was washed with petroleum ether and recrystallized from 95% ethanol to give 3.8 g (51.9%) of pure 15: mp 147–148°; nmr (CDCl$_3$) δ 7.41 (m, 10, aromatic H), 5.93 (d, 2, vinylic H), 5.61 (d, 2, bridgehead H), 1.60 (m, 4, CH$_2$C), 0.88 (t, 3, CH$_3$C), and 0.33 (t, 3, CH$_3$C).

Anal. Calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.85; H, 6.80; N, 7.65.

1,4-Dihydro-1,4-methanol-7,7-diethylpyrazolo[1,2-]pyridazine-6,8(7H)-dione (16).—From a mixture of 0.08 mol each of 1,3-cyclopentadiene, 1, and LTA was obtained a viscous liquid. Distillation gave a fraction, bp 120–140° (0.2 mm), yield 6.9 g (40.0%), of 16 which solidified on standing. Sublimation gave a pure sample of 16: mp 76–77°; nmr (CCl$_4$) δ 6.50 (m, 2, vinylic H), 5.20 (m, 2, bridgehead H), 2.07 (m, 2, bridging CH$_2$), 1.70 (m, 4, CH$_2$), 0.98 (m, 3, CH$_3$C), and 0.66 (t, 3, CH$_3$C).

Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.33; H, 7.13; N, 12.61.

1,4-Dihydro-1,4-ethanol-7,7-diethylpyrazolo[1,2-*a*]pyridazine-6,8(7H)-dione (17).—From a mixture of 0.08 mol each of 1,3-cyclohexadiene, 1, and LTA was obtained 21.4 g (76.1%) of 17 after washing with petroleum ether and drying. Sublimation at 0.1 mm pressure gave an analytical sample of 17: mp 105–106°; nmr (CCl$_4$) δ 6.55 (m, 2, vinylic H), 5.03 (m, 2, bridgehead H), 1.60 (m, 8, CH$_2$C), 0.89 (t, 3, CH$_3$C), and 0.61 (t, 3, CH$_3$C).

Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.83; H, 7.87; N, 11.77.

1,4-Dihydro-1,4-(1-isopropylethano)-3-methyl-7,7-diethylpyrazolo[1,2-*a*]pyridazine-6,8(7H)-dione (18).—From a mixture of 0.12 mol each of α-phellandrene, 1, and LTA was obtained 22.5 g of a liquid. Distillation gave a fraction, bp 141–143° (0.2 mm), yield 14.4 g (41.4%), of 18. Redistillation gave an analytical sample of 18: $n^{23}{}_{\mathrm{D}}$ 1.5071; nmr (CCl$_4$) δ 6.01 (m, 1, vinylic H), 4.85 (m, 2, bridgehead H), 1.93 (s, 3, allylic CH$_3$) 1.90 [s, 1, (CH$_3$)$_2$CH)], 1.6 (m, 4, CH$_2$C), 1.2–0.8 [m, 9, (CH$_3$)CH and CH$_3$CH$_2$], and 0.60 (t, 3, CH$_3$-CH$_2$).

Anal. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.21; H, 9.17; N, 9.54.

1,6-Etheno-1,2,3,4,5,6-hexahydro-9,9-diethylpyrazolo[1,2-*a*]-[1,2]diazocine-8,10(9H)-dione (19).—From a mixture of 0.06 mol each of 1,3-cyclooctadiene, 1, and LTA was obtained 4.8 g of a liquid. After the liquid was allowed to stand for 3 months, a quantity of crystals appeared. These crystals were filtered and dried to yield 3.3 g (21.0%) of 19. Sublimation gave an analytical sample of 19: mp 134–136°; nmr (CDCl$_3$) δ 6.13 (m, 2, vinylic H), 0.97 (t, 3, CH$_3$C), and 0.80 (t, 3, CH$_3$C).

Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.56; H, 8.16; N, 10.82.

5,10-*o*-Benzo-5,10-dihydro-7,7-diethylpyrazolo[1,2-*a*]pyridazine-6,8(7H)-dione (20).—From a mixture of 0.02 mol each of anthracene, 1, and LTA was obtained a solid residue. The residue was washed with methanol and filtered to give 2.3 g of anthracene (63.9% recovery). The filtrate was evaporated under reduced pressure and the residue was sublimed to give 0.9 g of 20 (13.6%) which contained a trace of anthracene. Preparative thin layer chromatography (Mallinckrodt Chromosorb Ar Sheet 1000) gave an analytical sample of 20: mp 222–224° dec; nmr (CDCl$_3$) δ 7.28 (m, 8, aromatic H), 6.41 (s, 2, bridgehead H), 1.61 (m, 4, CH$_2$C), and 0.38 (t, 6, CH$_3$C).

Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.90; H, 6.06; N, 8.43. Found: C, 75.83; H, 6.21; N, 8.32.

1,4-Dihydro-2,3-dimethyl-7,7-diethylpyrazolo[1,2-*a*]pyridazine-6,8(7H)-dione (13) (Nitrogen Tetroxide Oxidation).—To a mixture of 0.02 mol of 1 and 20 g of anhydrous sodium sulfate in 150 ml of methylene chloride at 0° was added gaseous nitrogen dioxide with stirring until all of the hydrazide 1 had dissolved. The reaction mixture was neutralized by the addition of 35 g of sodium bicarbonate and filtered into a stirred solution of 0.03 mol of 2,3-dimethyl-1,3-butadiene in 50 ml of methylene chloride at 0°. The resulting solution was stirred at 0° until the characteristic color of 2 had faded. The solution was filtered, and the solvent was evaporated under reduced pressure to give 2.6 g (55.3%) of 13.

1,4-Dihydro-1,4-methano-7,7-diethylpyrazolo[1,2-*a*]pyridazine-6,8(7H)-dione (16) (Nitrogen Tetroxide Oxidation).—To a mixture of 0.04 mol of 1 and 30 g of anhydrous sodium sulfate in 200 ml of methylene chloride at 0° was added gaseous nitrogen dioxide with stirring until all of the hydrazide 1 has dissolved. The reaction mixture was neutralized with 50 g of sodium bicarbonate and filtered into a stirred solution of 0.06 mol of freshly distilled cyclopentadiene in 50 ml of methylene chloride at 0°. The resulting solution was stirred at 0° until the characteristic color of 2 had faded. The solution was filtered and the solvent was evaporated under reduced pressure to give a dark liquid. The liquid was distilled to give a fraction, bp 135–148° (0.75 mm), yield 1.4 g (15.9%), of 16.

Attempted Preparation of 1,10,4-ethylidene-7,7-diethyl-1,2,3,4-tetrahydropyrazolo[1,2-*a*]cyclopropa[*d*]pyridazine-6,8(7H)-dione. LTA Oxidation.—From a mixture of 0.1 mol each of norbornadiene, 1, and LTA was obtained a 11.5-g mixture of the oxidized diene,[15] bp 94–114° (0.6 mm), and 1.9 g of 3.

Nitrogen Tetroxide Oxidation.—To 0.04 mol of 1 and 40 g of anhydrous sodium sulfate in 20 ml of methylene chloride at 0° was added gaseous nitrogen dioxide with stirring until all of the hydrazide 1 had dissolved. The reaction mixture was neutralized with 50 g of sodium bicarbonate and filtered into a solution of 0.06 mol of norbornadiene in 50 ml of methylene chloride at 0°. The resulting solution was stirred at 0° until the characteristic color of 2 had faded (2 weeks). The solution was filtered and the solvent was evaporated under reduced pressure to give 2.0 g of 3 plus polymeric material.

***cis-endo*-2,3-Dimethyl-1,2,3,4-tetrahydro-7,7-diethylpyrazolo-[1,2-*a*]pyridazine-6,8(7H)-dione (21).**—To a slurry of 0.1 g of 5% palladium on carbon in 25 ml of 95% ethanol was added a solution of 2.44 g (0.01 mol) of 13 in 25 ml of 95% ethanol. The slurry was stirred under hydrogen at 25° and 1 atm until the theoretical amount of hydrogen had been absorbed (14 hr). The catalyst was removed by filtration and the solvent was evaporated under reduced pressure to give 2.3 g (96.6%) of 21 as a viscous oil. Evaporative distillation gave pure 21: nmr (CDCl$_3$) δ 3.48 (d, 4, NCH$_2$), 2.18 (m, 4, CH$_2$), 1.02 (d, 6, CH$_3$C), and 0.80 (t, 6, CH$_3$CH$_2$).

Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.30; N, 11.75. Found: C, 65.48; H, 9.04; N, 11.89.

1,4-Methano-1,2,3,4-tetrahydro-7,7-diethylpyrazolo[1,2-*a*]-pyridazine-6,8(7H)-dione (22).—To a slurry of 0.1 g of 5% palladium on carbon in 25 ml of 95% ethanol was added a solution of 1.74 g (0.0079 mol) of 16 in 25 ml of 95% ethanol. The slurry was stirred under hydrogen at 25° and 1 atm until the theoretical amount of hydrogen had been absorbed (30 min). The catalyst was removed by filtration and the solvent was evaporated under reduced pressure to give 1.60 g (91.4%) of 27 as a viscous oil. Evaporative distillation gave pure 22: nmr (CDCl$_3$) δ 4.83 (s, 2, bridgehead H), 1.5–2.0 (m, 10), and 0.93 (t, 6, CH$_3$CH$_2$).

Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.86; H, 8.16; N, 12.60. Found: C, 64.67; H, 8.13; N, 12.65.

1,4-Ethanol-1,2,3,4-tetrahyro-7,7-diethylpyrazolo[1,2-*a*]pyridazine-6,8(7H)-dione (23).—To a slurry of 0.1 g of 5% palladium on carbon in 25 ml of 95% ethanol was added a solution of 1.0 g (0.0043 mol) of 17 in 25 ml of 95% ethanol. The slurry was stirred under hydrogen at 25° and 1 atm until the theoretical amount of hydrogen had been absorbed (30 min). The catalyst was evaporated under reduced pressure to give 0.95 g (94.1%) of 23 as a white solid. Sublimation gave pure 23: mp 98–98.5°; nmr (CDCl$_3$) δ 4.50 (s, 2, bridgehead H), 1.97 (s, 8, ethanol H), 1.77 (m, 4, CH$_3$CH$_2$), and 0.86 (t, CH$_3$CH).

Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 66.28; H, 8.30; N, 12.05.

Registry No.—**1**, 4744-72-3; **2**, 21367-52-2; **3**, 6495-34-7; **4**, 21367-54-4; **5**, 510-20-3; **7**, 21367-56-6; **10**, 21367-57-7; **11**, 21367-58-8; **13**, 21367-59-9; **14**, 21367-60-2; **15**, 21367-61-3; **16**, 21367-62-4; **17**, 21367-63-5; **18**, 21367-64-6; **19**, 21367-65-7; **20**, 21367-66-8; **21**, 21449-60-5; **22**, 21367-67-9; **23**, 21367-68-0; 1-(diethylacetyl)-4-4-diethylpyrazolidine-3,5-dione, 21367-56-6.

Acknowledgment.—The authors wish to acknowledge the assistance of the National Science Foundation in providing for departmental use a Cary 14 spectrophotometer, upon which all ultraviolet spectra were taken.

Notes

The Condensation of Succinic Anhydride with Benzylidinemethylamine. A Stereoselective Synthesis of *trans*- and *cis*-1-Methyl-4-carboxy-5-phenyl-2-pyrrolidinone

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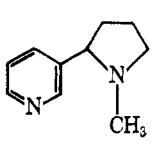
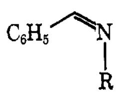
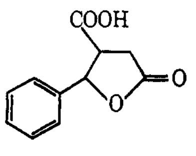
Our interest in examining structural parameters associated with the peripheral and central activities of the tobacco alkaloid nicotine (**1**) has led to a consideration of potentially versatile synthetic routes to substituted 2-arylpyrrolidines. As part of this program, we wish to report our studies on the condensation of benzylidinemethylamine (**2**) with succinic anhydride. By analogy with the Perkin condensation[1] of benzaldehyde and succinic anhydride to form the phenylparaconic acid (**3**), this reaction would be expected to yield the carboxypyrrolidinone system (**4**) and thus provide a facile entry to uniquely substituted nicotine analogs.



1



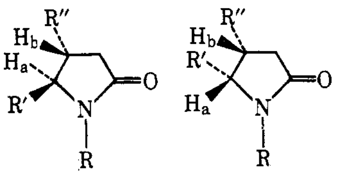
2, R = CH_3
12, R = C_6H_5



3

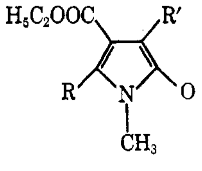
The spectral data of the crude isolate obtained from this reaction corresponded to the lactam system, **4**. Fractional crystallization separated the reaction product into two $C_{12}H_{13}NO_3$ acids, A (major) and B (minor). The nmr spectra of the two isomers can be readily interpreted in terms of the *trans*- and *cis*-carboxypyrrolidinones, **4a** and **4b**, respectively. A doublet centered near 5.0 ppm in both spectra is attributed to proton $\mathbf{H_a}$ based on its coupling with $\mathbf{H_b}$ and by analogy with the corresponding assignments reported for related 5-substituted-2-pyrrolidinones.[2] From the estimated dihedral angles, H_{a-b} (120°, *trans* isomer, and 0°, *cis* isomer), and the Karplus relationship,[3] the coupling constants, J_{a-b} (5 Hz, isomer A, and 9 Hz, isomer B) support the assignments of compound A as the *trans* isomer, **4a**, and compound B as the *cis* isomer, **4b**. Similar stereochemical conclusions were recently reported for the related 4-aryl-5-ethoxycarbonyl-2-pyrrolidinone system, **5**.[2b,c] Protons $H_{b,c,d}$ of **4a** form a complex multiplet centered near 3.4 ppm while the corresponding signals for **4b** are separated into three quartets; the lowest field quartet (3.85 ppm) can be assigned to $\mathbf{H_b}$ since irradiation of the low field doublet (due to $\mathbf{H_a}$) caused the quartet to collapse to a triplet (J = 9 Hz).

Confirmation of the above structure assignments was obtained by an independent synthesis of the *cis* acid. The condensation[4] of diethyl oxalacetate with benzaldehyde and methylamine gave the pyrrolinone, **6**. Attempted borohydride and catalytic reductions of 6

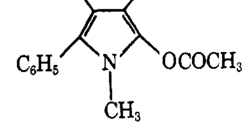


a **b**

4, R = CH_3; R′ = C_6H_5; R″ = COOH
5, R = H; R′ = $COOC_2H_5$; R″ = Aryl
8, R = CH_3; R′ = H; R″ = $COOC_2H_5$
11, R = CH_3; R′ = C_6H_5; R″ = $COOC_2H_5$
14, R = R′ = C_6H_5; R″ = COOH



6, R = C_6H_5; R′ = OH
7, R = H; R′ = $OCOCH_3$
9, R = C_6H_5; R′ = $OCOCH_3$



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