THE MECHANISM OF FORMATION OF TRIS(PHENYLHYDRAZONES) ON TREATMENT OF CYCLOHEXANE-1,3-DIONES WITH PHENYLHYDRAZINE*†

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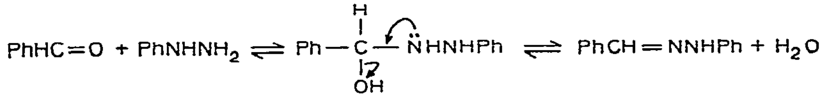
ABSTRACT

Treatment of the enolic cyclohexane-1,3-diones in aqueous acetic acid with an excess of phenylhydrazine at room temperature gave mixtures of the corresponding 2-oxo-1,3-bis(phenylhydrazone) and tris(phenylhydrazone) derivatives in low to moderate yield. E.s.r. study of the reaction path indicated that free-radical anionic intermediates are partially involved. Treatment of an enolic cyclohexane-1,2-dione (or of α-hydroxy or α-acetoxycyclohexanones) with phenylhydrazine gave mixtures of the corresponding mono- and bis(phenylhydrazones); formation of radical-anions was also observed in these reactions.

INTRODUCTION

The mechanism of formation of sugar phenylosazones, or the related bis(phenylhydrazones) from α-hydroxycarbonyl or dicarbonyl compounds (cyclic or acyclic), respectively, has been under study for over eighty years. Since the first preparation of a sugar osazone[1] and the pioneer work by Emil Fischer on the mechanism of formation of sugar osazones[2], their formation has been extensively studied[3,4]. The mechanism of formation of the sugar osazones remains of continuing interest[3].

A recent kinetic study[5] clarifies the mechanism of formation of the aromatic phenylhydrazones. For example, in formation of benzaldehyde phenylhydrazone, as in formation of semicarbazones, thiosemicarbazones, oximes, and Schiff bases, attack of the nucleophile is rate-determining under slightly acidic conditions, and dehydration of the carbinolamine intermediate is rate-determining under neutral and basic conditions. Dehydration of the carbinolamine intermediate exhibits both acid-catalyzed and pH-independent reactions, and the overall reaction is catalyzed by hydrated protons, carboxylic acids, phenylhydrazinium ions, and water.



$$PhHC{=}O + PhNHNH_2 \rightleftharpoons Ph-\overset{H}{\underset{OH}{C}}-\ddot{N}HNHPh \rightleftharpoons PhCH{=}NNHPh + H_2O$$

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During the last three decades, considerable progress has been achieved in elucidating the pathways of formation of the sugar osazones. Beginning with a direct oxidation mechanism of Fischer[2,3], the stepwise mechanism of Weygand[6] is now generally favored. Two pathways of this mechanistic approach[6], that involve tautomerizations (an Amadori rearrangement[3]), probably involve also such key reaction-intermediates as a hydrazino enol–keto imine (path A)[3] or a hydrazino hydrazone-ene bis(hydrazine) compound (path B)[3]; both of these pathways require elimination of aniline and ammonia.

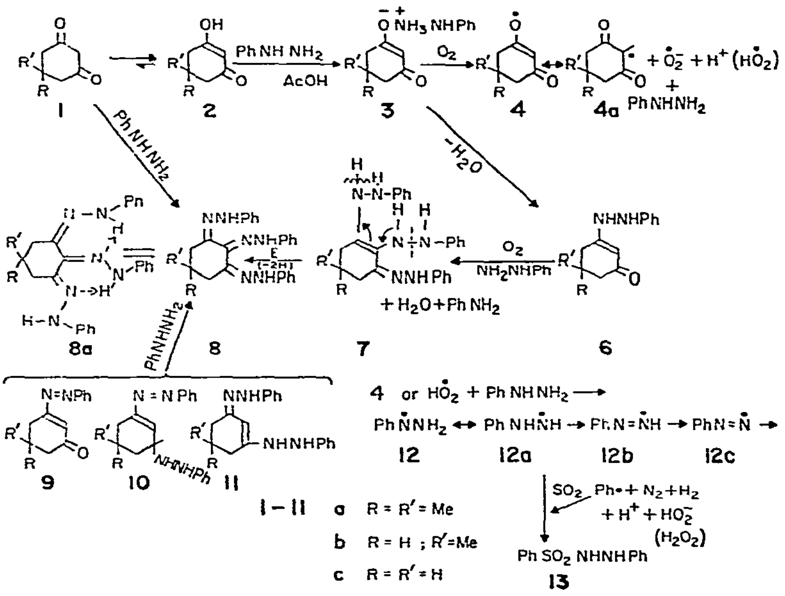
Recent studies on this subject have been concerned with formation of the cyclic bis(phenylhydrazones); arylazoalkenes have been postulated as intermediates in the formation of bis(phenylhydrazones) from α-acetoxycyclohexanone[7,8] or from α-substituted ketosteroids[9]. However, *none* of these studies on mechanism adequately considered two important points: (1) the role of atmospheric oxygen in the formation of bis(phenylhydrazones), and (2) the possible participation of free-radical intermediates. For example, Iffland and coworkers[10a] studied the kinetics of conversion of aromatic hydrazones into azo derivatives following treatment with lead tetraacetate; these authors formulated a free-radical mechanism. Norman and coworkers[10b] studied the same reaction by application of e.s.r. spectrometry and found an ionic mechanism. The auto-oxidation of phenylhydrazones at room temperature to produce phenylazo-hydroperoxides is now well established[3,11].

In the formation of sugar osazones, participation of atmospheric oxygen is somewhat less apparent, and, from our preliminary e.s.r. studies, it appears that the formation of sugar or inosose osazones may not involve a free-radical intermediate. However, the formation of cyclic bis(phenylhydrazones), as in the cyclohexane or steroid series, indeed involves oxygen participation, and probably proceeds through free-radical intermediates. Consequently, some of the ionic mechanisms previously reported should be reexamined.

RESULTS AND DISCUSSION

It was observed in this laboratory that, when colorless solutions of enolic cyclohexane-1,3-diones (compounds **1a** to **1c**) in glacial or aqueous acetic acid, benzene, or chloroform (see Experimental) are mixed with phenylhydrazine and kept in air (or even in sealed ampoules), the solutions soon turned orange and then deep red. Gradual dilution of these colored solutions with water (after they were 24–48 h old) gave at first yellow, microcrystalline powders identified as tris(phenylhydrazones) (compounds **8a**–**8c**) in 5–48% yield. Monitoring of each solution by its visible spectrum or by t.l.c. showed the presence of at least two colored components: a yellow one [a tris(phenylhydrazone)] and a red one; the nature of the latter will be discussed later in this paper.

Monitoring of these solutions, particularly those prepared in aqueous acetic acid, by e.s.r. spectrometry showed a five-line pattern; the paramagnetic species was the phenylazo radical **12c**, identified by its coupling constant (a^N ~4.7 gauss), by trapping with nitrosobenzene[12], and by direct isolation[13] as *N*-phenyl-*N*-phenylsulfonylhydrazide (compound **13**). A reasonable reaction-mechanism for the formation of the tris(phenylhydrazone) (**8**) involves the enol **2** and an anion **3**. Competition for the anion **3** leads to two simultaneous reactions: (1) an electron exchange with oxygen to give a free radical (**4**↔**4a**) that is involved in the formation of compound **17a**, and (2) formation of a phenylhydrazino intermediate **6**. The latter, on further interaction with phenylhydrazine (or its anion) via intermediates **9**, **10**, and **11** would give the unsaturated bis(hydrazino)-hydrazone **7**. Thence, the reaction can proceed directly to the tris(hydrazone) **8a** by an ionic mechanism, either by the Weygand path B (splitting of a molecule of aniline, which actually was found in the reaction mixture), or by an elimination reaction and the chelate-ring stabilization effect.



Scheme 1

The foregoing mechanism is supported by the fact that compounds **6**, **9**, **10** (not isolated), and **11**, on treatment with phenylhydrazine and acetic acid, give as the sole product the tris(phenylhydrazone) **8** (see Experimental), presumably by an ionic, 1,4-addition of phenylhydrazine to the conjugated ene-azo system[7,14]. This ionic mechanism is supported by the failure to detect, in these solutions, paramagnetic species such as were observed for cyclohexane-1,3-diones.

The presence of acetic acid (or phenylhydrazinium acetate) was found necessary for the conversion of compounds **6**, and **9**–**11** into the tris(phenylhydrazone) **8**; no formation of **8** was observed when the reaction with phenylhydrazine in methanol, benzene, or chloroform was conducted without acetic acid or in the presence of a stronger acid. The catalytic effect of acetic acid was also observed in the conversion of 1-phenylhydrazino-2-cyclohexene into the 1,2-bis(phenylhydrazone)[7].

Mixing cyclohexane-1,3-diones with phenylhydrazine in nonpolar solvents produced red solutions that showed (e.s.r.) little or no paramagnetic component

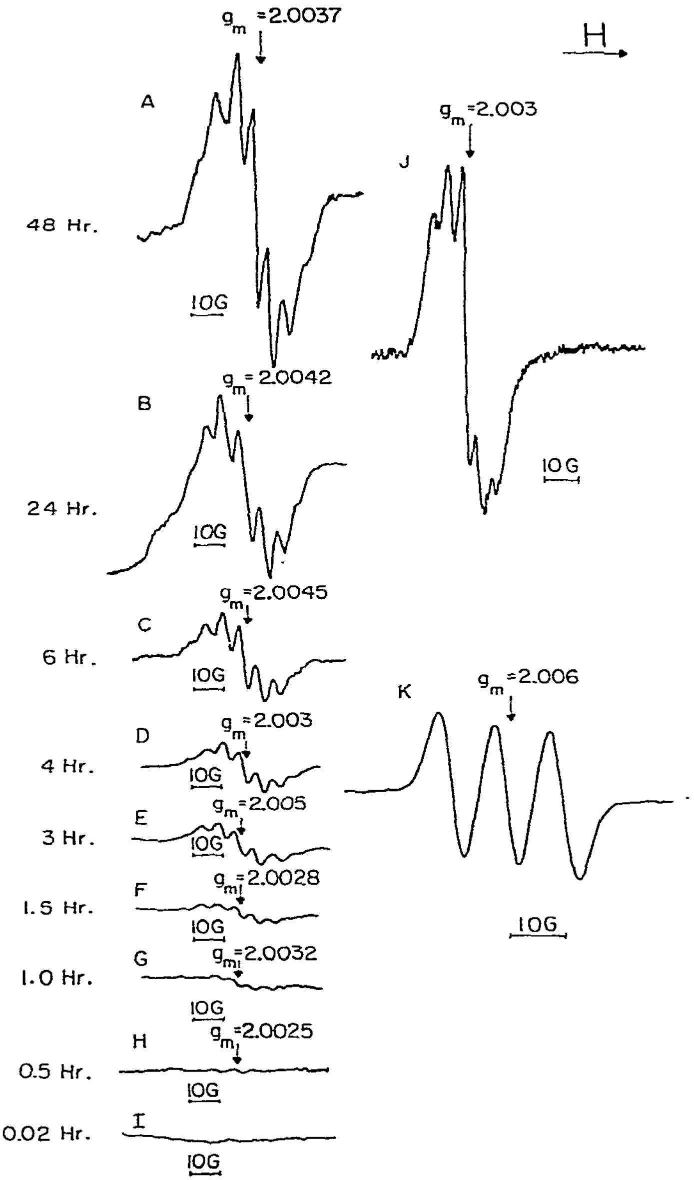
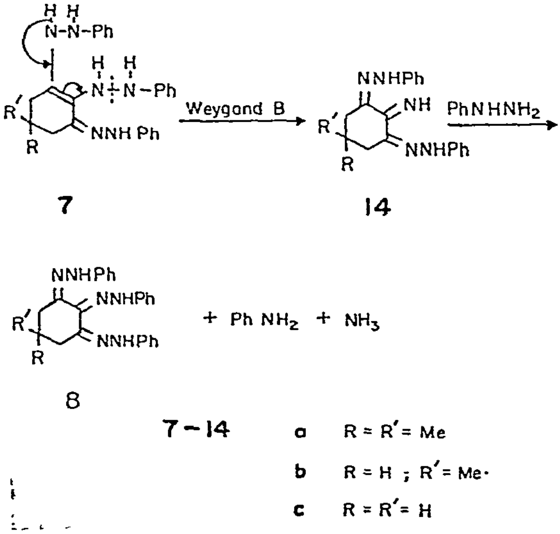


Fig. 1. E.s.r. spectra (I to A) of the paramagnetic species formed in a 10 mM mixture of **1a** and phenylhydrazine in glacial acetic acid; J is a similar spectrum derived from **1b**; K is for a benzene-nitroxide radical (trapping of radicals I to A).

present. For example, a mixture of dimedone and phenylhydrazine in chloroform showed after 24 h only a small peak in the e.s.r. spectrum, and a still smaller peak was observed in benzene. This may be ascribed to instability of the observed radical-anions in nonpolar solvents and their ready interaction with oxygen to give peroxides.

The actual "growth" of the paramagnetic species with time for an approximately 10 mM, 1:1 mixture of 5,5-dimethyl-1,3-cyclohexanedione (**1a**) and phenylhydrazine in glacial acetic acid is shown in Fig. 1 (e.s.r. spectra I to A). The presence of this paramagnetic species was noted less than 30 min after mixing, and the intensity of the e.s.r. spectrum was still increasing, 48 h afterwards. Spectrum K demonstrates an experiment on trapping of this radical with nitrosobenzene[12]; the e.s.r. spectrum shows a three-line pattern ascribed to the benzene–nitroxide radical[12,15] (a^N 10.2G).

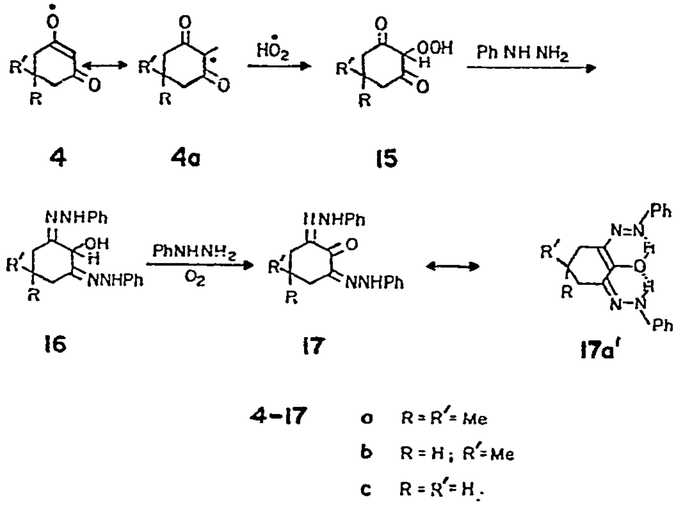
To account for the source of aniline present in the reaction mixture, the ene-bis(hydrazino) intermediate **7** must have split out a molecule of aniline via Weygand path B, to give the imine **14**, which, on further reaction with phenylhydrazine, would give the tris(phenylhydrazone) **8**.



Scheme 2

The reaction mixtures (with **1a**–**1c**) contained in each case about equal proportions (t.l.c.) of red components. These products were identified, by direct isolation and comparison of their i.r., u.v., and n.m.r. spectra, as compounds **17a**–**17c** respectively. The possible free-radical path for the formation of these side-products is depicted.

Treatment of a solution of enolic cyclohexane-1,2-dione in acetic acid with phenylhydrazine at room temperature gives a mixture of the mono- and bis(phenylhydrazones). E.s.r. examination of the reaction mixture after 24 h revealed the presence of a paramagnetic species that gave a six-line pattern (spectrum B' Fig. 2). However, analogous treatment of 2-acetoxy-1-cyclohexanone, which is also enolic, gave mainly the bis(phenylhydrazone) and a paramagnetic species having a seven-line pattern (C′, Fig. 2).



Scheme 3

Fig. 2 shows the e.s.r. spectra A′, B′, and C′ to be derived through apparent interaction of the phenylhydrazino anion ($\mathrm{PhNH\bar{N}H}$) with the corresponding paramagnetic species **4a**–**4c**, **18a**, and **19a**; direct interaction of the anion with oxygen would not differentiate between the reaction products (**12a**–**12c**, spectra A′, B′, and C′, Fig. 2).

The phenylazo radical **12c** (A and J of Fig. 1, and A′ of Fig. 2) is produced in a reaction mixture containing the highly enolic cyclohexane-1,3-diones[16] (**2a**–**2c**) (see also Experimental) and phenylhydrazine; the less acidic cyclohexane-1,2-dione[16a] (nonparamagnetic **18a**, Fig. 2, see also Experimental) gives predominantly the phenylhydrazinium radical **12b**, B′, Fig. 2), whereas 2-acetoxy-1-cyclohexanone (nonparamagnetic **19a**, Fig. 2) produces the phenylhydrazino radical **12a** (C′, Fig. 2).

Loss of an electron from **12b** would produce a reactive phenyldiazene (diimide) PhN=NH, which is an acidic and oxygen-sensitive compound. In basic medium it is rapidly transformed[16b] into a diazenyl anion $\mathrm{PhN{=}NH+OH^-\rightarrow PhN{=}N^-+H_2O}$, which decomposes via a carbanion, producing a hydrocarbon by addition of a proton $\mathrm{PhN{=}N^-\rightarrow N_2+Ph^-\xrightarrow{H^+}C_6H_6}$. Its reaction with oxygen is a homolytic fragmentation[17]: $\mathrm{PhN{=}NH+{\cdot}O{-}O{\cdot}\rightarrow PhN{=}\dot{N}+HOO{\cdot}}$; $\mathrm{PhN{=}\dot{N}\rightarrow Ph{\cdot}+N_2}$.

Formation of the different paramagnetic species (**12a**–**12c**) from the same phenylhydrazino anion ($\mathrm{PhNH\bar{N}H}$) can be explained in part as being due to the different acidity of the cyclic enols involved; the acid strength of these enols is in the order **2a**–**2c** > cyclohexane-1,2-dione > 2-acetoxy-1-cyclohexanone[16a].

Examination of the e.s.r. spectra (A′, B′, C′ of Fig. 2) permits a number of conclusions to be drawn about the structure and properties of the free-radical species

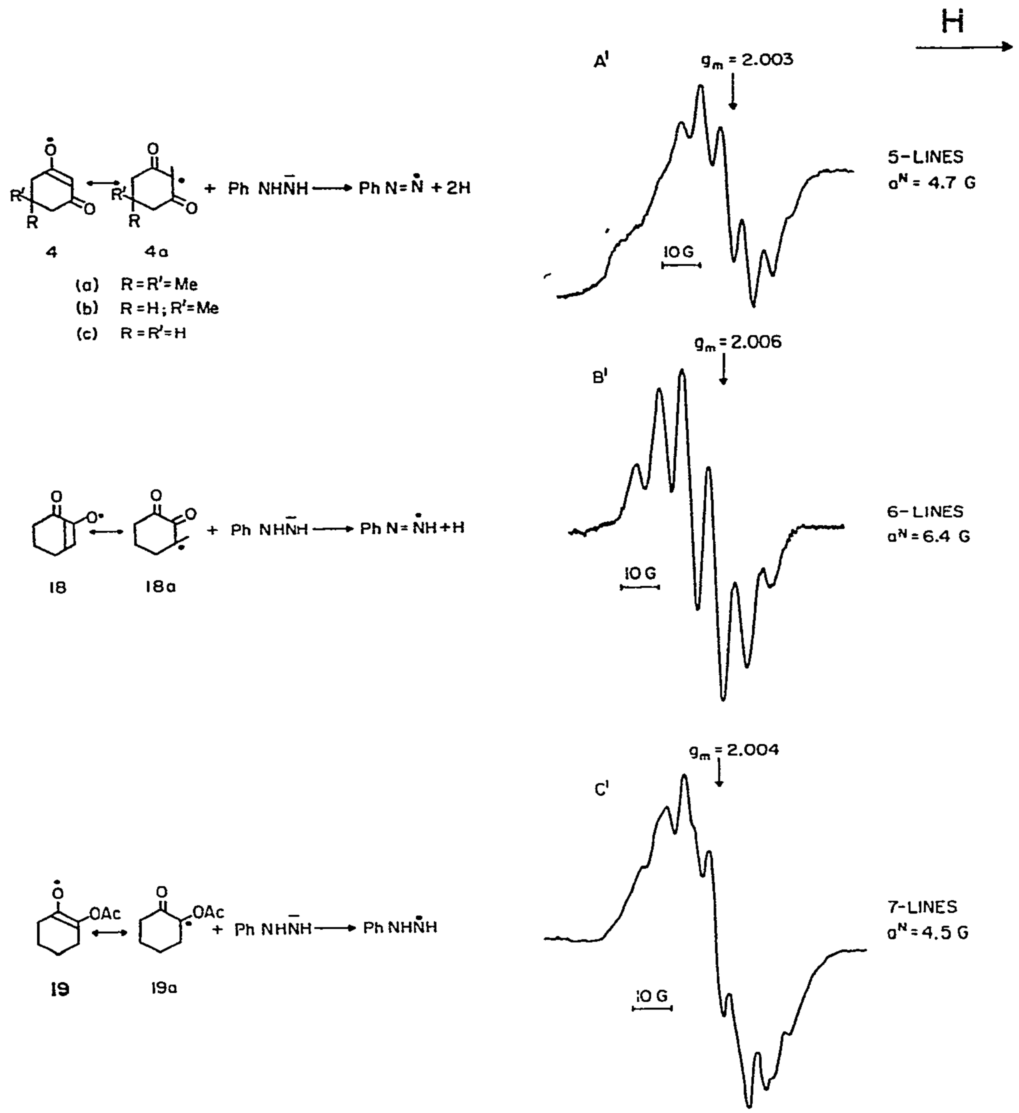


Fig. 2. E.s.r. spectra of the free radicals formed on interaction of the phenylhydrazino anion (PhNHN̄H) and the paramagnetic species derived from **4a–4c**, **18c**, and **19a** (10 mM mixture, spectra A', B' and C', respectively).

(**12a–12c**). The five-component e.s.r. spectrum (A') having relative intensities 1:2:3:2:1 can be explained as due to the interaction of an unpaired electron with two magnetically equivalent nitrogen atoms ($I = 1$); this characteristic accords with species **12c** ($PhN{=}\dot{N}$, $a^N = 4.7$ and 4.7 G) or its anion $PhN{=}\bar{N}$. The instability of a neutral, paramagnetic, phenylazo species ($PhN{=}\dot{N}$) has been reported[17a].

Treatment of cyclohexane-1,2-dione with phenylhydrazine produces a six-component e.s.r. spectrum (B′, Fig. 2) having the relative intensities of 1:3:5:5:3:1. The observed six-line hyperfine structure can be explained as due to the interaction of an unpaired electron with two equivalent nitrogen atoms ($I = 1$) and a proton ($I = 1/2$), and this spectrum is consistent with $a^N = 6.4$ and 6.4 G, $a^H = 6.4$ G. The shape and the parameters of this e.s.r. spectrum resemble that of the tetraphenylhydrazine cation-radical [$(\mathrm{Ph_2N\overset{H}{-}NPh_2})^{+\cdot}$, $a^N = 6.5$ and 6.5 G, $a^H = 6.5$ G, with relative intensities of 1:3:5:5:3:1][18]. This result indicates that the structure of the phenylhydrazinium radical-anion **12b** (B′, Fig. 2) can be represented by the resonance structures $\mathrm{Ph\bar{N}{-}\dot{N}H \leftrightarrow Ph\dot{N}{-}\bar{N}H \leftrightarrow PhN{=}\dot{N}H}$. These structures are isoelectronic with that of the tetraphenylhydrazinium radical-cation[18]. Moreover, the structure of the radical-anion **12b** was further confirmed by direct trapping from the reaction mixture as *N*-phenyl-*N*-phenylsulfonylhydrazide[13] (**13**).

Treatment of 2-acetoxy-1-cyclohexanone with phenylhydrazine produces a somewhat overlapped seven-line e.s.r. spectrum (C′, Fig. 2) having the relative intensities of 1:3:6:7:6:3:1. The observed hyperfine structure is consistent with an interaction of an unpaired electron with two equivalent nitrogen nuclei (I=1) and two protons (I=1/2), $a^N = 4.5$ and 4.5 G, $a^H = 4.5$ and 4.5 G. The structure of this radical was confirmed by its conversion into compound[13] **13**.

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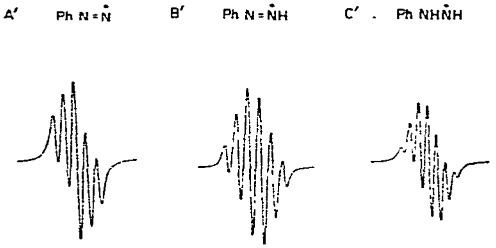

Fig. 3. Computed e.s.r. spectra, as drawn by a CALCOMP plotter, for five, six, and seven Lorentzian components having relative intensity of 1:2:3:2:1, 1:3:5:5:3:1, and 1:3:6:7:6:3:1, corresponding to the free radicals A′, B′, and C′, Fig. 2; values of the splittings (a^N) used for computations are shown in Fig. 2.

For comparison, the theoretically calculated e.s.r. spectra are shown (Fig. 3) for five, six, and seven Lorentzian components having relative intensities of 1:2:3:2:1, 1:3:5:5:3:1, and 1:3:6:7:6:3:1, corresponding to the free radicals A′, B′, and C′ of Figs. 2 and 3; the other parameters used are discussed in the text. The small non-correspondence between the experimental and the theoretical e.s.r. spectra shows that the shape of the experimental lines, particularly in spectrum C′ (Fig. 2), is not purely Lorentzian, due to an apparent interaction of the original spectrum with other paramagnetic species (possibly $\dot{O}_2^-$) present in the reaction mixture. A reasonable fit was achieved for the calculated e.s.r. spectra of the radical anions A′ and B′ (Figs. 2 and 3).

The foregoing studies show that formation of 2-oxo-1,3-bis(phenylhydrazones) and tris(phenylhydrazones) from cyclohexane-1,3-diones, and of bis(phenylhydrazones) from cyclohexane-1,2-diones, following treatment with phenylhydrazine in polar and nonpolar solvents, most probably proceeds by a concerted process, involving both ionic and free-radical pathways.

EXPERIMENTAL

General. — The n.m.r. spectra were recorded with a Varian A-60 spectrometer*. Positions are reported in p.p.m. from tetramethylsilane (δ-scale) and abbreviations used are s (singlet), m (multiplet), d (doublet), q (quartet), and t (triplet). E.s.r. spectra were recorded with a Varian Model 4500 ESR spectrometer with 100 kHz field-modulation and detection. The klystron frequency was measured with a transfer oscillator and a frequency counter. The magnetic field was measured by a proton gaussmeter monitored by the same frequency.

The solutions were examined in a Varian Model V-4548 aqueous-solution sample-cell. The path of reaction was carefully monitored by t.l.c. on nonactivated Silica Gel G (5 × 20 or 20 × 20 cm) plates. In all cases, freshly prepared solvent mixtures were used; 4:1 (v/v) heptane–ethyl acetate (solvent *A*); 1:1:8 (v/v) glacial acetic acid-ethyl acetate–heptane (solvent *B*) or 9:1 (v/v) glacial acetic acid–water (solvent *C*) and a spray (3M sulfuric acid in methanol). Solvents *A* and *B* were used to resolve mixtures containing the 1,3-bis- or 1,2,3-tris(phenylhydrazones); solvent *C* was used to resolve slow-moving components or the complex mixtures. Sulfuric acid spray was useful in obtaining distinct spots from the 1,3-bis(phenylhydrazones) because of the colored cation formed[19]. Column chromatography was performed on Florisil (100–200 mesh, Floridan Company, Philadelphia, Pennsylvania).

Reference compounds and their n.m.r. data. — 2-Chloro-1-cyclohexanone was a commercial preparation (Aldrich Chemical Company), n.m.r. ($CDCl_3$) δ 1.85–2.35 (m, 8, CH_2-ring), 4.4 (m, 1 C-H); 2-hydroxy-1-cyclohexanone (Aldrich Company) n.m.r. (Me_2SO-d_6) δ 1.4 (m, 8, CH_2-ring), 3.8 (s, 1, C–H, 3.9 (s, 1, -OH, exchangeable with D_2O); 2-acetoxy-1-cyclohexanone (prepared on treatment of 2-chloro-1-cyclohexanone with silver acetate[20]) n.m.r. ($CDCl_3$) δ 1.9 (m, 4, CH_2-ring), 2.15 (s, 3, CH_3), 2.40 (m, 4, CH_2-ring), 5.20 (m, 1 C-H); 2-acetoxy-1-cyclohexanone phenylhydrazone (prepared on treatment of 2-acetoxy-1-cyclohexanone with phenylhydrazine[20]) n.m.r. ($CDCl_3$) δ 1.78 (m, 4, CH_2-ring), 2.05 (d, 3, CH_3), 2.50 (m, 4, CH_2-ring), 7.15 (m, 5, ArH), 7.70 (s, 1, N–H, shifting to δ 8.8 on mixing with Me_2SO-d_6.

2-Cyclohexene-1-one (Aldrich Company) had n.m.r. ($CDCl_3$) δ 2.3 (m, 6, CH_2-ring), 5.85 (2d, 1, C–H), 6.95 (m, 1, C–H); 5-methyl-1,3-cyclohexanedione

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*Certain commercial instruments or chemicals are mentioned in this paper; this does not imply recommendation or endorsement by the National Bureau of Standards.

(prepared by Professor F. A. H. Rice, American University), n.m.r. ($DCCl_3$) δ 1.1 (s, 3, CH_3), 2.25 (m, 4, CH_2-ring), 3.36 (m, 1, C–H), 5.02 (s, 1, C–H), 11.55 (s, 1, enol OH, exchangeable with D_2O); enol content ($CDCl_3$) was found about 92% as calculated by the described n.m.r. method for the enolic β-diketones[21].

5-Methyl-2-oxo-1,3-bis(phenylhydrazono)cyclohexane (**17b**) was prepared as described later, n.m.r. ($CDCl_3$) δ 1.02 (d, 3, CH_3), 2.36 (m, 4, CH_2-ring), 3.75 (m, 1, $>$C–H), 7.18 (m, 10, ArH), 14.08 (s, 1, chelated N–H); 5-methyl-1,2,3-tris(phenylhydrazono)cyclohexane (**8b**) (prepared as described later), n.m.r. ($CDCl_3$) δ 1.0 (d, 3, CH_3), 2.18 (m, 4, CH_2-ring), 3.68 (m, 1, $>$C–H), 7.20 (m, 15, ArH), 12.67 (s, 1, chelated N–H), 13.50 (s, 1, chelated N–H); 5,5-dimethyl-2-oxo-1,3-bis(phenylhydrazono)cyclohexane (**17a**) (prepared by the procedure reported[23]), n.m.r. ($CDCl_3$) δ 1.05 (s, 6, CH_3), 2.10–2.42 (m, 4, CH_2-ring), 7.10 (m, 10, ArH), 13.95 (s, 1, chelated N–H); 5,5-dimethyl-1,2,3-tris(phenylhydrazono)cyclohexane (**8a**) (prepared by the method described[23] from 5,5-dimethyl-1,3-cyclohexanedione, enol content ~90% in $CDCl_3$), n.m.r. δ 1.00 (d, 6, CH_3), 2.12–2.45 (2s, 4, CH_2-ring), 7.1 (m, 15, ArH), 12.50 (s, 1, chelated N–H), 13.60 (s, 1, chelated N–H); on addition of Me_2SO-d_6, a new peak appeared at δ 9.1 (nonchelated N–H); 2-oxo-1,3-bis(phenylhydrazono)cyclohexane (**17c**) (prepared by the procedure described[22a]), n.m.r. ($CDCl_3$) δ 1.95–2.65 (m, 6, CH_2-ring), 7.2 (m, 10, ArH), 13.96 (s, 1, chelated N–H); 1,2,3-tris(phenylhydrazono)cyclohexane[23] (**8c**) (prepared from cyclohexane-1,3-dione, enol content in $CDCl_3$ ~88%), n.m.r. ($CDCl_3$) δ 1.84–2.70 (m, 6, CH_2-ring), 7.20 (m, 15, ArH), 12.77 (s, 1, chelated N–H), 13.58 (s, 1, chelated N–H); cyclohexane-1,2-dione (Aldrich Company), n.m.r. (Me_2SO-d_6) δ 2.10 (m, 8, CH_2-ring), 6.00 (t, 1, C=CH), 7.95 (s, 1, enol OH, exchangeable with D_2O); n.m.r. ($CDCl_3$), δ 2.20 (m, 8, CH_2-ring), 6.10 (t, 1, C=CH), 6.28 (s, 1, enol OH, enol content in $CDCl_3$ ~36%).

1-Phenylhydrazono-2-cyclohexanone, prepared by the reported procedure[20], had n.m.r. (Me_2SO-d_6) δ 1.90–3.55 (m, 8, CH_2-ring), 7.25 (m, 5, ArH), 9.90 (s, 1, nonchelated N–H); 1,2-bis(phenylhydrazono)cyclohexane (prepared according to the published procedure[20], see also later) n.m.r. ($CDCl_3$) δ 1.80–2.35 (m, 8, CH_2-ring), 7.15 (m, 10, ArH), 7.50 (s, 1, nonchelated N–H), 13.10 (s, 1, chelated N–H); on addition of Me_2SO-d_6 there is a shift to δ 9.00 (nonchelated N–H) and δ 13.37 (chelated N–H); 1,4-bis(phenylhydrazono)cyclohexane (prepared by treatment of cyclohexane-1,4-dione with phenylhydrazine) n.m.r. ($CDCl_3$) δ 2.5 (m, 8, CH_2-ring), 7.05 (m, 10, ArH), 8.00 (s, 1, nonchelated N–H), Compounds **6a**, **6c**, **9a**, and **9c** were prepared as previously described[22], see also later; their n.m.r. spectra were also recorded[22]. Compounds (**11a–11c**) were prepared as described in the literature[23a].

Treatment of cyclohexane-1,2-dione or 2-acetoxy-1-cyclohexanone (in methyl alcohol or acetic acid) with phenylhydrazine at room temperature, gave a mixture of a yellow 1,2-cyclohexanedione 1,2-bis(phenylhydrazone), m.p. 152–154°, and an orange 1-phenylhydrazono-2-cyclohexanone (**19a**), m.p. 179–182°. The mixture could be partially separated by extraction with warm chloroform to remove the more soluble bis(phenylhydrazone); final purification was accomplished by preparative t.l.c. (Silica Gel G) and column chromatography [Florisil, 1:4 (v/v) ethyl alcohol–chloro form or solvent *B*]. Surprisingly, treatment of 2-hydroxy-1-cyclohexanone in glacial acetic acid (25–50°) with phenylhydrazine gave almost pure cyclohexanedione 1,2-bis-(phenylhydrazone), m.p. 151–152° (85% yield), and only a trace of the mono(phenylhydrazone) (t.l.c., solvent *B*). Mono(phenylhydrazono) derivatives (**6a**–**6c**) could be prepared readily by mixing of an ethanolic solution of the corresponding cyclohexane-1,3-diones with 1–1.5 mol. of phenylhydrazine (room temperature); the yield of the product was over 90%.

Conversion of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (**1a**) *into the tris(phenylhydrazone)* **8a**. — A solution of dimedone (0.2 g) in glacial acetic acid (10 ml) was diluted with water (20 ml) and mixed with phenylhydrazine (1.5 g). The colorless solution, after stirring for 30 min at room temperature, turned orange-yellow. As indicated by t.l.c., the solution contained at least two colored components, a cherry-red one R_F 0.66 and a yellow one R_F 0.50 (solvent *B*). The solution was diluted with more water (150 ml) and stirred for an additional 60 min to give an orange-yellow precipitate of a crude product (0.05 g) . Recrystallization from 95% ethanol gave pure **8a** (0.035 g), m.p. 196–198°, identical with an authentic sample[23]. The filtrate was kept for an additional 24 h at room temperature to give a second crop of crude **8a** (0.12 g).

In another experiment, a solution of dimedone (0.8 g, 5.7 mmoles) in 20% aqueous acetic acid (250 ml) was treated with phenylhydrazine (8 g, 75 mM) and the product was collected in several crops; the first after 24 h (0.076 g, 3.2%) (50 ml washings were combined with the filtrate); the second after 120 h (0.125 g, 5.3%) (100 ml washings), and the third after 240 h (0.860 g, 36.5%); total yield of crude **8a**, 1.06 g (45%).

Similarly the tris(phenylhydrazone) **8b** (R_F 0.48, solvent *B*) was obtained in 42% yield and the analog **8c** [R_F 0.35 (solvent *A*); R_F 0.44 (solvent *B*)] in 48% yield.

Conversion of cyclohexane-1,3-dione into the 2-oxo-1,3-bis(phenylhydrazone) **17c** *and tris(phenylhydrazone)* **8c**; *isolation of the components*. — A solution of cyclohexane-1,3-dione (1 g) in 0.4M aqueous acetic acid (600 ml) was mixed with phenylhydrazine (9 g) and kept for 200 h at room temperature. The orange-red solid (0.95 g) was separated, and the dark-red filtrate, after dilution with water (500 ml), was extracted with 5:1 (v/v) ethyl acetate–chloroform (5 × 100 ml). The extract, after washing with 5% aqueous $NaHCO_3$ and water, was dried (Na_2SO_4) and concentrated. The combined residue and solid, dissolved in ethyl acetate, was placed on a Florisil column (3 × 40 cm) and eluted successively with solvent *A*, and then with 9:1 (v/v) ethyl acetate–95% ethanol. The red band was isolated and recrystallized from warm methanol to give dark-red prisms of **17c** (0.038 g), m.p. 131–133°, identical with an authentic sample[23]; t.l.c. cherry-red spot [R_F 0.72 (solvent *A*); R_F 0.60 (solvent B)] changing to a deep-purple color on spraying with 3M H_2SO_4 in methanol[19]. The yellow band, after isolation and recrystallization from 95% ethanol, gave yellow-orange **8c** (0.044 g, m.p. 185–186°).

Similarly, the 2-oxo-1,3-bis(phenylhydrazones) **17a** (0.035 g) (R_F 0.66, solvent *B*) and **17b** (0.04 g) (R_F 0.63, solvent *B*) were isolated (see also later).

T.l.c. study of the reaction products obtained on mixing dimedone with phenylhydrazines in nonpolar solvents. — When colorless solutions of enolic cyclohexane-1,3-diones (compounds **1a** to **1c**) in benzene or chloroform were mixed with phenylhydrazine and kept in the air, the solutions acquired a deep-red color in a few min. The chemical changes associated with the color changes were monitored by visible spectra, e.s.r., and by t.l.c. (on activated Silica Gel G plates, solvent *B*, and 3M sulfuric acid in methanol for detection). Solutions (3–5%) of dimedone in chloroform or 2–4% in benzene were mixed with anhydrous phenylhydrazine (1:3.5 molar ratio) and the progress of the reaction was monitored by t.l.c. The mixture in benzene after 6 min gave three spots (in addition to some crystalline monophenylhydrazino derivative **6a**); at R_F 0.64 (red, on spraying changed to a deep purple spot, corresponding to **17a**); at R_F 0.52 (yellow-green, on spraying changed to a deep-blue spot, corresponding to **7a**); at R_F 0.47 (light-yellow, did not change on spraying, corresponding to **8a**), and at R_F 0.05 (pink spot, unknown ionic-type component that moved with the solvent *C*; on spraying it changed into a blue spot). The mixture in chloroform after 12 min showed, in addition to a red component at R_F 0.64, a light-yellow spot at R_F 0.47 (did not change on spraying) and only a trace of a component having R_F 0.52; this observation indicates that the reaction in chloroform proceeds with a faster rate of decomposition of an intermediate having R_F 0.52, to give the tris(phenylhydrazone) **8a**. The mixture in benzene showed, after 1.5 h (t.l.c.), a progressive increase in the concentration of a tris(phenylhydrazone) component (R_F 0.47) and a corresponding diminution of the component having R_F 0.52. Direct isolation of the intermediate having R_F 0.52 by extraction of the t.l.c. spot with methanol verified the observed interconversion of R_F 0.52 into R_F 0.48.

Examination of the visible spectrum of the foregoing red reaction-mixture showed a band at λ_{max} 485 nm, characteristic[23a] of **17a**; the n.m.r. (neat red solution +tetramethylsilane) did not show a well resolved pattern, presumably because of the presence of paramagnetic species. Usually, mixtures of cyclohexane-1,3-diones and phenylhydrazine in benzene or chloroform could be used after 24 h for larger-scale preparations of the corresponding 1,3-bis- and 1,2,3-tris(phenylhydrazones) (column chromatography on Florisil with solvent *B*).

Interception of the phenylhydrazino radical in a mixture of dimedone and phenylhydrazine. — A slow stream of oxygen (or air) was passed into a stirred mixture of dimedone (300 mg) and phenylhydrazine (5 g) in 4M aqueous acetic acid (150 ml) for 1 h at 10°. (A mixture prepared at room temperature and kept for 24 h could also be used.) More solvent was added (in case of evaporation) to the red, paramagnetic solution, and the oxygen was replaced by a stream of sulfur dioxide (60 min). The stoppered reaction-mixture was kept for 24 h at room temperature. The resulting mixture on concentration, followed by a column chromatography on Florisil [solvent *B*, 1:4 (v/v) ethyl acetate–cyclohexane], gave compounds **17a**, **8a**, and colorless crystals of *N*-phenyl-*N*-benzenesulfonylhydrazide (**13**, 18 mg, from ethanol), m.p. 155–156°; n.m.r. (Me_2SO-d_6) 9.47 p.p.m. (N–H); t.l.c. (activated silica gel, solvent *B*) R_F 0.25 (pink spot on spraying); the compound was identical with an authentic sample[13].

Repetition of the experiment without dimedone failed to give compound **13**. Similarly, compound **13** was isolated from the mixtures of other cyclohexane-1,3-diones, or cyclohexane-1,2-dione, with phenylhydrazine in aqueous acetic acid.

Conversion of 5,5-dimethyl-3-oxo-1-phenylhydrazino-1-cyclohexene (**6a**) *into the tris(phenylhydrazone)* **8a**. — A solution of **6a** (ref. 22) (0.2 g) in glacial acetic acid (5 ml) was mixed with phenylhydrazine (1.2 g) and diluted with water to incipient turbidity. The turbidity was removed with a little methanol and the clear solution was kept for 24 h at room temperature. Bright yellow needles of the tris(phenylhydrazone) **8a** crystallized out; yield 85%, m.p. 196–197° (CH_3OH). The deep-red filtrate was analyzed by t.l.c. (nonactivated Silica Gel G plates, solvent *B* and sulfuric acid spray). It showed a trace amount of **17a**, a red spot at R_F 0.64 (changing to a deep-purple on spraying), some **8a**, a yellow spot at R_F 0.47, and some ionic material at the origin of a spot (R_F 0.05, red spot that migrated with solvent *C*). The filtrate did not contain any significant amount of the azo derivative[22] (**9a**) at R_F 0.46 (brown-red spot that did not change on spraying). When the original reaction mixture was placed for 5 min in a boiling water-bath and then kept for 1 h at room temperature, compound **8a** was isolated in 80% yield.

Similarly, the monophenylhydrazines **6b** and **6c** were converted into **8b** and **8c** in over 85% yield. Likewise, the azo-derivatives (**9a**–**9c**) were converted into the derivatives **8a**–**8c** in even higher yields (92–95%), and compounds **11a**–**11c** (see ref. 23b) into **8a**–**8c** in 84–89% yield.

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REFERENCES

1 E. Fischer, *Ber.*, 17 (1884) 579.
2 E. Fischer, *Ber.*, 20 (1887) 821.
3 H. El Khadem, *Advan. Carbohyd. Chem.*, 20 (1965) 139; J. Buckingham, *Quart. Rev.*, 23 (1969) 37.
4 H. Simon, G. Heubach, and H. Wacker, *Chem. Ber.*, 100 (1967) 3106 and references therein.
5 L. Amaral and M. P. Bastos, *J. Org. Chem.*, 36 (1971) 3412 and references cited therein.
6 F. Weygand, *Chem. Ber.*, 73 (1940) 1284; F. Weygand, H. Simon, and J. F. Klebe, *ibid.*, 91 (1958) 1567.
7 J. Caglioti, G. Rosini, and F. Rossi, *J. Amer. Chem. Soc.*, 88 (1966) 3865.
8 H. Simon and W. Moldenhauer, *Chem. Ber.*, 102 (1969) 1191.
9 J. Buckingham and R. D. Guthrie, *Chem. Commun.*, (1966) 781; A. Hassner and P. Catsoulacos, *Chem. Commun.*, (1967) 121; *Tetrahedron Lett.*, (1967) 489.
10 (a) D. C. Iffland, L. Salisbiny, and W. R. Schaefer, *J. Amer. Chem. Soc.*, 83 (1961) 747; (b) M. J. Harrison, R. O. C. Norman, and W. A. F. Gladstone, *J. Chem. Soc.* (*C*), (1967) 735.
11 H. G. Yao and P. Resnick, *J. Org. Chem.*, 30 (1965) 2832; A. J. Bellamy and R. D. Guthrie, *J. Chem. Soc.*, (1965) 2788; W. F. Taylor, H. A. Weiss, and T. J. Wallace, *J. Org. Chem.*, 34 (1969) 1759; E. G. E. Hawkins, *J. Chem. Soc.* (*C*), (1971) 1474.

12 S. Terabe and R. Konaka, *J. Amer. Chem. Soc.*, 91 (1969) 5655.

13 F. L. Scott and J. A. Barry, *Tetrahedron Lett.*, (1968) 2461.

14 L. Caglioti, A. Dondoni, and G. Rosini, *Chimica Industria*, 50 (1968) 122.

15 A. B. Forrester, J. M. Hay, and R. H. Thomson, *Organic Chemistry of Stable Free Radicals*, Academic Press, New York, 1968, pp. 195-217.

16 (a) E. S. Gould, *Mechanism and Structure in Organic Chemistry*, Henry Holt, New York, 1959, p. 376; B. Eistert and E. Merkel, *Chem. Ber.*, 86 (1953) 896; B. Eistert, E. Merkel, and W. Reiss, *ibid.*, 87 (1954) 1513; (b) E. M. Kosower, *Accounts Chem. Research*, 4 (1971) 193.

17 (a) A. Heesing and B. Kaiser, *Tetrahedron Lett.*, (1970) 2845; (b) J. M. Nicholson and S. G. Cohen, *J. Amer. Chem. Soc.*, 88 (1966) 2247; P. C. Huang and E. M. Kosower, *ibid.*, 89 (1967), 3911; J. B. Aylward, *J. Chem. Soc.* (*C*), (1969) 1663; T. Carty and J. M. Nicholson, *Tetrahedron Lett.*, (1970) 4155.

18 G. A. Razuvaev, G. A. Abakumov, and V. A. Pestunovich, *J. Struct. Chem.*, 5 (1964) 278; Ref. 15, pp. 122-125.

19 H. S. Isbell and A. J. Fatiadi, *Carbohyd. Res.*, 11 (1969) 303.

20 H. Simon and W. Moldenhauer, *Chem. Ber.*, 101 (1968) 2124.

21 J. L. Burdett and M. T. Rogers, *J. Amer. Chem. Soc.*, 86 (1964) 2105; G. K. Schweitzer and E. W. Benson, *J. Chem. Eng. Data*, 13 (1968) 452.

22 A. J. Fatiadi, *J. Org. Chem.*, 35 (1970) 831.

23 (a) A. J. Fatiadi and H. S. Isbell, *Carbohyd. Res.*, 5 (1967) 302; (b) B. Eistert, G. Kilper, and J. Göring, *Chem. Ber.*, 102 (1969) 1379.