2218 BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 44, 2218—2221 (1971) [Vol. 44, No. 8

The Bromination of 2-Methoxytropone and Its Bromo Derivatives

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(Received February 25, 1971)

The reaction of 2-methoxytropone and its bromo derivatives with bromine was examined in various solvents. The treatment of 2-methoxytropone or 5-bromo-2-methoxytropone with bromine in methanol gave an addition product, 2,6-dibromo-7,7-dimethoxy- (II) or 2,4,6-tribromo-7,7-dimethoxy-2,4-cycloheptadien-1-one (XIV) respectively, together with the substitution products. On the contrary, the treatment of 2-methoxytropone with bromine in anhydrous ethanol, chloroform, or carbon tetrachloride gave a reddish complex compound. In aqueous ethanol or acetic acid, however, it gave 3,5,7-tribromotropolone. A possible reaction mechanism involving the nucleophilic attack of a methanol molecule on 2-methoxytropones at the 2-position is presented to account for the formation of the addition products.

It has been established that, on bromination with bromine, tropolone generally gives substitution products,[1-3] whereas tropone gives addition products which are only changed to substituted tropones upon heating in the presence of sodium acetate[4]; this fact is chemical evidence for the concept that the aromatic character of tropone is less than that of tropolone. On the other hand, in the case of 2-methoxytropone(I),[3,5,6] it is expected that its aromatic character is less than that of tropolone because of the localization of the double bonds, while its stability is larger than that of tropone because of the contribution of the mesomeric effect due to the methoxyl group; consequently, the behavior of I in regard to bromine is expected to be intermediate between that of tropolone and that of tropone. In order to find chemical evidence of this, the reaction of I and its bromo derivatives with bromine was examined.

Results and Discussion

The treatment of 2-methoxytropone(I) with bromine in methanol at 0—5°C gave an oily mixture, from which a dibromo compound(II), $C_9H_{10}O_3Br_2$, was subsequently isolated by crystallization. The chromatography of the mother liquor in an alumina column afforded a dibromo compound(III), $C_8H_6O_2Br_2$, together with 3,7-dibromo-2-methoxytropone (IV)[5] and 3,5,7-tribromo-2-methoxytropone(V).[5] The relative yields of these products varied in accordance with the molar ratio of bromine used, but II was always formed as the major product.

The infrared spectrum of II exhibits an absorption at 1692 cm^{-1} characteristic of the conjugated carbonyl group and absorptions at 1147, 1106, and 1070 cm^{-1} corresponding to the ether linkage. The NMR spectrum of II reveals two singlets, at 3.25 (3H) and 3.42 ppm (3H), corresponding to two methoxyl groups, and two doublets, at 4.75 (1H, J=7.5 Hz) and 7.25 (1H, J=9.0 Hz), and two double doublets, at 5.94 (1H, J=9.0, 12.0 Hz) and 6.37 ppm (1H, J=7.5, 12.0 Hz), corresponding to a partial structure, $-\overset{|}{\underset{|}{C}}CHBr-CH=CH-CH=\overset{|}{C}-$. Moreover, II was easily changed to IV when its chloroform solution was passed through an alumina column. Judging from these facts, II must be assigned the structure of 2,6-dibromo-7,7-dimethoxy-2,4-cycloheptadien-1-one. The ultraviolet absorption spectrum is also consistent with this structure.

Compound II was stable under acidic treatment in spite of its ketal structure; that is, the treatment of II with concentrated hydrobromic acid resulted only in the recovery of the original compound, except for the formation of a small amount of IV. On the other hand, II was sensitive to alkaline treatment; that is, II was easily changed to IV by treatment with alumina, as has been described above. Moreover, the treatment of II with sodium methoxide easily gave methyl 2,6-dibromobenzoate(VI),[7] a rearrangement product, in a nearly quantitative yield, while treatment with sodium acetate in methanol gave IV and VI.

Compound III gave 3,5-dibromotropolone(VII)[1] upon hydrolysis with hydrobromic acid. Moreover, the treatment of III with hydrazine afforded hydrazinotropone(VIII), which in turn gave 2,4,7-tribromotropone(IX)[8] upon oxidative decomposition with copper sulfate in the presence of hydrobromic acid. From these facts, III was assigned the structure of 5,7-dibromo-2-methoxytropone. The ultraviolet absorption spectrum is also consistent with this structure.

When a solution of 2-methoxytropone(I) in anhydrous ethanol was treated with bromine, neither an addition product nor a substitution product was obtained; instead, a reddish compound (X) was formed. The same compound was also obtained on the treatment of I with bromine in chloroform or carbon tetrachloride. On the contrary, when I was treated with bromine in aqueous ethanol or acetic

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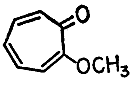
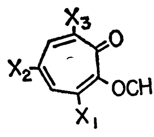
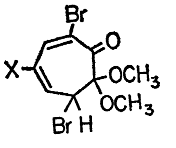
acid, 3,5,7-tribromotropolone (XI)[1-3] was easily produced in a good yield. Compound X gave the addition compound, II, when dissolved in methanol, whereas it gave XI on treatment with water. On the other hand, the original compound, I, was reproduced when X was treated with water containing sodium hydrogen sulfite. These facts suggested that X must be a complex compound similar to that of tropone[4] or tropolone.[1,2]



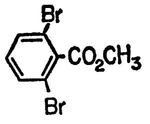
I



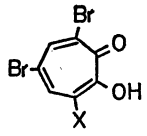
III: X_1=H, X_3=X_2=Br
IV: X_2=H, X_1=X_3=Br
V: X_1=X_2=X_3=Br
XII: X_2=X_3=H, X_1=Br
XIII: X_1=X_3=H, X_2=Br
XV: X_1=X_2=H, X_3=Br



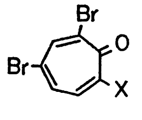
II: X=H
XIV: X=Br



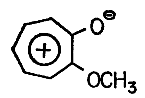
VI



VII: X=H
XI: X=Br



VIII: X=$NHNH_2$
IX: X=Br



Ia

The reaction of bromo derivatives of 2-methoxytropone with bromine was also examined. The treatment of 3-bromo-2-methoxytropone(XII)[9] with bromine in methanol at 0—5°C afforded the substitution products, IV or V, by the use of one or two molar equivalents of the reagent respectively, but no addition product was isolated. On the other hand, a similar treatment of 5-bromo-2-methoxytropone(XIII)[5] with bromine gave an addition product (XIV), $C_9H_9O_3Br_3$, together with small amounts of IV and V. The infrared spectrum of XIV shows absorptions at 1706 cm^{-1} and at 1115 and 1071 cm^{-1}, corresponding to the conjugated carbonyl and the ether linkage respectively. The NMR spectrum reveals two singlets, at 3.25 (3H) and 3.40 ppm (3H), due to the methoxyl groups, and two doublets, at 4.71 (1H, J=4 Hz) and 7.53 (1H, J=2 Hz), and a double doublet, at 6.80 ppm (1H, J=9, 2 Hz), corresponding to a partial structure, $-\overset{|}{\underset{|}{C}}-CHBr-CH=CBr-CH=\overset{|}{C}-$. Moreover, it was easily changed quantitatively to V on being passed through an alumina column. From these facts, it is reasonable to assign the structure of 2,4,6-tribromo-7,7-dimethoxy-2,4-cycloheptadien-1-one to XIV.

The treatment of 7-bromo-2-methoxytropone(XV)[9] with bromine in methanol at 0—5°C resulted in the recovery of the original compound, but that at room temperature over a long period afforded IV. The dibromo compound, IV, and the tribromo compound, V, did not show any change when treated similarly.

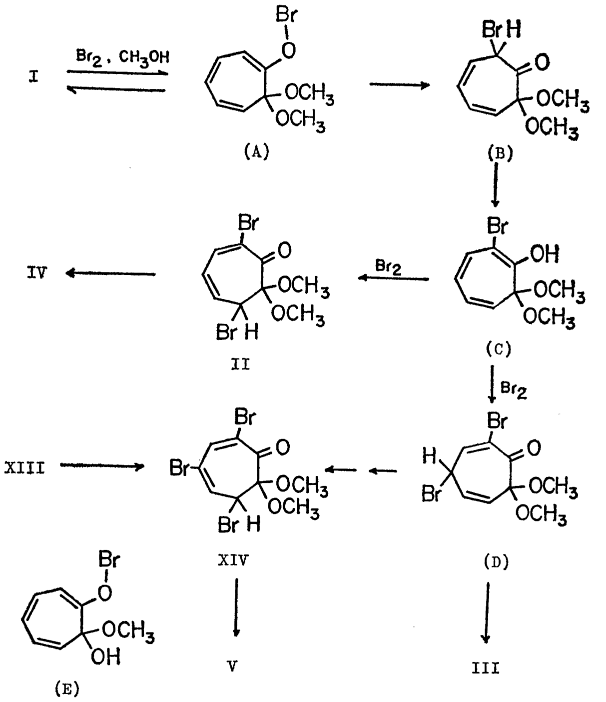


Chart 1. A possible mechanism for the reaction of 2-methoxytropone (I) with bromine in methanol.

From the findings described above, it is clear that the reaction of 2-methoxytropone(I) with bromine is markedly affected by the kind of the solvent used. It was also observed that the bromo substituents affected the reactivity of 2-methoxytropones toward bromine. Because of the rather large contribution of the polar structure(Ia),[5] the cationoid substitution can be expected to be difficult on I, for it is different from anisole. This is true when either anhydrous ethanol, chloroform, or carbon tetrachloride is used as the solvent, and I gave only a complex compound, X, as has been described previously. On the other hand, it was found that the treatment of I with bromine in methanol gave the addition compound, II, plus small amounts of the substitution products, IV and V. The formation of II is very interesting in the reaction mechanism. Although II has a structure corresponding to that consisting of the addition of a methanol molecule on IV, it is disproved that II is formed by the addition of methanol to IV, since IV did not show any change, at least under the present experimental conditions. Any possible mechanism for the formation of II would involve the nucleophilic attack of a methanol molecule on the 2-position of I, an attack which is facilitated by the coordination of the bromonium ion or its equivalent species on the carbonyl group, thus giving an intermediate (A), as is shown in Chart 1. The intermediate (A) changes immediately to a bromoketone-

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[9] T. Nozoe, Y. Kitahara, K. Yamane, and A. Yoshikoshi, *Proc. Japan Acad.*, **27**, 18 (1951).

type intermediate (B), which can then enolize to an enol-type intermediate (C). Although the two intermediates, (B) and (C), have structures consisting of the addition of a methanol molecule to 7-bromo-2-methoxytropone (XV), they are probably not produced through XV, since XV does not react with bromine under reaction conditions such as those under which I gave II. The reaction of bromine with the intermediate (C) affords the compound II. The substitution products, III, IV, and V, are assumed to be produced by the elimination of a methanol molecule from the corresponding addition compounds, (D), XIV and II respectively, which are formed through the intermediate (C). The addition compound XIV is also assumed to be formed from XIII through a similar reaction course.

In aqueous solvents, it is thought that a water molecule should attack the 2-position of I to give a hemiketal-type intermediate (E), which is similar to the intermediate (A). However, the intermediate (E) easily loses a methanol molecule, thus affording tropolone, which can then be easily brominated to give 3,5,7-tribromotropolone (XI).[1-3] On the other hand, in anhydrous ethanol it is presumed that an ethanol molecule can not attack the 2-position of I; consequently, probably no addition compound is formed. The reason for this has not yet been clear, but it seems to be due to the lesser nucleophilicity and/or to the greater sterical bulkiness of the ethanol molecule than that of the methanol molecule.

Experimental

All the melting points are uncorrected. The ultraviolet absorption spectra were taken on a Beckman DU spectrophotometer, and the infrared spectra, on a Shimadzu IR-27 infracord apparatus. The NMR spectra were determined with a Varian A-60 spectrometer on samples dissolved in deuteriochloroform and containing tetramethylsilane as an internal standard.

Bromination of 2-Methoxytropone(I) in Methanol. To a stirred solution of I (816 mg) in methanol (20 m*l*), a solution of bromine (1.0 g) in the same solvent (1 m*l*) was added under cooling at 0—5°C, after which the mixture was allowed to stand overnight in a refrigerator. The subsequent addition of water separated an oily material, which was then extracted with chloroform and dried over anhydrous sodium sulfate. The evaporation of the solvent left an oily residue (1.405 g), which was then crystallized by the addition of a small amount of methanol. The crystals (375 mg), mp 130—135°C, collected by filtration were recrystallized from benzene to give 2,6-dibromo-7,7-dimethoxy-2,4-cycloheptadien-1-one(II) as pale yellow prisms; mp 138—139°C.

Found: C, 33.32; H, 3.10%. Calcd for $C_9H_{10}O_3Br_2$: C, 33.47; H, 3.42%. UV (MeOH): λ_{max} nm ($\log \varepsilon$); 330 (3.75).

All the filtrates were combined, and then the evaporation of the solvent left an oily material (870 mg) which was subsequently chromatographed on an alumina column. The fraction, when eluted with benzene, gave colorless crystals (130 mg). Recrystallization from methanol afforded 5,7-dibromo-2-methoxytropone(III) as colorless needles; mp 206—207°C.

Found: C, 32.72; H, 2.32%. Calcd for $C_8H_6O_2Br_2$: C, 32.01; H, 2.06%. UV (MeOH): λ_{max} nm ($\log \varepsilon$); 275 (4.41), 320 (3.96), 335 (4.03), 373 (3.84).

Further elution with ether gave pale yellow crystals (85 mg). Recrystallization from ethyl acetate afforded 3,7-dibromo-2-methoxytropone(IV) as pale yellow needles, mp 134—135°C, which were identified with an authentic sample, mp 133—134°C,[5] by admixture and by a comparison of the infrared spectra.

A similar treatment of I (816 mg) with two or three molar equivalents of bromine gave II (839 mg), III (65 mg), IV (79 mg), and 3,5,7-tribromo-2-methoxytropone(V) (23 mg), mp 123—124°C,[5] and II (529 mg) and V (200 mg) respectively.

Treatment of II with Alumina. A solution of II (100 mg) in chloroform was passed through an alumina column. The subsequent evaporation of the solvent from the effluent gave IV (96 mg) as pale yellow needles; mp 134—135°C.

Treatment of II with Hydrobromic Acid. A solution of II (296 mg) in methanol (15 m*l*) containing concentrated hydrobromic acid (1 m*l*) was refluxed for 4 hr. The solution was concentrated to a small volume; the crystals thereby formed were then collected by filtration to give the original compound, II (265 mg), mp 138—139°C. The filtrate was diluted with water and extracted with chloroform. The subsequent evaporation of the solvent from the extract and the recrystallization of the residue from methanol gave IV (5 mg) as pale yellow needles; mp 134—135°C.

Treatment of II with Sodium Methoxide. A solution of II (592 mg) in methanol (20 m*l*) containing sodium methoxide (216 mg) was refluxed for 6 hr. The solvent was then evaporated, and the residue was dissolved in chloroform, washed with water, and dried over anhydrous sodium sulfate. The subsequent evaporation of the solvent left crystals (420 mg), mp 58—60°C, which were then recrystallized from petroleum ether to give methyl 2,6-dibromobenzoate(VI) as colorless needles; mp 63—64°C. This was identified with an authentic sample, mp 61—62°C[7] by admixture and by a comparison of the infrared spectra.

Treatment of II with Sodium Acetate. A mixture of II (1.48 g) and anhydrous sodium acetate (820 mg) in methanol (40 m*l*) was refluxed for 2.5 hr. The solution was then concentrated to a small volume, and to this was added water (30 m*l*). The precipitates thereby formed were collected by filtration and recrystallized from ethyl acetate to give IV (852 mg) as pale yellow needles; mp 134—135°C.

The subsequent evaporation of the solvent from the filtrate left an oily material (380 mg) which was then chromatographed on an alumina column and eluted with ether to give VI (354 mg) as colorless needles; mp 63—64°C.

3,5-Dibromotropolone (VII). A solution of III (60 mg) in methanol (30 m*l*) containing concentrated hydrobromic acid (4 m*l*) and water (4 m*l*) was refluxed for 3 hr. The subsequent evaporation of the solvent left crystals which were then recrystallized from methanol to afford VII (55 mg) as pale yellow needles; mp 152—153°C. VII was identified with an authentic sample, mp 152—153°C,[1] by admixture and by a comparison of the infrared spectra.

5,7-Dibromo-2-hydrazinotropone (VIII). To a suspension of III (294 mg) in ether (4 m*l*), 80% hydrazine hydrate (80 mg) was added under cooling at 0—5°C, after which the mixture was stirred for 9 hr. The orange crystals thereby formed were collected by filtration and recrystallized from ethyl acetate to give VIII (294 mg) as yellow needles; mp 155—156°C.

Found: C, 28.14; H, 2.56; N, 9.88%. Calcd for $C_7H_6ON_2Br_2$: C, 28.50; H, 2.05; N, 9.49%.

2,4,7-Tribromotropone (IX). Into a mixture of VIII

(260 mg) and concentrated hydrobromic acid (2 m*l*) being heated in a boiling water bath, a hot solution of 40% aqueous cupric sulfate solution was stirred; a vigorous evolution of nitrogen gas thus occurred. After the mixture had been heated for 5 min, it was allowed to cool to room temperature, diluted with water, and extracted with chloroform. After the chloroform solution had been dried over anhydrous sodium sulfate, the solvent was evaporated and the residue was dissolved in ether and passed through a short column of alumina. The subsequent evaporation of the solvent from the effluent, followed by the recrystallization of the residue from methanol, gave IX (60 mg) as pale yellow needles; mp 177—178°C. This was identified with an authentic sample, mp 177—178°C,[8] by admixture and by a comparison of the infrared spectra.

Reaction of I with Bromine in Anhydrous Ethanol. To a stirred solution of I (816 mg) in anhydrous ethanol (2 m*l*), a solution of bromine (1.0 g) in the same solvent (1 m*l*) was added under cooling at 0—5°C. A few minutes later, reddish orange precipitates were separated out. After being stirred for 5 min, the precipitates were collected by filtration to afford X (1.5 g) as a reddish powder.

Treatment of X with Methanol. A sample of X (500 mg) was dissolved in methanol (10 m*l*) and then allowed to stand overnight. The subsequent evaporation of the solvent left an oily material (384 mg) which was then crystallized by the addition of a few drops of methanol. The crystals (120 mg); mp 128—133°C, when collected by filtration, were recrystallized from ethyl acetate to give II (98 mg) as pale yellow prisms; mp 138—139°C.

All the filtrates were combined, the solvent was evaporated, and the oily residue (260 mg) was dissolved in ether and chromatographed on an alumina column. The fraction eluted with ether gave IV (83 mg) as pale yellow needles, mp 134—135°C, and V (56 mg) as yellow needles, mp 123-124°C.

Treatment of X with a Sodium Sulfite Solution. To a suspension of X (100 mg) in chloroform (2 m*l*), a 10% aqueous sodium hydrogen sulfite solution (9.5 m*l*) was added. After being stirred for 1 hr, the aqueous layer was separated and extracted with chloroform. All the chloroform layers were combined and dried over anhydrous sodium sulfate. The subsequent evaporation of the solvent left an oily material (43 mg) which was identified with 2-methoxytropone, I, by a comparison of the infrared spectra.

Treatment of X with Water. A suspension of X (200 mg) in water (5 m*l*) was stirred for 5 hr; the reddish color gradually disappeared, and pale yellow precipitates were formed. The product was collected by filtration and recrystallized from methanol to give 3,5,7-tribromotropolone (XI) (82 mg) as yellow needles, mp 121—122°C, which were identified with an authentic sample[1] by admixture and by a comparison of the infrared spectra.

Bromination of I in Ethanol. To a stirred solution of I (816 mg) in ethanol (10 m*l*) containing a small amount of water, a solution of bromine (3.10 g) in ethanol (10 m*l*) was added under cooling at 0—5°C. When a half of the bromine solution had been added, reddish precipitates were separated out; they gradually dissolved upon stirring for 1 hr. After being allowed to stand overnight, the reaction mixture was diluted with water (100 m*l*) and extracted with chloroform and the chloroform layer was dried over anhydrous sodium sulfate. The subsequent evaporation of the solvent left crystals (2.327 g) which were recrystallized from ethanol to afford XI (1.628 g) as yellow needles; mp 121—122°C.

Bromination of I in Acetic Acid. To a solution of I (816 mg) in acetic acid (10 m*l*), a solution of bromine (2.12 g) in the same solvent (5 m*l*) was added under cooling at 0—5°C. After being allowed to stand overnight, the reaction mixture was treated in a manner similar to that described above; this gave XI (1.10 g) as yellow needles; mp 121—122°C.

Bromination of 3-Bromo-2-methoxytropone (XII). To a solution of XII (215 mg) in methanol (2 m*l*), a solution of bromine (160 mg) in the same solvent (1 m*l*) was added under cooling at 0—5°C, after which the mixture was allowed to stand overnight at room temperature. The reaction mixture was diluted with water, and the precipitates thereby formed were collected by filtration and recrystallized from methanol to give IV (250 mg) as pale yellow needles; mp 134—135°C.

A similar treatment of XII (215 mg) with bromine (320 mg) gave V (205 mg) as yellow needles; mp 123—124°C.

Bromination of 5-Bromo-2-methoxytropone (XIII). To a solution of XIII (215 mg) in methanol (15 m*l*), a solution of bromine (350 mg) in the same solvent (2 m*l*) was added under cooling at 0—5°C. After being allowed to stand overnight, the reaction mixture was diluted with water and extracted with chloroform, and the organic layer was dried over anhydrous sodium sulfate. The subsequent evaporation of the solvent left an yellow oil (481 mg), which was crystallized by the addition of a small amount of methanol. Recrystallization from methanol gave 2,4,6-tribromo-7,7-dimethoxy-2,4-cycloheptadien-1-one (XIV) as pale yellow prisms; mp 107—108°C.

Found: C, 26.98; H, 2.38%. Calcd for $C_9H_9O_3Br_3$: C, 26.69; H, 2.24%. UV (MeOH): λ_{max} nm ($\log \varepsilon$); 333 (3.73).

A solution of XIV (100 mg) in chloroform was passed through an alumina column. The subsequent evaporation of the solvent from the effluent gave V (76 mg) as yellow needles; mp 123—124°C.

Reaction of 7-Bromo-2-methoxytropone (VII) with Bromine. a) To a stirred solution of VII (107 mg) in methanol (8 m*l*), a solution of bromine (80 mg) in the same solvent (2 m*l*) was added under cooling at 0—5°C, after which the mixture was allowed to stand overnight in a refrigerator. The reaction mixture was diluted with water (50 m*l*) and extracted with chloroform. The subsequent evaporation of the solvent gave the original compound, VII (92 mg).

b) To a stirred solution of VII (214 mg) in methanol (15 m*l*), a solution of bromine (240 mg) in the same solvent (5 m*l*) was added under cooling at 0—5°C, after which the mixture was allowed to stand for 7 days in a refrigerator and then for a few days at room temperature. Then, the reaction mixture was diluted with water; the precipitates thereby formed were collected by filtration to afford pale yellow crystals (89 mg), which later gave IV (56 mg); mp 134—135°C, by recrystallization from methanol.

This research has been financially supported by grants from the Japanese Ministry of Education and the Sankyo Co., Ltd.