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Zinc-Induced Reactions of Bromo Ketones. 6,7-Dihydrodibenzo- and 6,7-Dihydrodithieno[*a,c*]cyclooctene-5,8-diones and Their Dehydro Derivatives

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Abstract: The synthesis of 6,7-dihydrodibenzo- and 6,7-dihydrodithieno[*a,c*]cyclooctene-5,8-diones (**4**–**7**) by the use of a novel zinc-induced cyclization of bis(bromoacyl)biphenyls and -bithienyls is reported. The synthesized compounds serve as precursors of the fully conjugated, dibenzo and dithieno analogues **8**, **9**, and **11** of cyclooctatetraenoquinone. The latter compounds were found to undergo some specific reactions: dibenzo[*a,c*]cyclooctene-5,8-dione (**8**) adds acetic anhydride by a 1,4-addition, whereas the corresponding 6,7-dimethyl derivative **9** rearranges in acidic conditions to fluorene, spiroannelated with a γ-lactone (**22**). The conformational preferences of the stereoisomeric *cis*- and *trans*-6,7-dihydro-6,7-dimethyldibenzo-[*a,c*]cyclooctene-5,8-diones (**5** and **6**) have been investigated and their inversion barriers have been determined: the cis stereomer **5** has a higher energy barrier for inversion and is thermodynamically the more stable of the two isomers.

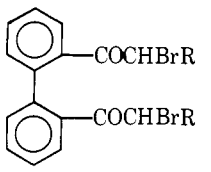
The synthetic importance of α-keto radicals, generated from ketones by the action of light,[1] peroxides,[2] or metallic ions[3] has been generally limited to addition reactions to unsaturated systems. Intermolecular dimerizations involving these radicals and leading to 1,4-diketones[4] have been found to be of rather limited synthetic value.[5] Moreover, the peroxide-initiated reactions of aliphatic 1,3- and 1,4-diketones did not afford cyclic diketones via a potential intramolecular coupling.[6] Recently it was found that aromatic α-ketomethylene radicals, generated by the action of zinc on bromo ketones, could undergo an intermolecular coupling.[7] This method was applied with advantage to the synthesis of six-membered cyclic diketones, by free-radical cyclizations involving two vicinal bromoacyl groupings attached to heterocyclic substrates.[8] The same approach has been extended now to further separated bromoacyl groupings, attached to aromatic or heteroaromatic substrates, thus providing a method for the synthesis of annelated medium-sized cyclic 1,4-diketones.

Results and Discussion

Treatment of 2,2′-bis(bromoacetyl)biphenyl (**1**) and of the 4,4′-bis(bromoacetyl)bithienyl (**3**) with zinc–copper couple in dimethyl sulfoxide (Me_2SO), in the presence of sodium iodide and sodium bicarbonate, resulted in an intramolecular coupling leading to the annelated cyclooctadienediones **4** and **7** in yields of ca. 50%. These cyclizations, although limited at present to aromatic or heteroaromatic diketones, appear to be the first reported intramolecular coupling reactions to involve α-ketomethylene groups and to lead to medium-sized cyclic 1,4-diketones.

The structure of **4** (and **7**) was established on the basis of spectral and chemical properties. The absence of methyl signals in the NMR spectrum of **4**, together with its elemental analysis, indicated a tricyclic diketone structure. The NMR spectrum showed one singlet for the cyclic methylene protons (at δ 2.82), unchanged down to −50°, and these data, associ-

ated with the great similarity of the uv spectra of **4** and of 2,2′-diacetylbiphenyl, suggested a high degree of conformational flexibility around the pivotal biphenyl bond of the former.[9]



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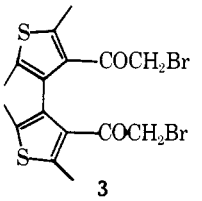
2, R = CH_3



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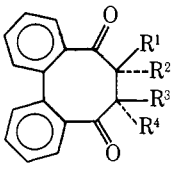
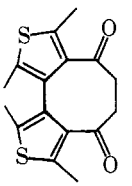


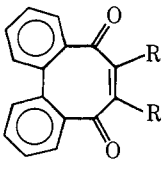


7

4, $R^1 = R^2 = R^3 = R^4 = H$
5, $R^1 = R^3 = CH_3$; $R^2 = R^4 = H$
6, $R^1 = R^4 = CH_3$; $R^2 = R^3 = H$
20, $R^1 = R^4 = CH_3$; $R^2 = H$, $R^3 = Br$
(or $R^1 = R^3 = CH_3$; $R^2 = H$, $R^4 = Br$)

Compound **4** provides a facile access to dibenzocyclooctatetraene derivatives and to annelated cyclooctatetraenoquinones. The former are obtained as the bis-enol ethers of **4** and the bis(trimethylsilyl) ether **12** is an example of this class of compounds. The "expanded quinone" system **8** is a dibenzo derivative of cyclooctatriene-1,4-dione (**10**), a potentially aromatic $(4n + 2)$ π electron system in its neutral or protonated state.[10,11] The chances for aromaticity in **8** could, however, be expected to be rather small because of annelation and of strong deviation from planarity.

The conversion of **4** into **8** was achieved by bromination and dehydrobromination (60% yield); similarly, diketone **7** was converted into **11**. No extended conjugation is observed in the uv spectra of these compounds. In the NMR spectra the vinylic protons appear at δ 6.85 and 6.51 for **8** and **11**, respectively, with no indication of a diamagnetic shift. A downfield shift is, however, observed when the spectra are recorded in deuteriotrifluoroacetic acid (δ 7.21 and 6.91, respectively) suggesting a possible contribution from a mono- or diprotonated aromatic species.[12] A significant reaction of the unsaturated system **8** was observed on treatment of this compound with acetic anhydride, in the presence of boron fluoride etherate. A 1,4-addition of acetic anhydride to the unsaturated diketone occurred affording compound **14** which corresponded to the assumed intermediate of the Thiele reaction of benzoquinones.[13] The second step of the latter reaction, which consists in a second enolization and formation of a triacetoxy aromatic derivative, does not occur in **14**, probably because of the absence of a driving force for aromatization.[14] Spectral and analytical properties confirmed the structure of **14** although some ambiguity arose in relation to its NMR spectrum, in which both the vinyl and the neighboring proton appeared as one sharp singlet at δ 5.75. The use of pyridine as solvent, or addition of a shift reagent, [Eu(fod)$_3$], to the $CDCl_3$ solution, resulted, however, in a resolved AB pattern for these protons.



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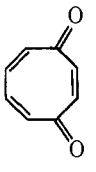
9, R = CH_3



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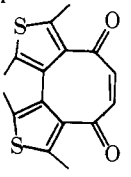

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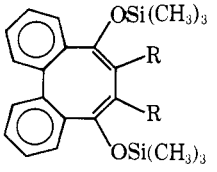
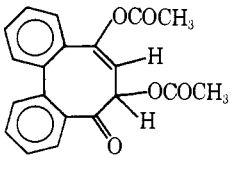


12, R = H
13, R = CH_3

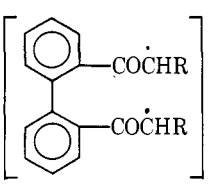


14

Conformational Analysis. The readiness with which the eight-membered ring bridged biphenyls could now be obtained prompted us to investigate their conformational preferences and the rates of ring inversion. In substituted seven-, eight-, and nine-membered ring bridged biphenyls the inversion barriers can be sometimes sufficiently high (above 20 kcal/mol), so as to allow the separation of enantiomeric conformers and to study their racemization or mutarotation.[15] The introduction of carbonyl groups in the α position to the aromatic rings should, however, eliminate a strong directed interaction between the hydrogens at these positions which occurs in the transition state of the interconversion and thus increase the flexibility of the system.[16]

The conformational mobility could best be studied on the 6,7-dimethyl derivatives of **4**. These were prepared as follows. Bromination of 2,2′-dipropionylbiphenyl with phenyltrimethylammonium perbromide[17] (PTAB) in THF gave a 3:2 mixture of two diastereomeric dibromides (**2**), which could be partly separated by chromatography. Each of the dibromides, when subjected to the coupling reaction, yielded the same mixture composed of diketone **5** (one isomer; 64% yield) and epoxy ketone **17** (14% yield). This identity of results in the coupling reaction of both isomers is in agreement with the assumed free radical pathway[8] by which the biradical **15**, derived from either of isomers **2**, can change its configuration before ring closure, to give the more stable isomer.

The epoxy ketone **17** is formed in a side reaction, probably by an intramolecular nucleophilic attack of the enolate ion from one bromoacyl grouping on the carbonyl carbon of the other grouping (via **16**), with displacement of bromine. Intermolecular reactions leading to similar results have been reported.[18] The structure of **17** was confirmed by its conversion with base to the dibenzotropone **18**, with a uv spectrum almost identical with that of **19**, independently prepared by base



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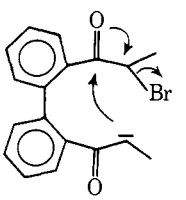

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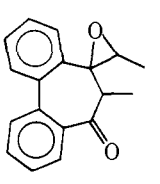

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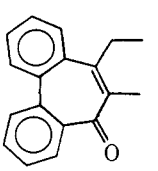

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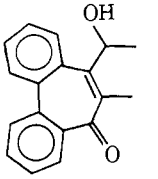


18

treatment of 2,2′-dipropionylbiphenyl. The NMR spectrum of **18** at room temperature exhibits poorly defined broad methyl signals which are resolved at lower temperatures (−30°) into two methyl doublets at δ 1.28 and 1.68 (J = 6 Hz, ratio ~3:2, side-chain methyl) and two methyl singlets at δ 2.14

and 2.25 (ratio ~2:3, ring methyl). The two sets of signals result from slow rotation, in the NMR time scale, via a planar transition state around the pivotal biphenyl bond. At 60° an increase in the inversion rate results in the coalescence of the signals to one methyl doublet (δ 1.47, J = 6 Hz, side-chain methyl) and one methyl singlet (δ 2.22, ring methyl).

The main product of the coupling reaction, diketone **5**, was found to be the *cis*-dimethyl isomer on the basis of hydrogenation experiments (cis hydrogenation of the unsaturated diketone **9** over platinum on barium sulfate to give **5**), NMR evidence, and comparison with the *trans*-dimethyl isomer. The NMR spectrum of **5** indicated an unsymmetrical structure with two methyl doublets (δ 1.03 and 1.22) and two methine doublet quartets (δ 2.68 and 3.47). Spin decoupling experiments interrelated these signals and showed them to belong to a single compound. Examination of models supports indeed an unsymmetrical structure for the *cis*-dimethyl isomer and a twofold symmetry for the trans isomer. The preparation of such a symmetrical isomer provided a confirmation of these assumptions. The proper method for this preparation, which afforded diketone **6** exclusively, was found to be the acid hydrolysis of the bis(trimethylsilyl) enol ether (**13**) of **5**. It is noteworthy that the cis isomer is recovered from the acid hydrolysis of the bis-enol acetate of **5** or of the monotrimethylsilyl ether of **5**. Treatment of diketone **5** with potassium *tert*-butoxide resulted also in the recovery of the starting diketone, although the bis-enol has been formed, as found by D_2O hydrolysis. The presence of a twofold axis of symmetry in diketone **6** follows from the ^1H NMR spectrum (δ 1.25, d, two methyls) and the ^{13}C NMR spectrum (δ 14.8, 2 methyls, and 191.9, two carbonyls); a further confirmation for this symmetry was obtained by the determination of the space group in which the molecule crystallizes.[19]

The temperature-dependent NMR spectra of the *cis*- and *trans*-dimethyl isomers allowed a quantitative determination of dynamic phenomena. The cis diketone **5** should interconvert between two enantiomeric conformations (Figure 1, nonequivalent methyls in ab′ or a′b positions), while the rotation about the biphenyl bond in the trans isomer **6** should involve two diastereomeric conformations (Figure 1, equivalent methyls in aa′ or bb′ positions). The conformational mobility in the cis isomer **5** is sufficiently low as to provide a well-resolved NMR spectrum in the range of −40 to 30 °C and to allow the detection of enantiomeric nonequivalence. Addition of 0.6 equiv of tris(3-trifluoroacetyl-*d*-camphorato)europium(III)[20] to a $CDCl_3$ solution of **5** resulted in the splitting of the methyl doublets with enantiomeric shift differences ($\Delta\Delta\delta$) of 2.7 and 2.0 Hz for the higher and lower field methyl signals, respectively. At higher temperature a simplified spectrum consisting of one well-resolved methyl doublet and one broad methine signal is obtained, the coalescence occurring at 63° for the methyl doublets and at 95° for the methine signals. The calculated[21] activation energy for inversion, based on either set of signals ($\Delta\nu$ = 7 and 80 Hz, respectively) was found to be of 18 kcal/mol, considerably lower than that found for systems with sp^3 methylene groups in the 5 and 8 positions.[15] The NMR spectrum of the trans isomer shows at −40° the expected unequal distribution between two nonequivalent conformations, with two methyl doublets (9:5 ratio) at δ 1.38 and 1.22 and two broad methine signals (same ratio) at δ 3.07 and 2.89. By irradiating the methyl region these methine bands were transformed into sharp singlets ($W_{1/2}$ = 2 Hz), not showing any mutual coupling. The calculated energy difference between the two conformations is thus $\Delta G°$ = 0.28 kcal/mol. The signals of **6** coalesce at 18 °C to one methyl doublet and one broad methine singlet and, notwithstanding the small $\Delta G°$ value, this corresponds to an inversion barrier of ~14 kcal/mol. The relatively low barrier to the rotational process is justified by a weaker nonbonded interaction in the transition state between the *trans*-dimethyl groupings as compared with a strong eclipsed interaction between the *cis*-methyls in **5**.

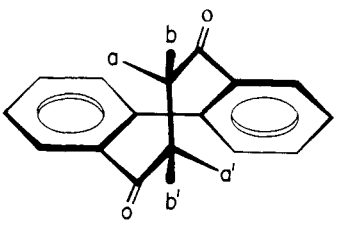
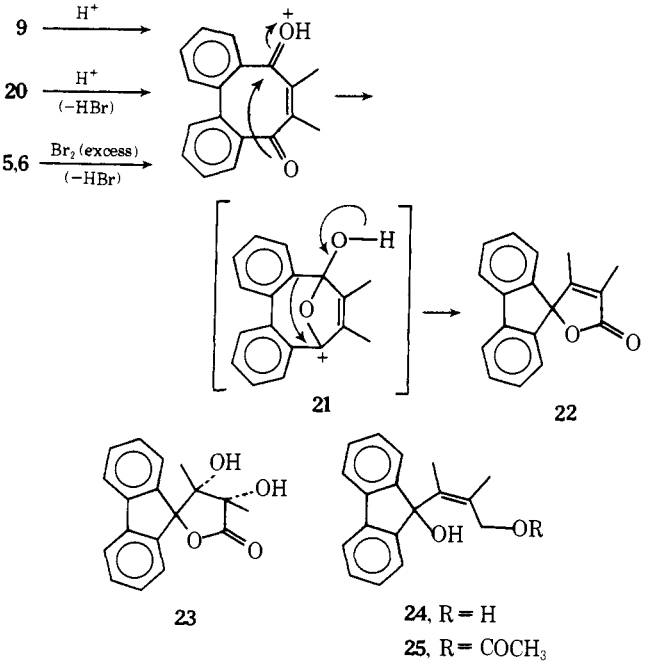


Figure 1.

Each of the isomeric diketones could be equilibrated (30 min, 200°, under nitrogen) to a 4:1 mixture of **5** (cis) and **6** (trans). Isomerization occurred via enolization, as evidenced by the incorporation of deuterium in the 6 and 7 positions, when equilibration was carried out in a sealed tube in the presence of D_2O. This difference in free energy between the two isomers, which is reflected also in the preferential formation of **5** in the coupling reaction, may be accounted for by the interference between the methyl groups and the aromatic rings in one of the trans conformers and the eclipsing of the methyls in the other conformer (Figure 1, methyls in aa′ or bb′ position, respectively). Such interactions occur to a lesser extent in the cis isomer.

Transannular Rearrangements. Eight-membered ring cyclic diketones could be expected to undergo transannular reactions, and an unusual rearrangement was indeed observed when **5** or **6** was treated with an excess of bromine in dioxane, or when the unsaturated diketone **9** was subjected to acid treatment. Compound **22**, in which an unsaturated γ-lactone is spiroannelated with fluorene, was formed in high yield as a single product. Monobromide **20**, when exposed to acid, was also converted to **22**. The pathway for the rearrangement of **9** involves probably protonation at one of the carbonyls and the intermediacy of **21**. When starting from **20**, the loss of hydrogen bromide precedes this step. The structure of **22** follows from spectroscopic evidence and was confirmed by chemical degradation. The ir spectrum displayed a peak at 1752 cm^{-1}, compatible with the absorption of a carbonyl group in an α,β-unsaturated γ-lactone, and the uv spectrum had a pattern characteristic of fluorenes. The ^1H NMR spectrum exhibited slightly split (J = 1 Hz) methyl signals, one of which is relatively shielded (δ 1.44) due to its position above the fluorene moiety. The ^{13}C NMR spectrum also confirmed the presence



of the unsaturated lactone (δ 174.9 for the lactone carbonyl and δ 159.75 for the olefinic carbon β to carbonyl). The presence of a tetrasubstituted double bond follows from the reaction of **22** with osmium tetroxide, affording the diol **23,** which exhibits in its ir spectrum the peak of a saturated γ-lactone (1765 cm^{-1}). Reduction of **22** with lithium aluminum hydride resulted in the cleavage of the lactone and formation of the diol **24,** in which the presence of a primary and a tertiary hydroxyl group was confirmed by acetylation to the monoacetate **25.**

Finally, ozonolysis of **24** followed by workup in oxidative conditions resulted in the formation of fluorenone.

Experimental Section

Melting points were determined on a hot-stage microscope and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 237**B** instrument and ultraviolet spectra were measured on a Cary 14 spectrophotometer. NMR spectra were obtained on Varian A-60 and Bruker 90 spectrometers. The Bruker instrument was used also for the recording of ^{13}C NMR spectra. Deuteriochloroform was used as solvent in NMR work unless specified otherwise. Mass spectra were recorded on a MAT-64 spectrometer. Merck silica gel G was employed for column chromatography; the ratio of silica to substrate was 30:1, unless specified otherwise.

2,2′-Bis(bromoacetyl)-1,1′-biphenyl (1). To a solution of 2,2′-diacetyl-1,1′-biphenyl[22] (2.38 g, 10 mmol) in dry THF (20 ml) was added 7.52 g (20 mmol) of phenyltrimethylammonium perbromide[17] (PTAB) dissolved in 50 ml of THF. The mixture was stirred for 15 min at room temperature, the precipitate was removed by filtration, and the filtrate was concentrated under vacuum. The residue afforded on crystallization (MeOH) 3.4 g of dibromide (85%), mp 100–102 °C: NMR δ 4.18 (4 H, br d), 7.10–7.95 (8 H, m). Anal. ($C_{16}H_{12}Br_2O_2$) C, H, Br.

2,2′-Bis(α-bromopropionyl)-1,1′-biphenyl (2). The treatment of 2,2′-dipropionylbiphenyl[22] (13.3 g, 50 mmol) with PTAB (37.6 g, 100 mmol) as described above gave a mixture of diastereomeric dibromides (20.67 g, 97%) in a 3:2 ratio (NMR). A part of the major isomer (6.4 g) was separated by direct crystallization (EtOH), mp 136 °C: NMR δ 1.60 (d, 3 H, J = 7 Hz), 4.78 (q, 1 H), 7.07–7.90 (m, 8 H). Anal. ($C_{18}H_{16}Br_2O_2$) C, H, Br.

Chromatography of the mother liquor (ratio of silica gel to substrate, 100:1; eluting with 10–20% benzene in hexane) afforded in the late fractions a second isomer, mp 119 °C (from EtOH): NMR δ 1.66 (d, 3 H, J = 7 Hz) 4.79 (q, 1 H), 7.10–7.95 (m, 8 H). Anal. ($C_{18}H_{16}Br_2O_2$) C, H, Br.

4,4′-Bis(bromoacetyl)-2,2′,5,5′-tetramethyl-3,3′-bithienyl (3). Treatment of 4,4′-diacetyl-2,2′,5,5′-tetramethyl-3,3′-bithienyl[24] (15.3 g, 50 mmol) with PTAB (37.6 g, 100 mmol) as described above afforded **3** (18.5 g, 80%), mp 105–106 °C (MeOH): NMR δ 2.19 (s, 6 H), 2.60 (s, 6 H), 3.78 (s, 4 H). Anal. ($C_{16}H_{16}O_2S_2Br_2$) C, H, Br.

6,7-Dihydrodibenzo[*a,c*]cyclooctene-5,8-dione (4). To a stirred mixture of Zn–Cu couple[23] (6.6 g, 100 mmol), NaI (1.50 g, 10 mmol), $NaHCO_3$ (1.68 g, 20 mmol), and **1** (3.96 g, 10 mmol), dry Me_2SO (100 ml) was added through a dropping funnel after flushing the reaction flask with nitrogen. The stopped flask was kept for 30 min in an oil bath at 60°, with efficient magnetic stirring. Dilution with cold NH_4Cl solution and extraction (ether–chloroform 4:1) gave the crude product which was purified by chromatography (pentane and 40% ether). Crystallization (chloroform–hexane) afforded 1.14 g (48%) of **4**, mp 140–141 °C (EtOH): NMR δ 2.84 (s, 4 H), 7.05–7.80 (m, 8 H); uv λ_{max} (EtOH) 245 sh (ϵ 10 200), 290 (ϵ 2100); mol wt, 236 (MS). Anal. ($C_{16}H_{12}O_2$) C, H.

6,7-Dihydro-2′,2″,5′,5″-tetramethyl-3′,3″-dithieno[*a,c*]cyclooctene-5,8-dione (7). Dibromide **3** (5 g, 10.7 mmol) was reacted with Zn–Cu couple (7.6 g, 107 mmol) in conditions used for the preparation of **4** (oil bath temperature: 70°). The crude product was purified by chromatography and afforded, on elution with hexane and 20% ether, 1.8 g (56%) of **7**, mp 133–135 °C (hexane–ether): NMR δ 2.08 (s, 6 H), 2.54 (s, 6 H), 2.75 (s, 4 H); ir ($CHCl_3$) 1680 cm^{-1} (C=O); MS *m/e* 304 (M^+), 263, 248, 171, 138. Anal. ($C_{16}H_{16}O_2S_2$) C, H.

***cis*-6,7-Dihydro-6,7-dimethyldibenzo[*a,c*]cyclooctene-5,8-dione (5).** A mixture of disastereomers **2** (10.8 g, 25 mmol) was allowed to react with Zn–Cu couple (16.5 g, 250 mmol) in the presence of $NaHCO_3$ (4.2 g, 50 mmol) and NaI (3.75 g, 25 mmol) in Me_2SO (200 ml) as described for the preparation of **4.** Crystallization of the crude product (MeOH) afforded 3.5 g of **5**, mp 145 °C; chromatography of the mother liquor from crystallization afforded by elution with pentane and 20% ether an additional 0.73 g of **5** (64% total yield): NMR δ 1.03 (d, 3 H, J = 7 Hz), 1.22 (d, 3 H, J = 7 Hz), 2.68 (d q, 1 H), 3.47 (d q, 1 H), 7.1–8.2 (m, 8 H). Spin decoupling experiments: irradiation at δ 2.68 converted the doublet at δ 1.03 into a singlet, while irradiation at δ 3.47 converted the doublet at δ 1.22 into a singlet. Inversely, irradiation of each of the methyl signals converted the corresponding double quartet into a narrow doublet, J = 3 Hz. Likewise, irradiation of each of the double quartets converted the other into a quartet, J = 7 Hz. ^{13}C NMR δ 210 and 201 (2 C=O), 52.6 and 46.8 (C-6 and C-7), 14.6 and 8.1 (methyls); MS *m/e* 264 (M^+), 235, 208, 180. Anal. ($C_{18}H_{16}O_2$) C, H.

Chromatography of the crude product afforded, prior to **5** (elution with pentane and 10% ether), 0.92 g (14%) of 6,7-dihydro-5-epoxyethylidene-6-methyl-dibenzo[*a,c*]cycloheptene-7-one (**17**), mp 121–122 °C (EtOH): NMR δ 0.67 (d, 3 H, J = 5 Hz, side-chain methyl), 1.24 (d, 3 H, J = 7 Hz, 6-methyl), 2.64 (q, 1 H, J = 7 Hz), 3.12 (q, 1 h, J = 5 Hz), 7.25–7.76 (m, 8 H); ir (KBr) 1678 cm^{-1} (C=O); uv λ_{max} (EtOH) 235 (ϵ 24 700) 255 sh (ϵ 9550), 295 (ϵ 1500); MS *m/e* 264 (M^+), 220, 203, 201, 181, 165. Anal. ($C_{18}H_{16}O_2$) C, H.

The separated isomers **2** were also submitted to the coupling conditions and afforded indentical results with those shown above (NMR evidence).

5-(1-Hydroxyethyl)-6-methyldibenzo[*a,c*]cyclohepten-7-one (18). The epoxy ketone **17** (120 mg, 0.45 mmol) in *t*-BuOH (3 ml) was added to a solution of *t*-BuOK (from 30 mg of potassium in 5 ml of *t*-BuOH) under nitrogen. After 30 min, water was added and the mixture was extracted with ether. Chromatography of the crude product (pentane and 20% ether) afforded 92 mg of **18** (76%), mp 139–140 °C (chloroform–hexane): NMR δ 1.1–1.7 (br, 3 H), 2.01 (OH), 2.18 (s, 3 H), 5.02 (q, 1 H), 7.18–7.74 (m, 8 H); ir (KBr) 1662 cm^{-1} (C=O); uv λ_{max} (EtOH) 233 (ϵ 32 000), 320 (ϵ 2460); MS *m/e* 264 (M^+), 221, 203, 193, 189, 178. Anal. ($C_{18}H_{16}O_2$) C, H.

5-Ethyl-6-methyldibenzo[*a,c*]cyclohepten-7-one (19). To a solution of EtONa (from 100 mg of Na in 10 ml of EtOH) was added 2,2′-diacetylbiphenyl (0.64 g, 2.7 mmol) in EtOH (10 ml). After 30 min of refluxing, the solution was diluted with water and extracted with ether. Chromatography of the crude product (pentane and 10% ether) afforded **19** (0.21 g, 32%), mp 100–101 °C (from hexane): NMR δ 1.02 (t, 3 H), 2.16 (s, 3 H), 2.72 (q, 2 H), 7.25–7.90 (m, 8 H); uv λ_{max} (EtOH) 237 (ϵ 32 500), 325 (ϵ 2950). Anal. ($C_{18}H_{16}O$) C, H.

6,7-Dibenzo[*a,c*]cyclooctene-5,8-dione (8). Diketone **4** (0.6 g 2.5 mmol), in 18 ml THF was brominated using 1 equiv of PTAB (0.96 g, 2.5 mmol) in THF (8 ml) as shown above. The crude product was dehydrobrominated by elution from a silica gel column (hexane and 10% ether) affording 0.36 g (60%) of **8**, mp 212 °C (from EtOH): NMR δ 6.85 (s, 2 H), 7.08–7.70 (m, 8 H); in CF_3COOD, δ 7.21 (s, 2 H), 7.10–7.70 (m, 8 H); uv λ_{max} (EtOH) 225 sh (ϵ 21 000), 285 sh (ϵ 2600), 365 sh (ϵ 200); ir (KBr) 1675 cm^{-1} (C=O); MS *m/e* 234 (M^+), 205, 178, 171. Anal. ($C_{16}H_{10}O_2$) C, H.

2′,2″,5′,5″-Tetramethyl-3′,3″-dithieno[*a,c*]cyclooctene-5,8-dione (11). To 0.23 g (0.75 mmol) of diketone **7** in THF (4 ml) was added PTAB (0.29 g, 0.75 mmol) in 2 ml of THF. A precipitate which formed after a few minutes was removed by filtration, and the filtrate was concentrated under vacuum. To the residue was added a mixture of $CaCO_3$ (60 mg), HMPA (7 ml), and 0.15 ml of trimethylammonium dimethyl phosphate. After stirring at 80° for 3 h the mixture was diluted with water and the yellow crystals that formed were filtered, dissolved in chloroform, and dried ($MgSO_4$); the solvent was removed under vacuum. Pure **11** was obtained by chromatography of the residue (elution with pentane and 5% ether; 71 mg, 30%), mp 184–185 °C (MeOH): NMR δ 2.16 (s, 6 H), 2.32 (s, 6 H), 6.56 (s, 2 H); in CF_3COOD the signals are shifted to δ 2.21, 2.38, 6.91; uv λ_{max} (EtOH) 232 sh (ϵ 26 200), 295 (ϵ 2950), 360 (ϵ 1200); ir (KBr) 1668 cm^{-1}; mol wt, 302 (MS). Anal. ($C_{16}H_{14}O_2S_2$) C, H.

5,8-Bis(trimethylsilyloxy)dibenzo[*a,c*]cyclooctene (12). The diketone **4** (0.72 g, 3 mmol) in dry DMF (20 ml) was added to an excess of chlorotrimethylsilane (3.26 g, 30 mmol) and triethylamine (8.2 ml, 60 mmol) in 20 ml of DMF. The mixture was stirred overnight at 80° and extracted with pentane[25] to yield 0.57 g (50%) of **12**, mp 42 °C (cold MeOH): NMR δ −0.14 (s, 18 H), 5.36 (s, 2 H), 7.2–7.6 (m, 8 H). Anal. ($C_{22}H_{28}O_2Si_2$) C, H.

5,8-Bis(trimethylsilyloxy)-6,7-dimethyldibenzo[*a,c*]cyclooctene (13) was prepared from **5** (0.79 g, 3 mmol) using the same amounts of reagents as above. Compound **13** crystallized on cooling, mp 62 °C (0.8

g, 64%): NMR δ −0.32 (s, 18 H), 1.66 (s, 6 H), 7.15–7.5 (m, 8 H). Anal. ($C_{24}H_{32}O_2Si_2$) C, H.

6,8-Diacetoxy-6,7-dihydrodibenzo[*a,c*]cyclooctene-5(6*H*)-one (14). The diketone **8** (0.2 g) was dissolved with slight warming in acetic anhydride (7 ml) and boron trifluoride etherate (0.2 ml) was added to the solution. After the mixture was allowed to stand for 20 h at room temperature, water was added and the mixture stirred for 1 h. The precipitated crystals were filtered and washed with water (120 mg). Extraction with ether gave an additional 30 mg of the same product (52%), mp 145–146 °C (EtOH): NMR δ 2.06 and 2.17 (two acetoxy methyl singlets), 5.76 s (coincidence of C-6 and C-7 protons), 7.1–8.2 (m, 8 H). The two-proton singlet is resolved in pyridine into a close AB quartet. On addition of Eu(fod)$_3$ to the $CDCl_3$ solution of **14** an AB pattern is also obtained (J = 9 Hz); ir (KBr) 1779, 1754, 1698, 1229, 1190 cm^{-1}; mol wt, 336 (MS). Anal. ($C_{20}H_{16}O_5$) C, H.

***trans*-6,7-Dihydro-6,7-dimethyldibenzo[*a,c*]cyclooctene-5,8-dione (6).** The bis(silyl) ether **13** (0.4 g) was dissolved in methanol (10 ml) to which 0.1 ml of concentrated HCl was added. After 30 min, water was added and the precipitated crystals were filtered. Two crystallizations (EtOH) afforded 136 mg (50%) of **6**, mp 202 °C: NMR δ 1.24 (d, 6 H, J = 6 Hz), 2.94 (br, 2 H, $W_{1/2}$ = 16 Hz), 7.16–7.76 (m, 8 H); ^{13}C NMR δ 191.9 (2 C=O), 52.6 (C-6 and C-7), 14.6 (two methyls); ir (KBr) 1692 cm^{-1}; MS m/e 264 (M$^+$), 235, 221, 208, 180, 165. Anal. ($C_{18}H_{16}O_2$) C, H.

6,7-Dimethyldibenzo[*a,c*]cyclooctene-5,8-dione (9). A solution of diketone **5** (2.64 g, 10 mmol) in dioxane (40 ml) was treated dropwise with bromine (1.6 g, 10 mmol). After stirring for 5 min the mixture was poured into diluted cold CO_3HNa solution and extracted with ether. The residue was crystallized (MeOH), affording 2.8 g (82%) of monobromide **20**, mp 131–132 °C: NMR δ 1.48 (d, 3 H, J = 6 Hz), 1.72 (s, 3 H), 3.46 (q, 1 H), 7.10–8.10 (m, 8 H). Anal. ($C_{18}H_{15}O_2Br$) C, H.

Dehydrobromination of **20** (2.1 g, 6.3 mmol) was carried out, in conditions described for **11**, in HMPA (60 ml) to which $CaCO_3$ (0.6 g) and trimethylammonium dimethyl phosphate (1.5 ml) were added. Chromatographic purification (pentane and 10% ether) afforded 1.12 g (70%) of **9**, mp 212 °C (EtOH): NMR δ 2.12 (s, 6 H), 6.90–7.60 (m, 8 H); ir (KBr) 1669, 1625 cm^{-1}. Anal. ($C_{18}H_{14}O_2$) C, H.

Hydrogenation of **9** (160 mg) in ethyl acetate with 5% platinum on barium sulfate (140 mg) under atmospheric pressure gave a mixture consisting mainly of diketone **5** and containing unchanged **9** and traces of **6** (NMR). Chromatographic separation (elution with hexane and 30% ether) gave 124 mg of a mixture of **5** (75%) and **9** (25%, by integration of NMR peaks).

Equilibration of Diketones 5 and 6. Compound **6** (50 mg) was placed in a nitrogen-flushed glass tube which was then sealed. After 30 min at 200° the tube was opened and the product was dissolved in $CDCl_3$; the NMR spectrum showed a 4:1 ratio of isomers **5** and **6**. Addition of one drop of D_2O before sealing resulted in a simplified two-singlet spectrum for the methyl groups of **5**.

Heating of isomer **5** in the above conditions afforded an identical ratio of the isomeric diketones.

3′,4′-Dimethylspiro[fluorene-9,2′-furan]-5′-one (22). A solution of **9** (100 mg, 0.38 mmol) in benzene (10 ml), to which a few crystals of *p*-toluenesulfonic acid were added, was refluxed for 1 hr. Addition of water and extraction with ether afforded **22** (91 mg, 90%), mp 181–182 °C (MeOH): NMR δ 1.44 and 2.02 (two methyls, split s, $J \simeq$ 1 Hz), 7.05–7.85 (m, 8 H); ir (KBr) 1752 cm^{-1}; ^{13}C NMR δ 174.9 (C=O lactone), 159.75 (-*C*=CCO), 9.16 and 10.66 (two methyls); uv λ_{max} 227 (ϵ 34 600), 234 (ϵ 28 100), 274 (ϵ 11 900), 285 (ϵ 9900); MS m/e 262.09 (M$^+$), 247, 219, 202, 191, 180. Anal. ($C_{18}H_{14}O_2$) C, H.

Compound **22** was also obtained from diketones **5** or **6** (0.52 g, 2 mmol) in dioxane (10 ml) by dropwise addition of an excess of bromine (0.64 g, 8 mmol). Addition of water and extraction with ether, after standing for 15 min at room temperature, afforded, by crystallization from methanol, 0.35 g (76%) of **22**.

Reflux of bromide **20** (0.34 g, 1 mmol) in benzene (10 ml) in the presence of a catalytic amount of *p*-toluenesulfonic acid also afforded **22** (0.2 g, 88%).

9-Hydroxy-9-(1,2-dimethyl-3-hydroxy-1-propenyl)fluorene (24). To a suspension of lithium aluminum hydride (38 mg, 1 mmol) in THF (5 ml) was added a solution of **22** (120 mg, 0.46 mmol), in THF (5 ml). The mixture was stirred at room temperature for 1 h and refluxed for 30 min. Standard workup and crystallization (chloroform–hexane) afforded 84 mg of **24** (71%), mp 156–157 °C: NMR δ 1.05 and 1.82 (2 methyls, split s, $J \simeq$ 1 Hz), 3.5 (br, 1 H, OH), 4.36 (s, 2 H), 7.20–7.80 (m, 8 H); MS m/e 266 (M$^+$), 248, 233, 181. Anal. ($C_{18}H_{18}O_2$) C, H.

Acetylation of **24** in standard conditions (pyridine, acetic anhydride) gave the monoacetate **25** (oil), homogeneous on TLC: NMR δ 1.14 (s, 3 H), 1.76 (s, 3 H), 2.05 (s, 3 H), 4.1 (br, 1 H, OH), 5.33 (s, 2 H), 7.20–7.80 (m, 8 H), mol wt, 308 (MS).

3′,4′-Dihydroxy-3′,4′-dimethylspiro[fluorene-9,2′-furan]-5′-one (23). Osmium tetroxide (250 mg, 1 mmol) dissolved in ether (3 ml) was added to a solution of **22** (120 mg, 0.46 mmol) in dry pyridine (3 ml). After being allowed to stand for 48 h, the mixture was diluted with dry ether; the precipitate was filtered, washed with ether, and dissolved in chloroform. The solution was saturated with hydrogen sulfide with some external cooling, and after 1 h the solvent was removed under vacuum. Chromatography of the residue (elution with chloroform) gave 85 mg of **23**, (63%) mp 161 °C (from chloroform–hexane): NMR δ 0.96 (s, 3 H), 1.78 (s, 3 H), 7.05–7.90 (m, 8 H); ir (KBr) 1765 cm^{-1}, mol wt, 296 (MS). Anal. ($C_{18}H_{16}O_4$) C, H.

Ozonolysis of 24. Ozone was introduced into a solution of **24** (50 mg) in CH_2Cl_2 (10 ml) until an excess of reagent was present. The solvent was then removed and a mixture of 0.5 ml of formic acid and 0.1 ml of H_2O_2 (30%) was added to the residue. After 2 h the peroxides were destroyed with $FeSO_4$ and the mixture was diluted with water and extracted with ether. Fluorenone (22 mg, 61%) crystallized directly from the crude product and was found identical with an authentic sample.

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Nucleophilic Substitution Reactions of *trans*-3-Methoxy-4′-substituted Acrylophenones[1,2]

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Abstract: Aminations of *trans*-3-methoxy-4′-substituted acrylophenones (**1–5**) to 3-substituted amino-4′-substituted acrylophenones in water solution are characterized by (1) rates which are first order in amine and first order in acrylophenone, (2) a deuterium solvent kinetic isotope effect $k(D_2O)/k(H_2O) = 1$, (3) $\rho = 1$, (4) a Bronsted-type catalytic coefficient $\beta = 0.37$ for glycine ethyl ester, aminoethanol, and *n*-butylamine, (5) a 90-fold decrease in reactivity when a β-methyl group is substituted for a hydrogen atom, (6) formation of cis product from trans reactant for reaction of the 4′-nitro derivative with aniline, (7) formation of trans product from trans reactant for reaction of the 4′-chloro derivative with *N*-methylaniline. In light of these results, the nucleophilic addition–elimination reactions are visualized as proceeding via rate-determining nucleophilic attack of the amine at the β carbon of 4′-substituted acrylophenones.

Introduction

Nucleophilic addition–elimination reactions (eq 1) of electrophilic olefins (Y = CO, CN, NO_2, C=N–, etc.) having electronegative atoms (X = O, N, halogen) at the β carbon

$$AH + X\text{—}\overset{\beta}{C}\text{=}\overset{\alpha}{C}\text{—}Y \longrightarrow A\text{—}C\text{=}C\text{—}Y + XH \quad (1)$$

appear to be important reactions in bioorganic chemistry. Candidate examples are the methylation of 2′-deoxyuridylate to give thymidylate catalyzed by thymidylate synthetase,[3] the alkylation of biomacromolecules by plant-derived tumor inhibitors such as jatrophone,[4] and the alkylation of aspartate amino transferase by the antibacterial L-2-amino-4-methoxy-*trans*-3-butenoic acid, an irreversible k_{cat} enzyme inhibitor which is activated via ketimine formation with the pyridoxal phosphate cofactor of the enzyme.[5]

The details of mechanism of nucleophilic addition–elimination reactions of aliphatic and aromatic compounds, in particular the role of catalysis in these reactions, are of current interest.[6-12] Results show there is a general requirement for catalysis in electrophilic olefins possessing relatively poor leaving groups (X, eq 1);[9,10] this has been interpreted to entail proton transfer from zwitterionic intermediates formed from reactions of amines (AH = R_1R_2NH, eq 1) with electrophilic olefins to acceptor bases (a second amine molecule), followed by protonation of the leaving group to facilitate X–C (eq 1) bond cleavage. Here we report the kinetics results of the reactions of *trans*-3-methoxy-4′-substituted acrylophenones (**1–5**) with primary and secondary amines to give 3-substituted amino-4′-substituted acrylophenones:

$$4'\text{-}XC_6H_4COCH\text{=}CHOCH_3 + R_1R_2NH \longrightarrow 4'\text{-}XC_6H_4COCH\text{=}CHNR_1R_2 + CH_3OH$$

We were attracted to this study because of: the possibility of detecting catalysis among the reactions of **1–5** and our desire to understand the role of catalysis in such reactions; the possibility of distinguishing between a concerted nucleophilic displacement reaction and a nucleophilic addition–elimination reaction, still a disputable feature of mechanism, based on ρ; and finally the resemblance of **1–5** to electrophilic reagents of biological interest and the likelihood that the chemistry of **1–5** would contribute to an understanding of the bioorganic chemistry of similar small molecule–large molecule interactions.

Experimental Section

Apparatus. The apparatus used was previously described.[13]

Reagents and Compounds. Fisher Certified ACS grade inorganic salts and hydroxylamine were used. Aminoethanol, imidazole, *tert*-butylamine, ethyl glycinate, morpholine (Eastman Organic Chemicals), 4-methoxy-3-buten-2-one, aniline, *N*-methylaniline (Aldrich Chemicals), deuterium oxide, deuteriochloric acid (Stohler Isotope Co.) were used. *trans*-3-Methoxy-4′-substituted acrylophenones [$N(CH_3)_2$ (**1**), OCH_3 (**2**), H (**3**), Cl (**4**), NO_2 (**5**)] were previously synthesized.[13] 3-Methoxy-4′-nitrocrotonophenone (**6**) was prepared by the method of Weygand.[14]

Kinetics. The reactions of **1–6** with various amines were monitored by recording the decrease or increase in absorbance vs. time at the analytical wavelength (nm): **1**, 370; **2**, **3**, 360; **4**, 345; **5**, 365; **6**, 360. Reactions were carried out under pseudo-first-order conditions (**1–6** = 10^{-4}–10^{-5} M) at 30 ± 0.1 °C, and ionic strength was calculated to be 0.1 M (KCl). The pH of each solution was measured before and after all runs and remained constant (±0.02 pH unit). Cuvettes (3 ml) were filled to the stopper level with appropriate solutions and allowed to come to thermal equilibrium (20–30 min). Reactions were initiated by adding a known amount of **1–6** in methanol[15] or tetrahydrofuran from a calibrated syringe to reaction solutions. Reactions were followed to at least 2 half-lives and were found to be pseudo-first-order. Pseudo-first-order rate constants, k_{obsd}, were obtained by multiplying the slopes of plots of log $(OD_\infty - OD_i)/(OD_\infty - OD_t)$ for absorbance increase and log $(OD_i - OD_\infty)/(OD_t - OD_\infty)$ for absorbance decrease vs. time by 2.303. pD was calculated by adding 0.4 to pH meter readings of pH.[16] Reactions were carried out in aqueous amine–amine hydrochloride buffers prepared by addition of calculated quantities of 1 N HCl to weighed quantities of amine.

Product Analysis.[34] Formation of *cis*-3-substituted amino-4′-substituted acrylophenones from reactions of **1–6** with various primary amines was assumed from the following experiments.

***cis*-4-Anilino-3-buten-2-one.** *trans*-4-Methoxy-3-buten-2-one (6 mmol) was added to aniline (6 mmol) suspended in water. The reaction mixture was stirred for several hours at room temperature. The