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BIS(BROMOMETHYL) COMPOUNDS

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The direct bromination of two aromatic methyl groups is a very unsatisfactory procedure. The yields are low, and in most cases a mixture of isomers of similar properties is formed, from which the isolation of definite compounds is difficult. Even in the most favorable cases, the bromination of the xylenes, the yields of xylylene bromides vary in wide limits. According to Atkinson and Thorpe (1) *o*-xylene is the only compound where direct dibromination is feasible. The *m*- and *p*-isomers yield mixtures from which only about 30% (1, 8) of the dibromo compounds are isolated by tedious procedures. In polycyclic compounds the procedure of direct bromination is even less satisfactory. For example, the bromination of small amounts of *o,o'*-bitolyl (I) is reported to give about 35% of *o,o'*-bis(bromomethyl) biphenyl (II) (4). Even the improved method of Hall, Lesslie, and Turner (2) gave only 43%, so that these authors had to resort to a rather involved synthesis, starting from diphenic acid, in order to prepare sufficient quantities of II. Obviously, the high temperatures required for direct bromination have a detrimental effect on the reaction product, and with the increased periods of time needed for greater amounts of starting material, this effect becomes disastrous.

Since considerable amounts of II were needed for the investigation of dihydro derivatives of dibenz[*c,e*]azepine (12), a more satisfactory method for the preparation of bis(bromomethyl) compounds had to be found. This led to the investigation of the reaction of N-bromosuccinimide with aromatic dimethyl compounds. Karrer and Schmid (3) have shown that N-bromosuccinimide brominates toluene in the side chain in the presence of benzoyl peroxide.

When two moles of N-bromosuccinimide are allowed to react with a dimethyl compound, a variety of products can theoretically be formed. The first bromine atom may enter the side chain as in the bromination of toluene. The second bromine atom could replace a hydrogen of the newly formed bromomethyl group to yield a dibromomethyl derivative. It could also replace a hydrogen of the nucleus, or finally, it could enter into the second methyl group to form a bis(bromomethyl) derivative.

The investigation showed that the last possibility is the preferred reaction, thus enabling the preparation of the desired bis(bromomethyl) compounds in good yields. To prove the structure of the dibromination product of *o,o'*-bitolyl, the compound was converted over the diacetoxy into the dihydroxy derivative, which on oxidation yielded diphenic acid.

To study the influence of the constitution of the parent compounds, a number of aromatic dimethyl compounds were subjected to the reaction. The three isomeric xylenes did not give uniformly the corresponding xylylene bromides. A considerable amount of monobrominated xylene is always found as by-product;

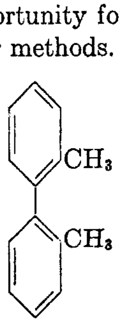
but, although the yields of the desired xylylene bromides were not quantitative, this method of preparation is vastly superior to the older procedure of direct bromination. By one distillation, or even by mere cooling of the crude products, yields of 60% and more of the xylylene bromides are easily obtained.

Whereas direct dibromination of more complex dimethyl compounds in general gives considerably lower yields of dibromo derivatives than that of xylenes, the bromination with N-bromosuccinimide in these cases occurs with higher yields than that of the xylenes. 2,3-Dimethylnaphthalene (V) and the two bitolyls (I and III) give yields of about 80% of the bis(bromomethyl) compounds (II, IV, and VI).

The side chain brominations with N-bromosuccinimide in the above-mentioned cases show some particular features which require attention. They do not start immediately, and some unknown influence (besides the peroxide catalysis) must play a role in the initiation of the reaction. In the case of the xylenes gentle refluxing on the steam-bath may continue for periods of a few minutes up to an hour, when suddenly a rather vigorous reaction occurs. It subsides after a few minutes, and the bromination is then finished. Polycyclic dimethyl compounds likewise may reflux for several hours without reaction. When reaction starts, it is, however, not characterized by vigorous boiling. Only by interruption of the refluxing is it possible to judge the progress of the reaction, because the succinimide rises to the surface. In many experiments, apparently conducted under identical conditions, the bromination of *o,o'*-bitolyl (I) started after irregular periods of boiling of from ½ to 10 hours; but in all cases refluxing overnight resulted in complete reaction.

In order to determine the influence of further substituents in the parent compounds on the reaction, two halogen-substituted dimethyl compounds were brominated. 4,4'-Dichloro-3,3'-bitolyl (9) reacted much slower than did the unchlorinated compound. In the course of the experiment some elementary bromine is formed which is used probably in nuclear bromination. Complete reaction of the N-bromosuccinimide required about 30 hours of refluxing. 4,4'-Dichloro-2,2'-bitolyl (6) reacted even more difficultly and it was impossible to complete the bromination; only a small yield of the dibrominated derivative VII was obtained.

The bis(bromomethyl) compounds, accessible in the manner described, offer the opportunity for the preparation of derivatives which are difficult to obtain by other methods. Some of these reactions are under investigation.



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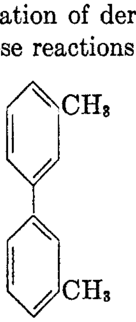

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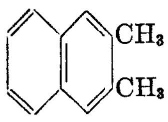

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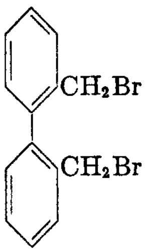

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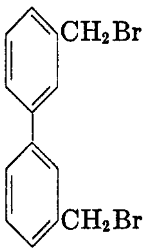

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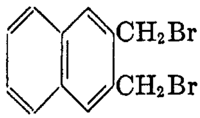

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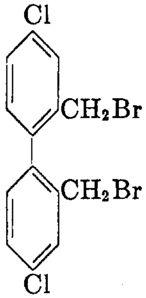
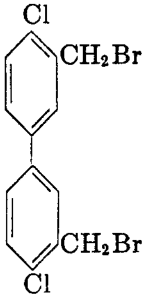


VII



VIII

Acknowledgment. I wish to thank Dr. A. Steyermark for the microanalyses reported in this paper.

EXPERIMENTAL

The melting points are uncorrected.

A. INTERMEDIATES

Since the method of Ullmann and Meyer (11) proved to be unsuitable for the preparation of larger batches of *o,o'*-bitolyl, the procedure discovered by May (7) and described in detail by Kornblum (5) for *m,m'*-bitolyl was used with good results.

1. *m-Tolidine.* *m*-Tolidine was prepared from *o*-nitrotoluene essentially according to Schultz and Rohde (10) in the following manner:

o-nitrotoluene (200 g.) was refluxed with stirring in 200 cc. of alcohol. The heating bath was removed, and 150 g. of zinc dust was added at such a rate that refluxing was maintained at a steady rate. When all of the zinc was added, a solution of 30 g. of sodium hydroxide in 150 cc. of 65% alcohol was cautiously dropped in. After complete addition, another 150 g. of zinc dust was added in portions. The mixture was then refluxed for about 2 hours. The solution was acidified slowly with 2400 cc. of 20% hydrochloric acid. Heating was continued to dissolve the excess of zinc. After standing overnight, *m*-tolidine dihydrochloride had crystallized. It was filtered and dissolved in about 2 liters of water. The hot solution was filtered through charcoal. To the filtrate 500 cc. of conc'd hydrochloric acid was added, precipitating *m*-tolidine dihydrochloride. After drying, the yield was 150–160 g. For the preparation of *o,o'*-bitolyl this material is sufficiently pure.

2. *o,o'-Bitolyl.* *m*-Tolidine dihydrochloride (212 g.) (or an equivalent amount of the commercially available material, for instance, from Carvin Co., North Haven, Conn.) was stirred with 2 liters of water. After addition of 210 cc. (250 g.) of conc'd hydrochloric acid, which precipitates the hydrochloride of the base in finely divided form, the mixture was cooled to 0–5°. At this temperature 145 g. of 95% sodium nitrite in 250 cc. of water was slowly added. A clear solution of the tetrazonium salt formed. It was added with stirring

to 1350 cc. of 30% hypophosphorous acid at 0–5°. The mixture was kept in the ice-bath until the ice melted. The next day the dark oil floating on the surface was separated, and the aqueous layer was extracted with three portions of 250 cc. of benzene. The oil and the benzene extracts were combined and extracted with about 500 cc. of 3% sodium hydroxide to remove some phenolic by-products. The solution was then filtered and distilled to remove the benzene. The residue was distilled *in vacuo*, yielding about 150 g. (*ca.* 88%) of *o,o'*-bitolyl of b.p.$_{18-20}$ 135–140°. Redistillation gave 140 g. of entirely colorless material. On standing in the refrigerator for several hours, the *o,o'*-bitolyl solidified to a crystalline solid, m.p. 17°.

3. *2,3-Dimethylnaphthalene.* Technical dimethylnaphthalene (Kodak) (1 kg.) was kept for one week at −15°. About 100 g. of crystals separated. They were filtered and recrystallized repeatedly from alcohol, yielding about 40 g. of pure 2,3-dimethylnaphthalene, m.p. 102–103°.

4. *4,4'-Dichloro-3,3'-bitolyl. o*-Tolidine dihydrochloride 56% (Carvin Co., North Haven, Conn.) (125 g.) was converted according to Schultz (9) into 4,4'-dichloro-2,2'-bitolyl. The compound distilled at 176–180°/10–15 mm. It solidified on cooling and melted at 49–50°. The yield was 46–50 g.

5. *4,4'-Dichloro-2,2'bitolyl. m*-Tolidine dihydrochloride (60 g.) was diazotized in 150 cc. of conc'd hydrochloric acid and 1800 cc. of water with 30 g. of sodium nitrite at 0°. The resulting solution was added dropwise to a stirred boiling solution of 100 g. of cuprous chloride in 1 liter of 2% hydrochloric acid. The next day the mixture was extracted with ether. The ether solution was filtered, washed with dilute sodium hydroxide and water, and dried over calcium chloride. The ether was evaporated, and the remaining dark oil was fractionated *in vacuo*, yielding 45 g. of 4,4'-dichloro-2,2'-bitolyl, b.p.$_{10-15}$ 180–185°. The compound solidified on cooling and melted at 42–43°. Le Fèvre and Vine (6) report m.p. 48°.

B. BIS(BROMOMETHYL) COMPOUNDS

6. *o,o'-Bis(bromomethyl)biphenyl* (4). N-Bromosuccinimide (103 g.) and 1 g. of benzoyl peroxide were added to 50 g. of *o,o'*-bitolyl dissolved in 125 cc. of carbon tetrachloride. The mixture was stirred and refluxed gently. If after 1 hour reaction had not started (visible by short interruption of the heating, whereupon succinimide rises to the surface), another 1-2 g. of benzoyl peroxide was added. Refluxing was then continued for several hours. After about 15 hours (overnight), reaction was always complete. The solution was cooled to room temperature and the succinimide was filtered off. The light yellow filtrate was distilled to dryness in a partial vacuum at a bath temperature not exceeding 50°. The residue was a heavy oil, which on standing at room temperature for several hours partly crystallized. To isolate the compound, the partly crystallized residue was stirred up with ligroin and was filtered. About 50–60 g. of almost pure *o,o'*-bis(bromomethyl)biphenyl were thus obtained. The mother liquor contains more of the compound.

Small amounts, up to 40–50 g., of the oily bromo compound can be crystallized within a few minutes by shaking with ice-cold alcohol and scratching. With larger amounts this procedure is not recommended, because the bis(bromomethyl)compound reacts slowly with alcohol.

The crude compound was best recrystallized from benzene-petroleum ether, m.p. 82–83°.

Anal. Calc'd for $C_{14}H_{12}Br_2$: C, 49.44; H, 3.56; Br, 46.72.
Found: C, 49.69; H, 3.84; Br, 46.99.

Recrystallization was accompanied by considerable losses.

7. *o,o'-Bis(hydroxymethyl)biphenyl. o,o'*-Bis(bromomethyl)biphenyl (10 g.) was dissolved in 30 cc. of acetone. The solution was slowly added to 8 g. of anhydrous potassium acetate in 100 cc. of glacial acetic acid at 80–90°. After heating for 10 hours on the steam-bath the mixture, which contained crystals of potassium bromide, was distilled to dryness *in vacuo*. The residue was shaken with water and ether, and the dried ether extract was distilled to dryness. The residue was distilled *in vacuo*, yielding pure *o,o'*-bis(acetoxymethyl)biphenyl as an oil, b.p.$_{20}$ 215–220°.

Anal. Calc'd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08.
Found: C, 72.39; H, 5.79.

The acetyl compound was saponified in methanol with an excess of potassium hydroxide. After neutralization with dil. acetic acid, filtration, and distillation to dryness a yellow oil remained, which was extracted with ether. The dried ether solution was distilled to dryness. The residue solidified. Recrystallization from benzene gave pure *o,o'*-bis(hydroxymethyl)biphenyl, m.p. 103–104°. Hall, *et al.* (2) give m.p. 112–113°.

Anal. Calc'd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59.
Found: C, 78.13; H, 6.60.

8. *Oxidation of o,o'-bis(bromomethyl)biphenyl.* In order to determine whether nuclear bromination accompanies the formation of *o,o'*-bis(bromomethyl)biphenyl, 10 g. of the latter was converted in the manner described in Exp. 7 over the diacetoxy and dihydroxy derivative into diphenic acid, but in this case without isolation of these intermediates, in order not to lose any nuclear brominated material in the recrystallization mother liquors. The crude *o,o'*-bis(acetoxymethyl)biphenyl was directly saponified, and the resulting crude *o,o'*-bis(hydroxymethyl)biphenyl was, without crystallization, oxidized in a solution of 20 g. of sodium hydroxide in 200 cc. water by stirring and heating to 80–90° with 12 g. of potassium permanganate. After filtration of manganese dioxide, the solution was acidified. The crude acid was purified by dissolving it in sodium bicarbonate solution, filtration, and reacidification. A yield of 5 g. of pure diphenic acid, m.p. 228–230°, was obtained. No brominated diphenic acid was found.

9. *m,m'-Bis(bromomethyl)biphenyl.* *m,m'*-Bitolyl (5) (25 g.), 51 g. of N-bromosuccinimide, and 1 g. of benzoyl peroxide were refluxed in 100 cc. of carbon tetrachloride. The reaction was complete after 5 hours. The succinimide was filtered while the solution was still hot. On cooling, large crystals formed which were filtered (20–25 g.) and recrystallized from benzene, yielding pure *m,m'*-bis(bromomethyl)biphenyl, m.p. 103–104°.

Anal. Calc'd for $C_{14}H_{14}Br_2$: C, 49.44; H, 3.56.
Found: C, 49.83; H, 3.64.

10. *2,3-Bis(bromomethyl)naphthalene.* 2,3-Dimethylnaphthalene (8 g.), 18.5 g. of N-bromosuccinimide, and 1 g. of benzoyl peroxide were refluxed in 80 cc. of carbon tetrachloride. After 10 hours, the solution was filtered hot. The filtrate was cooled in the refrigerator for 12 hours, yielding 6 g. of crude 2,3-bis(bromomethyl)naphthalene. Recrystallization from benzene gave the pure compound, m.p. 164–165°.

Anal. Calc'd for $C_{12}H_{10}Br_2$: C, 45.89; H, 3.21.
Found: C, 45.97; H, 3.37.

11. *o-Xylylene bromide.* *o*-Xylene (32 g.), 110 g. of N-bromosuccinimide, and 1 g. of benzoyl peroxide were refluxed in 300 cc. of carbon tetrachloride. After about ½ hour, the mixture started to boil vigorously for several minutes. When the reaction had subsided, the solution was filtered. The filtrate was distilled to dryness *in vacuo* at about 50°. The residue was covered with petroleum ether. The *o*-xylylene bromide crystallized slowly. It was filtered after one day; yield 45–48 g.; m.p. 98–99°. The filtrate contains *o*-xylyl bromide which is best isolated by fractional distillation.

12. *m-Xylylene bromide.* From 32 g. of *m*-xylene the bromination with N-bromosuccinimide in the same manner as described for *o*-xylene yielded about 100 g. of crude product which on fractionation gave 27 g. of b.p.$_{12-15}$ 105–125° (mostly *m*-xylyl bromide) and 40 g. of b.p.$_{12-15}$ 150–165° (crude *m*-xylylene bromide). Recrystallization of the latter gave 35 g. of pure *m*-xylylene bromide, m.p. 70–72°.

13. *p-Xylylene bromide.* In the manner described for *o*-xylylene bromide, the bromination of 32 g. of *p*-xylene resulted in the formation of 50 g. of crude *p*-xylylene bromide of b.p.$_{10-12}$ 155–158°. Recrystallization from alcohol yielded the pure compound, m.p. 142–144°.

14. *3,3'-Bis(bromomethyl)-4,4'-dichlorobiphenyl.* 4,4'-Dichloro-3,3'-bitolyl (20 g.), 29 g. of N-bromosuccinimide, and 1 g. of benzoyl peroxide were refluxed in 250 cc. of carbon tetrachloride for 12 hours. Another 1.5 g. of benozyl peroxide was added and refluxing continued. Some bromine vapors developed in the first hours. The reaction was complete after

refluxing overnight and the solution was filtered while hot; 10 g. crystallized in the refrigerator. The mother liquor was distilled to dryness, and the oily residue was stirred with ligroin and a few cc. of carbon tetrachloride, yielding another 10 g. of crystals. Recrystallization from carbon tetrachloride gave pure 3,3′-bis(bromomethyl)-4,4′-dichlorobiphenyl, m.p. 148–150°.

Anal. Calc'd for $C_{14}H_{10}Br_2Cl_2$: C, 41.11; H, 2.46.

Found: C, 40.77; H, 2.33.

15. *2,2′-Bis(bromomethyl)-4,4′-dichlorobiphenyl.* 4,4′-Dichloro-2,2′-bitolyl (10 g.), 40 cc. of carbon tetrachloride, 15 g. of N-bromosuccinimide, and 1 g. of benzoyl peroxide were refluxed on a steam-bath. After 15 hours of refluxing, another 0.5 g. of benzoyl peroxide was added, and refluxing was continued for 15 more hours (overnight). Only then was bromination complete. The hot solution was filtered and the filtrate was distilled to dryness. On standing at room temperature, the viscous dark residue partly crystallized. The crystals were filtered and were recrystallized twice from benzene-petroleum ether; yield 3 g. The 2,2′-bis(bromomethyl)-4,4′-dichlorobiphenyl melted at 114–116°.

Anal. Calc'd for $C_{14}H_{10}Br_2Cl_2$: C, 41.11; H, 2.46.

Found: C, 40.87; H, 2.49.

SUMMARY

The bromination with N-bromosuccinimide is a convenient procedure for the preparation of bis-bromomethyl derivatives from aromatic dimethyl compounds.

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