[CONTRIBUTION NO. 314 FROM THE RESEARCH LABORATORIES
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6,7-DIHYDRO-5*H*-DIBENZ[*c*,*e*]AZEPINE DERIVATIVES

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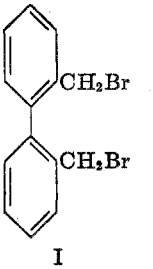
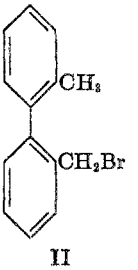
o,*o*'-Bis(bromomethyl)biphenyl (I) (1) has become easily accessible by the bromination method using N-bromosuccinimide (4), allowing the extension of the earlier work (3) to derivatives of 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine (V) containing more complex substituents in position 6. In order to reduce the handling of the aggressive lachrimator I to a minimum, the use of the crude material, obtained by simply distilling to dryness the bromination solution in carbon tetrachloride, was investigated. Whereas crude bromination products prepared with elementary bromine are generally of poor quality and need purification before they can be used for further reaction, crude *o*,*o*'-bis(bromomethyl)biphenyl made with N-bromosuccinimide is of high purity and is entirely satisfactory for the preparation of derivatives. The yields are even higher because isolation of pure *o*,*o*'-bis(bromomethyl)biphenyl is attended by considerable loss.

The azepine derivatives prepared with crude *o*,*o*'-bis(bromomethyl)biphenyl generally contained small amounts of α-amino-*o*,*o*'-bitolyl derivatives of formula IV, proving that the crude starting material contains some α-bromo-*o*,*o*'-bitolyl (II). The constitution of one of these amines as a secondary base was established by conversion of the allyl derivative (VII) into the urea derivative (III).

The free bases (IV) cannot be separated from the azepine derivatives (V) by ordinary fractional distillation, because both boil at about the same temperature. However, the salts (phosphate, hydrochloride) of II are generally much more soluble in alcohol than the corresponding salts of V, thus enabling separation by recrystallization.



I



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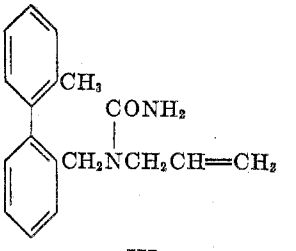

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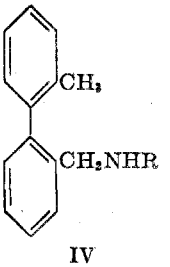
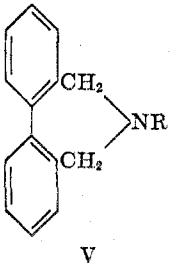


IV



V

VII R = $CH_2CH{=}CH_2$
X R = $CH(CH_3)_2$
XIV R = $CH_2CH_2CH_2OCH_3$

VI R = $CH_2CH{=}CH_2$
IX R = $CH(CH_3)_2$
XI R = $CH_2C_6H_5$
XII R = $CH_2CH_2C_6H_5$
XIII R = $CH_2CH_2CH_2OCH_3$

XV R = $CH_2CH_2CH_2OCH(CH_3)_2$
XVI R = Cyclohexyl
XVII R = $CH_2CH_2N(C_2H_5)_2$
XVIII R = CH_2CH_2OH
XIX R = H

The new derivatives of 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine are mostly water-insoluble liquids. They are quite stable compounds. Even the 6-(β-phenethyl) and the 6-(γ-isopropoxypropyl) derivative distill without decomposition *in vacuo*.

The benzyl derivative was catalytically debenzylated, yielding the unsubstituted 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine (XIX) which was obtained previously (3) in poor yield by the reaction of *o*,*o'*-bis(bromomethyl)biphenyl with ammonia.

The pharmacological properties of some of the compounds have been described by Randall and Smith (2).

EXPERIMENTAL

The melting points are uncorrected.

1. *Crude o,o'-bis(bromomethyl)biphenyl* (I). *o*,*o'*-Bitolyl[1] (100 g.) was brominated according to the procedure described earlier (3). The bromination solution was distilled to dryness, and the crude *o*,*o'*-bis(bromomethyl)biphenyl was dissolved in benzene. The solution, which may be kept indefinitely, was used as starting material for the preparation of the dibenzazepine derivatives. For the calculation of the amounts of primary amines needed, the content of the benzene solution was considered as corresponding to a quantitative yield of *o*,*o'*-bis(bromomethyl)biphenyl from the *o*,*o'*-bitolyl used.

2. *6-Allyl-6,7-dihydro-5H-dibenz[c,e]azepine* (VI). *2-Allylaminomethyl-2'-methylbiphenyl* (VII). From a solution of crude *o*,*o'*-bis(bromomethyl)biphenyl corresponding to 100 g. of *o*,*o'*-bitolyl and 105 g. of allylamine, about 100–105 g. of crude, distilled 6-allyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine, b.p. 180–195°/15 mm. was obtained according to the procedure described earlier (3). Neutralization with phosphoric acid in 400 ml. of alcohol yielded 120 g. of pure 6-allyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine phosphate of m.p. 205–206°. The concentrated mother liquor on standing in the refrigerator gave about 7 g. of 2-allylaminomethyl-2'-methylbiphenyl phosphate (VII) of m.p. 164–165°.

Anal. Calc'd for $C_{17}H_{19}N \cdot H_3PO_4$: C, 60.89; H, 6.61; N, 4.17.
Found: C, 60.60; H, 6.43; N, 4.32.

When 100 g. of crude distilled allyl derivative was neutralized in 200 ml. of abs. alcohol with 50 ml. of 8 *N* hydrochloric acid in abs. alcohol, 95–100 g. of the hydrochloride of VI of m.p. 208–210° was obtained. The mother liquor was concentrated to about 100 ml. and kept in the refrigerator for several days. The hydrochloride of 2-allylaminomethyl-2'-methylbiphenyl (VII) crystallized. After recrystallization from little alcohol it melted at 129–130°.

Anal. Calc'd for $C_{17}H_{19}N \cdot HCl$: C, 74.57; H, 7.36; N, 5.12.
Found: C, 74.58; H, 7.11; N, 5.04.

[1] In the previous year paper (4) the starting material for *o*, *o'*-bitolyl was mistakenly given as *o*-nitrotoluene. It should read *m*-nitrotoluene.

2-Allylaminomethyl-2′-methylbiphenyl hydrochloride (5 g.) was dissolved in 25 ml. of water. A solution of 2 g. of potassium cyanate in 10 ml. of water was added. After one day crystals of N-[2-(*o*-tolyl)benzyl]-N-allylurea (III) had formed and were filtered off. The compound melted at 78–79°.

Anal. Calc'd for $C_{18}H_{20}N_2O$: C, 77.38: H, 7.21; N, 10.03.
Found: C, 77.11; H, 7.20; N, 9.99.

3. *6-Isopropyl-6,7-dihydro-5H-dibenz[c,e]azepine* (IX). *2-Isopropylaminomethyl-2′-methyl-biphenyl* (X). Crude *o,o′*-bis(bromomethyl)biphenyl from 50 g. of *o,o′*-bitolyl and 50 g. of isopropylamine were allowed to react in about 400 ml. of benzene. In the manner described earlier (3), 55 g. of crude 6-isopropyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine of b.p. 195–205°/20–24 mm. were isolated. Neutralization with alcoholic hydrobromide acid in abs. alcohol yielded 40 g. of 6-isopropyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine hydrobromide (IX) of m.p. 248–250°.

The mother liquor was distilled to dryness and the residue was redissolved in water. The solution was extracted with water to removed some oily impurities. On standing in the refrigerator, about 4 g. of the azepine derivative IX separated and was filtered. The filtrate was made alkaline with ammonia. The base was extracted with ether. The dried solution was neutralized with alcoholic hydrobromic acid, precipitating 3 g. of colorless crystals. Recrystallization from isopropyl alcohol yielded 2.5 g. of 2-isopropylaminomethyl-2′-methylbiphenyl hydrobromide of m.p. 219–221°.

Anal. Calc'd for $C_{17}H_{21}N \cdot HBr$: C, 63.90; H, 6.42; N, 4.37.
Found: C, 63.88; H, 6.19; N, 4.57.

4. *6-Benzyl-6,7-dihydro-5H-dibenz[c,e]azepine* (XI). Crude *o,o′*-bis(bromomethyl)biphenyl from 50 g. of *o,o′*-bitolyl and 90 g. of benzylamine were mixed in 300 ml. of benzene. After filtration of benzylamine hydrobromide, the benzene solution was extracted with 2% hydrochloric acid. From the acid extract an oil separated which on standing crystallized. Recrystallization from 98% alcohol yielded 6-benzyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine hydrochloride (XI) semihydrate of m.p. 205°.

Anal. Calc'd for $C_{21}H_{19}N \cdot HCl \cdot 1/2H_2O$: C, 76.23; H, 6.40; N, 4.23.
Found: C, 76.63; H, 6.21; N, 4.49.

In another experiment the acid extract together with the oil was made alkaline, and the base was extracted with benzene. After removal of the solvent the base was distilled *in vacuo*, yielding 40 g. of the base of b.p. 195–200°/0.1 mm. Neutralization with alcoholic hydrobromic acid in ether gave pure 6-benzyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine hydrobromide of m.p. 196–197°.

Anal. Calc'd for $C_{21}H_{19}N \cdot HBr$: C, 68.54; H, 5.50; N, 3.82.
Found: C, 68.40; H, 5.38; N, 3.84.

The *methiodide*, prepared from the base and methyl iodide in ether, was crystallized from alcohol-ether and melted at 188–190°.

Anal. Calc'd for $C_{22}H_{22}IN$: C, 61.83; H, 5.19.
Found: C, 61.56; H, 5.37.

5. *6-(β-Phenethyl)-6,7-dihydro-5H-dibenz[c,e]azepine* (XII). *o,o′*-Bis(bromomethyl)biphenyl (7 g.) and 8 g. of β-phenylethylamine were combined in 100 cc. of benzene. After one day β-phenylethylamine hydrobromide was filtered off. On shaking the filtrate with 2% hydrochloric acid the hydrochloride of the new base formed; it remained in the benzene layer. Evaporation of the benzene solution gave a crystalline product, which was washed with ether and was recrystallized from alcohol-ether, yielding 5 g. of 6-(β-phenethyl)-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine *hydrochloride* (XII) of m.p. 221°.

Anal. Calc'd for $C_{22}H_{21}N \cdot HCl$: C, 78.67; H, 6.60; N, 4.17.
Found: C, 78.82; H, 6.41; N, 4.32.

In another experiment, the crude base obtained from 17 g. of *o,o′*-bis(bromomethyl) biphenyl and 19 g. of β-phenylethylamine was fractionated *in vacuo*, yielding 9 g. of 6-(β-phenethyl)-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine (XII) of b.p. 250–255°/0.1 mm. Neutraliza-

tion of the base with alcoholic hydrobromic acid in ether gave 12 g. of the *hydrobromide semihydrate* of m.p. 105–106°.

Anal. Calc'd for $C_{22}H_{21}N \cdot HBr \cdot \frac{1}{2}H_2O$: C, 67.86; H, 5.95; N, 3.60.
Found: C, 67.99; H, 6.12; N, 3.57.

The *methiodide*, prepared in ether and recrystallized from alcohol, melted at 122°.

Anal. Calc'd for $C_{23}H_{24}IN$: C, 62.95; H, 5.48; N, 3.17.
Found: C, 63.19; H, 5.49; N, 2.75.

6. *6-(γ-Methoxypropyl)-6,7-dihydro-5H-dibenz[c,e]azepine* (XIII). *2-(γ-Methoxypropylaminomethyl)-2'-methylbiphenyl* (XIV). Crude *o,o'*-bis(bromomethyl)biphenyl from 25 g. of *o,o'*-bitolyl and 38 g. of γ-methoxypropylamine (American Cyanamid Co.) were allowed to react in 100 ml. of benzene. The amine was isolated in the usual manner and purified by distillation *in vacuo*, yielding 22 g. of base of b.p. 195–200°/10–15 mm. The *phosphate* prepared by neutralization with 85% phosphoric acid in alcohol melted at 171–172°.

Anal. Calc'd for $C_{18}H_{21}NO \cdot H_3PO_4$: C, 59.17; H, 6.62; N, 3.83.
Found: C, 59.35; H, 6.56; N, 3.62.

The mother liquor was kept for two days in the refrigerator yielding 3 g. of 2-(γ-methoxypropylaminomethyl)-2'-methylbiphenyl phosphate (XIV) of m.p. 133–134°.

Anal. Calc'd for $C_{18}H_{23}NO \cdot H_3PO_4$: C, 58.84; H, 7.13; N, 3.81; P, 8.43.
Found: C, 58.49; H, 7.14; N, 3.74; P, 8.51.

7. *6-(γ-Isopropoxypropyl)-6,7-dihydro-5H-dibenz[c,e]azepine* (XV). Crude *o,o'*-bis(bromomethyl)biphenyl from 25 g. of *o,o'*-bitolyl and 50 g. of γ-isopropoxypropylamine (American Cyanamid Co.) were allowed to react in 300 ml. of benzene. In this case no crystals formed. After extraction with water the base was extracted with 2% hydrochloric acid. Vacuum distillation of the liberated amine yielded 25 g. of the pure base of b.p. 205–210°/1.0 mm.

The *phosphate*, prepared in and recrystallized from isopropyl alcohol, melted at 45–46°.

Anal. Calc'd for $C_{20}H_{25}NO \cdot H_3PO_4 \cdot \frac{1}{2}H_2O$: C, 59.69; H, 7.26; N, 3.48.
Found: C, 59.54; H, 7.24; N, 3.51.

The *hydrochloride*, which is rather soluble in benzene, melted at 156°.

Anal. Calc'd for $C_{20}H_{25}NO \cdot HCl$: C, 72.38; H, 7.90; N, 4.22.
Found: C, 72.23; H, 8.04; N, 4.30.

The *methiodide* was crystallized from acetone and melted at 129–130°.

Anal. Calc'd for $C_{21}H_{28}INO$: C, 57.67; H, 6.45.
Found: C, 57.71; H, 6.30.

8. *6-Cyclohexyl-6,7-dihydro-5H-dibenz[c,e]azepine*, XVI). *o,o'*-Bis(bromomethyl)biphenyl (7 g.) and 6 g. of cyclohexylamine were allowed to react in 80 ml. of benzene. The base was isolated in the usual manner. The *hydrobromide* prepared in ether and recrystallized from 90% alcohol melted at 262–264°.

Anal. Calc'd for $C_{20}H_{23}N \cdot HBr$: C, 67.04; H, 6.75; N, 3.91.
Found: C, 67.37; H, 7.41; N, 4.22.

9. *6-(β-Diethylaminoethyl)-6,7-dihydro-5H-dibenz[c,e]azepine* (XVII). *o,o'*-Bis(bromomethyl)biphenyl (7 g.) was allowed to react with 3 g. of β-diethylaminoethylamine in 65 ml. of benzene. The product was extracted with dil. hydrochloric acid. The free base was liberated with an excess of sodium hydroxide. It was neutralized in ether solution with alcoholic phosphoric acid. The crude amorphous *phosphate* was dissolved in water. Upon addition of acetone it slowly crystallized. It contained 2 moles of water of crystallization and melted at 278–230°.

Anal. Calc'd for $C_{20}H_{26}N_2 \cdot 2H_3PO_4 \cdot 2H_2O$: C, 45.63; H, 6.89; N, 5.32.
Found: C, 45.79; H, 6.34; N, 5.77.

10. *6-(β-Hydroxyethyl)-6,7-dihydro-5H-dibenz[c,e]azepine* (XVIII). Crude *o,o'*-bis(bromomethyl)biphenyl from 50 g. of *o,o'*-bitolyl was stirred in 250 ml. of benzene. A solution of 55 g. of β-aminoethanol in 150 ml. of dioxane was slowly added at 40–60°. The free base isolated from an acid extract of the residue of the reaction mixture was purified by vacuum

distillation to give 35 g. of 6-(β-hydroxyethyl)-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine of b.p. 235–240°/20–22 mm.. The *hydrochloride* prepared in alcohol-ether melted at 190–192°.

Anal. Calc'd for $C_{16}H_{17}NO \cdot HBr$: C, 60.01; H, 5.66.
Found: C, 60.17; H, 5.33.

The *phosphate* prepared in alcohol melted at 180–181°.

Anal. Calc'd for $C_{16}H_{17}NO \cdot H_3PO_4$: N, 4.15. Found: N, 4.13.

11. *6,7-Dihydro-5H-dibenz[c,e]azepine* (XIX). 6-Benzyl-6,7-dihydro-5*H*-dibenz[*c*,*e*]-azepine hydrochloride (1.6 g.) was hydrogenated in 160 ml. of alcohol with 0.5 g. of palladium charcoal (10%) at about 25° and 30 lbs. pressure. The residue of the filtered solution was recrystallized from alcohol, yielding 1 g. of 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine hydrochloride of m.p. 286–288° (3).

Anal. Calc'd for $C_{14}H_{13}N \cdot HCl$: C, 72.56; H, 6.09.
Found: C, 72.55; H, 6.12.

Acknowledgment. I wish to thank Dr. Steyermark and his staff for the microanalyses.

SUMMARY

o,*o*′-Bis(bromomethyl)biphenyl when prepared with N-bromosuccinimide can be used in the crude state for the preparation of dibenzazepine derivatives. The only by-product of the crude *o*,*o*′-bis-(bromomethyl)biphenyl is α-bromo-*o*,*o*′-bitolyl.

Several new derivatives of 6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine are described.

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REFERENCES

(1) KENNER AND TURNER, *J. Chem. Soc.*, **99**, 2101, 2108 (1911).
(2) RANDALL AND SMITH, *J. Pharmacol. Exptl. Therap.*, **103**, 10 (1951).
(3) WENNER, *J. Org. Chem.*, **16**, 1475 (1951).
(4) WENNER, *J. Org. Chem.*, **17**, 523 (1952).