Bromination of Ethyl Diacetosuccinate

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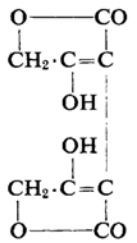
Although the synthesis of 1, 4, 7-cyclononatrione has been realized by us[1], it was isolated only as its trissemicarbazone in a poor yield. We have now chosen another course to attain this cyclic triketone, thus intending at first to obtain ethyl 1, 4, 7-cyclononatrione-2, 3, 6, 8-tetracarboxylate through the condensation of γ,γ'-dibromodiacetosuccinate (II) and ethyl disodioacetonedicarboxylate. This attempt, however, failed presumably owing to the false constitution (II) of the so-called γ,γ'-dibromodiacetosuccinate. Consequently, the bromination of ethyl diaceto succinate (I) had to be reinvestigated and the present paper presents some new aspects as an exceptional example of the bromination of β-ketoesters.

Informations concerning II can be summarized as follows: Wolff et al.[2] treated ethyl diacetosuccinate (I) with two moles of bromine and ascribed formula II to the pale yellow reaction product because of the fact that the substance in question, when heated at 150~160°C, gave bistetronic acid (V) by giving up two moles of ethyl bromide. On the other hand, Hirst et al. treated the same bromination product with hydrazine and concluded from the estimation of the nitrogen gas evolved that the bromide was a mixture of 21% of α,α'-dibromo compound III and 79% of γ,γ'-dibromo compound II[3], in other words, an equilibrium mixture due to an α,γ-shift of bromine atoms[3-5].

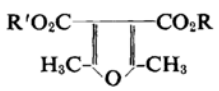
$$RCH_2\cdot CO\cdot \underset{\displaystyle Br}{\underset{|}{C}}R'\cdot CO_2C_2H_5$$

$$RCH_2\cdot CO\cdot \underset{\displaystyle Br}{\underset{|}{C}}R'\cdot COC_2H_5$$

(I) R=R'=H
(II) R=Br, R'=H
(III) R=H, R'=Br
(IV) R=R'=Br



(V)



(VI) R=H, R'=C_2H_5
(VII) R=R'=H
(VIII) R=R'=CH_3
(IX) R=R'=C_2H_5

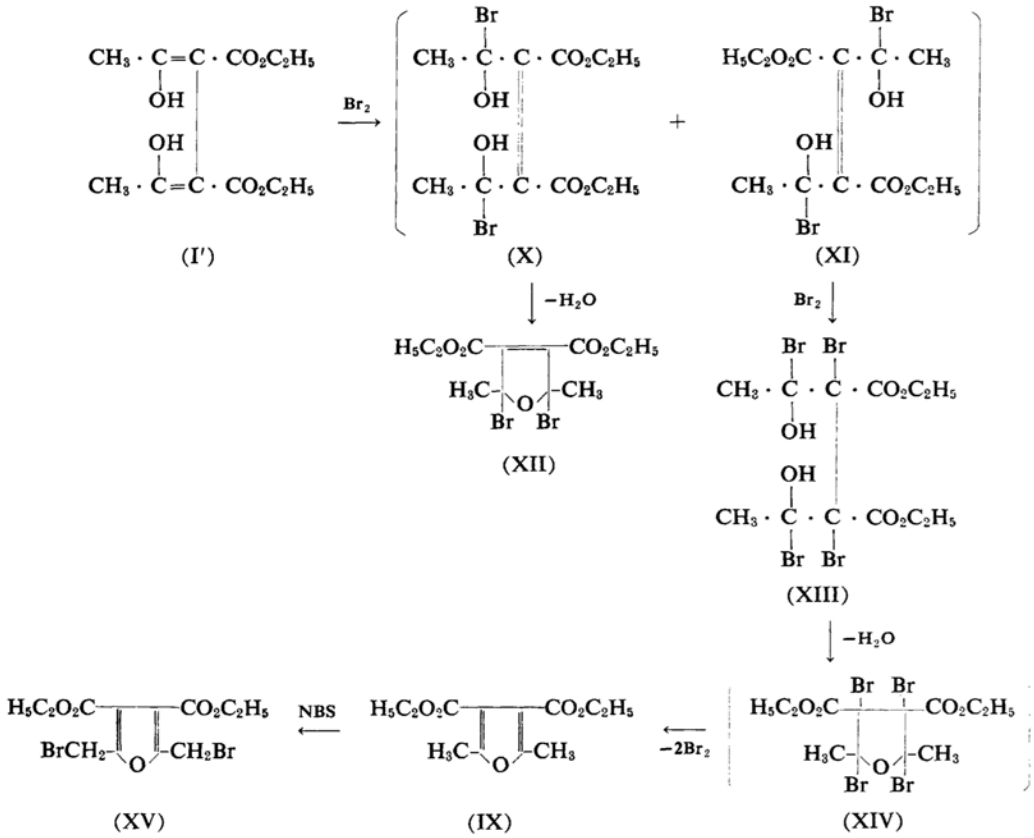
In fact, we could obtain a pale orange yellow viscous oil without hydrogen bromide evolution when we brominated compound I after Wolff's method[2], but the vacuum distillation of this

1) S. Kawai, S. Tanaka, K. Terai, M. Tezuka and T. Nishiwaki, This Bulletin, 33, 669 (1960).
2) L. Wolff and H. Junker, *Ann.*, 399, 311 (1913).
3) E. L. Hirst and A. K. Macbeth, *J. Chem. Soc.*, 121, 2169 (1922). Their conclusion was deduced from the fact that the bromine atom of the α-bromide is so reactive that it decomposes hydrazine with the evolution of nitrogen gas quantitatively but the γ-bromide remains intact.
4) (a) C. Duisberg, *Ann.*, 213, 137 (1882). (b) A. Hantsch, *Ber.*, 27, 356, 3168 (1894). (c) M. Conrad, ibid., 29, 1024 (1896). (d) A. K. Macbeth and D. Trail, *J. Chem. Soc.*, 127, 1118 (1925). (e) M. S. Kharasch, E. Sternfeld and F. R. Mayo, *J. Am. Chem. Soc.*, 59, 1655 (1937). (f) F. Kröhnke and H. Timmler, *Ber.*, 69, 614 (1939).
5) A. Becker, *Helv. Chim. Acta*, 32, 1114, 1584 (1949).

oil gave only a little amount of a distillate at 150~170°C (bath temperature) and then met with a sudden rise of the pressure obviously due to decomposition. The distillate contained monoethyl 2, 5-dimethylfuran-3, 4-dicarboxylate (VI), and the residue included 2, 5-dimethylfuran-3, 4-dicarboxylic acid (VII) as one of its constituents.

Then, we gave up vacuum distillation, and kept the viscous oily bromination product of compound I (it shall be called "I-bromide" hereafter) in a cool place during one month. Crystals which gradually appeared in the meanwhile were collected at appropriate intervals and at least four new compounds, i.e. I-tetrabromide (XIII), monoester VI, dicarboxylic acid VII and the dibromide of diester IX, were isolated.

The I-bromide gave neither any indole derivative when heated with a mixture of aniline and aniline hydrobromide[6], nor a *p*-nitrophenylpyridazine derivative when treated with *p*-nitrophenylhydrazine[5]. These results show the absence of a γ,γ'-dibromide such as II or IV. Since the I-bromide, when heated with resorcinol or with α-naphthol, did not give any bromophenol or bromonaphthol, the bromine atom is not so "positive"[7]. Thus the presence of α,α'-dibromide derivatives such as III or IV is excluded. The I-bromide, when heated with absolute methanol, gave dimethyl 2, 5-dimethylfuran-3, 4-dicarboxylate (VIII), and a desmotropic form[8] of diacetosuccinic acid (I, H instead of C_2H_5) when heated with sodium methoxide. When treated with concentrated sulfuric acid[5,9] the I-bromide did not show any sign of a ketonic hydrolysis but gave the free acid VII. The I-bromide gave no definite product when heated with aqueous potassium carbonate[10]. On the other hand, compound I gave diethyl 2, 5-dimethylfurandicarboxylate (IX) on treatment with concentrated sulfuric acid and acetonylacetone on heating with aqueous potassium carbonate, both in good yields. When hydrogen bromide gas was passed through a benzene solution of compound I, only a very little



6) J. R. Catch and E. R. H. Jones, *J. Chem. Soc.*, **1948**. 272, 276.

7) R. Altschul and P. B. Bartlett, *J. Org. Chem.*, **5**, 623 (1942).

8) Thirteen isomeric forms are theoretically possible for diacetosuccinic acid, but only three are known [L. Knorr, *Ber.*, **22**, 170 (1889); *Ann.*, **293**, 103 (1896)]. The compound obtained above does not agree in the melting point with any of the three.

9) P. Ruggli, A. von Wartburg and H. Erlenmeyer, *Helv. Chim. Acta*, **30**, 348 (1947).

10) L. Knorr, *Ber.*, **33**, 1219 (1900).

amount of VII was obtained and the major part of compound I remained unchanged. Therefore, the two compounds, VI and VII, which were isolated from the I-bromide, should never have been derived from the starting material (I) through the catalytic action of the little amount of hydrogen bromide generated during the bromination of compound I.

As has already been mentioned, there is no positive proof for the existence of α,α'-dibromide III and γ,γ'-dibromide II. Hence, the elucidation of the constitution of the I-tetrabromide, found as one constituent of I-bromide, appeared difficult. We are now forced to assume that the dienediol form I′ of compound I gave a mixture of *cis*-dibromide X and *trans*-dibromide XI as the result of 1,4-addition of bromine, and the former (X) passed over to a dihydrofuran XII while the latter (XI) took up another mole of bromine to produce tetrabromide XIII. Then, tetrabromide XIII underwent dehydration catalyzed by hydrogen bromide, thus yielding a tetrabromide XIV, which, as the result of spontaneous debromination, gave furan derivative IX. Compound IX suffered partial and total hydrolysis catalyzed by hydrogen bromide, yielding compounds VI and VII. The precise structure of dibromide XII is further shown by the fact that it is quite different from dibromide XV obtained from the dimethylfuran derivative IX through *N*-bromosuccinimide. Thus, the I-tetrabromide in question may perhaps be represented by formula XIII, because this compound is so unstable that it decomposes (dehydration?) when merely heated or treated with water-miscible solvents.

The proof that the main course involved in this reaction belongs to bromine addition but not bromine substitution can be found in the following facts: (i) during the bromination of compound I evolution of hydrogen bromide was scarcely recognized: (ii) on the other hand, hydrogen bromide evolution was observed during the manipulation of recrystallization of crystals gathered from the I-bromide.

Both Wolff[1] and Hirst[2] observed that bromine substitution took place when ethyl diacetosuccinate was treated with bromine, which does not agree with our experiments. Our observation seems more reasonable, because the more stable conjugated dienediol-form I′ may predominate over the unconjugated diketo-form I in ethyl diacetosuccinate, and the reaction may start with the 1, 4- and further 2, 3-addition of bromine to the conjugated system but not with bromine substitution.

Experimental[11]

Bromination of Ethyl Diacetosuccinate.—To a solution of ethyl diacetosuccinate[12] (I) (140 g., 1 mol.) in chloroform (300 cc.) bromine (170 g., 1.95 mol.) was added dropwise in 2 hr. with ice-cooling and stirring, and the mixture was stirred for 2 hr. at room temperature. Hydrogen bromide was scarcely evolved, or estimated as only 0.53% of the value calculated for bromine substitution. The chloroform layer was washed successively with water, with 5% sodium thiosulfate and finally with water, dried and evaporated in vacuo on a water bath (below 38°C), giving "I-bromide" as a pale reddish orange substance containing a small amount of colorless crystals. Yield, 290 g.

I-Tetrabromide (XIII) of Ethyl Diacetosuccinate. — The small amount of colorless crystals, obtained above, were separated from the oily substance, washed with a small amount of petroleum ether (b. p. 40~50°C), dried and recrystallized from anhydrous benzene to yield the I-tetrabromide as colorless plates, m. p. 189°C (decomp.). Yield, 1.2g.

Found: C, 25.15; H, 2.59; Br, 55.83. Calcd. for $C_{12}H_{18}O_6Br_4$: C, 24.94; H, 3.14; Br, 55.31%.

When the above oily substance was left to stand, further crops of XIII were obtained during 2 or 3 days. The total yield was 2.7 g. On long heating in an attempt to recrystallize from aqueous benzene or anhydrous benzene, XIII changed to an indefinite substance with evolution of hydrogen bromide. On the other hand, when a water-miscible solvent such as methanol, alcohol and acetone, were used, XIII changed to VII.

Separation of VI, VII and XII from "I-Bromide". —When XIII was separated from the "I-bromide", and the oily substance was left to stand, crystals gradually separated out during 5~30 days. Addition of a small amount of ether promoted crystallization. Since the colection of the crystals by filtration was quite difficult because of the viscousness of the liquid, the whole was placed on a porcelain plate in spite of the loss of the yield or diluted with ether and then filtered. The solid thus obtained showed various melting points such as m. p. 60~90°C, m. p. 110~115°C (decomp.) and m. p. 130~140°C (partly decomp.), and was a mixture of VI, VII, XII, XIII and I as described below. When the oily substance was kept on standing for more than 3 months, hydrogen bromide and bromine were evolved gradually, yielding a solid which was mainly VII.

The solid obtained above was dissolved in anhydrous benzene, and then an insoluble substance was filtered off. The most soluble part was left to stand, a small amount of crystals being formed in the meanwhile. Filtration and recrystallization from petroleum ether (b. p. 40~50°C) gave VI[13] as colorless long plates, m. p. 83~84°C.

Found: C, 56.60; H, 5.83. Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70%.

The filtrate from VI was evaporated, yielding another crystalline substance. Recrystallization from petroleum ether (with active carbon) gave

11) All melting points are uncorrected.

12) (a) E. Fischer, "Anleitung zur Darstellung organischer Präparate", Berlin, Friedrich Vieweg u. Sonn. (1922), p. 48. (b) L. Knorr and F. Haber, *Ber.*, **27**, 1155 (1894). (c) L. Knorr, *Ann.*, **306**, 332 (1899).

13) (a) G. H. U. Harrow, *Ann.*, **201**, 152 (1880). (b) L. Knorr, *Ber.*, **17**, 2864 (1884); ibid., **22**, 153 (1889).

unchanged I as colorless scales, m. p. 92~93°C, which was identified by mixed melting point determination.

Found: C, 55.86; H, 6.98. Calcd. for $C_{12}H_{18}O_6$: C, 55.80; H, 7.03%.

When the crystals, separated from the part soluble in benzene, were recrystallized from anhydrous benzene, XII was obtained as colorless long pillars, m. p. 92~96°C (decomp.). It melted at 92~96°C with decomposition to a substance which melted at 128~130°C and gave the positive Beilstein halogen test.

Found: C, 36.20; H, 3.59. Calcd. for $C_{12}H_{16}O_5Br_2$: C, 36.03; H, 4.03%.

From the part more soluble in benzene than XII, a small amount of XIII, previously mentioned, was obtained.

From the part less soluble than XII and from the first insoluble part, a crude material of VII was obtained. During recrystallization XII partly changed to VII, and use of recovered benzene promoted the change. The latter was collected and recrystallized from aqueous methanol or water, yielding VII as colorless pillars of m. p. 234~236°C (partly decomp.).

Found: C, 49.70; H, 4.77. Calcd. for $C_8H_8O_5 \cdot \frac{1}{2}H_2O$: C, 49.74; H, 4.70%.

The yields of VI, I, XII and VII were 2.2 g., 0.8 g., 1.7 g. and 28.5 g., respectively.

Vacuum Distillation of "I-Bromide". — After removal of XIII, "I-bromide" (50 cc.) was heated under the reduced pressure of 5~6 mmHg. The pressure dropped to 30~40 mmHg at 150~170°C (bath-temperature) and again rose to 6~7 mmHg after 10 min. A pale orangish oily substance distilled out at ca. 200°C (bath-temperature). When the distillate was triturated with a small amount of ether, it solidified. Recrystallization from aqueous methanol gave VI as colorless long pillars of m. p. 83~84°C, b. p. 100~105°C/0.25~0.3 mmHg. Yield, 2.1 g. It was identified by a mixed melting pont with an authentic sample.

The residue was a very viscous reddish black syrup containing a small amount of a solid and had a distinct smell of hydrogen bromide and bromine. To the residue a small amount of ether was added, and the whole was kept standing in a stoppered flask for 2 or 3 days, yielding crystals gradually. These were collected on a filter and recrystallized from aqueous methanol (1 : 1) to give VII as colorless pillars, m. p. 234~236°C (partly decomp.). Yield, 3.8 g.

Hydrolysis of VI.—VI (1.2 g.) was dissolved in alcohol (60 cc.), and 50% sulfuric acid (5 cc.) was added, and the whole was refluxed for 4 hr. After removal of the alcohol, water was added. The precipitate, which formed in the meanwhile, was recrystallized from water, giving VII, m. p. 234~235°C (partly decomp.).

Reaction of "I-Bromide" with Methanol.—1) The oily "I-bromide" (2 g.), freed from all the crystals VI, VII, XII and XIII, was mixed with absolute methanol, and the whole was refluxed on a steam bath for 5 hr. After cooling a small amount of crystals were yielded. Recrystallization from water gave VII. The methanolic filtrate from VII was concentrated, giving first a small amount of a colorless substance of m. p. 100~110°C. Recrystallization from petroleum benzine (b. p. 60~75°C) gave colorless long pillars of m. p. 118~119°C, the amount being too little to be analyzed. From the last portion of the methanolic filtrate, colorless long plates of m. p. 45~46°C were obtained. Recrystallization from petroleum ether (b. p. 40~50°C) gave VIII[14] as colorless tetragonal plates, m. p. 58~61°C.

Found: C, 56.53; H, 5.70. Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70%.

2) The mixture of the oily "I-bromide" (2 g.), freed from all the crystals, with sodium methoxide (sodium 0.2 g., absolute methanol 50 cc.), was refluxed on a steam bath for 2 hr., and after the methanol was removed as much as possible and water was added, it was acidified with sulfuric acid to yield a white residue. Recrystallization from benzene (with active charcoal) gave a compound of m. p. 120~121°C (partly decomp.) as pale yellow plates, which were analyzed as diacetosuccinic acid.

Found: C, 47.59; H, 4.94. Calcd. for $C_8H_{10}O_6$: C, 47.53; H, 4.99%.

Hydrolysis of "I-Bromide".—1) The oily "I-bromide" (1 g.) freed from all the crystals was treated with concentrated sulfuric acid (5 cc.) and the whole was heated on a steam bath for 1 hr. Addition of water yielded grayish white precipitates, which, on recrystallization from benzene and then water, gave VII.

2) The oily "I-bromide" (6 g.) freed from all the crystals was dissolved in aqueous potassium carbonate (protassium carbonate 7 g., water 25 cc.) and the whole was boiled for 2 hr. After addition of water, the whole was acidified with sulfuric acid, and extracted with ether. The ethereal solution was washed with water, dried and evaporated, leaving a grayish white solid (0.2 g.). Recrystallization from ethylene chloride gave a material of m. p. 176~180°C (decomp.), which was not analyzed because of the impurity.

Cyclization of I by Hydrogen Bromide.—Through a cooled solution of I (12 g.) in anhydrous benzene (150 cc.) dried hydrogen bromide was passed for 30 min. The whole was placed in a stoppered flask, and kept standing overnight, yielding crystals. These were recrystallized from aqueous methanol to give 0.7g. of VII. When the benzene filtrate was concentrated, 8.5 g. of I was recovered and a small amount of colorless needles of m. p. 105~112°C were obtained, which could not be further investigated because of the scarcity of the sample.

Ethyl 1-*p*-Nitrophenyl-3, 6-dimethyl-1, 4-dihydropyridazine-4, 5-dicarboxylate (Anhydro-*p*-nitrophenylhydrazone of I).—A solution of I (2 g.) and *p*-nitrophenylhydrazine (1 g.) in 70% acetic acid, was kept standing for 1 hr. at room temperature. The crystals which were yielded were recrystallized from ethyl acetate, giving pale yellow long pillars, m. p. 122~123°C.

Found: N, 11.57. Calcd. for $C_{18}H_{21}O_6N_3$: N, 11.20%.

14) I. M. Heilbron, E. R. H. Jones, P. Smith and B. C. L. Weedon, *J. Chem. Soc.*, **1946**, 57.

Ethyl 2, 5-Di(bromomethyl)furan-3, 4-dicarboxylate (XV).—To a mixture of IX (9.6 g., 1 mol.), *N*-bromosuccinimide (14.3 g., 2 mol.) and carbon tetrachloride (100 cc.), benzoyl peroxide (ca. 0.1 g.) was added. The whole was refluxed gently on a steam bath for 5 hr and allowed to cool. Succinimide which separated was filtered off. The filtrate was concentrated, and the residue was distilled in vacuo, giving XV as a pale yellow, very viscous syrup of b. p. 170~180°C/3 mmHg. Yield, 14.5 g. (91%). When kept standing in an icebox, it solidified, but melted partly at room temperature. The solidified substance was recrystallized from petroleum ether (b. p. 40~50°C) (the solution was kept standing in an icebox to crystallize), giving XV as colorless long plates, m. p. 52~52.5°C.

Found: C, 36.13; H, 3.62. Calcd. for $C_{12}H_{14}O_5Br_2$: C, 36.19; H, 3.52%.

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