β,β,β′,β′-Tetrabromoazoethenes. Synthesis, Bromine Addition, and Molecular Decomposition

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Ahrens and Berndt[1] have recently succeeded in preparing the first example of a divinyl azo compound (or azoethene), namely, $(t\text{-Bu})_2C{=}CHN{=}NCH{=}C(t\text{-Bu})_2$ (**1**) (in only 4% yield). The uv spectrum of **1** is reminiscent of aromatic dyes and this azoethene was found to be stable upon heating to 180°C. It was of interest to prepare further examples of the azoethene series and to compare the physical properties and chemical reactivity of these compounds with those of aromatic and aliphatic azo compounds.

In the present paper, the debromination of perbrominated ketazines (PBK), $Br_3C{-}CR{=}N{-}N{=}CRCBr_3$ (**2**, R = Ph, and **3**, R = $CHBr_2$), to give β,β,β′,β′-tetrabromoazoethenes, $Br_2C{=}CRN{=}NCR{=}CBr_2$ (**4**, R = Ph, and **5**, R = $CHBr_2$), in 70–75% yield is described and the mechanism of this reaction in various solvents is discussed.

Perbromination of acetophenone azine to give 2,2,2-tribromoacetophenone azine, $Ph(CBr_3)C{=}N{-}N{=}C(CBr_3)Ph$ (**2**), and of acetone azine to give pentabromopropanone azine, $CBr_3(CHBr_2)C{=}N{-}N{=}C(CHBr_2)CBr_3$ (**3**), is accomplished by adding bromine directly to refluxing methylene chloride solutions of the original ketazines. Yields are in the vicinity of 50%. Conversion of **2** to bright red 1,1′-diphenyl-2,2,2′,2′-tetrabromoazoethene (**4**) is achieved by brief refluxing in a mixture of methanol, ethyl acetate, and cyclohexene. This debromination method is inapplicable for **3** apparently as a result of its extreme insolubility. Debromination of **3** is accomplished by refluxing overnight in cyclohexene to give grayish purple 1,1,1′,1′,3,3,3′,3′-octabromo-2,2′-azopropene (**5**).

Perbrominated ketazines **2** and **3** are interesting examples of "bromine carriers", that is, compounds which readily liberate Br_2 upon heating and are regenerated by bromine addition to the resultant olefin at room temperature. While no obvious advantages of these PBK as brominating agents over *N*-bromosuccinimide (NBS) are seen, the liberation of Br_2 by a nonradical mechanism in methanol (and, perhaps, less polar solvents) may have possible utility.

An efficient "bromine carrier" system requires (1) easy removal of Br_2 from a dibromide upon heating and (2) facile addition of bromine to the original double-bond system, i.e.

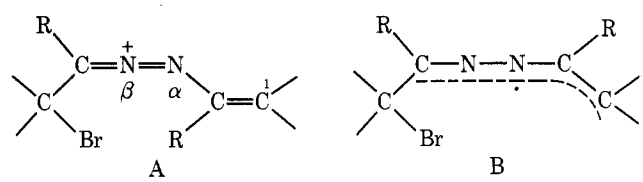
$$X + Br_2 \underset{\Delta}{\overset{\text{room temp}}{\rightleftharpoons}} X{-}Br_2$$

The low exothermicity of bromine addition to carbon double-bond systems (e.g., $CH_2{=}CH_2 + Br_2 \rightarrow CH_2BrCH_2Br$, $\Delta H° = -21.8$ kcal/mol)[2] and the relatively low C–Br bond energy (67 kcal)[3] suggest the possibility of facile removal of bromine from bromine-addition products at elevated temperatures.

A number of bromine carrier systems have been studied which consist of halogenated olefins such as tetrachloroethylene and their bromide-addition products.[4] The electron-withdrawing nature of the geminal halogen atoms in such bromine-addition products reduces the polarity of the $C^{\delta+}{-}Br^{\delta-}$ bond, thereby reducing the C–Br bond energy [e.g., *E* ($Br_3C{-}Br$) = 49 kcal].[3] The bromine transfer from these carriers to alkanes and alkenes appears to involve radical chain reactions and often requires radical initiation.

Unfortunately, the electron-poor double bonds of the halogenated olefins obtained upon loss of Br_2 are not prone to easy electrophilic bromine addition. In fact, bromine addition to such compounds is usually effected through a radical process with the generation of Br· from Br_2 by intense illumination.[5] Furthermore, the debromination of the addition product is not facilitated by the formation of well-stabilized intermediate cations or radicals. Thus, both the Br_2 addition and loss steps are not particularly facile for such haloalkene–alkane systems.

Perbrominated ketazines such as **2** and **3** appeared to be natural candidates for good bromine carriers as a result of (1) the weakening of the C–Br bonds owing to the inductive effect of the geminal bromine atoms, (2) the considerable steric strain resulting from the nonbonding geminal interaction of the CBr_3 and R groups, especially in **3**, and (3) the participation of the central C=N–N=C system to allow facile bromination and debromination through structures such as ionic intermediate A or radical intermediate B. The

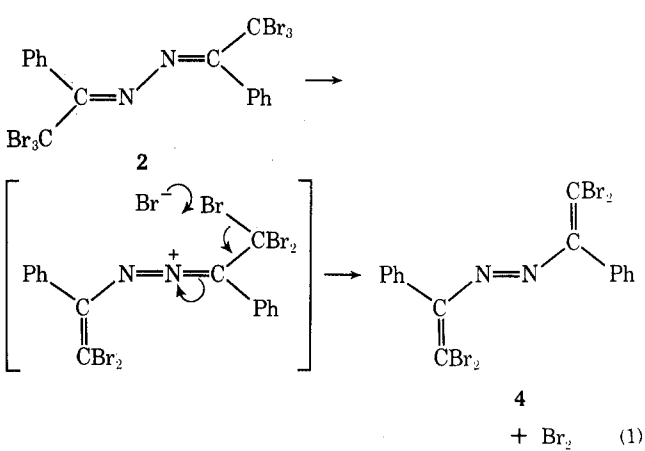


A B

role of structures of type A in the extremely facile solvolyses of α,α′-dichloroazoalkanes has been demonstrated in our earlier work.[6]

The debromination mechanism in the conversion of **2** to **4** was probed in mixed methanol–cyclohexene solvent. Heating **2** overnight at reflux in methanol–cyclohexene (70:30 v/v) gives 45% *trans*-1,2-dibromocyclohexane and 55% *trans*-1-bromo-2-methoxycyclohexane. These results are very close to those obtained by Chretien et al.[7] for the addition of Br_2 to cyclohexene–methanol mixtures and strongly indicate that an ionic reaction obtains in this reaction.

It has long been recognized that the allylic bromination of olefins by NBS involves attack of Br·;[8] NBS bromination of cyclohexene gives ca. 90% 3-bromocyclohexene and *no* addition product.[9] Therefore, the complete absence (<1%) of allylic products is further evidence that Br· is not produced in the initial debromination step. A reasonable ionic mechanism is



2 **4**

$$+ Br_2 \qquad (1)$$

It is interesting that the type A cation proposed in reaction 1 does not react by adding MeOH but rather undergoes 100% elimination. This behavior may be attributed, at least in part, to steric hindrance at C_1 and also to the localization of the positive charge on the β-N relative to C_1.

Debromination of **2** by heating in pure cyclohexene at reflux overnight either in ordinary room light or in the dark gives about 70% 3-bromocyclohexene and 30% 1,2-dibromo-

cyclohexane. This result does not lead to an unequivocal mechanistic conclusion.

McGrath and Tedder[10] found that the reaction of molecular bromine with cyclohexene in refluxing CCl_4 yields largely 3-bromocyclohexene. This reaction is very sensitive to the local Br_2 and HBr concentrations. The addition product, 1,2-dibromocyclohexane, was also found. The authors propose a radical mechanism for this reaction through Br·, though competing ionic addition and elimination reactions of Br_2 could also explain the observed results. At any rate, it is clearly impossible on this basis to decide whether Br· or Br_2 (or both) is the attacking species derived from **2** in pure cyclohexene, though the 30% yield of addition product is an indication that at least some Br_2 is formed by a nonradical process as the NBS radical bromination of cyclohexene does not give any additional product (vide supra).

It should be noted that the debromination of **2** in pure cyclohexene is a thermal and not a photoinduced process. Thus, a control solution of **2** held in cyclohexene for 24 hr under ordinary room illumination does not undergo any reaction.

Upon heating to 150° in *o*-dichlorobenzene for 30 min, pentabromopropanone azine (**3**) loses bromine in 80% theoretical yield. The bromine gas evolved may be collected by employing a gentle stream of nitrogen through the reaction solution and into a methylene chloride trap at 0°. The azooctabromide **5** is obtained upon cooling the solution. Thus, **3** is an efficient carrier of molecular bromine.

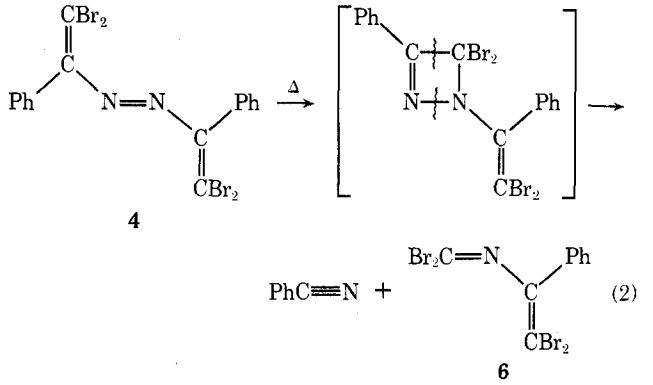
Attempts to follow the apparently first-order kinetics of the loss of Br_2 from **3** in *o*-dichlorobenzene–1-octene at 108° were unsuccessful as other colored products arise, probably from further reaction of **5**. A half-life of about 30 min can be estimated at this temperature by following the growth in the uv band at 502 nm for the products, **5**.

Both azoethenes **4** and **5** react quantitatively with Br_2 in CH_2Cl_2 solution at room temperature. The bromine addition to **4** is essentially instantaneous and with **5** requires 30 min for complete reaction; the sluggishness of **5** may be attributed to both the greater steric hindrance in the addition product **3** relative to **2** as well as to extreme insolubility of **5**. Azoethene **4** is inert to both Cl_2 and I_2 in CH_2Cl_2 at room temperature. The lack of reaction with Cl_2 is likely a result of the unfavorable interaction of highly electrophilic chlorine with the electron-poor double bonds in **4**. The failure of the addition of I_2 to **4** is probably due to steric hindrance and/or thermodynamic factors, i.e., the release of I_2 by the possible iodine-addition product of **4** proceeds more rapidly at room temperature than the I_2 addition.

The uv absorptions of these $\beta,\beta,\beta',\beta'$-tetrabromoazoethenes are reminiscent of aromatic azo compounds. Thus, for **4** (in benzene), λ_{max} 353 nm (log ϵ 4.36), 478 (2.59), for **5** (in benzene), λ_{max} 354 nm (log ϵ 4.38), 502 (2.52), and for (*E*)-azobenzene (in EtOH),[11] λ_{max} 319 nm (log ϵ 4.34), 443 (2.71).

Azoethene **1** was found to be stable upon heating to 180°C.[1] On the other hand, heating **4** at reflux in chlorobenzene for a few hours leads quantitatively to a colorless, crystalline product $C_9H_5NBr_4$ with the probable structure $Br_2C{=}NC(Ph){=}CBr_2$ (2-aza-3-phenyl-1,1,4,4-tetrabromo-1,3-butadiene, **6**). This same product may also be obtained by heating neat **3** to 190° in a test tube, whereupon melting with decomposition occurs; PhCN is obtained on the walls of the test tube. The ir, NMR, and uv spectral evidence is consistent with the proposed structure **6**; the ir bands at 1674 and 1623 cm^{-1} can be assigned to C=N and C=C bond stretching, respectively.

A possible mechanism for this molecular rearrangement involves prior conrotatory ring closure.



The rate of the first-order conversion of **4** to **6** at 119° in chlorobenzene subjected to prior bubbling with a nitrogen stream was followed by the disappearance of the peak at 478 nm and found to be 5.46×10^{-3} min^{-1}.

Azoethene **4** is stable upon heating neat to 190° but undergoes decomposition at 220°. Dibromoacetonitrile was not found among the decomposition products.

Experimental Section

2,2,2-Tribromoacetophenone Azine (2). A solution was prepared containing 10.0 g (0.042 mol) of acetophenone azine in 50 ml of CH_2Cl_2 in a round-bottomed flask equipped with a condenser. A dropping funnel with an equalizer arm was attached on top of the condenser. Bromine (41 g, 0.26 mol) was added dropwise over 40 min while the solution was heated at reflux with magnetic stirring. Heating at reflux was continued for 1 hr after bromine addition. The solvent was removed by rotary evaporation and the dark red mass remaining triturated with methanol. The unstable yellow crude product was collected on a Buchner funnel, then dissolved at room temperature in CH_2Cl_2 (10 ml per 1 g of crude product) and recrystallized at −20°, giving light yellow needles of **2** which slowly decompose upon standing in the air (11.9 g, 40%): mp 170° dec; ir (Nujol) 1715, 1610, 1592, 1449, 1250, 1080, 1028, 824, 781, 747, 730, 710, 650 cm^{-1}; NMR ($CDCl_3$) τ 2.50 (apparent s).

Anal. Calcd for $C_{16}H_{10}N_2Br_6$: C, 27.08; H, 1.42; N, 3.95; Br, 67.55. Found: C, 27.01; H, 1.36; N, 3.90; Br, 67.62.

Pentabromopropanone-2 Azine (3). This preparation, involving the bromination of acetone azine, was analogous to the preparation of **2** described above. After bromine addition, the reaction solution was heated at reflux overnight. The crude product was recrystallized from toluene (50 ml per 1 g of crude product) to give yellow needles of **3** (yields were about 60%), mp 227° dec, which are stable in the air: ir (KBr) 3010, 1660, 1610, 1390, 1150, 900, 785, 760, 730 cm^{-1}; MS (100 eV, 180° probe temperature) M^+ (rel intensity, 2, 11-line pattern for 10 Br), $(M - Br)^+$ (100), $(M - C_2H_2Br_4N)^+$ (70).

Anal. Calcd for $C_6H_2N_2Br_{10}$: C, 8.00; H, 0.22; N, 3.11; Br, 88.67. Found: C, 8.08; H, 0.19; N, 3.09; Br, 88.70.

1,1′-Diphenyl-2,2,2′,2′-tetrabromoazoethene (4). Crude **2** (10 g, 0.014 mol) was added to a mixture of 30 ml of methanol, 30 ml of ethyl acetate, and 0.5 ml of cyclohexene and heated to reflux. Shortly before the onset of reflux, bright red crystals appeared in the solution mixture and heating at reflux was continued for an additional 5–10 min until all **2** was debrominated, giving **4**. The solution was cooled rapidly and crude **4** was recrystallized from EtOAc–EtOH (2:1 v/v) (45 ml for 1 g) to give brilliant red platelets which are stable in a sealed evacuated ampoule, decompose after a few days in a closed nonevacuated vial, but are stable in the open air for about 1 month: mp 192° dec; 5.4 g (70%); ir (Nujol) 1540, 1265, 1180, 1092, 1080, 1035, 1005, 894, 811, 761, 703, 655 cm^{-1}; uv (benzene) λ_{max} 353 nm (log ϵ 4.36), 478 (2.59); NMR ($CDCl_3$) τ 2.5–3.0 (m). Bromine addition (in CH_2Cl_2): 1.2675 g of **4** gives 1.6358 g of **2** (99.99%).

Anal. Calcd for $C_{16}H_{10}N_2Br_4$: C, 34.95; H, 1.83; N, 5.09; Br, 58.13. Found: C, 35.01; H, 1.87; N, 5.10; Br, 58.05.

1,1,1′,1′,3,3,3′,3′-Octabromo-2,2′-azopropene (5). Crude **3** (3.0 g, 3.3 mmol) was added to cyclohexene and heated at reflux for 24 hr. The resulting red solution was cooled and grayish purple, circular platelets of **5** (1.83 g, 75%) were collected: mp 179° [from 10 ml of EtOAc–C_6H_6 (1:1 v/v) for 1 g]: ir (Nujol 1534, 1260, 1220, 1150, 938, 872, 739, 700 cm^{-1}; uv (benzene) λ_{max} 354 nm (log ϵ 4.38), 502 (2.52); NMR (CCl_4) τ 2.87 (s); MS (100 eV, 150° probe tempera-

ture) M^+ (rel intensity, 22, nine-line pattern for 8 Br) $(Br_2C{=}N{=}CBr_2)^+$ (100).

Anal. Calcd for $C_6H_2N_2Br_8$: C, 9.72; H, 0.27, N, 3.78; Br, 86.23. Found: C, 9.55; H, 0.25; N, 3.64; Br, 86.39.

2-Aza-3-phenyl-1,1,4,4-tetrabromo-1,3-butadiene (6). A sample of azoethene **2** (1.0 g, 1.8 mmol) was heated neat in a test tube to 190°. The black mass obtained was cooled and 5 ml of methanol was added. White square platelets (0.65 g, 80%) of azabutadiene **6** were obtained, mp 60° (MeOH). The liquid droplets condensed on the test tube wall were shown to be benzonitrile by ir.

Similarly, **6** was prepared by heating a solution of **2** (1.0 g, 1.8 mmol) in chlorobenzene at reflux for 4 hr until the originally deep red solution was practically colorless, evaporation of the solvent, and trituration with MeOH: yield 0.80 g of **6** (100%, 71% after MeOH); ir (CCl_4) 3062, 1674, 1623, 1490, 1447, 1060, 870, 697, 650 cm^{-1}; uv (methanol) end absorption; NMR (CCl_4) τ 2.61 (apparent s); MS (100 eV, 150° probe temperature) M^+ (rel intensity, 14, five-line pattern for 4 Br), $(M - Br_2CN)^+$ (100).

Anal. Calcd for $C_9H_5NBr_4$: C, 24.19; H, 1.13; N, 3.14; Br, 71.54. Found: C, 24.19; H, 1.25; N, 3.13; Br, 71.35.

Bromine Generation from Ketazine 3. A solution was prepared containing 12 g (0.033 mol) of ketazine **3** in 20 ml of *o*-dichlorobenzene in a 50-ml round-bottomed flask connected to a trap containing methylene chloride at 0°. The solution was heated at 150–170° for 30 min with a nitrogen stream bubbling through the system. The bromine collected in the trap was titrated with 850 mg of cyclohexene (10.3 mmol, 77%) and azopropene **5** (8.8 g, 89%) was recovered as a crystalline solid.

Registry No.—**2**, 56454-39-8; **3**, 56454-40-1; **4**, 56454-41-2; **5**, 56454-42-3; **6**, 56454-43-4; acetophenone azine, 729-43-1; bromine, 7726-95-6; acetone azine, 627-70-3.

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A Novel High-Yield Synthesis of γ Esters of Glutamic Acid and β Esters of Aspartic Acid by the Copper-Catalyzed Hydrolysis of Their Diesters

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Benzyl esters have a unique place in peptide synthesis for the reversible protection of side-chain carboxyl groups.[1] These esters are relatively stable to the mildly acidic and basic conditions of peptide synthesis, but can be easily removed at the end of the synthesis by strongly acidic or reductive cleavage.[2] A problem with benzyl esters, however, is that they are not completely stable to reagents commonly used to remove the α-NH_2 *tert*-butyloxycarboxyl protecting group (e.g., trifluoroacetic acid–dichloromethane, 1:1) and are slowly hydrolyzed by these reagents.[3]

This lability can cause difficulties in long syntheses, giving rise to cumulative loss of side-chain protection and hence to branching of the peptide chain. To prevent the occurrence of this problem, more stable carboxyl-protecting groups are needed. These groups are also useful for the solid-phase synthesis of protected peptide fragments, which can be achieved by the use of side-chain protecting groups[4] which are completely stable to the reagents used to cleave the peptide from the resin (e.g., HBr in acetic acid).

For these reasons, substituted benzyl esters have been used by several workers[5–7] for side-chain carboxyl protection, although the use of such esters has been hindered by a lack of methods for their facile preparation. For example, the *p*-nitrobenzyl esters of Schwarz and Arakawa[5] can best be prepared by the procedures of Ledger and Stewart,[6] which involve the preparation of the copper complex of the amino acid, and the subsequent esterification of this copper complex with *p*-nitrobenzyl halide. This method is lengthy, however, and yields are low. The selective hydrolysis of aspartic and glutamic acids diesters which is described in this communication provides a method for the preparation in high yield of a wide range of monoesters by a very simple procedure.

In this procedure the amino acid is converted to the appropriate diester salt, using well-established procedures.[1,8,9] Without further purification the diester is then hydrolyzed by aqueous copper sulfate, and the copper complex of the desired monoester is isolated by filtration. After the copper complex has been decomposed with EDTA by the method of Ledger and Stewart,[6] the monoester can be isolated in a pure form by a single recrystallization.

In a typical copper hydrolysis, glutamic acid dibenzyl ester *p*-toluenesulfonate (10 g, 20 mmol) was dissolved in ethanol (140 cm^3) and aqueous $CuSO_4 \cdot 5H_2O$ (20 g, 80 mmol in water, 350 cm^3) was added. The pH was raised to 8.0 with 1 *M* NaOH, and the solution was maintained at that pH and 32°C for 60 min. The pH was then lowered to 3.0 with 3 *M* HCl and the precipitate of the copper complex of Glu(γOBzl)[10,11] was filtered off and washed with water, ethanol, and ether. Ethylenediaminetetraacetic acid disodium salt (7.8 g, 21 mmol) in 100 cm^3 of water was added, the solution was boiled and filtered, and on cooling, glutamic acid γ-benzyl ester precipitated out. The product was collected by filtration and washed with water, ethanol, and ether: yield 3.5 g (14.8 mmol, 74%); mp 169–170°; $[\alpha]^{22}D$ +19.3° (*c* 5.49, acetic acid) (lit. mp 169–170°, $[\alpha]^{25}D$ +19.2).[6]

The yields for various esters of glutamic and aspartic acids are given in Table I.

Terashima et al.[12] have proposed a structure for the copper complexes of aspartic and glutamic acids where both the amino nitrogen and one of the carboxyl oxygens are coordinated to the copper atom only if a five-membered ring is formed. This proposal was confirmed by the absence in the hydrolysis product of any trace of the α-monoesters of aspartic and glutamic acid or of the free amino acids.[13]

The mechanism of the copper-catalyzed hydrolysis of amino acid esters has been suggested[14] to proceed by OH^- attack on the carbonyl group of the copper coordinated ester linkage. If this is the case, the rate of hydrolysis should be increased by electron-withdrawing substituents on the ester group. To test this hypothesis, the rate of the copper hydrolysis reaction for various glutamic acid diesters was measured. Samples of the reaction mixture were quenched with dilute acid, treated with EDTA, and chromatographed on silica gel plates, using a 1-butanol–acetic acid–pyridine–water (15:3:10:12) solvent. The γ-ester spots