

## The Syntheses of Pyridazino[1,2-*a*]pyridazine Derivatives of Furan, Pyridazine and Pyrrole by Diels-Alder Reactions

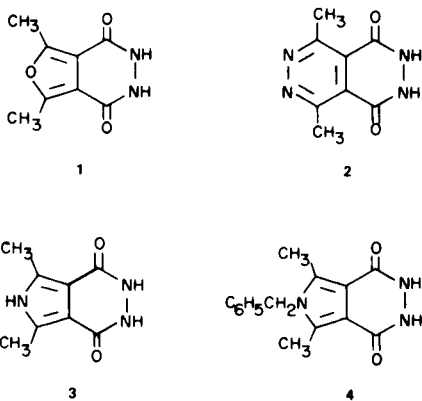
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Diels-Alder adducts were formed in the lead tetraacetate oxidations of substituted cyclic hydrazides of furan, pyridazine and pyrrole dicarboxylic acids in the presence of 1,3-cyclohexadiene or 1,3-cyclopentadiene. The products resulting were furo[3,4-*g*]pyridazino[1,2-*a*]pyridazine-6,10-diones, pyridazino[4,5-*g*]pyridazino[1,2-*a*]pyridazine-6,11-diones, and pyrrolo[3,4-*g*]pyridazino[1,2-*a*]pyridazine-6,10-diones, respectively. Some hydrogenations and ring opening reactions were studied.

Electron poor *cis*-azo compounds are known to be extremely reactive dienophiles in the Diels-Alder reaction and lead to the formation of pyridazine ring systems (1) when allowed to react with dienes. When oxidations of maleic and phthalic cyclic hydrazides to azo compounds were carried out in the presence of dienes, otherwise difficultly accessible pyridazino[1,2-*a*]pyridazines were formed in moderate yields (2), (3). The present investigation was undertaken to examine the extension of these reactions to systems as 1, 2, 3, and 4 which were expected to lead to the pyridazino[1,2-*a*]pyridazines fused to heterocycles and thence to study some further reactions of these adducts.



The lead tetraacetate oxidations of hydrazides 1, 2, and 4 in the presence of 1,3-cyclohexadiene and 1,3-cyclopentadiene indeed produced the title compounds 5-10 in moderate yields. Transitory azo intermediates, colored yellow, orange and red, respectively, were formed *in situ*, and trapped as Diels-Alder adducts by the reactive dienes. The pyrrole hydrazide 3, while forming a red solution in the presence of lead tetraacetate, did not form adducts

with dienes. Considerable 3 was recovered along with diene oxidation products. In the absence of dienes approximately half of the original amount of 3 was recovered along with brown insoluble tars in an equimolar reaction with the oxidant.

The replacement of the pyrrole hydrogen by the benzyl group as in 4 permitted the desired oxidation, so that Diels-Alder reactions occurred in good yields. This suggests that the oxidation of 3 occurred at the site of the pyrrole nitrogen-hydrogen bond rather than at some other site on the molecule. Otherwise, 4 analogously would have undergone the same oxidation as 3 rather than without azo formation, as observed.

Catalytic hydrogenation of the adducts occurred readily at room temperature and under one atmosphere of hydrogen. Although tertiary benzyl amines undergo hydrogenolysis under relatively mild conditions (4), the *N*-benzyl pyrrole adducts were reduced without debenylation. In spite of a hydrogen pressure of three atmospheres and the addition of acetic acid to the solvent, ethanol, 13 was recovered unchanged after several days over palladium-on-charcoal or platinum oxide catalyst. More drastic hydrogenations were not investigated.

In addition to hydrogenation of the adducts, some conversions to other ring systems were studied. When 11 was heated at reflux in excess hydrazine hydrate, 3,3'-dimethyl-4,4'-bis(2-pyrazolin-5-one) 15, was formed. One possible pathway for this reaction involves the displacement of 2,3-diazabicyclo[2.2.1]heptane by hydrazine with or without the formation of 1 followed by furan ring opening and recyclization with more hydrazine to 15. It has been reported that 15 was formed in high yield when 1 was heated at reflux with hydrazine hydrate (5).

In these new products, the furan ring was found to be strongly resistant to acid catalyzed ring opening. When 1

SCHEME I

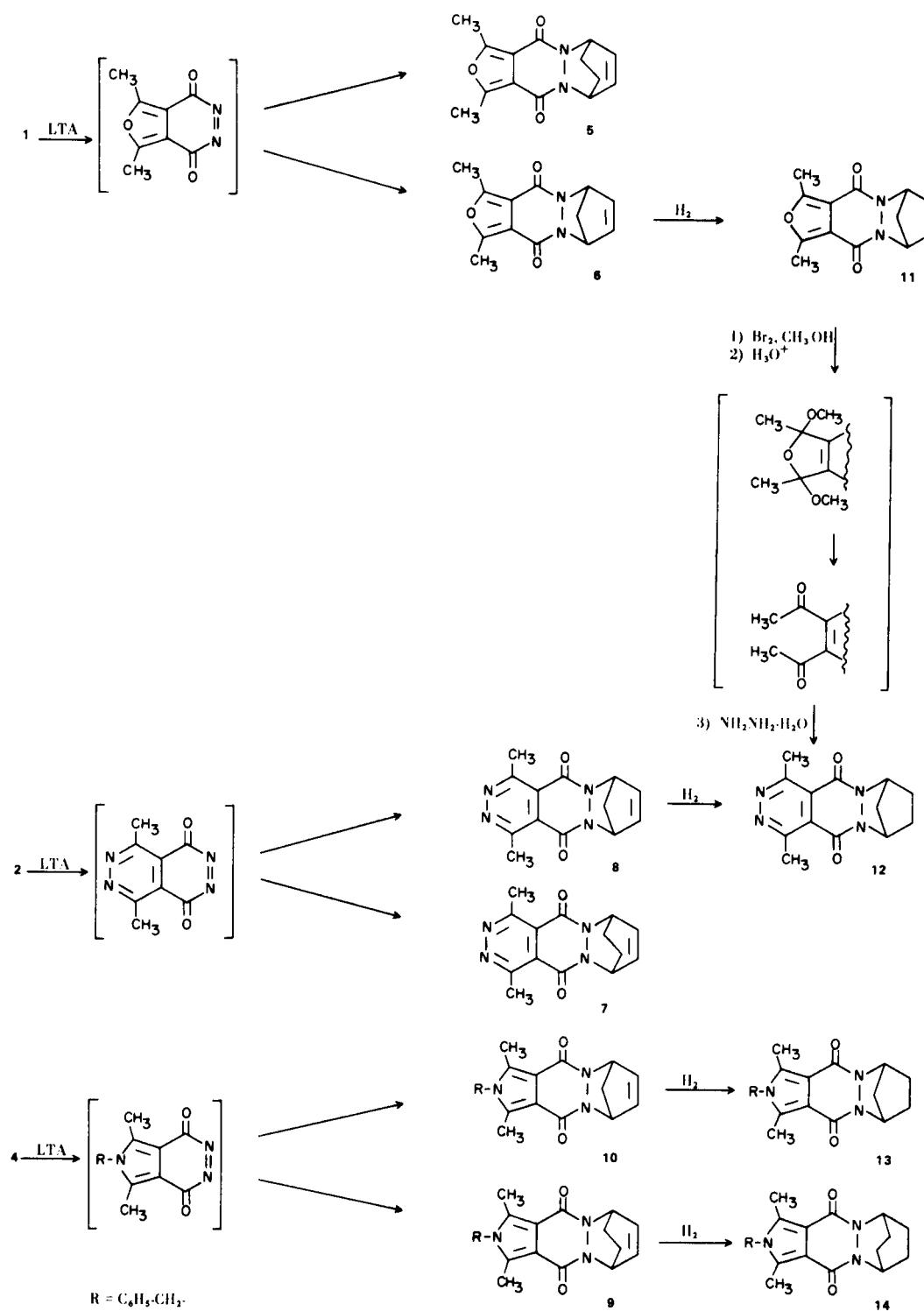


TABLE I  
NMR Spectra of Pyridazino[1,2-*a*]pyridazines (a)

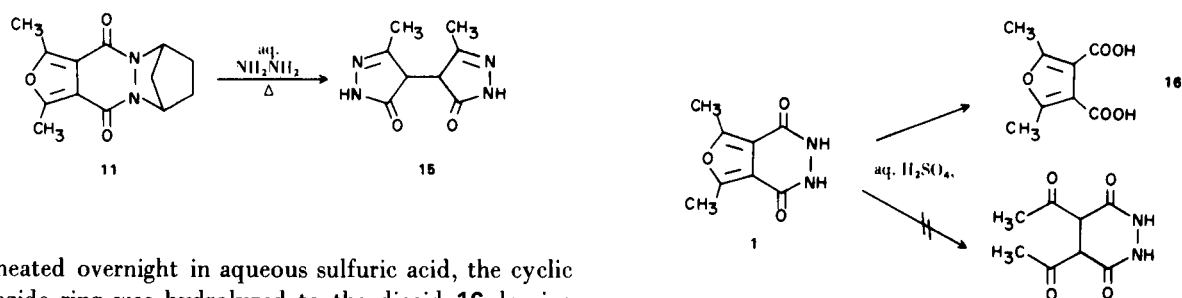
Compound	C-CH <sub>2</sub> -C	CH <sub>3</sub> -	Bridgehead	Vinyl	Benzyl	Phenyl
5	1.9 bm	2.54 s	5.80 bs	6.65 t	---	---
6	2.0 bm	2.61 s	5.75 m	6.64 t	---	---
7	2.0 bm	3.20 s	6.08 bs	6.79 t	---	---
8	2.25 m	3.15 s	5.99 m	6.85 t	---	---
9	1.80 bm	2.59 s	5.90 bs	6.65 t	5.16 s	7.1 m
10	2.00 m	2.53 s	5.75 m	6.60 t	5.16 s	7.1 m
11	1.98 bs	2.62 s	5.21 bs	---	---	---
12	2.10 bs	3.17 s	5.42 bs	---	---	---
13	1.96 bs	2.69 s	5.29 bs	---	5.20 s	7.1 m
14	1.98 bs	2.65 s	5.29 bs	---	5.20 s	7.1 m

(a) In deuteriochloroform, in ppm from TMS. The integrations of peak areas were consistent with the assigned structures; b is broad, s is singlet, m is multiplet, t is triplet.

TABLE II  
Ultraviolet Spectra of Pyridazino[1,2-*a*]pyridazines (a)

	5	6	7	8	9	10	11	12	13	14
$\lambda$ max	278	279	282	283	288	288	266 300 sh	283	276	278
$\epsilon/10^4$	1.04	1.16	0.44	0.50	1.46	1.45	0.96 0.60 sh	0.42	1.31	1.30

(a) In 95% ethanol, sh is shoulder.



was heated overnight in aqueous sulfuric acid, the cyclic hydrazide ring was hydrolyzed to the diacid **16**, leaving the furan ring intact. However, the furan ring was reactive toward bromination and **11** was converted to **12** (see Scheme I). This conversion indicates the possibility of forming additional ring systems fused to the pyridazino[1,2-*a*]pyridazines from intermediates formed along this pathway.

#### EXPERIMENTAL (11)

1,2,3,4-Tetrahydro-5,7-dimethylfuro[3,4-*d*]pyridazine-1,4-dione (**1**).

This compound was synthesized essentially by the method of Jones (5). From dimethyl 2,5-dimethyl-3,4-furandicarboxylate

(6) and 85% hydrazine hydrate in methanol was obtained a solid. After purification of the solid by reprecipitation from dilute sodium hydroxide by the addition of hydrochloric acid, a 63% yield of **1**, m.p. 345° dec. (lit. (5) m.p. 345° dec.) was obtained.

1,2,3,4-Tetrahydro-5,8-dimethylpyridazino[4,5-*d*]pyridazine-1,4-dione (**2**).

From diethyl 3,6-dimethylpyridazine-4,5-dicarboxylate (**7**) and 85% hydrazine hydrate using the method described above, was obtained a 51% yield of **2**, which does not melt below 350°, (lit. (5) m.p. 320° dec.).

1,2,3,4-Tetrahydro-5,7-dimethylpyrrolo[3,4-*d*]pyridazine-1,4-dione (**3**).

The method of Seka (**8**) was used. The diethyl 2,5-dimethylpyrrolo-3,4-dicarboxylate (**9**) was treated with hydrazine hydrate (85%). After purification of the resultant solid by reprecipitation from dilute sodium hydroxide by the addition of hydrochloric acid, **3**, m.p. 350°, (lit. (8) m.p. 359° dec.) was obtained in 55% yield.

6-Benzyl-1,2,3,4-tetrahydro-5,7-dimethylpyrrolo[3,4-*d*]pyridazine-1,4-dione (**4**).

To 46 g. (0.14 mole) of diethyl 1-benzyl-2,5-dimethylpyrrolo-3,4-dicarboxylate (**9**), m.p. 65-66°, was added 100 g. of 85% hydrazine hydrate. The mixture was heated at reflux until the ester layer dissolved and a gelatinous white solid appeared (2-3 days). Cooling of the solution and filtration of the solid furnished 25 g. (71%) of **4**. Reprecipitation of this product from dilute sodium hydroxide by the addition of hydrochloric acid yielded 21.7 g. (61%) of **4**. An analytical sample, prepared by recrystallization from a large volume of acetic acid, does not melt below 350°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>: C, 66.89; H, 5.61; N, 15.60. Found: C, 66.66; H, 5.44; N, 15.75.

General Procedure for the Diels-Alder Reactions of **1** and **4**.

1,4-Ethano-1,4,6,10-tetrahydro-7,9-dimethylfuro[3,4-*g*]pyridazino[1,2-*a*]pyridazine-6,10-dione (**5**).

To a stirred mixture of 5.0 g. (0.028 mole) of **1** and 2.2 g. (0.028 mole) of 1,3-cyclohexadiene in 75 ml. of methylene chloride was added dropwise a solution of 14.7 g. (0.028 mole) of 85% lead tetraacetate dissolved in 75 ml. of methylene chloride over a period of 30 minutes. Although a negative lead tetraacetate test was observed soon after complete addition, stirring was continued overnight. The solution was filtered, washed with water and saturated sodium bicarbonate solution, dried and concentrated under reduced pressure to yield 6.8 g. (95%) of crude yellow **5**, m.p. 230-235°. Recrystallization of this product from ethanol yielded 2.3 g. (33%) of **5**, m.p. 271-272°.

*Anal.* Calcd. for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: C, 65.10; H, 5.46; N, 10.85. Found: C, 64.89; H, 5.57; N, 10.84.

1,4-Methano-1,4,6,10-tetrahydro-7,9-dimethylfuro[3,4-*g*]pyridazino[1,2-*a*]pyridazine-6,10-dione (**6**).

By the above general procedure, from 5.0 g. (0.028 mole) of **1**, 1.8 g. (0.028 mole) of 1,3-cyclopentadiene and 14.5 g. (0.028 mole) of 85% lead tetraacetate, all cooled to 0-5°, was obtained 6.0 g. (90%) of yellow **6**, m.p. 183-188°. Recrystallization from ethanol of this material furnished 4.5 g. (67%) of **6**, m.p. 203.5-204°.

*Anal.* Calcd. for C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.80; H, 5.15; N, 11.55.

8-Benzyl-1,4-ethano-1,4,6,10-tetrahydro-7,9-dimethylpyrrolo[3,4-*g*]pyridazino[1,2-*a*]pyridazine-6,10-dione (**9**).

By the above procedure, from 5.0 g. (0.020 mole) of **4**, 1.6 g. (0.020 mole) of 1,3-cyclohexadiene and 9.1 g. (0.020 mole) of 94% lead tetraacetate was obtained 6.1 g. (93%) of **9**, m.p. 253-255°. Recrystallization of **9** from ethanol yielded 4.7 g. (71%) of **9**, m.p. 259-260°.

*Anal.* Calcd. for C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>: C, 72.60; H, 6.09; N, 12.01. Found: C, 72.39; H, 6.20; N, 11.98.

8-Benzyl-1,4,6,10-tetrahydro-1,4-methano-7,9-dimethylpyrrolo[3,4-*g*]pyridazino[1,2-*a*]pyridazine-6,10-dione (**10**).

By the above procedure, from 6.0 g. (0.024 mole) of **4**, 1.6 g. (0.024 mole) of 1,3-cyclopentadiene and 11.3 g. (0.024 mole) of 94% lead tetraacetate, all cooled to 0-5°, was obtained 6.6 g. (87%) of **10**, m.p. 206-211°. Recrystallization of **10** from ethanol resulted in 5.2 g. (68%) of **10**, m.p. 228-230°.

*Anal.* Calcd. for C<sub>20</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>: C, 72.05; H, 5.74; N, 12.60. Found: C, 72.15; H, 5.92; N, 12.41.

1,4-Ethano-1,4,6,11-tetrahydro-7,10-dimethylpyridazino[4,5-*g*]pyridazino[1,2-*a*]pyridazine-6,11-dione (**7**).

To a mixture of 5.0 g. (0.026 mole) of **2** and 2.1 g. (0.026 mole) of 1,3-cyclohexadiene in 100 ml. of glacial acetic acid was added in small portions, 12.3 g. (0.026 mole) of 94% lead tetraacetate. After stirring the reaction overnight, the solution was added to 500 ml. of water, and the aqueous layer extracted three or more times with 100 ml. portions of methylene chloride. The combined methylene chloride layers were washed with 200 ml. of water and once with saturated sodium bicarbonate solution, dried, and concentrated under reduced pressure to give 4.5 g. (64%) of crude yellow **7**, which does not melt below 350°. Recrystallization of **7** from ethanol afforded an analytical sample.

*Anal.* Calcd. for C<sub>14</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>: C, 62.20; H, 5.22; N, 20.73. Found: C, 62.11; H, 5.33; N, 20.75.

1,4-Methano-1,4,6,11-tetrahydro-7,10-dimethylpyridazino[4,5-*g*]pyridazino[1,2-*a*]pyridazine-6,11-dione (**8**).

By use of the method for the preparation of **7**, 5.0 g. (0.026 mole) of **2**, 1.7 g. (0.026 mole) of 1,3-cyclopentadiene, and 12.3 g. (0.026 mole) of 94% lead tetraacetate in 75 ml. of acetic acid and 25 ml. of methylene chloride, all cooled to 0-5°, gave 3.6 g. (55%) of crude yellow **8**. Recrystallization of **8** from ethanol gave 1.6 g. (31%) of **8**, m.p. 217-218°.

*Anal.* Calcd. for C<sub>13</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub>: C, 60.92; H, 4.69; N, 21.86. Found: C, 60.82; H, 4.80; N, 21.99.

General Procedure for Reduction of Diels-Alder Adducts **6**, **8**, **9**, **10**.

1,2,3,4,6,10-Hexahydro-1,4-methano-7,9-dimethylfuro[3,4-*g*]pyridazino[1,2-*a*]pyridazine-6,10-dione (**11**).

A stirred mixture of 4.8 g. of **6**, 0.1 g. of 10% palladium-on-charcoal, and 200 ml. of ethanol absorbed one equivalent of hydrogen in 4-6 hours. When the uptake of hydrogen was complete, the reaction mixture was filtered and the catalyst was washed with methylene chloride. The combined filtrates were concentrated under reduced pressure to yield 4.7 g. (98%) of **11**. Recrystallization of **11** from ethanol yielded 3.0 g. (62%) of **11**, m.p. 221.5-223°.

*Anal.* Calcd. for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: C, 63.40; H, 5.73; N, 11.37. Found: C, 63.50; H, 5.68; N, 11.46.

1,2,3,4,6,11-Hexahydro-1,4-methano-7,10-dimethylpyridazino[4,5-*g*]pyridazino[1,2-*a*]pyridazine-6,11-dione (**12**).

By the above procedure, 0.70 g. of **8** furnished 0.70 g. (99%) of **12**. Recrystallization of **12** from acetone containing a small amount of methanol, followed by sublimation of the product at 1 mm gave an analytical sample of **12**, m.p. 273-274° dec.

*Anal.* Calcd. for C<sub>13</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>: C, 60.44; H, 5.46; N, 21.69. Found: C, 60.63; H, 5.65; N, 21.54.

8-Benzyl-1,2,2,4,6,10-hexahydro-1,4-methano-7,9-dimethylpyrrolo-[3,4-*g*]pyridazino[1,2-*a*]pyridazine-6,10-dione (**13**).

By the above procedure, 4.3 g. of **10** gave 4.3 g. (99%) of **13**, a viscous oil which crystallized upon standing, m.p. 178.5-179.5°. Recrystallization of **13** from 2:1 ethanol-water solvent raised the melting point to 181.5-182.5°.

*Anal.* Calcd. for C<sub>20</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>: C, 71.61; H, 6.31; N, 12.53. Found: C, 71.44; H, 6.39; N, 12.36.

When 2.5 g. of **13** and 0.1 g. of 10% palladium-on-charcoal or platinum oxide in ethanol-acetic acid was placed under 40-45 psi of hydrogen for several days, all of **13** was recovered unchanged.

8-Benzyl-1,4-ethano-1,2,3,4,6,10-hexahydro-7,9-dimethylpyrrolo-[3,4-*g*]pyridazino[1,2-*a*]pyridazine-6,10-dione (**14**).

By the general procedure above 3.8 g. of **9** gave 3.7 g. (97%) of **14**, m.p. 237-238.5°. Recrystallization of this product from 2:1 ethanol-water solution did not raise the melting point.

*Anal.* Calcd. for C<sub>21</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>: C, 72.18; H, 6.63; N, 12.03. Found: C, 71.99; H, 6.65; N, 11.89.

#### Conversion of **11** to **12**.

A mixture of 1.0 g. (0.0041 mole) of **11**, 1.0 g. of sodium bicarbonate, and 15 ml. of methanol was stirred while 0.65 g. (0.0041 mole) of bromine was added dropwise. After a negative starch-iodide test for bromine, 3 *N* hydrochloric acid was added slowly to acidify the mixture. After stirring was continued for 15 minutes, sodium hydroxide was added to neutrality and 0.25 g. (0.0041 mole) of 85% hydrazine hydrate was added dropwise. After about 30 minutes, the cloudy solution was added to 25 ml. of water and extracted three times with 25 ml. portions of methylene chloride. The combined extracts of methylene chloride were dried and concentrated under reduced pressure yielding 0.98 g. (94%) of crude **12**. Recrystallization of this crude product from acetone containing a small amount of methanol followed by two sublimations at 1 mm yielded a small amount of **12**, m.p. 260-263°, which exhibited an infrared spectrum identical to the

product that resulted from the reduction of **8**. An equi-mixture of this product with that from reduction of **8**, melted 262-264° dec. 3,3'-Dimethyl-4,4'-bis(2-pyrazoline-5-one) (**15**).

A mixture of 1.0 g. of **11** and 10 ml. of 85% hydrazine hydrate was heated at reflux for 2.5 hours. The cooled solution was added to water and neutralized with hydrochloric acid. Upon standing 0.37 g. (47%) of **15** precipitated. This material which does not melt below 350°, exhibited an infrared spectrum identical to that solid resulting from the reaction of hydrazine hydrate with diethyl diacetyl succinate (**5**), which also does not melt below 350°. 2,5-Dimethylfuran-3,4-dicarboxylic Acid (**16**).

A mixture of 1.0 g. of **1** and 25 ml. of 6 *M* sulfuric acid was heated overnight on a steam bath. The cooled mixture was filtered and the precipitate was recrystallized from 1:4 ethanol-water solvent to yield 0.63 g. (61%) of **16**, m.p. 226-228.5°. The infrared spectrum of the product was identical to **16** prepared by saponification of the diester (**10**), m.p. 232-233°, (lit. (**10**) m.p. 232°). An equi-mixture of the two samples melted 231.5-233°.

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- (11) All melting points are corrected. Infrared spectra were obtained on a Beckman IR-8 or IR-20 double-beam spectrophotometer. The ultraviolet spectra were obtained with a Cary-14 spectrophotometer. The NMR spectra were observed with a Varian A-60 spectrometer. Analyses were performed by Dr. Alfred Bernhardt, Mulheim, West Germany.