TABLE I

RATES OF REACTION OF *N*-(X-PHENYL)IMINOTRIPHENYLPHOSPHORANES WITH SUBSTITUTED BENZALDEHYDES[a]

$(C_6H_5)_3P{=}NC_6H_4X + YC_6H_4CHO$

Registry no.	Y	X = *p*-CH_3O (14796-89-5)[a]	X = *p*-CH_3 (2327-67-5)[a]	X = H (2325-27-1)[a]	X = *p*-Br (14987-96-3)[a]	X = *m*-Cl (14796-87-3)[a]	X = *m*-NO_2 (14796-86-2)[a]
528-75-6	2,4-$(NO_2)_2$	27.6[b]	29.6[b]	29.9[b]	9.0[b]	5.4[b]	1.03[b]
555-16-8	*p*-NO_2	19.3	23.3	34.6	24.0	16.7	2.03
105-07-7	*p*-CN			27.9			
587-04-2	*m*-Cl			8.82			
100-52-7	H	0.83	0.96	1.37	1.10	0.67	0.23
104-87-0	*p*-CH_3			0.66			
123-11-5	*p*-CH_3O	0.13	0.14	0.17	0.18	0.10	Too slow

[a] Registry number. [b] Rate constants are $\times 10^2$ l./mol sec at 40.5° in absolute ethanol solution.

tion of the *N*-phenyl-substituted imines with each of the four benzaldehydes results in four similar "concave down" curves. Accordingly, it may be concluded that the change in rate-determining step in the reaction of *N*-phenyliminotriphenylphosphoranes with aldehydes is a general phenomenon.

The delicate balance in the rates of betaine formation and betaine decomposition in the imine–carbonyl reaction is a unique observation in the field of ylide chemistry. In the imine, electron-donating substituents are expected to increase the nucleophilicity of the nitrogen atom, but at the same time increase the electron density on the phosphorus atom, thereby decreasing its susceptibility to oxyanion attack (*i.e.*, increase k_1 and decrease k_2, respectively). Electron-withdrawing substituents are expected to decrease the nucleophilicity of the nitrogen atom but also decrease the electron density on the phosphorus atom, thereby increasing its susceptibility to oxyanion attack (*i.e.*, decrease k_1 and increase k_2, respectively). Thus, any imine substituent is expected to exert opposing effects on the two rate constants. The introduction of even a methyl group on the *N*-phenyl ring seems sufficient to increase k_1 to the point that betaine decomposition (oxyanion attack on phosphorus) becomes rate-determining. The difference in the effect exerted by an electron-donating substituent seems to indicate a far more effective transmission of electronic effect through a phenyl group to nitrogen than to phosphorus.

Coincidentally, the use of 2,4-dinitrobenzaldehyde has permitted the observation of a steric effect in the imine–carbonyl reaction heretofore not observed. Although such a carbonyl group should be more electrophilic than that of *p*-nitrobenzaldehyde, in the reactions with those imines *not* carrying electron-donating groups k_{obsd} is lower for the dinitrobenzaldehyde. These observations are consistent with betaine formation being the slow step of the reaction in the former cases, and therefore the steric hindrance being reflected in k_{obsd}, but with betaine decomposition being the slow step in the latter case, and the steric effect apparently not being reflected in k_{obsd}. Steric hindrance seems to be a significant factor only in betaine formation and seems to be detectable only in those reactions in which betaine formation is the rate-determining step.

Experimental Section

The iminophosphoranes (I) were prepared as described in our earlier report.[3] The benzaldehydes were commercial samples which were purified by crystallization or distillation. The rates of the reactions of the imines with the benzaldehydes were determined at 40.5° in absolute ethanol solution according to the procedure described in our previous work.

1,2-Diazacyclooctanes

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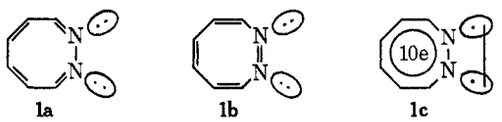
Received November 4, 1971

In light of the recent success of Trost and Cory[1] in uncovering an elegant route to 1,2-diazacyclooctatetraene (**1**), we have terminated our own studies in this



1a **1b** **1c**

area which were directed toward a synthesis of **1** *via* a classical halogenation–dehydrohalogenation sequence through the bis-protected diazacyclooctene **3**. Our interest in **1** derived from the conjecture that this compound might exist as the "aromatic" 10-π system **1c**.[2] Gund[3] has recently reported simple MO calculations on the classic structures **1a** and **1b** and has obtained delocalization energies similar to those calculated for cyclooctatetraene, whereas the "promoted" form **1c** leads to delocalization energies which are substantially higher. On the other hand, Trost's spectral results suggest nothing unusual about **1** but rather correlate well with structure **1a**.

Treatment of *cis*-1,6-dibromo-3-hexene (**2**) with *tert*-butyl hydrazodiformate and sodium hydride in dimethylformamide under relatively high dilution conditions gave **3** in 72% yield. A similar technique was used to obtain the saturated analog **7** (70%). Overberger and Stoddard[4] synthesized similarly the diethyl analog of **7**, although in only 22% yield.

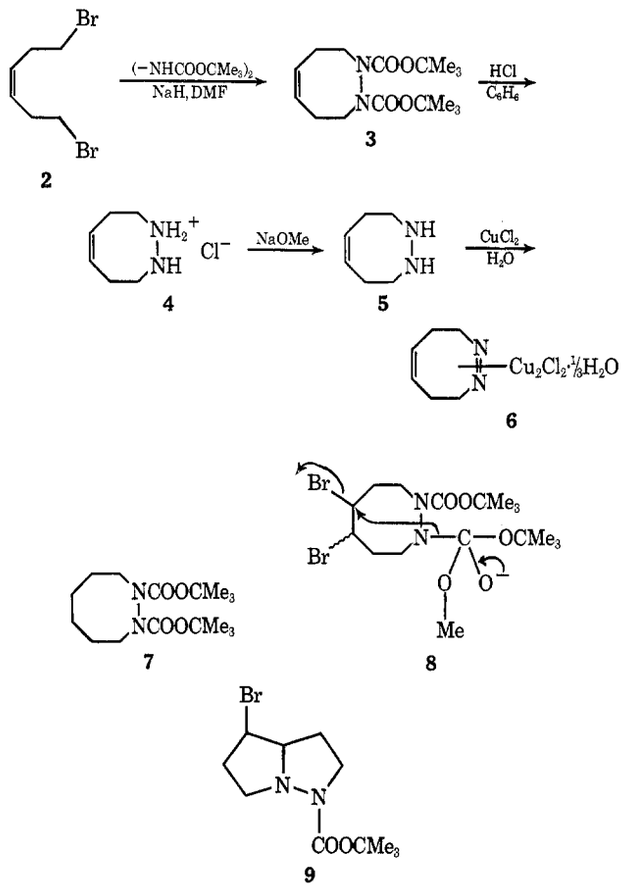
Preliminary attempts to introduce further unsaturation into **3** were carried out by bromination followed by treatment with various bases. Thus addition of bromine to a solution of **3** in ether followed by addition of potassium *tert*-butoxide led to debromination with recovery of **3** rather than dehydrobromination. The less bulky sodium methoxide apparently attacked one

(1) B. M. Trost and R. M. Cory, *J. Amer. Chem. Soc.*, **93**, 5572, 5573 (1971).

(2) For a consideration of a classical 10-π system which might also be obtainable *via* **3** see N. L. Allinger and G. A. Youngdale, *J. Org. Chem.*, **25**, 1509 (1960).

(3) P. H. Gund, Ph.D. Thesis, University of Massachusetts, Amherst, Mass., 1967.

(4) C. G. Overberger and J. W. Stoddard, *J. Amer. Chem. Soc.*, **92**, 4922 (1970).



of the carbo-*tert*-butoxy groups since in this case a compound tentatively identified as **9**, possibly derived from intermediate **8**, was the only product which could be isolated.[5,6]

Deblocking of **3** by the usual technique[7] gave the hydrazine hydrochloride **4** which was characterized by oxidation to the corresponding azo compound, isolated as the cuprous chloride complex.[8]

Experimental Section[9]

1,2-Dicarbo-*tert*-butoxy-1,2-diazacyclooct-5-ene.—To a 12-l. flask equipped with a mechanical stirrer and a nitrogen inlet tube there was added 6 l. of dry DMF followed by 50 g of *tert*-butyl hydrazodiformate.[10] After careful addition of 9 g of sodium hydride (60% in mineral oil) the mixture was stirred for 2 hr at room temperature and 52.2 g of *cis*-1,6-dibromo-3-hexene[11] in 50 ml of dry DMF was added in one portion. The mixture was stirred at room temperature for 24 hr, a second 9 g of NaH was cautiously added, and the stirring was continued for 72 hr at room temperature and 12 hr at 90°.

The volume was reduced to 1 l. at the water aspirator, 500 ml of water added, and the solution was extracted with seven 400-ml portions of ligroin (bp 61–70°). The combined extracts were washed with 500 ml of DMF–H_2O (1:1) and twice with 500-ml portions of H_2O. Removal of the solvent from the dried ($MgSO_4$) solution gave 56.6 g (83%) of crude oily hydrazide which was purified by column chromatography.[12] To a Florisil-packed column (15 × 200 cm) there was introduced 25 g of the above oil. Elution with ligroin (bp 35–60°)–acetone (9:1) gave after solvent removal a material which, if not crystalline, was stored in contact with 20 ml of ligroin (bp 61–70°) at −15° for 48 hr to aid in crystallization. Filtration followed by sublimation gave clear colorless crystals, mp 69.3–70°. The combined yield was 47.9 g (72%): ir ($CHCl_3$) 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.45 (s, 18 H, CH_3), 2.2 (br q, 4 H, CH_2), 3.08 (m, 2 H, CH_2), 3.9 (m, 2 H, CH_2), 5.78 (*t*, 2 H, =CH).

Anal. Calcd. for $C_{16}H_{28}N_2O_4$: C, 61.51; H, 9.03; N, 8.96; mol wt, 312.4. Found: C, 61.66; H, 9.01; N, 9.12; mol wt, *m/e* 312 ± 1 (mass spectrum).

1,2-Dicarbo-*tert*-butoxy-1,2-diazacyclooctane.—Treatment of 40 g of 1,6-dibromohexane with 30 g of *tert*-butyl hydrazodiformate[10] by the same technique as described above gave after column chromatography 40 g (70%) of an oil which was shown by glpc to be >95% pure. To obtain an analytical sample preparative glpc on a 10-ft column (25% SE-30 on 60/80 Chromasorb W) at 180° gave a solid which after sublimation gave clear colorless crystals: mp 47–49°; ir ($CHCl_3$) 1705 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.45 (s, 18 H, CH_3), 1.5 (m, 8 H, CH_2), 3.4 (m, 4 H, CH_2). The same compound was obtained in 65% yield from the 1,6-ditosylate and by catalytic reduction of **3** over palladium/carbon in a Parr apparatus.

Anal. Calcd. for $C_{16}H_{30}N_2O_4$: C, 61.08; H, 9.61; N, 8.90. Found: C, 61.30; H, 9.62; N, 9.18.

Treatment of 5,6-Dibromo-1,2-dicarbo-*tert*-butoxy-1,2-diazacyclooctane with Sodium Methoxide.—To a solution of 10 g of **3** in 100 ml of CH_3OH at 0° was added 5.2 g of Br_2. The solution was stirred at 0° for 0.5 hr and allowed to come to room temperature and 3.5 g of $NaOCH_3$ was added. After 2 hr, the solution was concentrated to one-third its volume and 50 ml of H_2O was added, and the mixture was extracted with two 30-ml portions of CH_2Cl_2. The oil obtained from the combined extracts was chromatographed on a 10 × 150 cm Florisil-packed column by elution with ligroin (bp 35–60°)–ethyl acetate (8:1). Concentration of appropriate fractions (tlc) gave a small amount of solid: mp 51–52°; ir ($CHCl_3$) 1698 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.48 (s, 9 H, CH_3), 2.0–4.0 (m, 9 H), 4.52 (m, 1 H).

Anal. Calcd for $C_{11}H_{19}N_2O_2Br$: C, 45.37; H, 6.57; N, 9.62; Br, 27.44. Found: C, 45.65; H, 6.56; N, 9.60; Br, 27.40.

1,2-Diazacyclooct-5-ene Hydrochloride.—Passage of gaseous HCl through a solution of 17.6 g of **3** in 200 ml of dry benzene at 0° gave 10 g (97%) of a salt, mp 89–91°, shown to be the dihydrochloride by nmr analysis. Sublimation at 20° (0.1 mm) gave the monohydrochloride: mp 120–122°; nmr (D_2O) δ 2.52 (m, 4 H, CH_2), 3.15 (m, 4 H, CH_2), 4.68 (s, 3 H, HOD), 6.0 (t, 2 H, =CH).

Anal. Calcd. for $C_6H_{13}N_2Cl$: C, 48.84; H, 8.81; N, 18.84. Found: C, 48.50; H, 8.80; N, 18.83.

1,2-Diazacyclooctane Hydrochloride.—Treatment of **7** with HCl by the method described above gave the dihydrochloride, mp 105–107°. Sublimation at 50° (0.1 mm) gave the monohydrochloride: mp 121–123°; nmr (D_2O) δ 1.68 (br s, 8 H, CH_2), 3.17 (m, 4 H, CH_2), 5.2 (s, 3 H, HOD).

Anal. Calcd. for $C_6H_{15}N_2Cl$: C, 47.83; H, 10.04; N, 18.09. Found: C, 48.10; H, 10.00; N, 18.32.

Liberation of the free base by means of trimethylamine gave a yellow oil, bp 89° (20 mm) [lit.[4] bp 71–74° (15 mm)], shown by spectral comparison to be the same as that independently obtained by Overberger and Stoddard[4] from the corresponding diethyl ester.

1,2-Diazacycloocta-1,5-diene–Cuprous Chloride Complex.—Sodium methoxide was added to a solution of 4.3 g of 1,2-diazacyclooct-5-ene dihydrochloride in 25 ml of H_2O until it was neutral to universal indicator paper. There was then added a solution of 6.7 g of $CuCl_2$ in 50 ml of H_2O. The dark red-brown precipitate was quickly filtered to give 1.1 g. (13.2%) of a complex: mp 191–197° dec; ir (KBr) 3350 (OH), 2910 (CH), 1430 cm^{-1} (N=N).

Anal. Calcd. for $C_6H_{10}N_2Cu_2Cl_2 \cdot {}^1/_3H_2O$: C, 22.94; H, 3.42; N, 8.91; Cl, 22.57; O, 1.70; Cu, 40.4. Found: C, 23.55; H, 3.46; N, 8.76; Cl, 22.70; O, 1.89; Cu, 39.6.

(5) Structure **9** is preferred over the alternate bicyclo[4.2.0] system on the basis of other transannular reactions in eight-ring systems.[6]

(6) A. C. Cope, H-H. Lee and H. E. Petree, *J. Amer. Chem. Soc.*, **80**, 2849 (1958); A. C. Cope, and P. E. Peterson, *ibid.*, **81**, 1643 (1959).

(7) L. A. Carpino, *ibid.*, **85**, 2144 (1963).

(8) For recent examples of the isolation of azo compounds as their cuprous chloride complexes, see E. L. Allred, J. C. Hinshaw, and A. L. Johnson, *ibid.*, **91**, 3382 (1969).

(9) Melting and boiling points are uncorrected. Infrared spectra were obtained on Beckman IR-10 and Perkin-Elmer 247B instruments and nmr spectra on a Varian A-60 unit. Preparative glpc was carried out on a Varian Aerograph 700 chromatograph. Elemental analyses were carried out by Charles Meade and associates, University of Massachusetts Microanalytical Laboratory.

(10) L. A. Carpino, *J. Amer. Chem. Soc.*, **79**, 4427 (1957).

(11) R. Lukes and V. Dudek, *Chem. Listy*, **52**, 1926 (1958).

(12) The same column could be reused at least five times by rinsing it after each separation with 2 l. of acetone followed by 2 l. of ligroin (bp 35–60°)–acetone (9:1).

The same compound was obtained by treatment of the dihydrochloride with trimethylamine, followed by oxidation of the free base with activated manganese dioxide[13] in dimethyl ether. This gave a crude sample of 1,2-diazacycloocta-1,5-diene which was distilled from a water bath at 10° to a receiver held at −78°. Without further purification of the free azo compound, treatment with a saturated solution of Cu_2Cl_2 in 10% HCl gave the same complex described above, identified by infrared spectral comparison.

Registry No.—**3**, 34201-71-3; **5** hydrochloride, 34201-72-4; **5** dihydrochloride, 34201-73-5; **6**, 11089-64-8; **7**, 34201-74-6; **9**, 34201-75-7; 1,2-diazacyclooctane monohydrochloride, 34201-76-8; 1,2-diazacyclooctane dihydrochloride, 34201-77-9.

Acknowledgment.—Thanks are due to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

(13) L. A. Carpino, *J. Org. Chem.*, **35**, 3971 (1970).

A Study of the Cyclization of 2′-Formamido-4′,5′-dimethoxypropiophenone with Ammonia

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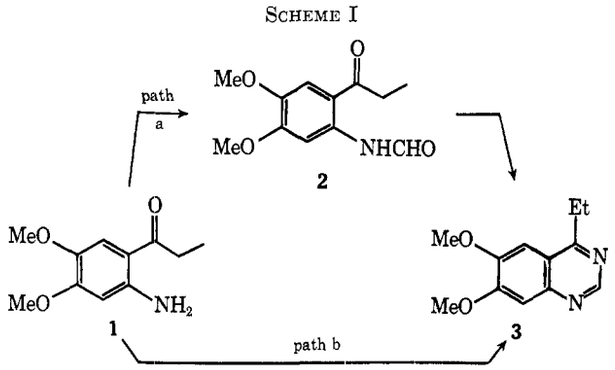
Received December 13, 1971

The compound [2-^{14}C]-6,7-dimethoxy-4-ethylquinazoline was required for metabolism studies. Scheme I shows the general approach considered for its

SCHEME I



synthesis. Previously, 6,7-dimethoxy-4-ethylquinazoline[1] (**3**) was prepared in these laboratories by formylation of 2′-amino-4′,5′-dimethoxypropiophenone[2] (**1**) with excess mixed formic–acetic anhydride, followed by heating the resulting 2′-formamido-4′,5′-dimethoxypropiophenone (**2**) in fused ammonium formate saturated with ammonia (path a),[3] or by heating **1** with formamide and formic acid (path b).[4] Compound **3** labeled at the 2 position could be made *via* path a if methods for the efficient incorporation of a [^{14}C]formyl group could be found. Certainly, the methods used previously for the conversions **1** to **2** or **1** to **3** would not be suitable because of the excesses of formic acid or formic acid derivatives used in each case. The synthesis of [^{14}C]formyl-**2** was easily accomplished by reaction of **1** with 1 equiv each of [^{14}C]formic acid and dicyclohexylcarbodiimide (DCC).

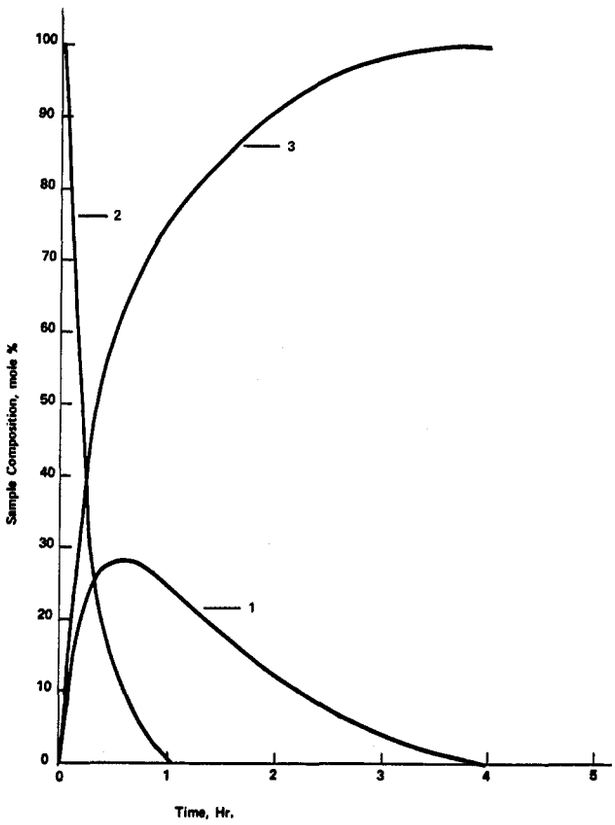


Figure 1.—The reaction of **2** with ammonia in ammonium formate at 125°. Mole per cent composition of the reaction mixture *vs.* time.

The question remaining concerned the fate of the label in **2**. Would it be lost in the conversion of **2** to **3**? The course of this reaction was studied by adding **2** with stirring to fused ammonium formate saturated with ammonia at 125° and withdrawing aliquots periodically. The samples were analyzed by glc, and the results are presented in Figure 1, in which the mole per cent composition of the sample is plotted against reaction time. Figure 1 indicates that **2** may proceed to **3** irreversibly, and/or it may equilibrate with **1**. Complete conversion to **3** is assured by the fact that it is formed essentially irreversibly. This experiment showed that ring closure of labeled **2** under these conditions would lose the label to the reaction medium.

As an alternate to the ring closure in fused ammonium formate, the reaction of **2** in ethanol saturated with ammonia in a sealed tube was investigated. The results of reactions at various temperatures and for various times are presented in Table I. It should be noted that here again the starting formanilide **2** equilibrates with the amine **1**, but the formic acid is captive and does not equilibrate with solvent.

In the actual synthesis of the labeled compound, using 23.5 mCi of [^{14}C]formic acid, in the DCC formylation procedure, 2′-formamido[^{14}C]-4′,5′-dimethoxypropiophenone was obtained, after recrystallization from methanol, in 82.8% yield. This material was

(1) The U. S. Adopted Name for this material is Quazodine.
(2) D. E. Ames and A. C. Lovesey, *J. Chem. Soc.*, 6306 (1965).
(3) J. L. Minielli and H. C. Scarborough, U. S. Patent 3,248,292 (1966).
(4) S. Palazzo, *Boll. Sedute Accad. Gioenia Sci. Natur. Catania*, **71**, 75 (1959); *Chem. Abstr.*, **55**, 12412 (1961).