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A STUDY OF THE INTERMEDIATES IN THE PREPARATION OF SYMPATHOL

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One of the most valuable substitutes for epinephrine is sympathol (synephrine), *p*-hydroxyphenyl-N-methylaminoethanol, $HOC_6H_4CHOHCH_2NHCH_3$. The substance is prepared commercially in several countries, under patents (1). Its preparation in the laboratory is extremely difficult. The classical epinephrine synthesis of Stolz, when applied to the preparation of sympathol, is quite inadequate, because of negligible yields. In seeking a satisfactory method, we accumulated much interesting material, some of which we consider sufficiently important to be published.

As an illustration of the poor yields obtained in the sympathol synthesis, we may cite the fact, that whereas Stolz (2) obtained a 61% yield of the methylamino ketone (adrenalone) by condensing 3,4-dihydroxy-α-chloroacetophenone with methylamine, Legerlotz (3) reported a yield of only 12% of *p*-hydroxy-α-methylaminoacetophenone when he treated *p*-hydroxy-α-chloroacetophenone with methylamine. The yield was appreciably increased when the phenolic group was benzoylated. The compound, *p*-benzoyloxy-α-bromoacetophenone, is frequently mentioned by Legerlotz, but we were unable to find any statement regarding its preparation in any of the Legerlotz patents which were available to us. Slotta (4), and Kindler and Peschke (5),[2] however, quote Legerlotz as having prepared *p*-benzoyloxy-α-bromoacetophenone by the condensation of phenyl benzoate with bromoacetyl bromide in the presence of aluminum chloride:

$$C_6H_5OCOC_6H_5 + BrCH_2COBr = BrCH_2COC_6H_5OCOC_6H_5 + HBr.$$

Working with phenyl benzoate and chloroacetyl chloride, we obtained, however, not the expected *p*-benzoyloxy-α-chloroacetophenone, but *p*-(chloroacetoxy)benzophenone:

$$C_6H_5OCOC_6H_5 + ClCH_2COCl = C_6H_5COC_6H_4OCOCH_2Cl + HCl.$$

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[2] Kindler and Peschke claim to have a convenient synthesis of sympathol from anisaldehyde.

p-Benzoyloxy-α-chloroacetophenone we prepared by benzoylating *p*-hydroxy-α-chloroacetophenone.

After repeating practically all the work embodied in the patents by Legerlotz, we found that one of the best methods of preparing sympathol was through the use of methylbenzylamine (6). Satisfactory yields were obtained by condensing *p*-benzoyloxy-α-chloroacetophenone with methylbenzylamine, hydrolyzing the *p*-benzoyloxy-α-methylbenzylaminoacetophenone with alcoholic hydrogen chloride, and reducing catalytically the *p*-hydroxy-α-methylbenzylaminoacetophenone to sympathol. Since *p*-benzoyloxy-α-chloroacetophenone was difficultly accessible, we attempted to replace it by *p*-benzyloxy-α-bromoacetophenone. We prepared this compound by the bromination of the benzyl ether of *p*-hydroxyacetophenone. Due, however, to the simultaneous formation of *p*-benzyloxy-α,α-dibromoacetophenone, $C_6H_5CH_2OC_6H_4COCHBr_2$, the isolation of the pure monobromo compound could be effected only with great difficulty, and with a poor yield. Far more easy to prepare, and with better yield, was the dibromo compound, which was readily formed from *p*-benzyloxyacetophenone and two moles of bromine. Treatment of *p*-benzyloxy-α-bromoacetophenone with methylbenzylamine yielded *p*-benzyloxy-α-methylbenzylaminoacetophenone.

While working on the bromination of the benzyl ether of *p*-hydroxyacetophenone, we became interested in studying the bromination of *p*-hydroxyacetophenone itself. We found that Nencki and Stoeber (7) had brominated *p*-hydroxyacetophenone and had obtained a dibromide, $C_8H_6Br_2O_2$, of unknown constitution. We have proved that the structure of this compound is 3,5-dibromo-4-hydroxyacetophenone, since oxidation of the methyl ether gave 3,5-dibromoanisic acid. By appropriate treatment with bromine, 3,5-dibromo-4-hydroxyacetophenone yielded 3,5-dibromo-4-hydroxy-α-bromoacetophenone and 3,5-dibromo-4-hydroxy-α,α-dibromoacetophenone, respectively. Similarly, the benzyl ether of 3,5-dibromo-4-hydroxyacetophenone could be converted into 3,5-dibromo-4-benzyloxy-α-bromoacetophenone and 3,5-dibromo-4-benzyloxy-α,α-dibromoacetophenone.

p-Benzyloxy-α-isonitrosoacetophenone was obtained in good yield by the Claisen condensation of *p*-benzyloxyacetophenone with two moles of sodium ethoxide and an excess of butyl nitrite. When hydrogen chloride was used as the catalyst, the only reaction-product isolated was a small amount of *p*-benzyloxybenzoic acid. This same product was also obtained by treatment of *p*-benzyloxy-α,α-dibromoacetophenone with alkali. A small amount of dibenzyloxybenzoic acid as a by-product was obtained by the action of sodium ethoxide and butyl nitrite on 3,4-dibenzyloxyacetophenone and 3,4-dibenzyloxypropiophenone. Catalytic reduction of *p*-benzyloxy-α-isonitrosoacetophenone by Hartung's method (8) gave *p*-benzyloxy-α-aminoacetophenone.

EXPERIMENTAL

Condensation of phenyl benzoate with chloroacetyl chloride. When 10 g. of phenyl benzoate, 5.6 g. of chloroacetyl chloride, and 0.8 g. of phosphorus oxychloride were refluxed with 15 cc. of benzene for 45 hours, the phenyl benzoate was isolated from the mixture in practically quantitative yield. A similar full recovery of the phenyl benzoate was obtained by heating for 6 hours 19.8 g. of phenyl benzoate, 11.2 g. of chloroacetyl chloride, and 20 g. of aluminum chloride, in 50 cc. of carbon disulfide. Repeating the latter experiment, but without the carbon disulfide, a slight evolution of hydrogen chloride was observed at 80–95°. After about an hour, the temperature was raised to 120°, and the reaction was allowed to proceed at this temperature for another two hours. The contents could be removed only by breaking the flask. The reaction-mass was powdered in a mortar and gradually introduced into 300 cc. of a water-ice mixture. On the addition of ether, about a gram of crystalline substance, m.p. 120–123°, separated. The ether extract was dried over anhydrous sodium sulfate, and the ether evaporated. A gum was obtained, which, when seeded with the crystalline substance, crystallized. The mass was stirred up with 75 cc. of alcohol, filtered, and crystallized from 75 cc. of alcohol, with the addition of 3 g. of activated charcoal. The yield of *p*-(chloroacetoxy)benzophenone was 4.0 g., m.p. 123°.

Anal. Calc'd for $C_{15}H_{11}ClO_3$: Cl, 12.93. Found: Cl, 12.92.

For hydrolysis, 10 cc. of fuming hydrochloric acid and 0.8 g. of the substance were kept together at room temperature for several days. Sixty cubic centimeters of water was added, and the mixture distilled with steam until a liter of distillate was collected. No benzoic acid was found in the distillate. The contents of the distilling-flask (about 250 cc.) was twice filtered hot from the tar. On cooling, 0.08 g. of needles, m.p. 128–130°, separated. The filtrate was evaporated to about 50 cc., and a second crop of crystals, 0.08 g., m.p. 130–132°, was obtained. The melting point of *p*-hydroxybenzophenone is recorded in the literature (9) as 134°. The two crops of crystals were mixed and analyzed.

Anal. Calc'd for $C_{13}H_{10}O_2$: C, 78.70; H, 5.05.
Found: C, 78.53; H, 5.06.

p-Benzoyloxy-α-chloroacetophenone (obtained from *p*-hydroxy-α-chloroacetophenone, benzoic acid, and phosphorus oxychloride in benzene solution) melted at 115°.

p-*Benzyloxyacetophenone* (I). Metallic sodium, 2.3 g., was dissolved in 45 cc. of absolute alcohol, and 13.6 g. of *p*-hydroxyacetophenone and 15.0 g. of benzyl chloride were added. The mixture was boiled under reflux for 5 hours. The alcohol was then distilled off, the sodium chloride dissolved in hot water, and the solid residue crystallized from 100 cc. of 95% alcohol. The yield was 19 g. of substance, m.p. 93°.

Anal. Calc'd for $C_{15}H_{14}O_2$: C, 79.64; H, 6.19.
Found: C, 79.82; H, 6.50.

The *o*-benzyloxyacetophenone was prepared in the same manner, and melted at 40°.

p-*Benzyloxy-α-bromoacetophenone* (II). One gram of (I) in 10 cc. of chloroform was treated with 0.7 g. of bromine dissolved in 5 cc. of chloroform. After about 15 minutes, the reaction was complete. An intermediate insoluble addition-product with hydrogen bromide appeared, which redissolved upon shaking the solution. The chloroform was removed under reduced pressure. The solid residue was washed with a little alcohol and recrystallized several times from 95% alcohol. The substance, 0.10 g., melted at 91°.

Anal. Calc'd for $C_{15}H_{13}BrO_2$: Br, 26.2. Found: Br, 26.8.

p-*Benzyloxy-α, α-dibromoacetophenone* (III). One gram of (I) in 15 cc. of chloroform was treated with 1.5 g. of bromine dissolved in 5 cc. of chloroform. After an hour, the chloroform was removed under reduced pressure. The solid residue (1.07 g., m.p. 82°) was washed with a little alcohol and crystallized from 95% alcohol. The yield was 0.25 g., m.p. 84°.

Anal. Calc'd for $C_{15}H_{12}Br_2O_2$: Br, 41.6. Found: Br, 41.6.

p-*Benzyloxy-α-methylbenzylaminoacetophenone* (IV). A solution of 10.5 g. of (II) in 25 cc. of absolute alcohol was treated with 8.6 g. of methylbenzylamine. The solution became hot. It was cooled and set aside. After 3 hours, a precipitate had separated. The next day, the alcohol was removed under reduced pressure. To the residue was added 150 cc. of water and 150 cc. of ether, and the two solutions were separated. On evaporation of the water solution, pure methylbenzylamine hydrobromide was obtained.

Anal. Calc'd for $C_8H_{12}BrN$: N, 6.93; Br, 39.56.
Found: N, 7.00; Br, 39.52.

The ethereal solution containing the *p*-benzyloxy-*α*-methylbenzylaminoacetophenone was shaken up in a separatory funnel with 100 cc. of 3% hydrochloric acid. The hydrochloride of the base precipitated out in the form of an oil. It was dissolved in chloroform, the solution dried over anhydrous sodium sulfate, and the chloroform distilled under reduced pressure. The *p*-benzyloxy-*α*-methylbenzylaminoacetophenone hydrochloride left behind was dried *in vacuo* but did not crystallize. It was obtained in the form of a glassy mass, which immediately liquefied on exposure to air. For conversion into the base, the hydrochloride was dissolved in a little acetone and treated with a concentrated solution of potassium carbonate. The free base was extracted with ether, the ethereal solution dried with anhydrous sodium sulfate, and the ether distilled. The *p*-benzyloxy-*α*-methylbenzylaminoacetophenone was obtained in the form of a gum.

Anal. Calc'd for $C_{23}H_{23}NO_2$: N, 4.07. Found: N, 4.02.

That this compound was actually *p*-benzyloxy-*α*-methylbenzylaminoacetophenone was proved by the formation of sympathol on catalytic reduction and by the fact that it closely resembled in physical properties *p*-benzoyloxy-*α*-methylbenzylaminoacetophenone, which we had previously prepared a number of times, but which we likewise could not obtain in crystalline form, although Legerlotz (6) claims the substance melts at 96°.

3,5-Dibromo-4-hydroxyacetophenone (V). To a solution of 6.0 g. of *p*-hydroxyacetophenone in 30 cc. of glacial acetic acid, 85 cc. of water was added. A solution of 14.0 g. of bromine in 30 cc. of 80% acetic acid was then gradually added, with efficient stirring. After standing for several hours, the precipitate was filtered and dried on the steam-bath. The yield was 12.2 g., m.p. 178°. The substance, after two recrystallizations from benzene, melted at 181°.

Anal. Calc'd for $C_8H_6Br_2O_2$: Br, 54.3. Found: Br, 54.6.

The *phenylhydrazone* melted at 147°.

Anal. Calc'd for $C_{14}H_{12}Br_2N_2O$: N, 7.3. Found: N, 7.3.

3,5-Dibromo-4-methoxyacetophenone (VI). This compound, which melted at 78°, was prepared from (V) by treatment with dimethyl sulfate and sodium hydroxide. For oxidation to 3,5-dibromo-4-methoxybenzoic acid, 3.0 g. of the ether was suspended in 200 cc. of concentrated nitric acid diluted with 300 cc. of water, and the mixture warmed on the water-bath for 14 hours. The solid was filtered from the cold solution, then dissolved in sodium carbonate, and the filtered solution acidified with hydrochloric acid. After crystallization from 50% alcohol, the 3,5-dibromo-4-methoxybenzoic acid melted at 213°. The melting point was not depressed by the addition of a pure sample of 3,5-dibromo-4-methoxybenzoic acid, m.p. 213°, obtained by bromination of anisic acid.

3,5-Dibromo-4-benzyloxyacetophenone (VII), m.p. 79°, was prepared from (V) and benzyl bromide, in a manner similar to that described for (I).

Anal. Calc'd for $C_{15}H_{12}Br_2O_2$: Br, 41.6. Found: Br, 42.3.

3,5-Dibromo-4-benzyloxy-α-bromoacetophenone (VIII). To a solution of 0.5 g. of (VII) in 5 cc. of chloroform was added 0.208 g. of bromine in 5 cc. of chloroform. Decolorization took place in about an hour. The chloroform solution precipitated some crystals, apparently a molecular addition-compound with hydrogen bromide. On spontaneous evaporation of the chloroform solution, large plates were obtained. After 3 recrystallizations from alcohol, the compound was obtained in the form of needles, m.p. 119°.

Anal. Calc'd for $C_{15}H_{11}Br_3O_2$: Br, 51.8. Found: Br, 52.6.

3,5-Dibromo-4-benzyloxy-α,α-dibromoacetophenone (IX), m.p. 104°, was prepared as was (VIII), using double the amount of bromine. The substance was very prone to form supersaturated solutions, so that scratching with a glass rod was necessary to cause precipitation from solution. This behavior is exactly like that of *p*-benzyloxy-*α*,*α*-dibromoacetophenone.

Anal. Calc'd for $C_{15}H_{10}Br_4O_2$: Br, 59.09. Found: Br, 59.06.

3,5-Dibromo-4-hydroxy-α-bromoacetophenone (X). To one gram of (V) in 30 cc. of warm chloroform was added 0.5 g. of bromine in 5 cc. of chloroform. After 30 minutes, the chloroform was allowed to evaporate spontaneously. The residue was washed with a little benzene and crystallized from 10 cc. of benzene. The substance melted at 128°. The bromination was also carried out in glacial acetic acid, and the same product was obtained.

Anal. Calc'd for $C_8H_5Br_3O_2$: Br, 64.0. Found: Br, 64.13.

3,5-Dibromo-4-hydroxy-α,α-dibromoacetophenone, (XI), m.p. 105°, was prepared as was (X), using twice the amount of bromine.

Anal. Calc'd for $C_8H_4Br_4O_2$: Br, 70.8. Found: Br, 70.16.

p-Benzyloxy-α-isonitrosoacetophenone (XII). In preparing the isonitroso ketones, care is taken to employ exactly one mole of sodium ethoxide and one mole of butyl nitrite for one mole of ketone. We have found, however, that the reaction was much quicker, and a better yield was obtained by using twice the amount of sodium ethoxide recommended. An excess of butyl nitrite likewise did not hurt the reaction. The sodium salt was not subjected to further action of the butyl nitrite because it was removed from the reaction by precipitation.

Sodium, 0.8 g., was dissolved in 20 cc. of absolute alcohol. To this was added 30 cc. of benzene, and then 4.0 g. of *p*-benzyloxyacetophenone. A clear solution resulted. Four grams of butyl nitrite was added, the bottle was tightly stoppered, and set aside for 48 hours. The sodium salt was filtered, washed with a little alcohol, then with benzene, and dried. It weighed 3.7 g. The sodium salt was suspended in water and decomposed with dilute hydrochloric acid, by rubbing the salt in a mortar until no pink particles remained. The isonitroso ketone, after crystallization from alcohol or benzene, melted at 149°.

Anal. Calc'd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49.
Found: C, 70.46; H, 5.20; N, 5.49.

p-*Benzyloxy-α-aminoacetophenone* (XIII). To a suspension of 1.0 g. of (XII) in

10 cc. of absolute alcohol was added 4.3 cc. of a solution of 10% hydrogen chloride in absolute alcohol, and 0.5 g. of 5% palladium-charcoal catalyst. In 20 minutes, two moles of hydrogen had been absorbed (190 cc.), and further shaking with hydrogen resulted in no additional reduction. The solution was filtered, and since from the filtrate only a very small amount (10 mg.) of reduced product was recovered, it was evident that the substance had precipitated from the solution, and was mixed with the catalyst. The charcoal was therefore extracted three times with 75 cc. of hot water. After concentrating the aqueous solution under reduced pressure to a volume of 30 cc., 0.75 g. of *p*-benzyloxy-α-aminoacetophenone hydrochloride, m.p. 226°, was obtained.

Anal. Calc'd for $C_{15}H_{16}ClNO_2$: N, 5.04. Found: N, 5.05.

p-*Benzyloxybenzoic acid from* p-*benzyloxyacetophenone.* A solution of 5.0 g. of *p*-benzyloxyacetophenone in 40 cc. of benzene was treated with 2.3 g. of freshly distilled butyl nitrite dissolved in 12 cc. of benzene. A current of dry hydrogen chloride was passed into the solution for 30 minutes. The solution was then set aside until the next day. After removal of the benzene under reduced pressure, a gum was obtained. Dilute alkali was added, and the resulting crystalline mass was filtered. The material on the filter was identified as unchanged *p*-benzyloxyacetophenone. The filtrate was acidified with dilute hydrochloric acid. The crude material weighed 0.65 g. It was crystallized from 25 cc. of 95% alcohol, and then melted at 187°.

Anal. Calc'd for $C_{14}H_{12}O_3$: C, 73.68; H, 5.30.
Found: C, 73.59; H, 5.42.

The substance was therefore *p*-benzyloxybenzoic acid (10). On treatment of (III) with alcoholic potassium hydroxide, a small amount of *p*-benzyloxybenzoic acid was also obtained.

3,4-Dibenzyloxybenzoic acid from 3,4-dibenzyloxypropiophenone and 3,4-dibenzyloxyacetophenone. In this experiment, one mole of sodium ethoxide and one mole of butyl nitrite were used for every mole of 3,4-dibenzyloxypropiophenone. To a sodium ethoxide solution prepared by dissolving 0.17 g. of sodium in 10 cc. of absolute alcohol, was added 1.3 g. of 3,4-dibenzyloxypropiophenone, and a solution of 0.4 g. of butyl nitrite in 5 cc. of benzene. The flask was stoppered and set aside for 24 hours. The precipitate was filtered, washed with benzene, and decomposed with dilute acetic acid. Only 0.04 g. of substance, m.p. 177°, was obtained by decomposing the precipitated sodium salt. This represented crude 3,4-dibenzyloxybenzoic acid, the sodium salt of which was rather soluble in the alcohol-benzene mixture. The solvent was allowed to evaporate spontaneously from the filtrate. The residue was taken up in water and ether. On acidifying the aqueous solution, 0.25 g. of a solid, m.p. 165°, was obtained. This was crystallized from 10 cc. of 95% alcohol, and yielded 0.11 g. of substance, m.p. 182°.

Anal. Calc'd for $C_{21}H_{18}O_4$: C, 75.5; H, 5.42.
Found: C, 75.5; H, 5.35.

3,4-Dibenzyloxyacetophenone, m.p. 98°, when treated with butyl nitrite and sodium ethoxide as condensing agent, also gave a small amount of 3,4-dibenzyloxybenzoic acid, m.p. 182°.

SUMMARY

The condensation reaction between phenyl benzoate and chloroacetyl chloride, in the presence of aluminum chloride, was studied. A number of new intermediates, useful in the synthesis of sympathol and related amino alcohols, have been prepared.

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