Bis-Pyrazolones as Azodienophiles

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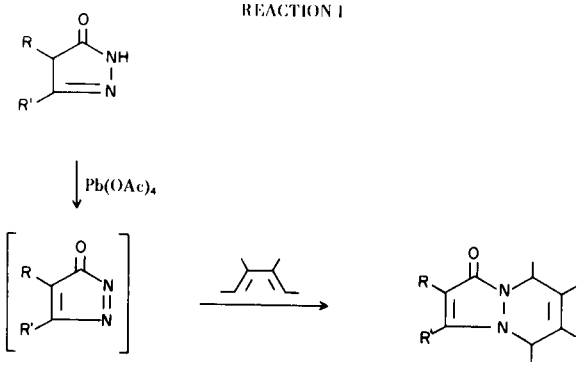
Lead tetraacetate oxidations of 2,3,3a,4,6,7,7a,8-octahydrobenzo[1,2-*c*:4,5-*c*']dipyrazolo-3,7-dione and 2,3,3a,4,5,5a,6,7-octahydrobenzo[2,1-*c*:3,4-*c*']dipyrazolo-3,6-dione in the presence of 1,3-cyclopentadiene, 1,3-cyclohexadiene, 2,3-dimethyl-1,3-butadiene or 1,4-diphenyl-1,3-butadiene have yielded octahydrodipyridazino[1,2-*a*:1,2-*a*']benzo[1,2-*c*:4,5-*c*']dipyrazolo-6,14-diones and octahydrodipyridazino[1,2-*a*:1,2-*a*']benzo[2,1-*c*:3,4-*c*']dipyrazolo-6,9-diones. In one of the eight Diels-Alder reactions two isomeric products were isolated.

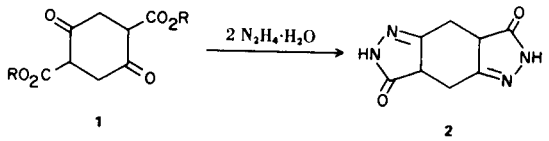
Oxidations of 2-pyrazolin-5-ones to pyrazol-3-ones in the presence of dienes have been shown to yield Diels-Alder adducts (1).

REACTION I

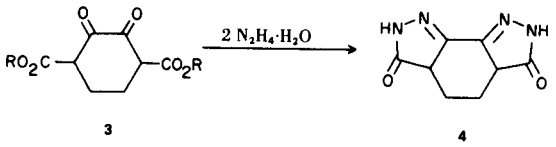


Similar adducts have been prepared by 1,4-dehydrohalogenation of 4-halo-2-pyrazolin-5-ones in the presence of dienes which presumably occurs through the same intermediate (2), (3). The present investigation was undertaken to test the extension of reaction I to certain fused-ring bis-pyrazolones which, if oxidized to bis-azodienophiles, might lead to novel ring systems, and thereby demonstrate the feasibility of forming Diels-Alder polymers with suitable polyenes.

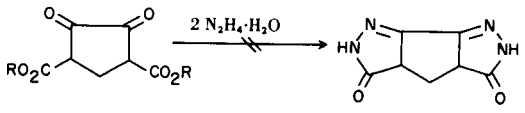
The availability of cyclic bis-ketoesters and the often facile pyrazolone formation by reaction with hydrazine hydrate offered an entry into the starting bis-pyrazolones.



1 2



3 4



5 6

R = Me or Et

Keto esters **1** and **3** underwent pyrazolone formation in essentially quantitative yields to give 2,3,3a,4,6,7,7a,8-octahydrobenzo[1,2-*c*:4,5-*c*']dipyrazolo-3,7-dione (**2**) and 2,3,3a,4,5,5a,6,7-octahydrobenzo[2,1-*c*:4,3-*c*']dipyrazolo-3,6-dione (**4**), respectively. However, 1-4-dicarbethoxy-2,3-cyclopentanedione (**5**) failed to yield the homologous 2,3,3a,4a,5,6-hexahydroclopenta[2,1-*c*:3,4-*c*']dipyrazolo-3,5-dione (**6**). The infrared spectrum and elemental analysis of the precipitate which immediately formed upon the addition of hydrazine hydrate to **5** was indicative of a mono-hydrazone hydrate. This material decomposed upon heating or long standing to brown, ash-like solids. In the somewhat similar reactions of either 2-carbethoxy-1-indanone or 1-carbethoxy-2-indanone, Carpino (3) failed to obtain the desired pyrazolones. Perhaps considerable bond stretching and bending would be required to form pyrazolones fused to these five-membered rings.

The lead tetraacetate oxidations of compounds **2** and **4** were exothermic and led to the formation of colored transitory intermediates which in the absence of dienes evolved gas and yielded amorphous brown, non-melting solids. These products were not characterized.

Compounds **2** and **4** were oxidized with lead tetraacetate in the presence of 1,3-cyclopentadiene, 1,3-cyclohexadiene, 2,3-dimethyl-1,3-butadiene or 1,4-diphenyl-1,3-butadiene to 2:1 Diels-Alder adducts in yields from six to fifty percent.

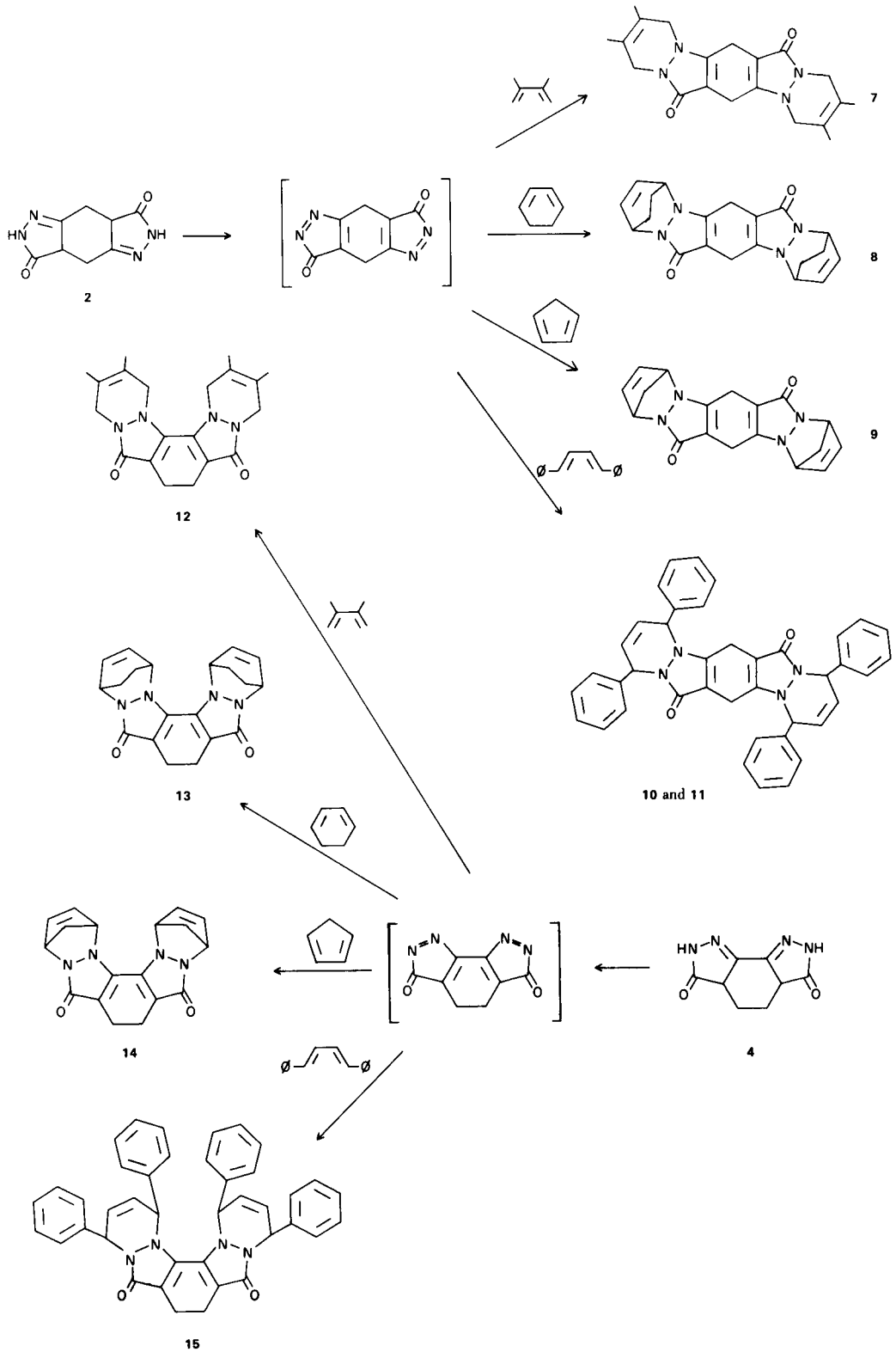


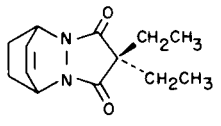
TABLE I

The Ultraviolet Data of 2:1 Diels-Alder Adducts in 95% Ethanol

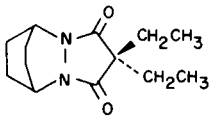
Diene	Compound	λ max	$\epsilon/10^4$	Compound	λ max	$\epsilon/10^4$
2,3-Dimethyl-1,3-butadiene	**7**	260	1.51	**12**	296	1.61
1,3-Cyclohexadiene	**8**	279	1.34	**13**	300 308	1.66 1.65
1,3-Cyclopentadiene	**9**	291 227	1.41 0.88	**14**	301 313 330 sh	1.35 1.34 0.99
trans-trans 1,4-diphenyl-1,3-butadiene	**10**	264	1.94	**15**	290	1.44
	11	264	1.66			

The occurrence of two diastereoisomers, differing in the configuration of the pyridazine rings, was anticipated for the oxidation of **2** in the presence of dienes, but in only one of these four Diels-Alder reactions of **2** was this observed. When the dienes used were 2,3-dimethyl-1,3-butadiene, 1,3-cyclohexadiene or 1,3-cyclopentadiene only one 2:1 adduct was isolated in each case. All of these adducts fluoresced blue-green in ultraviolet light allowing the ready detection and permitting facile chromatographic separation as a single, narrow fluorescing band on alumina or silica gel in each of these three cases. However, the oxidation of **2** in the presence of *trans-trans*-1,4-diphenyl-1,3-butadiene yielded two rather closely spaced fluorescing bands on alumina. Treatment of the chromatographed product-mixture with pyridine led to the separation of two products which both analyzed correctly for the expected 2:1 adduct and had virtually superimposable infrared spectra. Compound **10** was found to be soluble in polar organic solvents whereas **11**, higher melting by seventeen degrees, was either insoluble or nearly so in polar organic solvents. Neither was soluble in non-polar solvents. However, **11**, in addition to **10**, was found to be moderately soluble in phenols and the NMR spectrum of a saturated solution of **11** in *o*-bromophenol was compared to that of **10** at the same concentration in the same solvent. Attention was focused on the upfield portions of the two spectra which was assigned to be the doubly allylic protons of the center ring. In the case of **10** this region appeared as a broad multiplet, δ 2.5-3.8 centered at 3.1 ppm relative to tetramethylsilane. In **11** this region appeared as a broadened singlet, δ 2.8-3.2 centered at 3.0 ppm. When a time average computer was used to resolve these two regions, that of **10** was found to be a well defined AB pattern, $\Delta\nu_{AB}$ = 38 Hz, and that of **11** was a nearly coalesced AB pattern, $\Delta\nu_{AB}$ = 18 Hz. In each of the adducts **7**, **8** and **9**, the doubly allylic protons of the center ring were observed as singlets. One explanation is that the NMR spectra of isomers with *cis*- and *trans*-pyridazine rings are equivalent and products **7**, **8** and **9** are one or the other or an inseparable mixture of isomers. Another explanation of the singlet tendency of the doubly allylic protons in **7**, **8**, **9** and even **10** is that the shielding above and below the central rings in each case is equivalent, or nearly so, and each product is a single symmetric isomer having *trans* pyridazine rings. This is the favored explanation although no reason for the preferred *trans* isomers is apparent. In the unusual case of **11** it is suggested that the heavily substituted 1,4-cyclohexadiene ring was inverting sufficiently slowly between two slightly nonplanar forms so that a closely spaced AB pattern was observed. In the more polar and lower melting **10** the *cis* configuration is assigned. The greater perturbation of the doubly allylic protons occurred, as suggested, by the difference in the electronic environments above and below the center ring.

Support for the contention that an ethylene bond in this type of system could cause differences in the chemical shifts of remote protons was shown previously (4).



a



b

It was found that the NMR spectrum of **a** showed two clearly separated methyl groups whereas the two methyl groups of **b** were equivalent. The Alder endo-rule would predict that the ethylene bonds of the pyridazine rings would prefer the configuration endo to the rest of the molecule.

During the lead tetraacetate oxidation of **4** in the presence of dienes, the evolution of gas occurred unless the reaction was carried out below room temperature. By adding enough methylene chloride to prevent the freezing of the acetic acid solvent, the reactions were conducted at 0°.

Here again the crude adducts were chromatographed on alumina. In ultraviolet light the elution of one narrow, blue-green fluorescing band was observed in each case. Stereomodels of these 2:1 adducts, **12-15**, indicated that *trans* adduction was to be expected to the exclusion of *cis* adduction. Considerable steric interference would occur between the two pyridazine rings if both were on the same side of the molecule.

EXPERIMENTAL (7)

General Procedure for Diels-Alder Reactions of Compound **2**.

2,3,10,11-Tetramethyl-1,4,6,7,9,12,14,15-octahydrodipyridazino-[1,2-*a*:1,2-*a'*]benzo[1,2-*c*:4,5-*c'*]dipyrazolo-6,14-dione (**7**).

To a stirred mixture of 3.00 g. of **2** (0.0156 mole) and 2.12 g. (0.0313 mole) of 2,3-dimethyl-1,3-butadiene in fifty ml. of glacial acetic acid was added 13.5 g. (0.0313 mole) of 85% LTA over a period of about forty-five minutes. Although a negative test for LTA occurred almost immediately after its addition, stirring was continued overnight. The reaction mixture was then added to one-half liter of water and extracted three or more times with 200 ml. portions of methylene chloride. The combined methylene chloride layers were washed with saturated sodium bicarbonate, dried and concentrated to dryness yielding 3.2 g. (63%) crude **7**. Recrystallization from ethanol-water or chromatography on alumina with chloroform or on silica gel with chloroform-methanol 3:1, yielded 1-1.5 g. (20-30%) of gold needles, not melting below 360°. Thin layer chromatography showed one spot; nmr (deuterioacetic acid) δ 1.80 (s, 12, methyl), 3.52 (s, 4, doubly allylic), and 4.20 (broad singlet, 8, N–CH_2–).

Anal. Calcd. for $C_{20}H_{24}N_4O_2$: C, 68.16; H, 6.86; N, 15.90. Found: C, 67.98; H, 7.01; N, 16.05.

1,4-9,12-Diethano-1,4,6,7,9,12,14,15-octahydrodipyridazino[1,2-*a*:1,2-*a'*]benzo[1,2-*c*:4,5-*c'*]dipyrazolo-6,14-dione (**8**).

From a mixture of 0.0156 mole of **2**, 0.0313 mole of LTA, and 0.0313 mole of 1,3-cyclohexadiene was obtained 4.03 g. (74%) of crude **8**. Purification by recrystallization from water or by chromatography on alumina yielded 2.7 g. (50%) of yellow needles 298° dec. but when immersed in a hot oil bath merely darkens without melting below 350°; nmr (deuterioacetic acid) δ 1.51-2.25 (A_2B_2, 8, $-CH_2-CH_2-$), 3.50 (s, 4, doubly allylic), 5.07 and 5.41 (two broad singlets, 4, bridgehead), and 6.58 (possible triplet, 4, vinyl).

Anal. Calcd. for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.07; H, 5.92; N, 16.20.

1,4-9,12-Dimethano-1,4,6,7,9,12,14,15-octahydrodipyridazino-[1,2-*a*:1,2-*a'*]benzo[1,2-*c*:4,5-*c'*]dipyrazolo-6,14-dione (**9**).

A mixture of methylene chloride-glacial acetic acid was used as solvent and the reaction mixture was cooled to 0° to inhibit cyclopentadiene dimerization. From 0.0156 mole of **2**, 0.0313 mole of freshly distilled cyclopentadiene and 0.0313 mole of LTA was obtained 0.60 g. (12%) of **9**. Chromatography on alumina or recrystallization from ethanol afforded 0.3 g. (6%) of yellow crystals which begin to darken about 190° but do not melt. Thin layer chromatography showed one spot; nmr (trifluoroacetic acid) δ 2.74 (s, 4, CH–CH_2–CH), 4.00 (s, 4, doubly allylic), 5.70 and 5.88 (two s, 4, bridgehead), and 6.67 (broad singlet, 4, vinyl).

Anal. Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.42; H, 5.19; N, 17.30.

1,4,9,12-Tetraphenyl-1,4,6,7,12,14,15-octahydrodipyridazino[1,2-*a*:1,2-*a'*]benzo[1,2-*c*:4,5-*c'*]dipyrazolo-6,14-dione (**10** and **11**).

A mixture of 0.0156 mole of **2**, 0.0313 mole of *trans, trans*-1,4-diphenyl-1,3-butadiene and 0.0313 mole of LTA after standing 2-3 days was added to one-half liter of hot water, cooled to coagulate the product, filtered and dried. The precipitate was triturated several times with boiling ether and filtered to remove unreacted diene yielding 5.35 g. (57%) crude product. After chromatography on alumina with chloroform, the two closely-spaced bands were collected together and concentrated to dryness under reduced pressure. Treatment with warm pyridine followed by filtration, washing with ether and drying yielded 1.37 g. (15%) of **11** which melted at 329-329.5°.

Anal. Calcd. for $C_{40}H_{32}N_4O_2$: C, 79.97; H, 5.37; N, 9.33. Found: C, 79.77; H, 5.54; N, 9.31.

When several volumes of water were added to the pyridine filtrate, 2.05 g. (22%) of **10** precipitated, melting at 294-296.5°. Recrystallization from ethanol raised the melting point to 302-303.5°; nmr (deuteriochloroform) δ 2.65-2.97 (AB, 4, doubly allylic), 5.09 (broad singlet, 2, two of the four benzyl), 5.79-6.12 (m, 6, two benzyl and four vinyl), and 7.40 (s, 20, aromatic).

Anal. Calcd. for $C_{40}H_{32}N_4O_2$: C, 79.97; H, 5.37; N, 9.33. Found: C, 80.10; H, 5.32; N, 9.45.

2,3,3a,4,6,7,7a,8-Octahydrobenzo[1,2-*c*:4,5-*c'*]dipyrazolo-3,7-dione (**2**).

To a mixture of 0.1 mole 2,5-dicarbethoxy- or 2,5-dicarbomethoxy-1,4-cyclohexanedione (5) in ethanol was added 0.21 mole of hydrazine hydrate. Refluxing overnight resulted in 95-100% yield of **2** which precipitated from the ethanol. Compound **2** was dissolved in dilute sodium hydroxide and reprecipitated by the addition of hydrochloric acid to neutrality with 90+% recovery. The product did not melt below 360°.

Anal. Calcd. for $C_8H_8N_4O_2$: C, 49.99; H, 4.20; N, 29.15. Found: C, 49.90; H, 4.19; N, 29.34.

3,6-Dicarbomethoxy-1,2-cyclohexanedione (**3**, R = CH_3).

To a stirred mixture of 68 g. (0.575 mole) of dimethyl oxalate and 70 g. (1.3 moles) of freshly prepared sodium methoxide in 250 ml. of anhydrous ether was slowly added 100 g. (0.575 mole) of dimethyl adipate. The mixture was refluxed for about two days until the reaction mixture yielded a yellow solid. The ether was distilled off and the solid was slowly hydrolyzed in cold, dilute sulfuric acid. Extraction with several portions of methylene chloride and concentration under reduced pressure yielded upon standing 41.6 g. (32%) of **3**, R = Me, m.p. 105.5-107.5°, after recrystallization from methanol, m.p. 108°.

Anal. Calcd. for $C_{10}H_{12}O_6$: C, 52.62; H, 5.30. Found:

C, 52.66; H, 5.40.

2,3,3a,4,5,5a,6,7-Octahydrobenzo[2,1-*c*:4,3-*c'*]dipyrazolo-3,6-dione (**4**).

To a 0.1 mole of 1,4-dicarbethoxy (6) or 1,4-dicarbomethoxycyclohexanedione **3** in ethanol was added 0.21 mole hydrazine hydrate. Refluxing overnight resulted in 95-100% of **4** which precipitated from the ethanol. Compound **4** was dissolved in dilute sodium hydroside and reprecipitated by the addition of hydrochloric acid to neutrality, m.p. 319-321°. This material was used without further purification. Recrystallization from a large volume of 50:50 ethanol-water afforded an analytical sample, m.p. 322-323°.

Anal. Calcd. for $C_8H_8N_4O_2 \cdot H_2O$: C, 45.71; H, 4.80; N, 26.65. Found: C, 45.59; H, 4.91; N, 26.60.

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

2,3,12,13-Tetramethyl-1,4,6,7,8,9,11,14-octahydrodipyridazino-[1,2-*a*:1,2-*a'*]benzo[2,1-*c*:3,4-*c'*]dipyrazolo-6,9-dione (**12**).

To a stirred mixture of 10.0 g. (0.0520 mole) of **4**, 8.55 g. (0.104 mole) of 2,3-dimethyl-1,3-butadiene, 100 ml. of methylene chloride and 200 ml. of glacial acetic acid, all cooled to 0°, was added 54.8 g. (0.104 mole) of 85% LTA over about forty-five minutes. The mixture was allowed to warm to room temperature overnight, added to one liter of water and extracted three or more times with 200 ml. portions of methylene chloride. The combined methylene layers were washed with saturated sodium bicarbonate, dired over magnesium sulfate and concentrated to dryness under reduced pressure yielding 9.0 g. (49%) crude **12**. Chromatography on alumina with chloroform-methanol 3:1 or recrystallization methanol-water 50:50 afforded 4.0 g. (24%) of pure **12**, m.p. 308-309°; nmr (trifluoroacetic acid) δ 1.97 (s, 12, methyl), 2.95 (s, 4, $-CH_2-CH_2-$), 5.75 and 5.85 (two s, 8, $-CH_2-N$).

Anal. Calcd. for $C_{20}H_{24}N_4O_2$: C, 68.16; H, 6.86; N, 15.90. Found: C, 67.98; H, 6.97; N, 15.75.

1,4-11,14-Diethano-1,4,6,7,8,9,11,14-octahydrodipyridazino[1,2-*a*:1,2-*a'*]benzo[2,1-*c*:3,4-*c'*]dipyrazolo-6,9-dione (**13**).

From 0.0529 mole of **4**, 0.104 mole of 1,3-cyclohexadiene and 0.104 mole of LTA was obtained 16.3 g. (89%) of crude **13**. Chromatography or recrystallization from acetone containing a small amount of methanol yielded 7.2 g. (40%) of a solid which decomposes at 233°; nmr (deuteriochloroform) δ 1.4-2.6 (m, 12, $-CH_2-CH_2-$), 4.58 and 5.15 (two broad singlets, 4, bridgehead), and 6.00-6.62 (m, 4, vinyl).

Anal. Calcd. for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.83; H, 5.65; N, 16.23.

1,4-11,14-Dimethano-1,4,6,7,8,9,11,14-octahydrodipyridazino-[1,2-*a*:1,2-*a'*]benzo[2,1-*c*:3,4-*c'*]dipyrazolo-6,9-dione (**14**).

From 0.0260 mole of **4**, 0.0520 mole of freshly distilled cyclopentadiene and 0.0520 mole of LTA was obtained 5.44 g. (65%) crude **14**. Chromatography or recrystallization from chloroform-carbon tetrachloride yielded 2.6 g. (32%) of pure **14** which slowly darkens without melting above about 190°. Thin layer chromatography showed one spot; nmr (deuteriochloroform) δ 2.00-2.60 (m, 8, $-CH_2-$), 4.95 and 5.20 (two s, 4, bridgehead), and 5.90-6.23 (AB, J = 4.4, vinyl).

Anal. Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.48; H, 5.03; N, 17.48. Found: C, 67.51; H, 5.21; N, 17.35.

1,4,11,14-Tetraphenyl-1,4,6,7,8,9,11,14-octahydrodipyridazino-[1,2-*a*:1,2-*a'*]benzo[2,1-*c*:3,4-*c'*]dipyrazolo-6,9-dione (**15**).

A mixture of 0.0156 mole of **4**, 0.0313 mole of *trans-trans*-1,4-diphenyl-1,3-butadiene and 0.0313 mole of LTA after standing overnight were added to one-half liter of hot water, cooled to coagulate the product, filtered and dried. The precipitate was triturated several times with boiling ether and filtered to remove unreacted diene yielding 5.87 g. (63%) of crude **15**. Chromatography on alumina with chloroform yielded 1.66 g. (18%) melting at 226.5-229°. Recrystallization from ethanol containing a small amount of water raised the melting point to 229°; nmr (deuteriochloroform) δ 1.6-2.5 (m, 4, $-CH_2-CH_2-$), 5.48-5.69 (m, 4, benzyl), 6.10 (s, 4, vinyl), 7.29 and 7.44 (two s, 20, aromatic).

Anal. Calcd. for $C_{40}H_{32}N_4O_2$: C, 79.97; H, 5.37; N, 9.33. Found: C, 79.80; H, 5.28; N, 9.23.

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(7) 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 deuteriochloroform, deuterioacetic acid, or trifluoroacetic acid and tetramethylsilane as a reference standard. The ultraviolet spectra were taken with a Cary Model 14 Spectrophotometer. The alumina used was unactivated, 80-200 mesh, Fisher No. 540. The silica gel was 60-200 mesh, Fisher No. S-662.

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