[CONTRIBUTION FROM THE DANIEL SIEFF INSTITUTE AND THE GROSVENOR LABORATORY]

A NEW SYNTHESIS OF 1-(*m*- AND *p*-HYDROXYPHENYL)-2-METHYLAMINOETHANOL (*m*- AND *p*-SYMPATHOL)

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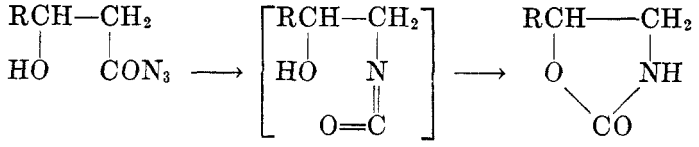
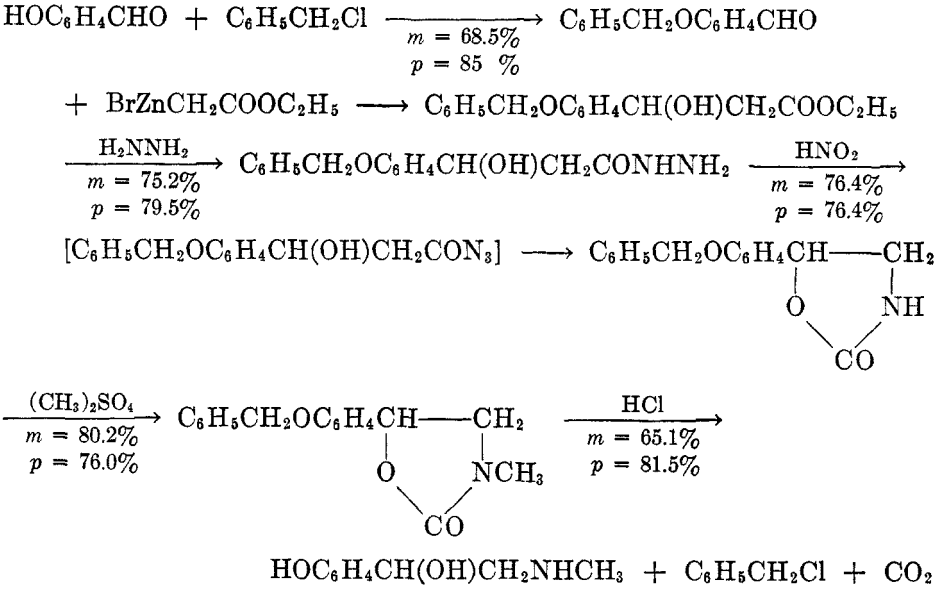
The isomerization to oxazolidones which takes place in the Curtius rearrangement of β-hydroxyacid azides was discovered by Schroeter (1) and recently has



been utilized in a number of cases (2–4) for the preparation of substances of possible pharmacological interest. It can be applied to a new synthesis of Sympathol (*meta*- and *para*-) according to the following Chart:



The N-methylation of the 5-(benzyloxyphenyl)2-oxazolidones recalls that of hydantoin and its derivatives (5) and of the oxazolidine-2,4-diones (6), but in both cases the NH is linked to two carbonyl groups; obviously, one carbonyl group is sufficient for the activation of the NH.

The treatment of the methylated oxazolidones with hydrochloric acid not only destroys the ring (liberation of carbon dioxide) but also causes debenzylation. In the *para*-series it is possible to separate these two reactions.

While the *acetoxy*-benzaldehydes did not react with ethyl bromoacetate and zinc, the above sequence of reactions could be carried out with *m*- and *p-methoxy*-

benzaldehyde, but the final demethylation proved difficult. Relatively good results (68% yield) were obtained with aniline hydrochloride [method of Klemenc (7)]. Also in model experiments with 4-methoxyacetophenone, a yield of only 60% could be obtained (at a conversion rate of 70%).

In the Curtius rearrangement of the hydrazide of 3-methoxyphenylhydracrylic acid, the expected oxazolidone was accompanied by a sparingly soluble by-product which—according to the analysis—was probably the trimeride of 2-(3′-methoxyphenyl)-2-hydroxyethyl isocyanate. Such trimerides do not seem to have been isolated before in the course of the Curtius rearrangement (8). However, trimerisation products of isocyanates are well known.

In the course of this investigation, another approach to the synthesis of the Sympathols was explored, *viz.* the reaction of 4-methoxystyrene chlorohydrin with methylamine, assuming that the reaction takes the same course as in the case of the unsubstituted styrene (9).

$$CH_3OC_6H_4CH(OH)CH_2Cl + CH_3NH_2 \rightarrow CH_3OC_6H_4CH(OH)CH_2NHCH_3$$

As, however, the yield of O-methyl-*para*-Sympathol in this reaction was only 32%, and as, moreover, the reaction of 4-methoxystyrene with hypochlorous acid gave under the best conditions only a 30% yield of the chlorohydrin (together with a large amount of resinous products), this route was abandoned. Also the analogous 4-methoxystyrene oxide could only be prepared in very unsatisfactory yield.

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EXPERIMENTAL PART

4-Benzyloxybenzaldehyde has been prepared before (10), but no experimental data were given. A mixture of 28 g. of 4-hydroxybenzaldehyde (0.23 mole), 32 g. of benzyl chloride (0.25 mole), 70 g. of anhydrous potassium carbonate, and 150 cc. of methyl ethyl ketone was refluxed for ten hours with stirring. The product was then poured into dilute potassium hydroxide solution and the upper layer separated, dried, and distilled. The product had b.p. 198°/11 mm.; from methyl alcohol, needles, m.p. 72°. Yield, 41.4 g. (85%).

Anal. Calc'd for $C_{14}H_{12}O_2$: C, 79.3; H, 5.7.
Found: C, 79.4; H, 6.0.

3-Benzyloxybenzaldehyde was prepared analogously in 68.5% yield [compare Rapson and Robinson (11)].

Hydrazide of 4-benzyloxyphenylhydracrylic acid. An initial 50 cc. of a mixture, consisting of 116.6 g. (0.55 mole) of 4-benzyloxybenzaldehyde, 100.2 g. (0.6 mole) of ethyl bromoacetate, and 100 cc. of benzene, was added to 39.2 g. (0.6 mole) of zinc wool, suspended in 200 cc. of benzene. The mixture was heated until reaction set in, and the balance of the reactants was gradually added. The mixture was then refluxed for two hours (until all the metal had disappeared) and decomposed with ice and dilute sulfuric acid. The benzene layer was washed with water, sodium bicarbonate, and water, and dried and concentrated *in vacuo* at a temperature not exceeding 50°. The crude hydroxyester remained as a slightly yellow oil, which crystallized quickly.

Without further purification, it was dissolved in 60 cc. of ethyl alcohol, and 80 g. of 50%

hydrazine hydrate (0.8 mole of hydrazine) was added. The exothermic reaction, which gave a white mass of crystals, was completed by heating at 50° for one hour. The product was washed with alcohol and recrystallized from butyl alcohol to give needles, m.p. 191–192°; yield, 125 g. (79.5% calculated on the 4-benzyloxybenzaldehyde employed).

Anal. Calc'd for $C_{16}H_{18}N_2O_3$: C, 67.1; H, 6.3; N, 9.8.
Found: C, 67.2; H, 6.1; N, 9.5.

Hydrazide of 3-benzyloxyphenylhydracrylic acid. From alcohol, needles, m.p. 161°; yield, 75.2%.

Anal. Calc'd for $C_{16}H_{18}N_2O_3$: C, 67.1; H, 6.3; N, 9.8.
Found: C, 67.1; H, 6.1; N, 9.4.

Hydrazide of 4-methoxyphenylhydracrylic acid. The methyl ester of the hydracrylic acid derivative was obtained as a slightly yellowish oil, yield, 95.0%. The hydrazide formed needles, m.p. 177°; yield, 84.0% (calculated on anisaldehyde employed).

Anal. Calc'd for $C_{10}H_{14}N_2O_3$: C, 57.1; H, 6.7; N, 13.3.
Found: C, 57.3; H, 6.2; N, 13.8.

Hydrazide of 3-methoxyphenylhydracrylic acid. The crude methyl ester (yield, 95.2%) gave a hydrazide which crystallized from methanol in needles. M.p. 148°; yield, 90.5% (calculated on 3-methoxybenzaldehyde employed).

Anal. Calc'd for $C_{10}H_{14}N_2O_3$: C, 57.1; H, 6.7; N, 13.3.
Found: C, 56.7; H, 6.4; N, 13.8.

5-(4'-Benzyloxyphenyl)-2-oxazolidone. A mixture of 71.5 g. (0.25 mole) of finely ground hydrazide (suspended in 400 cc. of water), 100 g. of chopped ice, and 40 cc. of glacial acetic acid, was placed in a separatory funnel. An aqueous solution of 35 g. (0.5 mole) of sodium nitrate was gradually added and the mixture shaken for about 20 minutes. The thick magma was diluted with 400 cc. of water and twice extracted with benzene, thus giving a light emulsion. The benzene solution was filtered from 4.0 g. of starting material (5.6%), dried, and concentrated to 100 cc. at ordinary pressure, nitrogen being split off at this stage. Upon cooling, the oxazolidine crystallized; from alcohol, colorless crystals, m.p. 145–146°; yield, 48.5 g. (76.4% calculated on hydrazide not recovered).

Anal. Calc'd for $C_{16}H_{15}NO_3$: C, 71.3; H, 5.6; N, 5.2.
Found: C, 71.2; H, 5.8; N, 5.5.

5-(3'-Benzyloxyphenyl)-2-oxazolidone was prepared analogously; from alcohol, m.p. 106–107°. Yield, 76.4% (5.6% of the starting material was recovered unchanged).

Anal. Calc'd for $C_{16}H_{15}NO_3$: C, 71.4; H, 5.6; N, 5.2.
Found: C, 71.6; H, 5.8; N, 5.3.

5-(4'-Methoxyphenyl)-2-oxazolidone was best obtained (93.3%) at 0°. The benzene was removed completely and the crystalline residue triturated with petroleum ether and recrystallized from dilute alcohol (1:9). M.p. 108–109°.

Anal. Calc'd for $C_{10}H_{11}NO_3$: C, 62.2; H, 5.7; N, 7.3.
Found: C, 62.1; H, 5.0; N, 7.1.

5-(3'-Methoxyphenyl)-2-oxazolidone was prepared in the same manner as the *para*-isomer. It was a yellow, viscous oil which could not be induced to crystallize. Yield, 69.4%. As a benzene-insoluble by-product, the trimeride of 2-(3'-methoxyphenyl)-2-hydroxyethyl isocyanata was obtained; from butyl alcohol, needles m.p. 202–203°; yield, 24.9%.

Anal. Calc'd for $C_{30}H_{33}N_3O_9$: C, 62.2; H, 5.7; N, 7.4; OCH_3, 16.1; Mol. wt., 579.
Found: C, 62.1; 62.0; H, 6.4; 6.2; N, 7.8; OCH_3, 16.1; Mol. wt., 604.

5-(4'-Benzyloxyphenyl)3-methyl-2-oxazolidone. A solution of sodium methoxide was prepared from 3.4 g. (0.15 mole) of metallic sodium and 100 cc. of methanol and after addition of 26.9 g. (0.1 mole) of the non-methylated oxazolidone the mixture was evaporated to dryness *in vacuo*. The residue was suspended in 60 cc. of dry toluene and 18.9 g. (0.15 mole) of freshly-distilled methyl sulfate was added with stirring and cooling. The reaction was completed at 100° (one hour) and the neutral product treated with water and, after drying, freed from the solvent *in vacuo*. The remaining oil solidified spontaneously; from alcohol or methanol

crystals, m.p. 101–102°; yield, 21.5 g. (76%). In contradistinction to the non-methylated product, the substance is easily soluble in cold benzene.

Anal. Calc'd for $C_{17}H_{17}NO_3$: C, 72.0; H, 6.0; N, 4.9.
Found: C, 72.3; H, 6.0; N, 4.6.

5-(3'-Benzyloxyphenyl)-3-methyl-2-oxazolidone, from dilute alcohol, m.p. 65–66°; yield, 80.2%.

Anal. Calc'd for $C_{17}H_{17}NO_3$: C, 72.0; H, 6.0; N, 4.9.
Found: C, 71.6; H, 5.8; N, 4.8.

5-(4'-Methoxyphenyl)-3-methyl-2-oxazolidone, from ether or aqueous alcohol (1:1), crystals, m.p. 75°; yield, 78.1%.

Anal. Calc'd for $C_{11}H_{13}NO_3$: C, 63.8; H, 6.3; N, 6.8.
Found: C, 63.4; H, 6.2; N, 7.1.

5-(3'-Methoxyphenyl)-3-methyl-2-oxazolidone, is a yellow oil, which could not be induced to crystallize; it could not be distilled without partial decomposition. Yield, 80.6 g.

O-Benzyl-p-Sympathol. At room temperature, 2.8 g. (0.01 mole) of 5-(4'-benzyloxyphenyl)-3-methyl-2-oxazolidone was added to 5 cc. of 40% hydrochloric acid. With effervescence, a precipitate of fine needles appeared. The mass was cooled at 0°, diluted with 5 cc. of concentrated hydrochloric acid, filtered, and the solid washed with cold anhydrous ether. The *hydrochloride* was recrystallized from a small volume of slightly aqueous acetone, m.p. 149°, yield, 2.5 g. (85.0%).

Anal. Calc'd for $C_{16}H_{20}ClNO_2$: C, 65.4; H, 6.9; N, 4.8; Cl, 12.1.
Found: C, 65.3; H, 6.7; N, 4.7; Cl, 12.4.

The *free base* was obtained by the addition of a cold concentrqted ammonia solution to the concentrated aqueous solution of the hydrochloride. M.p. 104–105°; yield, quantitative.

Anal. Calc'd for $C_{16}H_{19}NO_2$: C, 74.7; H, 7.5; N, 5.5.
Found: C, 74.5; H, 7.6; N, 5.4.

p-Sympathol. (a) A mixture of 2.9 g. (0.01 mole) of O-benzyl-*p*-Sympathol hydrochloride and 6 cc. of 40% hydrochloric acid was heated at 40° for 30 minutes in a closed pressure-bottle. The salt dissolved and drops of benzyl chloride separated. The latter was extracted with ether and the aqueous solution treated at 0° with an excess of concentrated ammonia. The precipitate was washed with dilute ammonia and anhydrous ether and dried to give a grayish powder, m.p. 184–185°; yield, 1.5 g. (89.8%). The base gives a brown-violet color with ferric chloride. *Hydrochloride*, from alcohol with ether, m.p. 150–152°.

(b) The addition of 25 cc. of 40% hydrochloric acid to 14.1 g. (0.05 mole) of 5-(4'-benzyloxyphenyl)-3-methyl-2-oxazolidone gave a vivid evolution of carbon dioxide. After addition of a further 25 cc. of acid to the resulting crystalline mass, the latter was kept at 25–30° for three hours and diluted with water. The supernatant benzyl chloride was removed with ether and the free base precipitated as above. Yield, 6.8 g. (81.5%).

m-Sympathol. A mixture of 11.2 g. (0.04 mole) of 5-(3'-benzyloxyphenyl)-3-methyl-2-oxazolidone and 20 cc. of 40% hydrochloric acid was heated at 60° for five hours; from time to time, the solution was replenished by the introduction of some gaseous hydrogen chloride. After dilution with 20 cc. of water and extraction of the benzyl chloride with ether, the solution was chilled and ammonia added. The base, which precipitated, was filtered, dried, and dissolved in absolute alcohol. Treatment with gaseous hydrogen chloride and addition of ethyl acetate gave the crystalline *hydrochloride*. M.p. 140–145° (decomp.), yield, 5.3 g. (65.1%).

Anal. Calc'd for $C_9H_{14}ClNO_2$: C, 53.0; H, 6.9; N, 6.9; Cl, 19.4; Mol. wt., 204.
Found: C, 52.7; H, 6.7; N, 6.8; Cl, 16.9; Mol. wt., 209 (by titration).

The *free base* is a microcrystalline powder having no sharp decomposition point (120°).

Anal. Calc'd for $C_9H_{13}NO_2$: C, 64.7; H, 7.8; N, 8.4.
Found: C, 64.3; H, 7.0; N, 7.7.

O-Methyl-p-Sympathol. At room temperature, 20.7 g. (0.1 mole) of 5-(4'-methoxyphenyl)-3-methyl-2-oxazolidone was added to 50 cc. of concentrated hydrochloric acid. The resulting

solution was filtered from a trace of resinous material and neutralized at 0° with concentrated potassium carbonate solution. Then a slight excess of potassium *hydroxide* solution was added, which precipitated the crystalline base. It was washed with water and dried; m.p. 106–107°; yield, 16.5 g. (91.2%). The substance quickly decomposes on contact with air.

Anal. Calc'd for $C_{10}H_{15}NO_2$: C, 66.3; H, 8.3; N, 7.7.

Found: C, 65.8; H, 8.3; N, 7.4.

Demethylation of O-methyl-p-Sympathol. In a series of systematic experiments, mixtures of 5.4 g. (0.03 mole) of O-methyl-*p*-Sympathol and 13.0 g. (0.075 mole) of anilinium bromide were heated at temperatures between 180 and 235° (at higher temperatures, water was split off) for a definite period of time. The product was treated with 30% hydrochloric acid, filtered, and made alkaline with an excess of 20% potassium hydroxide solution. Extraction with ether removed aniline, some N-methylaniline, and unchanged starting material; finally the alkaline solution was saturated with carbon dioxide and the precipitated *p-Sympathol* filtered, washed, and dried.

TEMPERATURE (°C.)	TIME (HOURS)	YIELD OF *p*-SYMPATHOL	
		G.	%
180	4	0.5	10.0
200	4	0.5	10.0
225	2	2.0	40.0
225	4	3.4	68.0
225	6	2.8	56.0
235	2	2.0	40.0
235	4	1.8	36.0

O-Methyl-m-Sympathol. Hydrolysis of 5-(3'-methoxyphenyl)-3-methyl-2-oxazolidone (20.7 g.) with concentrated hydrochloric acid (50 cc.) occurred only at 50°. The solution was filtered and neutralized at 0° with concentrated potassium carbonate solution. A small excess of potassium hydroxide was added and the base extracted with ether. The base is a viscous, yellow oil, which did not crystallize. Yield, 15.0 g. (82%).

SUMMARY

1. *m*- and *p*-Sympathol were synthesized from *m*- and *p*-benzyloxybenzaldehydes by the Reformatsky reaction with ethyl bromoacetate, rearrangement of the azides of the β-hydroxyacids so obtained to the 5-aryl-2-oxazolidones, methylation and acid decomposition of the latter, and finally debenzylation of the O-benzyl-Sympathols with strong hydrochloric acid. The five-step synthesis gave an over-all yield of 20.5 and 37.6%, respectively.

2. The same method was applied to *m*- and *p*-methoxybenzaldehydes, but the demethylation in the last step proved unsatisfactory.

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