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# Mixed Benzoins. X. Conversion of Benzanisoin into Anisbenzoin

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The only case of the direct transformation of a mixed benzoin produced by the cyanide method into its isomer, is that of the conversion of benzanisoin ($\alpha$-hydroxybenzyl 4-methoxyphenyl ketone) into anisbenzoin (4-methoxy-$\alpha$-hydroxybenzyl phenyl ketone).[1] Jenkins,[2] in a note just published, converts 4-methoxybenzyl phenyl ketone into the *ms*-bromo derivative and this into anisbenzoin. This conversion of benzanisoin into anisbenzoin depends on the (unusual) reduction of benzanisoin to the above ketone.[1a] Unless, therefore, a mixed benzoin can be reduced so that the CO group of the benzoin becomes the $CH_2$ group of the desoxy compound, the reaction is not applicable to the conversion of isomers. Few cases of such reductions are known.[1a,3] A possible route for the conversion of a mixed benzoin into its isomer depends on the course of the Tiffeneau vinyl dehydration of the hydrobenzoin.[4] In cases where this gives both desoxy compounds or where the desoxy compound formed corresponds to the exchange of the CO of the benzoin for $CH_2$, meso-halogenation and replacement of the halogen by hydroxyl, after the manner of Meisenheimer and Jochelson,[5] would give the isomeric mixed benzoin. A few such dehydrations have been observed.[3,4,6] Several instances of the reverse transformation are recorded (non-cyanide benzoin into cyanide benzoin).[6,7,8]

The present work was undertaken to find a general reaction capable of converting a mixed benzoin into its isomer, by an unequivocal route. Such a method has been found and it is possible to convert benzanisoin ($C_6H_5CHOHCOC_6H_4OCH_3$) into anisbenzoin ($C_6H_5COCHOHC_6H_4OCH_3$) in four simple steps. Doubtless the same series of reactions could also be used in the reverse sense, anisbenzoin to benzanisoin. The other methods which achieve this last type of change depend either on fission and recombination[1b] or on an intramolecular change of some kind.[6,7,8]

Preliminary work was carried out on benzoin itself. Benzoin was converted into benzoin-$\alpha$-oxime and the oxime reduced to $\alpha$-aminobenzylphenylcarbinol (diphenylhydroxyethylamine). After acetylation the prod-

(1) Buck and Ide. THIS JOURNAL, **55**, 855 (1933); (a) **53**, 1536 (1931); **54**, 3012 (1932); (b) **53**, 2350 (1931); (c) **53**, 3510 (1931); (d) **53**, 1912 (1931).

(2) Jenkins, *ibid.*, **55**, 3048 (1933).

(3) Jenkins, Buck and Bigelow, *ibid.*, **52**, 4495 (1930).

(4) Orékhoff and Tiffeneau, *Bull. soc. chim.*, **37**, 1410 (1925).

(5) Meisenheimer and Jochelson, *Ann.*, **355**, 249 (1907).

(6) Jenkins, THIS JOURNAL, **53**, 3115 (1931).

(7) Luis, *J. Chem. Soc.*, 2547 (1932).

(8) Julian and Passler, THIS JOURNAL, **54**, 4756 (1932).

uct was oxidized to α-acetaminobenzyl phenyl ketone. From this, on hydrolysis, α-aminobenzyl phenyl ketone (desylamine) was obtained, and this on treatment with nitrous acid gave benzoin. The yields at each stage are good except as might be expected for the oxidation where the yield is moderate. Although benzoin itself was obtained it is clear that the CO and CHOH groups must have been interchanged.

An exactly similar series of reactions was carried out using benzanisoin as the starting material. There was obtained anisbenzoin identical with the compound prepared by the method of Asahina and Terasaka.[9]

Subsequent work showed that protection of the amino groups during oxidation was not essential and that the α-aminobenzylphenylcarbinol could be oxidized to the corresponding ketone directly. This observation enables two stages to be eliminated from the original series of reactions.

The reduction of the benzoin oximes to the α-aminobenzylphenylcarbinols was carried out catalytically. This means of reduction which has not previously been applied to benzoin oximes gave excellent yields in most cases and is a convenient preparative method.

The oxidation of α-aminobenzylphenylcarbinols to α-aminobenzyl phenyl ketones represents a new method of preparation for the latter compounds. The method was also applied to the α-acetaminobenzylphenylcarbinols, the corresponding α-acetaminobenzyl phenyl ketones being obtained.

The reduction (catalytic) of 2-chloro-α-hydroxybenzyl-4-methoxyphenyl ketoxime (*o*-chlorobenzanisoin oxime) presented difficulties. The major part of the chlorine was stripped from the ring and there resulted a mixture of the hydrochlorides of 4-methoxy-α-aminobenzyl-2-chlorophenylcarbinol and 4-methoxy-α-aminobenzylphenylcarbinol together with unchanged oxime and other compounds. The lability of the chlorine atom is noteworthy, and has been observed before in a similar connection.[1c]

An interesting point is that N-acetylbenzoin-α-oxime and acetylbenzil-α-oxime, on catalytic reduction, both give considerable amounts of α-acetaminobenzylphenylcarbinol. Hydrolysis or alcoholysis is apparently not involved, since the reaction also takes place in benzene solution. Probably the simplest explanation is that the acetyl group is split off during the reduction and the α-aminobenzylphenylcarbinol formed, partially reacetylated. The equations are

$$C_6H_5COC(=NOCOCH_3)C_6H_5 \longrightarrow C_6H_5CHOHCHNHCOCH_3C_6H_5 \longleftarrow C_6H_5CHOHC(=NOCOCH_3)C_6H_5$$

The α-aminobenzyl phenyl ketones contain the group $COCHNH_2$ which often gives stable azomethylene compounds with nitrous acid.[10] No such compounds were sought for nor observed in the present work,

(9) Asahina and Terasaka, *J. Pharm. Soc. Japan*, **494**, 19 (1923).
(10) Angeli, *Ber.*, **26**, 1715 (1893).

although they were probably intermediates in the last stage[11] of the interconversion.

## Experimental

**α-Aminobenzylphenylcarbinols.**—The reductions were carried out in the usual Burgess-Parr apparatus, except that the bottle was heated electrically and the apparatus modified so that it could be used for 0.005 mole and upward of material;[12] 0.03 mole of the benzoin oxime, in 50 cc. of absolute alcohol, with 0.5 g. of platinum oxide (Adams) was reduced at 70–75°. The reductions were not satisfactory unless run hot. The theoretical amount of hydrogen was given in each case. The product was isolated by removing the catalyst, partially evaporating the solvent, and recrystallizing the material which separates out from the alcohol.

In the case of *o*-chlorobenzanisoin oxime, 0.04 mole (11.68 g.) was reduced in the above manner. The reduction mixture was cooled and a crop of 4-methoxy-α-aminobenzyl-2-chlorophenylcarbinol hydrochloride (2.8 g.) filtered off. The liquors were evaporated to dryness on the water-bath and the resulting crystalline mass washed well with ether; 3.9 g. of 4-methoxy-α-aminobenzylphenylcarbinol hydrochloride was so obtained. The remainder of the starting material was accounted for as unchanged, together with other compounds not identified. The bases were liberated from the aqueous solutions of the hydrochlorides by sodium hydroxide. The reduction of the acetyl oximes was carried out in a similar manner but at room temperature.

TABLE I

α-AMINOBENZYLPHENYLCARBINOLS AND DERIVATIVES

| | Compound reduced | Product, phenylcarbinol | Yield, % | M. p., °C. |
|---|---|---|---|---|
| 1 | Benzoin-α-oxime[13] | α-Aminobenzyl- | 86 | |
| 2 | Benzil-α-monoxime[14] | α-Aminobenzyl- | 85 | |
| 3 | Acetyl benzoin-α-oxime[13] | α-Acetaminobenzyl- | 19 | 197 |
| 4 | Acetyl benzil-α-monoxime[15] | α-Acetaminobenzyl- | 19 | |
| 5 | Benzanisoin oxime[1d] | 4-Methoxy-α-aminobenzyl | 66 | 123 |
| 6 | Dimethylaminobenzoin oxime[1d] | 4-Dimethylamino-α-aminobenzyl- | 80 | 151 |
| 7 | *o*-Chlorobenzanisoin oxime[1d] | Hydrochloride of 4-methoxy-α-aminobenzyl- | 35 | 233 dec. |
| 8 | *o*-Chlorobenzanisoin oxime[1d] | Hydrochloride of 4-methoxy-α-aminobenzyl-2-chloro- | 22 | 252 dec. |
| 9 | (From salt) | 4-Methoxy-α-aminobenzyl-2-chloro- . . | | 115 |

| | Solvent | Appearance | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|
| 3 | Alcohol | Glittering small needles | 75.25 | 74.91 | 6.71 | 6.43 |
| 5 | Alcohol | Flat rect. prisms | 74.03 | 74.09 | 7.04 | 7.05 |
| 6 | Alcohol | Small stout prisms | 74.95 | 75.04 | 7.86 | 7.75 |
| 7 | Alcohol | Tiny jagged needles | 64.38 | 64.20 | 6.49 | 6.68 |
| 8 | Alc.-ether | Felted hair-like needles | 57.32 | 57.56 | 5.45 | 5.31 |
| 9 | Aq. alcohol | Small stout prisms | 64.84 | 65.20 | 5.80 | 5.96 |

**Acetylation of α-Aminobenzylphenylcarbinols.**—The N-acetylation was accomplished readily by treating the carbinol with 2.5 times its weight of acetic anhydride.

(11) *Cf.* Schroeter, *Ber.*, **42**, 2345 (1909).
(12) Buck and Jenkins, THIS JOURNAL, **51**, 2163 (1929).
(13) Werner and Detscheff, *Ber.*, **38**, 69 (1905).
(14) Taylor and Marks, *J. Chem. Soc.*, 2305 (1930).
(15) Auwers and Meyer, *Ber.*, **22**, 545 (1889).

Heat was evolved and the mass solidified. After heating for ten minutes on the water-bath, the mixture was cooled, allowed to stand in the cold, ether added, and the product filtered off and recrystallized from alcohol. The compounds (except the *o*-chloro compound) are sparingly to moderately soluble in hot alcohol. The *o*-chloro compound is rather soluble in alcohol.

In the acetylation of α-aminobenzylphenylcarbinol, some α-acetaminobenzylphenylcarbinol acetate is usually produced. It melts at 219° (lit. 213°) and was checked against an authentic specimen.[16]

4-Methoxy-α-acetaminobenzyl-2-chlorophenylcarbinol, on account of its greater solubility, is best isolated by pouring the reaction mixture into water, and, after warming, allowing the mixture to stand in the cold.

TABLE II

α-ACETAMINOBENZYLPHENYLCARBINOLS

| | Compound, phenylcarbinol | Solvent | Yield, % | M. p., °C. |
|---|---|---|---|---|
| 1 | α-Acetaminobenzyl-[16] | Alcohol | 79 | 197 |
| 2 | 4-Methoxy-α-acetaminobenzyl- | Alcohol | 91 | 183 |
| 3 | 4-Methoxy-α-acetaminobenzyl-2-chloro- | Aq. alcohol | 79 | 122 |
| 4 | 4-Dimethylamino-α-acetaminobenzyl- | Alcohol | 94 | 187 |

| | Appearance | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|
| 1 | Glittering small needles | 75.25 | 74.91 | 6.71 | 6.43 |
| 2 | Felted tiny needles | 71.54 | 71.57 | 6.72 | 6.87 |
| 3 | Small thick prisms | 63.83 | 64.00 | 5.67 | 5.99 |
| 4 | Glittering felted needles | 72.44 | 72.48 | 7.44 | 7.59 |

**α-Acetaminobenzyl Phenyl Ketones (Acetyldesylamines.)**—The α-acetaminobenzylphenylcarbinol was dissolved in four times its weight of acetic acid. A solution of chromic acid (= one O) in a little aqueous acetic acid was added in portions. The temperature at the start was 40° and after the addition 70°. The mixture was kept at 70° for ten minutes, allowed to cool, and gradually diluted in the refrigerator. The product which separated was filtered off and fractionated from alcohol until pure.

**α-Aminobenzyl Phenyl Ketones (Desylamines).**—The oxidation of the (unacetylated) α-aminobenzylphenylcarbinols was carried out in dilute sulfuric acid solution, using chromic acid (= one O). For the unsubstituted carbinol 7 parts of 20% sulfuric acid were used and for the methoxy carbinol, 12 parts. After mixing at about 40° the reaction mixture was slowly (twenty minutes) heated to 70°. α-Aminobenzyl phenyl ketone readily separates as sulfate on adding further sulfuric acid to the mixture; yield, 59% as base, via the sulfate.

4-Methoxy-α-aminobenzyl phenyl ketone cannot be separated as sulfate. The oxidation mixture was therefore extracted with ether to remove non-basic material, made alkaline with ammonia, extracted with ether (very troublesome), the extract dried over anhydrous sodium sulfate, and the solution treated with hydrogen chloride. The hydrochloride which was precipitated was filtered off and dried *in vacuo*. The yield was 70% as hydrochloride, via the base. The free 4-methoxy-α-aminobenzyl phenyl ketone rapidly turns yellow when removed from solvent, and undergoes some change. For this reason a pure specimen was not isolated. The hydrochloride, however, is quite stable.

The same α-aminobenzyl phenyl ketones are obtained by the hydrolysis of the α-acetaminobenzyl phenyl ketones. For the unsubstituted compound (acetyldesylamine) digestion on the bath with eight times its weight of concd. hydrochloric acid for 3.6 hours

(16) Söderbaum, *Ber.*, **29**, 1210 (1896).

was found best. The yield was 91% (as hydrochloride). In the case of the methoxy compound much difficulty was encountered with hydrochloric acid. Ultimately it was found that refluxing for four and one-half hours with sulfuric acid (1 vol. concd. sulfuric acid to 5 vols. water) gave good results. The yield (isolated as hydrochloride, via the base) was 92%.

TABLE III

α-ACETAMINOBENZYL PHENYL KETONES AND α-AMINOBENZYL PHENYL KETONES

| | Compound, benzyl phenyl ketone | Solvent | Yield, % | M. p., °C. |
|---|---|---|---|---|
| 1 | α-Acetamino- | Aq. alcohol | 52 | 132 |
| 2 | 4-Methoxy-α-acetamino- | Aq. alcohol | 37 | 112 |
| 3 | 4-Methoxy-α-amino- | Ether | .. | soft 88 froth 94 |
| 4 | Hydrochloride of α-amino-[17] | Alc.–ether | 91 | 245 yellow, froth |
| 5 | Hydrochloride of 4-methoxy-α-amino- | Alcohol | 92 | 236 orange, froth |

| | Appearance | Carbon, % Calcd. | Found | Hydrogen, % Calcd. | Found |
|---|---|---|---|---|---|
| 1 | Glittering flat needles | 75.85 | 75.75 | 5.96 | 6.01 |
| 2 | Dull white nodules of tiny needle prisms | 72.05 | 72.04 | 6.05 | 6.14 |
| 3 | Yellow crust of tiny spheres | Nitrogen | calcd., | 5.80. | found, 5.81 |
| 4 | Bundles of thick glassy needles | 67.86 | 67.81 | 5.70 | 5.92 |
| 5 | Clusters of tiny jagged needles | 64.85 | 65.09 | 5.81 | 6.02 |

**Benzoin from α-Aminobenzyl Phenyl Ketone.**—2.7 g. of α-aminobenzyl phenyl ketone hydrochloride was dissolved in 40 cc. of water, cooled, and 3.0 cc. of concd. hydrochloric acid added. A solution of 1.4 g. of sodium nitrite (2 moles) in 15 cc. of water was then added in portions at room temperature. The mixture was warmed on the bath for a few minutes until the nitrogen was expelled. The yellowish oil which separated solidified on cooling and was filtered off; yield 91%. After recrystallization the product was pure white and was identified as benzoin (checked against authentic benzoin).

**Anisbenzoin from 4-Methoxy-α-aminobenzyl Phenyl Ketone.**—The reaction was carried out substantially as above, except that 8 cc. of concd. sulfuric acid was used in place of the 3 cc. of concd. hydrochloric acid and stronger heating was required to drive off the nitrogen. The oily product was extracted with ether, the ether evaporated, and the oil taken up in dilute alcohol. The anisbenzoin crystallized out on standing in the cold. It was checked, after recrystallization, against an authentic specimen.[9] For confirmation, it was oxidized (Fehling's solution) to benzanisil and this was then checked against an authentic specimen. The yield of anisbenzoin (crystalline) was about 50%, but this must be considered as minimal on account of the difficulty of crystallizing the compound in the presence of impurities.

It is not necessary to isolate the α-aminobenzyl phenyl ketones or their salts from the hydrolysis mixtures, as these can be treated (after extraction with ether) directly with sodium nitrite.

When the unacetylated compounds are oxidized, the oxidation mixture may, after extraction with ether, be treated directly with sodium nitrite and then heated. The resulting benzoin is extracted with ether. The cold liquors, treated with a second portion of sodium nitrite and again heated, give a further amount of the benzoin.

## Summary

1. A series of reactions is described whereby benzanisoin was converted into anisbenzoin. The reactions can probably be applied to other

(17) Pschorr and Brüggemann, *Ber.*, **35**, 2740 (1902).

mixed benzoins. Benzoin itself as starting material gave benzoin as the end product.

2. An expeditious method for the preparation of α-aminobenzylphenylcarbinols is the catalytic reduction of the oximes of benzoins.

3. α-Aminobenzyl phenyl ketones are produced by the oxidation of α-aminobenzylphenylcarbinols.

4. α-Acetaminobenzyl phenyl ketones are produced by the oxidation of α-acetaminobenzylphenylcarbinols. The acetyl group may be removed by hydrolysis.

5. In the catalytic reduction of 2-chloro-α-hydroxybenzyl-4-methoxyphenyl ketoxime, the chlorine is largely split from the nucleus.

TUCKAHOE, NEW YORK RECEIVED JULY 13, 1933
PUBLISHED OCTOBER 6, 1933

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# Action of Aromatic Alcohols on Aromatic Compounds in the Presence of Aluminum Chloride. VI. Condensation of Phenylpropylcarbinol and α-Chlorobutylbenzene with Phenol

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The work here described may be considered a continuation of that with Lewis and Grotemut[1] on the condensation of secondary alcohols with phenols.

The phenylpropylcarbinol used was prepared from propyl bromide and benzaldehyde by the Grignard reaction. A yield of 81% was obtained when the reactants were used in the proportion of one of propyl bromide to one of magnesium to four-fifths of benzaldehyde[2,3] and when the reaction mixture was cooled to a slight visible reaction during the preparation of the Grignard reagent and in ice during the addition of the benzaldehyde.[4] Because of the lack of agreement[5] as to the boiling point and density of this compound these constants were carefully redetermined: b. p. 94–96° (6 mm.), sp. gr. 18/4°, 0.974.

Condensation of one mole of phenylpropylcarbinol (or α-chlorobutylbenzene) with one mole of phenol in petroleum ether at 20–25°, by means of one-half mole of aluminum chloride,[6] gave a 20% yield of 4-(α-phenylbutyl)-phenol and a 6% yield of 2-(α-phenylbutyl)-phenol. These were separated by repeated fractionation at reduced pressure. Solution of the crude

(1) Huston, Lewis and Grotemut, THIS JOURNAL, **49**, 1365 (1927).
(2) Meisenheimer, *Ann.*, **442**, 180 (1925).
(3) Gilman and McCracken, THIS JOURNAL, **45**, 159 (1923).
(4) Rheinboldt and Roleff, *J. prakt. Chem.*, **109**, 175 (1925).
(5) Marshall and Perkin, *J. Chem. Soc.*, **59**, 885 (1891); Grignard, *Chem. Centr.*, II, 7622 (1901); Klages, *Ber.*, **37**, 2312 (1904); Puyal and Montague, *Bull. soc. chim.*, **27**, 857 (1920); Strauss and Grindel, *Ann.*, **439**, 276, 312 (1924).
(6) Huston, THIS JOURNAL, **46**, 2777 (1924).