Reactions of Squaric Acid with Phenylhydrazine: Structure and Nuclear Magnetic Resonance Spectroscopy of Cyclobutanetetraone Poly(phenylhydrazones)

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The reaction of squaric acid **1** with phenylhydrazine affords three cyclobutanetetraone poly(phenylhydrazones), *viz.* a tetrakis(phenylhydrazone) **3**, a tris(phenylhydrazone) **4a** ⇌ **4b** and a 1,3-bis(phenylhydrazone) **5**. The structure of these compounds has been determined by IR, MS and ^{1}H and ^{13}C NMR spectroscopy, including 2D COSY, and ^{1}H-detected, single- and multiple-bond 2D carbon–proton chemical-shift-correlation techniques. Chemical methods were also used to elucidate the structure of bis(phenylhydrazone) **5**, including its synthesis and that of its *N*-methyl-*N*-phenyl and *N*,*N*-diphenyl analogues **8** and **9** from cyclobutanetetraone, and the preparation of a quinoxaline **7** to establish the 1,3-arrangement of substituents.

Compounds in the squaric acid/semisquaric acid series are of considerable biological, synthetic, spectroscopic, and theoretical interest. For example, semisquaric acid (3-hydroxycyclobut-3-ene-1,2-dione) is produced by the mould *Fusarium moniliforme*, which has been isolated from corn seed damaged by Southern leaf blight.[1,2] This compound has growth-regulating and phytotoxic effects on plants and a toxic effect on mammals. Herbicidal effects of squaric acid and semisquaric acid derivatives have also been demonstrated.[2] Squaric acid diethyl ester has been identified as a new coupling reagent for the formation of drug–biopolymer conjugates.[3]

Since the synthesis of squaric acid (3,4-dihydroxycyclobut-3-ene-1,2-dione, **1**) in 1959,[4] its structure and reactions have been extensively studied.[5–12] Of particular relevance to the present work are the reactions of the free acid and its esters with nucleophiles such as aliphatic, aromatic, or heterocyclic amines[13–26] and hydrazines.[27–30] Reactions of squaric acid with amines produce 1,2- and 1,3-disubstituted squaraines, many of which are intensely coloured. There is no report in the literature of a direct reaction of squaric acid with phenylhydrazine. However, certain pseudo-oxocarbon[31,32] analogues of squaric acid exchange sulfur groups upon treatment with hydrazines. For example, it has been reported that potassium tetrathiosquarate, upon treatment with phenylhydrazine, yields cyclobutanetetraone tetrakis(phenylhydrazone).[33] Unfortunately, the product isolated was neither analysed nor purified, as is evident from the fact that the melting point reported is 72 °C lower than that found here. Another tetrasubstituted nitrogen derivative pertinent to this study is a bis(quinoxaline)[34–37] prepared by reaction of squaric acid with *o*-phenylenediamine.

Squaric acid and its derivatives have been converted into substituted aromatics by using transition metal-mediated processes[38,39] and into *o*-quinone methides by ring opening of allene-substituted squaric acid.[40–45]

The aim of the present work was to study the structures of the poly(phenylhydrazones) isolated from the reaction of squaric acid with phenylhydrazine, with the potential for finding useful chemical and biochemical applications of these highly coloured derivatives, and for shedding light on analogous oxidations that occur during formation of sugar osazones.

Results and Discussion

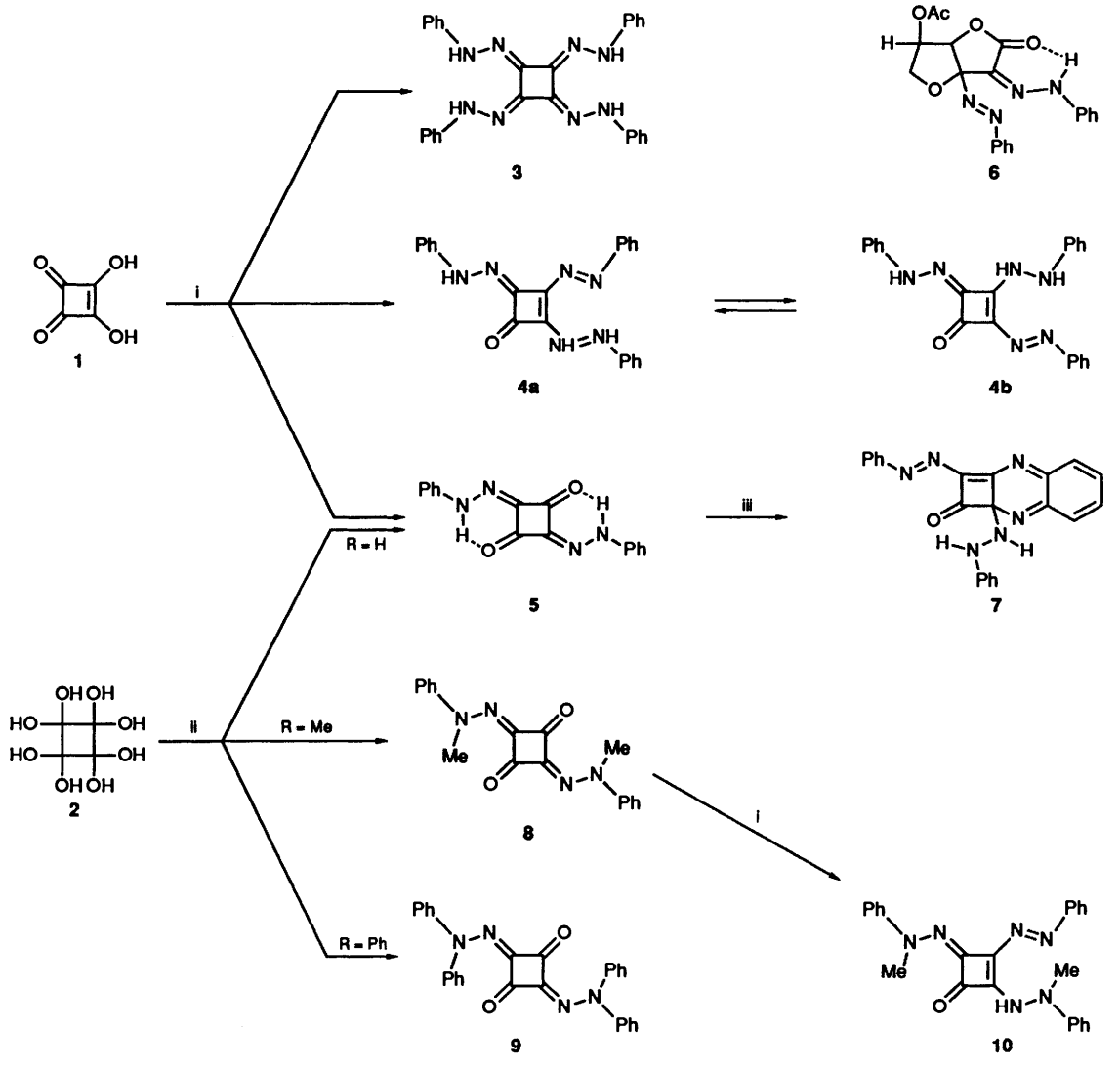
The reaction of squaric acid **1** with phenylhydrazine[46] affords three major coloured poly(phenylhydrazone) derivatives of cyclobutanetetraone[47] **2**, the oxidation product of squaric acid, namely, cyclobutanetetraone tetrakis(phenylhydrazone) **3**, tris(phenylhydrazone) **4a**/**4b**, and bis(phenylhydrazone) **5**, whose structures have been established by physical and by chemical methods. The physical methods included mass spectrometry, which in conjunction with the results of combustion analysis confirmed that the poly(phenylhydrazones) isolated were derivatives of cyclobutanetetraone.

IR spectroscopy provided information about the presence of carbonyl groups as well as of any intramolecular C=O···HN hydrogen bonding. The latter was detected by shifts in the carbonyl IR absorption bands to lower frequency as well as by shifts of the NH proton signals in the ^{1}H NMR spectra to lower field (from $\delta \leqslant 11$ to δ 12–14).

The predominant tautomeric structures and molecular symmetry of the products were established from (a) the number of NH signals in the ^{1}H NMR spectra, (b) the number of resonances observed for *ortho*, *meta* and *para* protons and carbon nuclei in the ^{1}H and ^{13}C NMR spectra of the phenyl groups, and (c) the number of resonances detected for the carbon nuclei in the four-membered ring. Other NMR techniques used were ^{1}H-coupled ^{13}C NMR, two-dimensional (2D) *CO*rrelation *S*pectroscop*Y*[48] (COSY), and 2D *H*eteronuclear *M*ultiple *Q*uantum *C*oherence[49] (HMQC) and 2D *H*eteronuclear *M*ultiple *B*ond *C*oherence[50] (HMBC).

Based on the ^{1}H assignments generated either by inspection of the ^{1}H NMR spectra or by analysis of 2D COSY ^{1}H–^{1}H chemical-shift correlation spectra, the 2D HMQC and HMBC techniques allowed the aromatic ^{13}C NMR signals to be assigned *via* the heteronuclear ^{1}H–^{13}C chemical-shift correlations over one bond, and over two or more bonds, respectively. The 2D HMQC method has the virtue of simple interpretation, since the spectra contain cross-peaks only for the carbon nuclei that are directly bonded to protons. On the other hand, the 2D HMBC spectra provide proton correlations with more distant carbons, including quaternary carbons, but are more subject to interpretation, especially because suppression of one-bond correlations is sometimes incomplete.

For the 2D HMBC method, most of the C–H correlations were mediated by $^3J_{CH}$ couplings, but some correlations *via* $^2J_{HNC}$ were also detected. In all cases, the C–H correlations developed by the 2D HMQC and HMBC methods confirmed one another. The sensitivity enhancement afforded by these inverse techniques (in which the ^{13}C connectivities are detected indirectly through the more highly magnetized protons) was particularly appropriate for the poly(phenylhydrazones), because of their limited solubility. However, the 2D HMQC and



Scheme 1 *Reagents:* i, $PhNHNH_2$; ii, $PhN(R)NH_2$; iii, $1,2\text{-}(H_2N)_2C_6H_4$

HMBC methods usually did not generate any assignments for the ^{13}C nuclei in the four-membered rings of the poly(phenylhydrazones), owing to the absence of non-exchanging protons that were either attached to, or near to, these rings. Additionally, the 2D spectra obtained by these methods often suffer from limited digital resolution in the ^{13}C dimension.

In order to characterize the three different types of phenyl substituents encountered in this work, ^1H chemical-shift data were measured for several model compounds. An oxidation product[51] **6** of didehydro-L-ascorbic acid bis(phenylhydrazone) acetate served as a model for the ^1H chemical shifts of phenyl-azo and -hydrazono groups, and azobenzene and phenylhydrazine provided additional data for the phenyl-azo and -hydrazino groups, respectively.

The chemical methods used in structure elucidation included direct synthesis of the products and some of their analogues from cyclobutanetetraone, and the preparation of a quinoxaline to distinguish 1,2- from 1,3-disubstituted derivatives. A summary of the synthesis and structures of the major products obtained when squaric acid is treated with phenylhydrazine is presented in the next section (see Scheme 1).

Structure of Cyclobutanetetraone Tetrakis(phenylhydrazone).—Cyclobutanetetraone tetrakis(phenylhydrazone) **3** can be obtained from a variety of substrates such as squaric acid esters and cyclobutanetetraone tris- and bis-(phenylhydrazone), but it is best prepared by reaction of squaric acid and phenylhydrazine, either without solvent or in refluxing dimethylformamide (DMF). The mass spectrum of compound **3** showed a molecular ion at m/z 472, and its IR spectrum showed no carbonyl absorption band, indicating that it must be fully substituted. Measurements of the ^1H NMR spectra of saturated solutions of compound **3** in three solvents at 400 MHz disclosed only one major type of NH group and only one type of phenyl group, which showed the doublet/triplet/triplet pattern that is characteristic of the *ortho*, *meta* and *para* protons, respectively. Change of solvent produces little variation of the chemical shift of the NH proton, which remains in the range δ 9.8–10.0 (see Table 1) that is characteristic of non-hydrogen-bonded NH protons. The presence of only one type of phenyl group was confirmed by ^{13}C NMR spectroscopy (see ^{13}C chemical shifts in Table 2). The assignments for the aromatic carbon signals C-1, C_o, C_m and C_p were defined by a 2D HMBC experiment, which showed long-range C–H correlations over three bonds together with a correlation of the NH proton with C-1 over two bonds ($^2J_{HNC}$).

The ^1H and ^{13}C NMR data for compound **3** are consistent with a tetrakis(phenylhydrazone) structure having four-fold symmetry, but not with cyclobutadienoid or phenylazocyclobutene tautomers, which would be expected to display the signals of multiple NH protons and phenyl groups.

Table 1 ^{1}H NMR chemical shifts[a] of cyclobutanetetraone poly(phenylhydrazones) and related derivatives

Compound	Solvent	Type	H_o	H_m	H_p	NH
3	$(CD_3)_2SO$	hydrazono	7.450	7.365	6.961	9.804, 8.172[b]
	$(CD_3)_2NCDO$		7.508	7.382	6.981	9.906
	C_5D_5N		7.483	7.413	7.048	9.988
4a, b	$(CD_3)_2SO$	azo	7.584	≈7.385	7.047	
		hydrazono	7.437	≈7.361	6.953	9.825
		hydrazino	7.385	≈7.385	7.047	10.311, 11.582
	$CDCl_3$	azo	7.319	7.377	7.085	
		hydrazono	7.221	7.391	7.095	9.926
		hydrazino	7.185	7.391	7.021	8.977, 9.947
5	$(CD_3)_2SO$	hydrazono	7.575	7.403	7.171	12.347[c]
6	$CDCl_3$[d]	azo	7.858	7.522	7.505	
		hydrazono	7.230	7.301	7.069	12.032
	$(CD_3)_2SO$[e]	azo	7.786	7.600	7.584	
		hydrazono	7.350	7.322	7.061	12.001
7	$CDCl_3$[f]	azo	8.496	7.597	7.410	
		hydrazino	7.057	7.270	6.944	6.701, 10.142
	$(CD_3)_2SO$[g]	azo	8.500	7.708	7.487	
		hydrazino	6.935	7.214	6.776	8.243, 10.611
8	$CDCl_3$[h]	hydrazono	7.629	7.416	7.250	
9	$(CD_3)_2SO$	hydrazono	7.207	7.396	7.308	
10	$CDCl_3$[i]	azo	7.523	7.372	7.107	
		hydrazono	7.421	7.468	7.195	
		hydrazino	7.098	7.304	6.914	10.729
Azobenzene	$CDCl_3$[j]	azo	7.922	7.521	7.471	
	$(CD_3)_2SO$[k]		7.905	7.599	7.617	
Phenylhydrazine	$CDCl_3$	hydrazino	6.821	7.243	6.824	≈3.67 (NH and NH_2)
	$(CD_3)_2SO$		6.762	7.081	6.564	6.620, 3.929 (NH_2)

[a] Ppm from internal tetramethylsilane. [b] Minor signal. [c] Broad signal. [d] Aliphatic protons at δ 5.322 (4-H), 5.406 (5-H), 4.414 (6-H), 4.290 (6-H′) and 2.065 (Me). [e] Aliphatic protons at δ 5.309 (4-H), 5.375 (5-H), 4.427 (6-H), 4.220 (6-H′) and 2.023 (Me). [f] Quinoxaline ring protons at δ 8.337 and 8.282 (3-H and 6-H), and 7.876 and 7.942 (4-H and 5-H). These assignments are simultaneously interchangeable, 3-H with 6-H, and 4-H with 5-H. [g] Quinoxaline ring protons at δ 8.398 and 8.299 (3-H and 6-H), and 7.976 and 8.056 (4-H and 5-H). These assignments are simultaneously interchangeable, 3-H with 6-H, and 4-H with 5-H. [h] δ 4.153 (Me). [i] δ 4.192 (Me) and 3.978 (Me). [j] Benzene had δ 7.359 in $CDCl_3$. [k] Benzene had δ 7.366 in [$^2H_6$]DMSO.

Table 2 ^{13}C NMR chemical shifts[a] of cyclobutanetetraone poly(phenylhydrazones) and related derivatives

Compound	Solvent	Type	C-1	C_o	C_m	C_p	CN (4-ring)	C=O
3	$(CD_3)_2SO$	hydrazono	143.47	113.49	129.11	121.07	150.94[b]	
4a, b	$(CD_3)_2SO$		143.00	114.50	129.33	122.87	145.52	181.35
			143.44	113.65	129.14	121.10	144.44	
			142.65	114.41	129.14	122.74	145.23	
5	$(CD_3)_2SO$	hydrazono	142.54	116.14	129.38	125.22	152.10	183[c]
7[d]	$CDCl_3$	azo	138.63	121.13	129.36	127.29	136.11	159.91
		hydrazino	147.74	114.11	129.27	121.54	134.52, 142.75	
8[e]	$CDCl_3$	hydrazono	145.59[f]	118.30	129.37	126.39	149.73	183.60
9	$(CD_3)_2SO$	hydrazono	143.99	122.77	129.61	129.42	151.95	180.18
10[g]	$CDCl_3$	hydrazino	146.62	113.15	129.09	120.95	144.73[f]	182.11
			146.21	116.35	129.50	123.65	146.71[f]	
			144.10	116.79	129.50	124.26	140.95[f]	

[a] Ppm from internal tetramethylsilane. [b] Tentative because of low signal:noise ratio. [c] Broad signal. [d] Quinoxaline ring carbons at δ_C 142.00 and 141.62 (C-1 and C-2), 130.09 and 129.51 (C-3 and C-6), 129.94 and 131.97 (C-4 and C-5). These assignments are simultaneously interchangeable, C-1 with C-2, C-3 with C-6 and C-4 with C-5. [e] δ_C 43.46 (Me). [f] Assignment confirmed by ^{1}H-coupled ^{13}C NMR spectrum. [g] δ_C 41.33 (Me) and 40.39 (Me).

Structure of Cyclobutanetetraone Tris(phenylhydrazone).—Cyclobutanetetraone tris(phenylhydrazone), represented by tautomeric structures **4a** and **4b**, is obtained in low yield by reaction of squaric acid with phenylhydrazine. It is best prepared by treatment of dibutyl squarate with the same phenylhydrazine, a reaction that bears on the use of squarate esters as coupling reagents.[3] The IR spectrum of tautomeric product **4a**/**4b**, showed a strong carbonyl absorption band at 1740 cm^{-1} and its mass spectrum a molecular ion at *m*/*z* 382. ^{1}H NMR spectra of **4a**/**4b** measured at 400 MHz displayed three types of imino protons and three different sets of phenyl ring protons, each set showing the typical doublet/triplet/triplet pattern of the *ortho*, *meta* and *para* protons.

The chemical shifts of the NH protons of **4a**/**4b** in [^{2}H]-chloroform solution (see Table 1) are within the range for non-hydrogen-bonded NH protons, which is consistent with the observation of a non-hydrogen-bonded C=O absorption in the IR at 1740 cm^{-1}. However, change of solvent to $(CD_3)_2SO$ ([$^2H_6$]DMSO) causes the three NH proton NMR signals to shift to lower field, which suggests that all of these protons are available for hydrogen bonding with the sulfoxide oxygen atoms. The ^{1}H NMR assignments within each aromatic proton

Table 3 ^{13}C–^{1}H NMR coupling constants (Hz) of quinoxaline derivative **7** of cyclobutanetetraone 1,3-bis(phenylhydrazone)

Coupling constant[a]	Quinoxaline ring	Phenylhydrazino group	Phenylazo group
$^{3}J_{HNCC=O}$		9.1	
$^{3}J_{C-1,3-H}$	5.5	8.7	10.2
$^{3}J_{C-1,5-H}$	10.1	8.7	10.2
$^{1}J_{C-2,2-H}$		155.5	164.7
$^{3}J_{C-2,4-H}$	9.8	*b*	7.6
$^{3}J_{C-2,6-H}$	5.7	*b*	5.4
$^{1}J_{C-3,3-H}$	165.3	156.8	162.9
$^{3}J_{C-3,5-H}$	7.4	8.6	8.3
$^{1}J_{C-4,4-H}$	162.9	160.6	163.2
$^{3}J_{C-4,2-H}$		7.4	7.4
$^{3}J_{C-4,6-H}$	9.4	7.4	7.4
$^{1}J_{C-5,5-H}$	162.2	156.8	162.9
$^{3}J_{C-5,3-H}$	9.4	8.6	8.3
$^{1}J_{C-6,6-H}$	165.2	155.5	164.7
$^{3}J_{C-6,2-H}$		*b*	5.4
$^{3}J_{C-6,4-H}$	7.5	*b*	7.6

[a] Assignments of coupling constants over one and three bonds were confirmed by 2D HMQC and 2D HMBC techniques, respectively. [b] Unresolved.

set were indicated by a 2D COSY spectrum. The presence of three types of phenyl groups was confirmed by ^{13}C NMR spectroscopy, which displayed three different sets of aromatic carbon signals. The nonsymmetrical four-membered ring of compound **4a**/**4b** was manifested by the observation of four non-equivalent, quaternary carbon signals, including one C=O signal at δ_C 181.3. The assignments for the aromatic carbon signals were indicated by 2D HMQC and HMBC experiments.

The NH proton of compound **4a**/**4b** at highest field (δ 9.83) in [$^{2}H_6$]DMSO solution shows cross-peaks with both C-1 and C_o of the attached phenyl ring, most likely reflecting correlations over two and three bonds, respectively. The ^{1}H and ^{13}C NMR data are consistent with asymmetrical cyclobutenone structures **4a** and **4b** having phenyl-azo, -hydrazono, and -hydrazino substituents.

Comparison of ^{1}H NMR data for azobenzene, benzene and phenylhydrazine (see Table 1) indicates that the hydrazino group has a shielding effect on the phenyl ring protons, whereas the azo group has a deshielding effect. The latter effect is expected to be most significant for the *ortho* protons and to a lesser extent for the *para* protons. Deshielding of the *ortho* protons of the phenylazo group is also exhibited by the ascorbic derivative **6**, and the data for this compound and the several cyclobutanetetraone poly(phenylhydrazones) in this study also suggest that the *ortho* protons of phenylhydrazono groups resonate at chemical shifts intermediate between those of the corresponding protons in the phenylazo and phenylhydrazino groups (see Table 1). Uniquely, however, the chemical shifts of the *ortho* protons of the phenyl-azo, -hydrazono, and -hydrazino groups in the tris derivative **4a**/**4b** are not markedly different (Table 1), suggesting that these shifts are time-averaged by a dynamic equilibrium of tautomers **4a** and **4b**.

Structure of Cyclobutanetetraone 1,3-*Bis*(*phenylhydrazone*).—Cyclobutanetetraone 1,3-bis(phenylhydrazone) **5** is produced in low yield from squaric acid and is best prepared from cyclobutanetetraone and phenylhydrazine. The mass spectrum of compound **5** showed a molecular ion at *m*/*z* 292 and the IR spectrum a strong carbonyl absorption band at 1650 cm^{-1}, shifted to lower frequency by intramolecular C=O--HN hydrogen bonding. The ^{1}H NMR spectrum showed the presence of only one type of phenyl group, as well as a broad, highly deshielded NH signal at δ 12.34 that confirms intramolecular C=O--HN chelation. This chemical shift is comparable with that (δ 12.0) of the NH proton of compound **6**, which is also favourably oriented for intramolecular C=O--HN hydrogen bonding. It seems that compound **5** is the only cyclobutanetetraone poly(phenylhydrazone) that exhibits hydrogen bonding, presumably because it is the least substituted. Chelation introduces an element of strain and rigidity on an already strained four-membered ring. The ^{13}C NMR spectrum of compound **5** in [$^{2}H_6$]DMSO displayed the signals of only one type of phenyl group and one type of C=N (see Table 2). Long scanning revealed a broad ^{13}C signal at δ_C 183 that was assigned to the C=O groups. The aromatic ^{13}C assignments were indicated by 2D HMQC and HMBC experiments. The HMBC spectrum showed five cross-peaks correlating aromatic protons and carbons, including one for the *meta* protons and C-1, but no HNC correlations were detected. The ^{1}H and ^{13}C NMR evidence demonstrates the chemical equivalence of the two phenylhydrazone residues in compound **5** and of pairs of carbon atoms in its four-membered ring, but is consistent with either symmetrical 1,2- or 1,3-diketo structures.

To determine the position of the phenylhydrazone groups, a chemical method was used that was based on the structure of the product formed on reaction with *o*-phenylenediamine. If the bis(phenylhydrazone) were 1,2-disubstituted, it would afford a symmetrical quinoxaline without a carbonyl group, whereas if it were 1,3-disubstituted it would form an asymmetrical quinoxaline such as compound **7**, having a carbonyl group. When the bis(phenylhydrazone) was treated with *o*-phenylenediamine, it indeed afforded the quinoxaline **7** having a strong carbonyl absorption at 1680 cm^{-1}, and a molecular ion at *m*/*z* 380, thus indicating a 1,3-bis(phenylhydrazone) structure.

Owing to the key role of the quinoxaline in establishing the structure of the bis(phenylhydrazone) **5**, its NMR parameters have been studied in detail.

Evidence for the nonsymmetrical nature of the quinoxaline **7** was obtained at the outset from the ^{1}H NMR spectrum, which shows the presence of (a) two types of phenyl groups having very different chemical shifts for the *ortho*, *meta* or *para* protons, (b) four non-equivalent, quinoxaline ring protons, and (c) two non-equivalent NH protons (see Table 1). By contrast, the symmetrical quinoxaline from a 1,2-diketo precursor would display equivalent phenyl groups, equivalent NH protons, and two pairs of chemically equivalent quinoxaline ring protons. In fact, the imino protons were observed as mutually spin-coupled doublets (J_{HNNH} 2.8 Hz) in the ^{1}H NMR spectrum of the quinoxaline in [$^{2}H_6$]DMSO solution, implying that the NH groups are vicinal and, therefore, not attached to different phenyl groups. The slow exchange of the NH protons in [$^{2}H_6$]DMSO suggests that they are not acidic, which is consistent with structure **7** in which the NH protons are not allylic to any of the double bonds in the tricyclic ring system. The proton NMR assignments were indicated by a 2D COSY spectrum.

Deshielding of the *ortho* protons of the phenylazo group by the azo moiety is much more pronounced in the quinoxaline than it is for azobenzene and compound **6** (see Table 1), thus suggesting that, in the quinoxaline, these protons are further deshielded by conjugation of the phenylazo group with the double bonds in the tricyclic ring system. The nonsymmetrical quinoxaline structure **7** was confirmed by ^{13}C NMR data (see ^{13}C chemical shifts in Table 2 and ^{13}C–H coupling constants in Table 3) which demonstrated the presence of six non-equivalent quinoxaline ring carbon atoms, two non-equivalent phenyl groups, and four non-equivalent carbons in the four-membered ring, including the C=O group. Methine carbon resonances were identified by a DEPT-90 experiment.[52] The ^{13}C chemical shift of the C=O group in compound **7** is about 20 ppm less than that of C=O groups in other poly(phenylhydrazones) in this

series (see Table 2). This is appropriate for a C=O group in which the cationoid character of the carbon atom is neutralized by electron donation from the conjugated double bond in structure **7**.

Based on the ^{1}H NMR assignments determined already, most of the ^{13}C assignments for the quinoxaline **7** were confirmed by 2D HMQC and 2D HMBC experiments. The long-range correlation of the NH proton at δ_H 10.14 with the ^{13}C=O at δ_C 159.1 is noteworthy and is reflected by the measurement of a sizeable coupling constant $^3J_{HNCC=O}$ 9.1 Hz (Table 3) from the ^{1}H-coupled ^{13}C NMR spectrum of compound **7**. ^{1}H–^{13}C coupling was not detected for the other three carbons in the four-membered ring. The $^1J_{CH}$-values for the phenylazo group are invariably larger than those of the phenylhydrazino group (Table 3), which is consistent with increased percentage s character[53] in the CH bonds of the phenylazo group caused by partial withdrawal of its p electrons by the conjugated double-bond system.

To study the effect of intramolecular hydrogen bonding in cyclobutanetetraone 1,3-bis(phenylhydrazone), two analogues of this compound, incapable of forming hydrogen bonds, were prepared. They are cyclobutanetetraone 1,3-bis-(*N*-methyl-*N*-phenylhydrazone) **8** and 1,3-bis-(*N*,*N*-diphenylhydrazone) **9** obtained by reaction of cyclobutanetetraone with the asymmetrically disubstituted hydrazines *N*-methyl-*N*-phenylhydrazine and *N*,*N*-diphenylhydrazine. The two products **8** and **9** showed carbonyl absorption bands (at 1672 and 1685 cm^{-1}, respectively) that were not shifted by chelation as was shown by compound **5**. The ^{1}H NMR spectrum of cyclobutanetetraone 1,3-bis-(*N*-methyl-*N*-phenylhydrazone) **8** disclosed only one type of phenyl group, one type of methyl group, and obviously no NH (see Table 1). The presence of only one type of phenyl group and one type of methyl group was confirmed by ^{13}C NMR spectra, which also displayed one type of C=N at δ_C 149.7, a value quite similar to that (δ_C 152.1) of 1,3-bis(phenylhydrazone) **5**. In contrast to 1,3-bis(phenylhydrazone) **5**, the ^{13}C=O resonance of compound **8** at δ_C 183.6 was not broadened by hydrogen exchange/tautomerism.

Measurements of the ^{1}H NMR spectrum of cyclobutanetetraone 1,3-bis(*N*,*N*-diphenylhydrazone) **9** in [$^2H_6$]DMSO solution displayed a mixture of sharp and broad components. The sharp set of signals indicated the presence of one type of phenyl ring (see Table 1). The ^{13}C NMR spectrum of compound **9** in [$^2H_6$]DMSO also displayed sharp and broad peaks, including one type of C=O at δ_C 180.2 and a non-protonated carbon (C=N) at δ_C 152.0. The sharp and broad spectral components may indicate restricted rotation about the N–N bond.

Cyclobutanetetraone 1,3-bis-(*N*-methyl-*N*-phenylhydrazone) reacts with phenylhydrazine to afford an analogue of tautomer **4a**, namely cyclobutanetetraone 1,3-bis-(*N*-methyl-*N*-phenylhydrazone)-2-phenylhydrazone **10**. Its IR spectrum showed a carbonyl absorption band at 1760 cm^{-1}, and in its mass spectrum a molecular ion at *m*/*z* 410. Measurement of the ^{1}H NMR spectrum disclosed one type of NH, three different phenyl groups, and two non-equivalent methyl substituents. The ^{1}H–^{1}H connectivities were indicated by a 2D COSY spectrum. The ^{13}C NMR spectrum of compound **10** in $CDCl_3$ was consistent with the ^{1}H NMR data. It contained the signals of three types of phenyl groups, two methyl signals, a C=O resonance, and the signals of three non-equivalent, non-protonated carbons in the four-membered ring. The NMR data indicates the unsymmetric cyclobutenone structure **10**.

The formation of cyclobutanetetraone derivatives during the reaction of squaric acid with phenylhydrazine bears a striking resemblance to the formation of osazones from aldoses. Both reactions are accompanied by oxidation of the substrate and reduction of phenylhydrazine to aniline and ammonia. Noteworthy is the fact that cyclobutanetetraone 1,3-bis(phenylhydrazone) is an analogue of aldosulose monophenylhydrazones, which are believed to be generated during formation of osazones.[54]

Experimental

General.—M.p.s were determined using a Kofler-block apparatus and are uncorrected. Mass spectra were recorded by means of a Hewlett Packard* 5995 GC/MS spectrometer in the EI mode. IR spectra were measured by use of a BIO-RAD FTS-7 (SPC-3200) FT-IR spectrophotometer calibrated with polystyrene. UV spectra were recorded on a Hewlett Packard 8452A Diode Array spectrophotometer with HP 89530A MS DOS-UV/VIS operating software. NMR spectra were acquired using a Bruker WM-400 spectrometer, equipped with an Aspect 3000 data system, a process controller, and a BFX-5 broadband amplifier. ^{1}H NMR spectra were measured at 400 MHz and at 300 K. Assignments of NH protons were confirmed by deuterium exchange, and integrals of ^{1}H NMR signal intensities agreed with the structures assigned. ^{1}H-coupled and -decoupled ^{13}C NMR spectra were recorded at 100.6 MHz and at 303 K, the data being obtained with the nuclear Overhauser effect by use of either gated or continuous composite pulse ^{1}H decoupling, respectively. 2D COSY[48] ^{1}H NMR spectra were acquired by use of 2048 (t_2) × 128 (t_1) point data sets, and a spectral width of 1.6 kHz in both dimensions. ^{1}H–^{13}C chemical-shift correlations over one bond and over multiple bonds were made by the ^{1}H-detected (inverse mode) 2D HMQC[49] and 2D HMBC[50] methods, respectively. Data sets of 2048 (t_2) × 256 (t_1) points were used together with spectral widths of 2.4 and 12 kHz in the F_2 (^{1}H) and F_1 (^{13}C) dimensions, respectively. All 2D data sets were zero-filled to twice the initial size in the t_1 dimension.

TLC was carried out using pre-coated sheets (Merck silica gel 60, layer thickness 0.2 mm, catalogue No. 5735) which, after development, were viewed in a Chromato-Vue UV illumination chamber. Merck silica gel 60 (0.063–0.200 mesh) was used for column chromatography. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan. Extracts were dried over $MgSO_4$.

Cyclobutanetetraone Tetrakis(phenylhydrazone) **3**.—(a) *Neat.* A suspension of squaric acid **1** (0.57 g, 5 mmol) in phenylhydrazine (2.16 g, 20 mmol) was boiled under reflux for 4 min. The brownish solid that formed upon cooling was stirred with ethanol (10 cm^3) for 1 h, and the red crystals which then separated were filtered off, washed successively with ethanol and diethyl ether, and dried (0.77 g, 33%). Recrystallization from CH_2Cl_2 gave *compound* **3** as red needles, m.p. 301–302 °C; (lit.,[43] 225 °C); R_f 0.95 in CH_2Cl_2, sparingly soluble in DMF, DMSO, tetrahydrofuran (THF), $CHCl_3$, and EtOH; λ_{max}-(CH_2Cl_2)/nm 474 (log ε 4.90), 322sh (4.69), 302 (4.76) and 278 (4.75); ν_{max}(KBr)/cm^{-1} 1597 and 1487 (phenyl ring), 1558 (NH bending) and 1260 (C–N); *m*/*z* 472 (M^+, 44%), 379 (10), 287 (20), 274 (14), 105 (42), 93 (65), 92 (82) and 77 (100) (Found: C, 71.1; H, 5.3; N, 23.6. $C_{28}H_{16}N_8$ requires C, 71.17; H, 5.12; N, 23.71%).

(b) *In DMF.* A solution of squaric acid (0.57 g, 5 mmol) in DMF (5 cm^3) was treated with phenylhydrazine (1.08 g, 10 mmol) and the mixture was boiled under reflux for 40 min. The

* Certain commercial equipment, instruments, or materials are identified in this paper to specify adequately the experimental procedure. Such identification does not imply recommendation by the National Institute of Standards and Technology, nor does it imply that the materials or equipment are necessarily the best available for the purpose.

tetrakis(phenylhydrazone) **3** that separated was filtered off, washed successively with methanol and diethyl ether, and then dried at room temperature (0.36 g, 15.2%). Recrystallization from CH_2Cl_2 gave compound **3** as red needles, m.p. and mixed m.p. 301–302 °C. Upon addition of water (30 cm^3), the filtrate of the reaction mixture afforded 1-anilino-3-(*N*,*N*-dimethylamino)cyclobutenediylium-2,4-diolate (0.09 g). Recrystallization from MeOH–$CHCl_3$ gave *yellow needles*, m.p. 273–274 °C (lit.,[9] 273.5–274 °C); ν_{max}(KBr)/cm^{-1} 1620–1590 (diolate); *m*/*z* 216 (M^+, 7%), 104 (91), 85 (40) and 77 (34) (Found: C, 66.4; H, 6.0; N, 12.9. $C_{12}H_{12}N_2O_2$ requires C, 66.66; H, 5.60; N, 13.08%).

Cyclobutanetetraone Tris(phenylhydrazone) **4a**/**4b**.—(a) *From squaric acid.* To a solution of squaric acid (0.57 g, 5 mmol) in methanol (100 cm^3) was added phenylhydrazine (0.86 g, 8 mmol), and the mixture was heated at 50 °C for 4 h. The solid that formed was filtered off, washed with methanol, and dried. The resulting dark brown solid was then dissolved in $CHCl_3$ (20 cm^3) and chromatographed on a column (2 × 20 cm) of silica gel eluted with CH_2Cl_2. The violet fraction was concentrated and the resulting crystals (120 mg, 6.2%) were recrystallized from $CHCl_3$ as *violet needles*, m.p. 231–232 °C, R_f 0.76 in CH_2Cl_2; soluble in $CHCl_3$, THF, DMF, and sparingly soluble in ethanol; λ_{max}(CH_2Cl_2)/nm 620sh (log ε 4.0), 526 (4.64), 330sh (4.09 and 278 (4.47); ν_{max}(KBr)/cm^{-1} 3256 (NH), 1740 (C=O), 1600, 1484 (phenyl ring) and 1260 (C–N); *m*/*z* 382 (M^+, 60%), 289 (14), 276 (10), 212 (18), 105 (18), 93 (60), 92 (100) and 77 (80) (Found: C, 68.85; H, 5.0; N, 21.65. $C_{22}H_{18}N_6O$ requires C, 69.09; H, 4.74; N, 21.97%).

(b) *From dibutyl squarate.* To a solution of dibutyl squarate (2.26 g, 10 mmol) in methanol (50 cm^3) was added phenylhydrazine (3.24 g, 30 mmol), and the mixture was kept at room temperature for 4 h. The crystals that separated were filtered off, washed with methanol, and dried (1.52 g, 40%). After purification by column chromatography and crystallization as before, the mixed product **4a**/**4b** had m.p. and mixed m.p. 231–232 °C.

Cyclobutanetetraone 1,3-*Bis(phenylhydrazone)* **5**.—A suspension of cyclobutanetetraone (0.92 g, 5 mmol) in methanol (20 cm^3) and phenylhydrazine (1.25 g, 1.15 mmol) was heated at 60 °C for 10 min. The blue crystals that separated on cooling were filtered off, washed successively with methanol and diethyl ether, and dried (0.80 g, 55%). Recrystallization from $CHCl_3$ gave *compound* **5** as dark blue needles, m.p. 196 °C; R_f 0.36 in CH_2Cl_2; soluble in THF and 1,4-dioxane, and sparingly soluble in ethanol; λ_{max}(CH_2Cl_2)/nm 570sh (log ε 3.86) and 540 (3.88); ν_{max}(KBr)/cm^{-1} 3215 (NH), 1650 (C=O), 1593, 1473 (phenyl ring) and 1274 (C–N); *m*/*z* 292 (M^+, 45%), 200 (18), 145 (25), 119 (39), 93 (100), 77 (72) and 65 (48) (Found: C, 65.6; H, 4.2; N, 19.1. $C_{16}H_{12}N_4O_2$ requires C, 65.75; H, 4.14; N, 19.19%).

Quinoxaline Derivative of Cyclobutanetetraone 1,3-*Bis(phenylhydrazone)*, *Compound* **7**.—To a solution of cyclobutanetetraone 1,3-bis(phenylhydrazone) (2 g, 6.8 mmol) in DMF (10 cm^3) was added *o*-phenylenediamine (0.74 g, 6.8 mmol), and the mixture was boiled under reflux for 1 h. The oily syrup remaining after evaporation was extracted twice with diethyl ether (20 cm^3), and once with methanol (10 cm^3). The solid formed (1.40 g, 52.9%) was recrystallized from $CHCl_3$ and then from ethanol to give the *quinoxaline* **7** as yellow needles, m.p. 222–223 °C; λ_{max}(95% EtOH)/nm 414 (log ε 3.81), 338 (4.10), 270sh (4.45) and 252 (4.74); ν_{max}(KBr)/cm^{-1} 3260 (NH) and 1680 (C=O); *m*/*z* 380 (M^+, 90%), 273 (100), 245 (46), 220 (12), 166 (10) and 77 (33) (Found: C, 69.55; H, 4.4; N, 22.0. $C_{22}H_{16}N_6O$ requires C, 69.46; H, 4.24; N, 22.09%).

Cyclobutanetetraone 1,3-*Bis*-(N-*methyl*-N-*phenylhydrazone*) **8**.—To a suspension of cyclobutanetetraone (0.92 g, 5 mmol) in ethyl alcohol (20 cm^3) containing conc. HCl (2 drops) was added a solution of *N*-methyl-*N*-phenylhydrazine (1.22 g, 10 mmol) in ethanol (10 cm^3), and the mixture was stirred at 60 °C for 10 min. The crystals that separated were collected, washed with methanol, and dried (270 mg, 16.9%). Recrystallization from $CHCl_3$ afforded compound **8** as magenta needles, m.p. 251–252 °C; λ_{max}(CH_2Cl_2)/nm 514 (log ε 4.0); ν_{max}(KBr)/cm^{-1} 1672 (C=O); *m*/*z* 320 (M^+, 15%), 214 (15), 159 (58), 132 (28), 106 (100) and 77 (85) (Found: C, 67.55; H, 5.1; N, 17.4. $C_{18}H_{16}N_4O_2$ requires C, 67.49; H, 5.03; N, 17.49%).

Cyclobutanetetraone 1,3-*Bis*-(N,N-*diphenylhydrazone*) **9**.—A mixture of cyclobutanetetraone (2 g, 10.8 mmol) in water (5 cm^3) and *N*,*N*-diphenylhydrazine hydrochloride (5.2 g) in methanol (30 cm^3) was heated at 60 °C for 10 min. The crystals that separated on cooling were filtered off, washed with methanol, and dried (1.58 g, 33%). Recrystallization from $CHCl_3$ furnished *title compound* **9** as dark green needles, m.p. 267–268 °C; λ_{max}(CH_2Cl_2)/nm 538 (log ε 4.9); ν_{max}(KBr)/cm^{-1} 1685; *m*/*z* 444 (M^+, 11%), 276 (32), 249 (25), 221 (55), 168 (100) and 77 (25) (Found: C, 75.5; H, 4.5; N, 12.6. $C_{28}H_{20}N_4O_2$ requires C, 75.66; H, 4.53; N, 12.60%).

Cyclobutanetetraone 1,3-*Bis*-(N-*methyl*-N-*phenylhydrazone*) 2-*Phenylhydrazone* **10**.—To a suspension of cyclobutanetetraone 1,3-bis-(*N*-methyl-*N*-phenylhydrazone) **8** (400 mg) in methanol (40 cm^3) was added a solution of phenylhydrazine (1.0 g) in methanol (10 cm^3). The mixture was boiled under reflux for 5 h, then left at room temperature overnight. The crystals that separated were filtered off, washed with methanol, and dried. Purification by chromatography on a column of silica gel (2 × 20 cm) eluted with CH_2Cl_2 afforded *title compound* **10** (60 mg, 11.7%), which on recrystallization from $CHCl_3$ gave violet needles, m.p. 229–230 °C; R_f 0.55 in CH_2Cl_2; λ_{max}(CH_2Cl_2)/nm 618sh (log ε 4.16), 504 (4.73), 326sh (4.32) and 278 (4.53); ν_{max}(KBr)/cm^{-1} 1760 (C=O); *m*/*z* 410 (M^+, 38%), 106 (100), 93 (21) and 77 (76) (Found: C, 70.2; H, 5.4; N, 20.3. $C_{24}H_{22}N_6O$ requires C, 70.22; H, 5.40; N, 20.47%).

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