# The reaction of phenylhydrazine with squaric acid: a model for carbohydrate osazone formation

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#### ABSTRACT

The reaction of squaric acid (1) with phenylhydrazine yields cyclobutanetetraone poly(phenylhydrazones) (2-4), as reported earlier, as well as squaric acid derivatives, reported here. The latter products are a salt, 1,3-dianilinocyclobutenediylium-2,4-diolate (5), and 1-anilino-2-phenylhydrazino-cyclobutene-3,4-dione (6), which upon oxidation yields tautomeric forms of cyclobutanetetraone 1-anilide-2-phenylhydrazone (7a and 7b). The structure of the compounds isolated was established by <sup>1</sup>H, <sup>13</sup>C, 2D COSY, and 2D J-resolved NMR spectroscopy. The similarity between the reaction of squaric acid (1) with phenylhydrazine and osazone formation can be seen from the analogy between compounds 2, 6, and 7b and intermediates produced during carbohydrate osazone formation, as well as from the fact that these compounds afford an osazone analog (4) when treated with phenylhydrazine. It was also found that compound 5 can be generated by a retro-osazone reaction when cyclobutanetetraone bis(phenylhydrazone) (2) is heated with aniline.

#### INTRODUCTION

In earlier work<sup>1,2</sup>, we found that the reaction of squaric acid (1) with phenylhydrazine is accompanied by oxidations similar to those that occur during osazone formation. Three derivatives of cyclobutanetetraone, the oxidation product of squaric acid, were isolated. These were cyclobutanetetraone bis-, tris-, and tetrakis(phenylhydrazone) (compounds 2, 3, and 4, respectively). The first derivative (2) proved to be an analog of an intermediate (A), produced during osazone formation<sup>2</sup>.

In the present work, we describe the isolation and structure elucidation of phenylhydrazine and aniline derivatives of squaric acid and of cyclobutanete-

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traone. The importance of aniline derivatives was emphasized by Micheel and Dijong<sup>3</sup>, who suggested that the osazone reaction starts with the formation of anilides.

# RESULTS

We describe here some squaric acid derivatives formed when squaric acid (1) is treated with phenylhydrazine. These are a phenylhydrazine salt obtained when the reaction is carried out in the cold, and two condensation products formed at higher temperatures. The latter products were identified as 1,3-dianilinocyclobutenediylium-2,4-diolate (5), a dianilide obtained previously<sup>4</sup> by treating squaric acid with aniline, and 1-anilino-2-phenylhydrazinocyclobutene-3,4-dione (6), which upon oxidation yielded two tautomers of a cyclobutanetetraone derivative (7a and b). The products isolated were converted into cyclobutanetetraone tetrakis(phenylhydrazone) (4) by heating with phenylhydrazine and two of them (6 and 7) were found to be analogs of osazone intermediates (C and D)<sup>3</sup> (see Scheme 1).

1,3-Dianilinocyclobutenediylium-2,4-diolate (5) was isolated in small amounts from the reaction of squaric acid with phenylhydrazine. It was also formed when cyclobutanetetraone 1,3-bis(phenylhydrazone) (2) was heated in aniline, by what seems to be a new retro-osazone reaction. Like other squaraines<sup>4,5</sup> (1,3-diaminosquaric acid derivatives), it does not exhibit any carbonyl absorption band in the IR spectrum. Simple <sup>1</sup>H and <sup>13</sup>C NMR spectra (one type of phenyl and ring C=O) were observed for 5 because of two-fold symmetry caused by contributions from resonance forms such as the bond delocalized **5a** (Scheme 2), which would exhibit internally equivalent pairs of anilino, ring C-N, and C-O groups<sup>5</sup> (for <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts, see Tables I and II, respectively).

The mixed aniline phenylhydrazine derivative, 1-anilino-2-phenylhydrazinocyclobutene-3,4-dione (6) was isolated in small amount by preparative column chromatography. Larger samples needed for structure elucidation were prepared by treating squaric acid methyl or butyl ester with aniline<sup>6,7</sup> and reacting the anilino ester thus formed with phenylhydrazine. The mass spectrum of 6 showed a molecular ion at m/z 279 and its IR spectrum two carbonyl absorption bands, which is characteristic of 1,2-disubstituted squaric derivatives. <sup>1</sup>H and <sup>13</sup>C NMR spectra of 6 in tetrahydrofuran- $d_8$  (THF- $d_8$ ) solution disclosed the presence of three NH groups, two types of phenyl groups and two different C=O groups and two different C-N groups in the four-membered ring. <sup>1</sup>H NMR assignments were established from two-dimensional (2D) COSY and J-resolved experiments and <sup>13</sup>C assignments were supported by measurements of <sup>1</sup>H coupled <sup>13</sup>C NMR spectra. Evidence of tautomeric forms of 6 was revealed by its spectra in Me<sub>2</sub>SO- $d_6$ solution which showed four broad NH signals having fractional intensities, and a sharp NH resonance with unit intensity.

Oxidation of 1-anilino-2-phenylhydrazinocyclobutene-3,4-dione (6) with p-benzoquinone afforded cyclobutanetetraone 1-anilide-2-phenylhydrazone (7). Its mass



Scheme 1.

spectrum showed a molecular ion at m/z 277, and its IR spectrum, a strong carbonyl absorption band at 1775 cm<sup>-1</sup>, with a shoulder at 1740 cm<sup>-1</sup>. The <sup>1</sup>H NMR spectrum of a solution of 7 in CDCl<sub>3</sub> indicated that it exists in CDCl<sub>3</sub> as a 92:8 mixture of two tautomers, unchanged after 66 h. In previous papers<sup>1,2</sup>, we reported that phenyl-azo, -hydrazono, and -hydrazino groups can often be distinguished by measurement of their <sup>1</sup>H chemical shifts, because the H<sub>o</sub> protons of



Scheme 2.

Derivative	Solvent	Туре	H <sub>o</sub>	H <sub>m</sub>	H <sub>p</sub>	NH
5	(CD <sub>3</sub> ) <sub>2</sub> SO	diylium	7.785	7.378	7.125	~ 11.034, 8.190 <sup>b</sup>
6	C <sub>4</sub> D <sub>8</sub> O	anilino	7.420	7.203	6.920	7.525
		hydrazino	6.958	7.244	6.901	9.299, 8.260
	$(CD_3)_2SO$	anilino	7.393	7.311	7.030	10.307, 9.620
		hydrazino	6.856	7.232	6.847	9.129, 9.021, 8.267
7 <b>a</b> (92%)	CDCl <sub>3</sub>	azo	7.981	~ 7.579	~ 7.579	
	5	anilino	~ 7.562	7.470	7.298	10.047
<b>7b</b> (8%)		hydrazono	7.896			8.798
		anilide	7.709		7.342	
7b (55%)	$(CD_3)_2SO$	hydrazono	7.773	~ 7.602	~ 7.602	12.108
	· -	anilide	7.706	7.504	7.330	
7a (45%)		azo	8.060	~ 7.647	~ 7.647	11. <b>460</b>
		anilino	7.583	7.475	7.315	

 TABLE I

 <sup>1</sup>H NMR chemical shifts <sup>a</sup> of squaric acid derivatives

<sup>a</sup> Measured in ppm from internal tetramethylsilane. <sup>b</sup> Minor signal of possible tautomer.

#### TABLE II

<sup>13</sup>C NMR chemical shifts <sup>a</sup> of squaric acid derivatives

Derivative	Solvent	Туре	C-1 (phenyl)	C <sub>o</sub>	C <sub>m</sub>	C <sub>p</sub>	CN (4-ring)	C=0
5	(CD <sub>3</sub> ) <sub>2</sub> SO	diylium	Ь	119.66	128.84	123.31	Ь	159.70 (C-O)
6 <sup>c</sup>	C <sub>4</sub> D <sub>8</sub> O	anilino hydrazino	149.54 140.34	119.30 115.04	129.95 129.69	123.25 122.19	165.40 170.61	181.51 182.88
7a <sup>d</sup>	CDCl <sub>3</sub>	anilino azo	153.13 136.11	120.00 123.90	129.96 129.68	126.92 133.79	167.52 172.39	186.31 190.03
7b <sup>d</sup>		anilide hydrazono		120.55 123.83	129.55 129.37			

<sup>a</sup> Measured in ppm from internal tetramethylsilane. <sup>b</sup> Not detected because of low solubility. <sup>c</sup> <sup>1</sup>H coupled <sup>13</sup>C NMR spectra showed triplets  $[J(C-1, H_m) 8.9 \text{ Hz}]$  for C-1 of the phenyl rings, doublets [J(C-N, NH) 4.1 and 7.3 Hz] for the C-N carbons, a singlet and a doublet [J(C=O, NH) 5.2 Hz] for the C-O carbons, and appropriate values for <sup>1</sup>J(CH) of the phenyl rings. <sup>d</sup> Some assignments were confirmed by <sup>1</sup>H coupled <sup>13</sup>C NMR spectra, which showed triplets  $[J(C-1, H_m) 6.2 \text{ and } 9.3 \text{ Hz}]$ , respectively] for the C-1 carbons of the phenyl groups, singlets for the CN carbons and one of the C=O groups.

Fig. 1. Partial <sup>1</sup>H NMR spectrum of cyclobutanetetraone, 1-anilide-2-phenylhydrazone tautomers 7a and 7b in  $Me_2SO-d_6$  solution at 400 MHz; (A) 1D spectra and 2D COSY-45 contour spectrum showing connectivities of the aromatic protons, and (B) 2D *J*-resolved contour spectrum showing separation of overlapped spin multiplets and the unique *J*-spectra of the virtually coupled spin-system. The o, m, and p protons of the anilino and anilide groups are primed, while those of the phenylazo and phenylhydrazono groups are unprimed.



these groups tend to resonate in the ranges  $\delta$  7.5–8.5, 7.2–7.6, and 6.7–7.1, respectively. Shielding of H<sub>a</sub> in phenylhydrazino groups is borne out by the data for compound 6 ( $\delta \sim 6.9$ , see Table I). The intense H<sub>a</sub> doublet at lowest field ( $\delta$ 7.98) in the spectrum of 7 was assigned to a preponderant phenylazo cyclobutene tautomer 7a and the minor signals at the 8% level were assigned to the phenylhydrazone anilide tautomer 7b. The <sup>13</sup>C NMR spectrum of 7 in CDCl<sub>3</sub> displayed major signals for two C=O groups, two CN groups, and two phenyl groups, together with four minor signals ( $C_o$  and  $C_m$ ) in the protonated aromatic carbon region (see Table II). Quite different proportions of tautomers were observed for solutions of 7 in Me<sub>2</sub>SO- $d_6$ . The <sup>1</sup>H NMR spectrum of 7 in this solvent shows two strong NH resonances at low field, with an integration ratio of 55:45 (see Table I). The aromatic proton region (see Fig. 1A) displays four types of phenyl resonances that can be paired into two sets having relative intensities of 55:45, unchanged by storage of the solution for 27 h. The two  $H_{o}$  multiplets at lowest field are of the virtually coupled type<sup>8,9</sup> due to strong coupling (severe overlap, large  $J/\delta$  ratio) of H<sub>m</sub> and H<sub>n</sub> on the same phenyl ring. These multiplets may be recognized by the presence of strong lines in the center of the multiplet. Several of the overlapped multiplets shown in Fig. 1A were separated by a 2D J-resolved experiment (see Fig. 1B), although the non-first order character of the virtually coupled spin systems causes the essentially isochronous  $H_m$  and  $H_p$  spins to appear with complex multiplet patterns that are very different to those of the well separated first order  $H_m$  and  $H_p$  triplets at higher field. The internal <sup>1</sup>H assignments for the four types of phenyl groups were indicated by a 2D COSY spectrum (see Fig. 1A), which shows clearly resolved cross multiplets of the two first order  $H_{a}$  doublets with their respective H<sub>n</sub> protons, but only combination cross multiplets of the virtually coupled  $H_{a}$  protons with their corresponding isochronous  $H_{m}H_{n}$  pairs. In Me<sub>2</sub>SO- $d_6$  solution, the H<sub>a</sub> multiplet at lowest filed ( $\delta$  8.06) is the less intense, thus indicating that in this solvent, the phenylazoene 7a is the minor tautomer, in contrast to its preponderance in CDCl<sub>3</sub>.

### DISCUSSION

The accepted mechanisms of osazone formation<sup>10</sup> fall into two main categories. The first proceeds by oxidation of the saccharide moiety with phenylhydrazine salts<sup>11,12</sup>. This is exemplified by the mechanism of Micheel and Dijong<sup>3</sup>, in which 1-anilino-1,2-dideoxy-2-phenylhydrazino-glycosene (C), an analog of compound **6** is oxidized by phenylhydrazine hydrochloride to give an imino hydrazone (D), which is an analog of compound **7b**. In the second type of mechanism<sup>13</sup>, the aldose phenylhydrazone undergoes tautomerization to a 1-deoxy-1-phenylhydrazino ketose, and oxidation by atmospheric oxygen to an aldosulose monophenylhydrazone<sup>14</sup> (**A**), an analog of compound **2** (or elimination of aniline to give an imino ketose<sup>13</sup>), before reacting with phenylhydrazine to give osazones (**B**).

From the foregoing discussion, it is seen that the reaction of squaric acid with phenylhydrazine affords analogs 2, 6, and 7 of osazone intermediates A, C, and D,

respectively, which suggests that the mechanisms of the two reactions are quite similar. There are, however, two differences. One is the ability of phenylhydrazine base to react with squaric acid to give cyclobutanetetraone tetrakis(phenylhydrazone) (4), but not with aldoses to afford osazones. This is because phenylhydrazones enolize in acid media but not in basic media<sup>15,16</sup>, so the strongly acidic squaric acid phenylhydrazone is able to enolize in the presence of phenylhydrazine base, whereas aldose phenylhydrazones need an acid such as phenylhydrazine hydrochloride to do so. Secondly, there is no report in the carbohydrate literature of a retro-osazone reaction such as the one observed when cyclobutanetetraone 1,3-bis(phenylhydrazone) (2) was heated with aniline to give compound 5. The conversion of a carbohydrate osazone to an Amadori compound with aniline has never been reported, and when attempted in this work, did not succeed. The reason for this might be the greater susceptibility of carbohydrate derivatives to the high temperatures used in this reaction. A plausible mechanism for the conversion of cyclobutanetetraone 1,3-bis(phenylhydrazone) (2) to a squaric acid derivative, namely 1,3-dianilino-cyclobutenediylium-2,4-diolate (5), by heating with aniline would start with the addition of aniline to one of the phenylhydrazone residues to give a mixed 1-anilino-1-phenylhydrazino derivative (8), which is an analog of 1,1-bis(anilino)aldoses generated during osazone formation<sup>3</sup>. Loss of the

phenylhydrazino group by formation of nitrogen and benzene, affords 1-anilino-3phenylhydrazinocyclobutene-4-one-2-ol (9), which can readily undergo transamidation to give 1,3-dianilinocyclobutenediylium-2,4-diolate (5).

# EXPERIMENTAL

General. — Melting points were determined with a Kofler-block apparatus and are uncorrected. Mass spectra were recorded by using a Hewlett-Packard\* 5995 GC-MS spectrometer in the EI mode. Infrared spectra were measured by use of a BIO-RAD FTS-7 (SPC-3200) FT-IR spectrophotometer calibrated with polystyrene. NMR spectra were acquired by means of a Bruker Instruments Model WM-400 spectrometer, equipped with an Aspect 3000 data system, and a process controller. 1D <sup>1</sup>H NMR spectra were measured at 400 MHz and at 300 K, by using a 30° pulse (3.3-4.0  $\mu$ s), a spectral with of 8.065 kHz, a pulse recycle time of 5-6 s, and a 32768 point data set. <sup>1</sup>H-decoupled, 1D <sup>13</sup>C NMR spectra were recorded at 100.6 MHz and at 303 K. <sup>1</sup>H coupled <sup>13</sup>C NMR data were obtained with the nuclear Overhauser effect by use of gated decoupling. 2D COSY <sup>1</sup>H NMR spectra were acquired by use of a 45° mixing pulse (3-5  $\mu$ s), 1024, 2048, or 4096 ( $t_2$ ) × 512 or 1024 ( $t_1$ ) point data sets, zero-filled to 1024 or 2048 points in the  $t_1$  dimension. 2D J-Resolved <sup>1</sup>H NMR spectra were measured using 4096 or 8192 ( $t_2$ ) × 128 ( $t_1$ )

<sup>\*</sup> Certain commercial equipment, instruments, and materials are identified in this paper in order 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.

point data sets, zero-filled to 256 points in the  $t_1$  dimension. Thin layer chromatography was carried out using pre-coated sheets (Merck Silica Gel 60, layer thickness 0.2 mm, catalog no. 5539) purchased from Thomas Scientific Co. and viewed in a Chromato-Vue UV illumination chamber, and for column chromatography, Merck Silica Gel 60 (0.063–0.200 mesh) was used. Microanalyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Michigan.

Starting materials and reagents. — Dimethylsquarate was prepared by treating the silver salt of squaric acid with MeI as described by Cohen and Cohen<sup>17</sup>, and 1,3-dianilinocyclobutenediylium-2,4-diolate was prepared by heating squaric acid with aniline in N,N-dimethylformamide (DMF) under reflux<sup>4</sup>.

Bis(phenylhydrazinium) squarate. — This salt was obtained by adding an ice-cold solution of squaric acid (1.14 g, 10 mmol) in DMF (6 mL) to a precooled solution of phenylhydrazine (2.16 g, 20 mmol) in DMF (4 mL) and keeping the clear solution in an ice bath for 10 min. Ether (25 mL) was then added to precipitate the salt (3.14 g, 95%), which was filtered, washed with MeOH and ether, and recrystallized from water as plates, mp 139°C. Anal. Calcd for  $C_{16}H_{18}N_4O_4$ : C, 58.17; H, 5.49; N, 16.96. Found: C, 58.06; H, 5.85; N, 16.93.

When a solution of the salt (2.36 g) in MeOH (100 mL) was refluxed for 4 h, cyclobutanetetraone tetrakis(phenylhydrazone) (4) precipitated. It was filtered, washed successively with MeOH and ether, and dried; (0.28 g, 17%). Higher yields were obtained by adding phenylhydrazine to the mixture. After recrystallization from  $CH_2Cl_2$ , the red crystals of 4 had mp and mixed mp 301–302°C (lit.<sup>1,2</sup> mp 301–302°C).

Formation of 1,3-dianilinocyclobutenediylium-2,4-diolate (5). — (a) From squaric acid and phenylhydrazine. A solution of squaric acid (1.14 g, 10 mmol) and phenylhydrazine (2.16 g, 20 mmol) in methanol (50 mL) was refluxed for 24 h. The reddish crystals that separated were filtered, washed with methanol, and dried. Some compound 4 was removed from the mixture by extraction with THF and the yellow residue was then recrystallized from Me<sub>2</sub>SO or DMF as needles mp > 350°C. The IR spectrum was identical with that of an authentic sample of 5, prepared by refluxing squaric acid with aniline<sup>4</sup>.

(b) By a retro-osazone reaction. A suspension of cyclobutanetetraone 1,3bis(phenylhydrazone) (2) (200 mg 0.7 mmol) in aniline (1 mL) was heated at 155°C for 15 min. The yellowish solid that formed was washed with THF, recrystallized from Me<sub>2</sub>SO, and dried (29 mg, 17%, mp > 350°C. The product was identical in all respects with the authentic sample prepared before. Anal. Calcd for  $C_{16}H_{12}N_2O_2$ : C, 72.72; H, 4.58; N, 10.60. Found: C, 72.78; H, 4.62; N, 10.61.

1-Anilino-2-phenylhydrazinocyclobutene-3,4-dione (6). — To a solution of 1anilino-2-butoxycyclobutene-3,4-dione<sup>18</sup> (0.71 g, 5 mmol) in DMF (5 mL) was added phenylhydrazine (0.53 g, 2.9 mmol). The solution was heated at 70°C for 30 min and then kept at room temperature for a further 30 min. After cooling in an ice bath, water (30 mL) was added and the solid formed was collected, washed with MeOH, and dried (0.74 g, 91.4%). An identical product was obtained by reacting 1-anilino-2-methoxycyclobutene-3,4-dione with phenylhydrazine in the same way. Both products were recrystallized from THF as white needles; mp 210–212°C;  $\nu_{max}^{KBr}$ 1785 (C=O), 1670 (C=O), and 1600 cm<sup>-1</sup> (phenyl ring);  $\lambda_{max}$  406 (2.81), 316 (3.5), 296 (sh) (3.48), and 228 (3.28) nm (log  $\epsilon$ ), and  $\lambda_{min}$  256 (2.9), and 376 (3.9) nm (log  $\epsilon$ ) in 95% EtOH. Anal. Calcd for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>: C, 68.81; H, 4.69; N, 15.04. Found: C, 68.78; H, 4.78; N, 15.09.

Treatment of this product with phenylhydrazine yielded cyclobutanetetraone tetrakis(phenylhydrazone) (4), mp and mixed mp 301-302°C.

Oxidation of 6 to cyclobutanetetraone 1-anilide-2-phenylhydrazone (7). — To a solution of 1-anilino-2-phenylhydrazinocyclobutene-3,4-dione (6) (1.40 g, 5 mmol) in THF (50 mL) was added p-benzoquinone (0.54 g, 5 mmol), and the solution was boiled under reflux for 10 min. Evaporation of the mixture followed by extraction of the residue with EtOH afforded 7 in 52% yield. It was recrystallized from THF as red needles; mp 175–176°C;  $\nu_{max}^{KBr}$  1775 (C=O) and 1740 cm<sup>-1</sup> (C=O);  $\lambda_{max}$  292 (3.34) and 432 (3.29) nm (log  $\epsilon$ ), and  $\lambda_{min}$  360 (2.86) nm (log  $\epsilon$ ) in CH<sub>2</sub>Cl<sub>2</sub>. Anal. Calcd for C<sub>16</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>: C, 69.30; H, 4.00; N, 15.15. Found: C, 69.21; H, 4.05, N, 15.09.

Treatment of 7 with phenylhydrazine yielded cyclobutanetetraone tetrakis-(phenylhydrazone) (4).

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