

Substituted Benzylquinolines^{1, 2}

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The purpose of the preparation of 6-(p-bromobenzyl)-quinaldine and -lepidine was to study certain reactions involving the halogen atom in the benzyl group. Both 6-(p-bromobenzyl)-4-hydroxyquinaldine and 6-(p-bromobenzyl)-4-methylcarbostyryl were prepared according to the method described previously (3). The hydroxy quinolines were converted readily to the corresponding chloro compounds by treatment with phosphoryl trichloride but unexpected difficulties were encountered in removal of the chlorine atom by catalytic reduction. In the catalytic reduction of 6-(p-bromobenzyl)-4-chloroquinaldine under the usual conditions, both the chlorine and the bromine atoms were removed to give 6-benzylquinaldine. Under less drastic conditions. The substance was recovered unchanged.

Catalytic reduction of 6-(p-bromobenzyl)-2-chlorolepidine (V) gave two substances, neither of which was the expected product. One substance was an ether soluble material containing no halogen, therefore was 6-benzyllepidine. The other product was insoluble in ether and melted at a high temperature over a considerable range. From this was isolated a substance which contained the correct percentage of halogen for 6-p-bromobenzyllepidine but the melting point, 240-42°, is not compatible with the structure of the substance. A molecular weight determination gave a value of 557 which is almost twice that for 6-p-bromobenzyllepidine. It would appear that bimolecular reduction had occurred during removal of the chlorine atom. Such bimolecular reductions have been reported by Busch and Weber (1). The substance contained bromine therefore it is in all probability 2, 2'-bis-6-(p-bromobenzyl)-lepidine. No attempt was made at structure proof. Catalytic reduction of V under less drastic conditions gave further mixtures. The ether soluble portion of the reduction products contained as much as 11-13% halogen and the ether insoluble portion could not be purified to yield a material of short melting point range.

Experimental

4-p-Bromobenzylaniline (I), 6-(p-bromobenzyl)-4-methylcarbostyryl (II) and 6-(p-bromobenzyl)-4-hydroxyquinaldine (III) were prepared according to the method described previously (2, 3).

6-(p-Bromobenzyl)-4-chloroquinaldine (IV).—Fifty-two grams (0.158 mole) of III was mixed with 150 g. (0.97 mole) of phosphoryl

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trichloride and the substances heated in a boiling water bath for two hours. The contents of the flask were then poured onto 200-250 g. of cracked ice and the solution neutralized with concentrated ammonia water. After removal of the solid, it was recrystallized from 100 ml. of 80% ethyl alcohol. IV was obtained as fine white needles. The yield was 35 g. (71%); the substance melted at 90-93°. The melting point could not be raised above 95-96° by three recrystallizations from ethyl alcohol.

Anal. Calc'd for $C_{17}H_{13}BrClN$: BrCl, 33.29%. Found: BrCl, 33.16%.

6-(p-Bromobenzyl)-2-chlorolepidine (V).—Phosphoryl trichloride (50 g., 0.325 mole) was added to 20 g. (0.061 mole) of II and the mixture heated in a boiling water bath until all of the solid was dissolved, then the solution poured onto 200-250 g. of ice. After standing for two hours, the solid was removed by filtration and washed until the acid was removed. The yield of tan-colored solid was 20 g. (94%), m.p. 103-106°. The substance melted at 107.5-108.5° after recrystallization from ethyl alcohol.

Anal. Calc'd for $C_{17}H_{13}BrClN$: BrCl, 33.29%. Found: BrCl, 33.05%.

Reduction of 6-(p-Bromobenzyl)-4-chloroquinaldine (IV).—Three grams of palladium-charcoal catalyst (4) was added to a solution of 9 g. (0.023 mole) of IV dissolved in 200 ml. of glacial acetic acid containing 8 g. of anhydrous sodium acetate. The hydrogenation was carried out at 65-70° and at 40 p.s.i. pressure. The hydrogenation was continued until there was no further drop in pressure (4-5 hours). After removal of the catalyst by filtration, most of the acetic acid was removed by vacuum distillation, ice was added and then the residue was made slightly alkaline with sodium hydroxide. The yield of dry crude solid was 5 g. (92%), which melted at 78-81°. After two recrystallizations from 30-40% ethyl alcohol, the substance was obtained as slightly yellow needles, which melted at 81-82°.

Neither the crude nor the purified substance gave slightest test for halogen, therefore the reduction product must have been 6-benzylquinaldine.

Anal. Calc'd for $C_{17}H_{15}N$: N, 6.01%. Found: N, 6.05%.

Reduction of 6-(p-bromobenzyl)-2-chlorolepidine (V).—Thirteen grams (0.038 mole) of V was reduced catalytically in exactly the same procedure as for the reduction of IV. After removal of the acetic acid and neutralization with sodium hydroxide, there was obtained an oil and a solid. The oil was soluble in ether and the solid (VI) was not appreciably soluble in the latter solvent. After drying and distillation of the ether, the residue distilled at 215-222° at 8 mm. pressure; the yield was 4 g. The oil gave a positive test for halogen. After standing for several days, large crystals appeared; these were removed, washed with a small amount of cold ether. The crystals weighed 1.2 g. After recrystallizations from dilute ethyl alcohol, the substance melted at 63.5-

65°. The test for halogen was negative; it must be presumed the substance is 6-benzyllepidine.

Recrystallization of the solid VI (5.8 g.) several times finally gave 0.8 g. of a white crystalline substance which melted at 240-242°.

Anal. Calc'd for $C_{21}H_{18}N_2Br_2$: Br, 25.7%; Mol. Wt., 622. Found: Br, 25.42%; Mol. Wt., 557.

Methyl 4, 4'-Methylenebis-(β -anilinoanilino) crotonate (VII).—A solution of 99 g. (0.5 mole) of 4, 4'-diaminodiphenylmethane (2) and 147 g. (1.27 moles) of methyl acetoacetate in 300 ml. of methylene chloride containing one drop of dilute hydrochloric acid was refluxed with a trap for liquids heavier than water attached. After the theoretical amount of water had separated, the methylene chloride was removed by distillation and the residual liquid mass poured into 200 ml. of cold ligroin. The solid was removed by filtration after it had been allowed to stand in a refrigerator over night. The yield of crude VII was 190 g. (96.4%); the substance melted at 93-97°. Purification of a ten-gram portion through recrystallization from a benzene-ligroin solution (1 to 20 by volume) gave white silky needles which melted at 101.5-102°.

Anal. Calc'd for $C_{23}H_{26}N_2O_4$: N, 7.10%. Found: N, 7.03%.

6,6'-Methylenebis-(4-hydroxyquinaldine) (VIII).—A solution of 50 g. (0.127 mole) of VII in 70 ml. of di-n-butyl phthalate at 70° was added slowly by means of a separatory funnel to vigorously stirred butyl phthalate which was maintained at 260-270°. The heating was continued, after VII was added, until no further distillation of methyl alcohol occurred. After the solution cooled, the solid was removed by filtration and washed, successively with a ligroin-butyl phthalate solution (1:1), then with ligroin and finally the solid was refluxed with benzene. The yield of crude dark tan colored VIII was 40 g. (95%) and it melted at 410-415° with decomposition. No solvent could be found for purification of the substance by recrystallization but it was soluble in a large excess of 3 N hydrochloric acid crystallized partially from the cold solution. Addition of alkali to the acid filtrate precipitated any VIII which remained in the hydrochloric acid.

Anal. Calc'd for $C_{21}H_{18}N_2O_2$: N, 8.48%. Found: N, 6.59%.

6,6'-Methylenebis-(4-chloroquinaldine) (IX).—A mixture of 50 g. (0.325 mole) of phosphoryl trichloride and 30 g. (0.09 mole) of VIII was heated for four hours in a boiling water bath. After the mixture had been poured onto about 200 g. of ice then the solution neutralized with concentrated ammonia water, the aqueous layer was decanted from the tarry semi-solid mass. The dark colored solid was dissolved in boiling ethyl alcohol, filtered and cooled to crystallize the crude IX as dark tan needles. The yield was 16 g. (48%). After three recrystallizations from ethyl alcohol, the substance melted at 159-160°.

Anal. Calc'd for $C_{21}H_{16}Cl_2N_2$: Cl, 19.32%. Found: Cl, 19.13%.

6,6'-Methylenebis-(4-methoxyquinaldine).—Twenty-four grams (0.065 mole) of IX was added to a solution of 23 g. (1 mole) of sodium in 360

ml. of absolute methanol, then the mixture heated to reflux temperature and benzene added while the methyl alcohol was removed by distillation. The mixture was heated for 40-50 minutes, then poured into one liter of water. The liquid was filtered to remove the solid, then the benzene layer separated and distilled. The solid residues were combined and recrystallized from 100 ml. of ethyl alcohol. The yield was 22 g. (98%). After recrystallization from alcohol and from dioxane, the substance melted at 222.5-224°.

Anal. Calc'd for $C_{23}H_{22}N_2O_2$: N, 7.82%. Found: N, 7.60%.

Summary

The preparation of 6-(p-bromobenzyl)-2-chlorolepidine and 6-(p-bromobenzyl)-4-chloroquinaldine from the corresponding 2-, and 4-hydroxy compounds has been reported. Catalytic reduction of 6-(p-bromobenzyl)-4-chloroquinaldine over palladium on charcoal gave 6-benzylquinaldine. Reduction of 6-(p-bromobenzyl)-2-chlorolepidine by the same method gave 6-benzyllepidine and a substance believed to be 2,2'-bis-6-(p-bromobenzyl)-lepidine.

Condensation of 4,4'-diaminodiphenylmethane with methyl acetate according to the modified Conrad-Limpach method gave 6,6'-methylenebis-4-hydroxyquinaldine. This substance was converted to the corresponding 4-chloro compound using phosphoryl trichloride. Treatment of 6,6'-methylenebis-4-chloroquinaldine with sodium methoxide in boiling benzene gave the corresponding 4-methoxy compound.

Literature Cited

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