Experimental[13]

Ethyl β-Aminoglutarate Hydrochloride.—Absolute ethanol was saturated with dry ammonia and diethyl glutaconate[14] (15 g., 0.08 mole) was added in one portion. The temperature was maintained at 50–55° while ammonia was passed through the solution continually for 36 hours. Removal of ammonia and ethanol *in vacuo* afforded a slightly green-yellow oil which was taken up in 100 ml. of dry ether. Some gummy material remained; it was removed from the solution and washed with two 50-ml. portions of ether. The washings were combined with the ethereal solution and upon addition of dry hydrogen chloride an oil separated which soon crystallized. Dissolution in chloroform followed by reprecipitation with ether afforded a total of 12.0 g. (62%) of ethyl β-aminoglutarate hydrochloride, m.p. 83.5–84.5°.

Anal. Calcd. for $C_9H_{18}NO_4Cl$: C, 45.1; H, 7.52; N, 5.85. Found: C, 44.80; H, 7.58; N, 6.00.

β-Aminoglutaric Acid.—The crude amino ester was heated with excess 37% hydrochloric acid on the steam-bath for two hours. The solution was then concentrated *in vacuo* to a thick slurry, distilled water was added and the resulting solution evaporated *in vacuo* to dryness. Any unchanged glutaconic acid was extracted with boiling ether and the residue was then redissolved in water. The amino acid precipitated when the *p*H was adjusted to about 3.5 with base. Crystallization with water in the presence of Norite and Celite gave β-aminoglutaric acid, m.p. 295° dec. (lit.[2] value 276–280° dec.). An additional amount of the acid was obtained by extracting the Norite and Celite residue several times with boiling water. The total yield was 69%.

Anal. Calcd. for $C_5H_9O_4N$: C, 40.81; H, 6.17; N, 9.52. Found: C, 40.35; H, 6.27; N, 9.50.

β-Aminoadipic Acid.—Ammonia was passed continually through a reaction mixture containing 210 ml. of 28% ammonium hydroxide and 21.2 g. (0.2 mole) of 3-hexenedinitrile which had been recrystallized from both benzene and water. The temperature was raised slowly to 75° where it was maintained for about 24 hours. Ammonia and water were then removed *in vacuo* and this operation was repeated by adding and evaporating more water until all of the ammonia was removed. The remaining oil was hydrolyzed at reflux with 200 ml. of 18% hydrochloric acid in the presence of Norite and Celite. The precipitate was extracted with two 100-ml. portions of distilled water and the extracts combined with the filtrate from the hydrolysis. The solution then was concentrated *in vacuo* and this operation was repeated by adding additional amounts of water until the excess hydrochloric acid was removed. A thick slurry remained from which the isolation of the free amino acid was carried out in two ways:

(a) On dissolving the above slurry in water and on adjusting the *p*H to about 3.5 with base, a total of 13.1 g. (40.5%) of β-aminoadipic acid m.p. 190–193° dec., precipitated from the solution on standing for several weeks in a refrigerator. An additional 8% of slightly impure acid, m.p. 180–185° dec. (lit.[2,6] values 186–187° dec. and 189–190.5° dec.), was obtained on concentrating the mother liquor, adding a mixture of alcohol and ether and washing the precipitate free of ammonium chloride with ice-cold water, methanol and finally ether.

(b) The above slurry was dissolved in 200 ml. of distilled water and passed through a column of the basic ion-exchange resin, Amberlite IR-4-B. The eluate was basic and was concentrated until the excess ammonia was removed. The concentrate was diluted with water and the fresh solution passed again through the exchange resin. This procedure had to be repeated several times to remove all inorganic matter. In doing this a certain amount of Amberlite had been dissolved by the water and concentration of the final eluate gave a red-brown, gummy semi-solid. Trituration of this magma with 150 ml. of methanol at 25° left 18.7 g. of crude β-aminoadipic acid, m.p. 185–187° dec. Additional amounts of the acid were isolated by evaporating the aqueous methanolic solution and triturating the residue with fresh methanol. The total yield was 20.0 g. (62%).

Acknowledgment.—We are indebted to the Office of Naval Research for the financial support of this work and to E. I. du Pont de Nemours and Company for a generous sample of 3-hexenedinitrile.

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(13) All melting points are uncorrected.

(14) E. P. Kohler and G. H. Reid, THIS JOURNAL, **47**, 2807 (1925).

Dehydrocyclization of *o*-Ethyl-, *o*-Allyl- and *o*-Isopropylphenols

BY B. B. CORSON, H. E. TIEFENTHAL, J. E. NICKELS AND W. J. HEINTZELMAN

RECEIVED APRIL 21, 1955

Hansch and co-workers[1,2] recently described this dehydrocyclization reaction, but their yields were low (4–11% for benzofuran over palladium-on-charcoal and chromia-on-charcoal at 600–625°, 8–18% for 3-methylbenzofuran over chromia–copper-on-charcoal at 540–600° and 15–31% for 2-methylbenzofuran over palladium-on-charcoal and platinum-on-charcoal at 525–625°). They reported chromia–alumina to be unsatisfactory due to excessive decomposition of the phenols. On the contrary, we found chromia–alumina to be an effective catalyst, especially in the presence of diluent steam.

The use of diluent steam was found to be beneficial in these dehydrocyclizations, increasing the per pass yield of benzofuran from 16 to 48%, that of 2-methylbenzofuran from 31 to 48%, and that of 3-methylbenzofuran from 12 to 54%. The ultimate yields were increased proportionally. The use of diluent benzene vapor increased the per pass yield of benzofuran from 16 to 21% but decreased the yield of 3-methylbenzofuran from 12 to 7% (again the ultimate yields varied in similar manner). The superiority of steam over benzene vapor as diluent agrees with the findings of Nickels and Corson[3] in the dehydrogenation of ethylnaphthalene.

Certain by-products were identified: phenol and *o*-cresol from *o*-ethylphenol; phenol, *o*-cresol, *o*-ethylphenol and benzofuran from *o*-allyl- and *o*-isopropylphenols. Dihydrobenzofurans were not found.

The dehydrocyclization of these *o*-substituted phenols makes benzofuran and alkylbenzofurans readily available for the first time from easily obtainable starting materials.

Catalyst and Materials.—The chromia–alumina catalyst, 15% Cr_2O_3–85% Al_2O_3, was in the form of $1/8'' \times 1/8''$ pills, purchased from the Harshaw Chemical Co. *o*-Ethyl- and *o*-isopropylphenols were supplied by the Koppers Co., Inc. *o*-Allylphenol was prepared in 83% yield by the rearrangement of *o*-allylphenyl ether.

Apparatus, Analysis and Procedure.—The catalytic apparatus was similar to that described previously.[4] The starting materials and catalysates were distilled through a 27-plate glass column packed with glass helices, and analyzed by infrared absorption.

Procedure A.—The phenol was passed over the catalyst in the absence of diluent. The catalysate was dissolved in 500 cc. of ether, and the solution was extracted with 700 cc. of cold 10% aqueous sodium hydroxide in three portions.

(1) C. Hansch, W. Saltonstall and J. Settle, THIS JOURNAL, **71**, 943 (1949).

(2) C. Hansch, C. Scott and H. Keller, *Ind. Eng. Chem.*, **42**, 2114 (1950).

(3) J. E. Nickels and B. B. Corson, *ibid.*, **43**, 1685 (1951).

(4) J. E. Nickels, G. A. Webb, W. J. Heintzelman and B. B. Corson, *ibid.*, **41**, 563 (1949).

TABLE I

DEHYDROCYCLIZATION OF CERTAIN *o*-SUBSTITUTED PHENOLS OVER Cr_2O_3–Al_2O_3 AT 600°

1 sec. contact time; atmospheric pressure; 12-hour runs.

Phenol, g.	Diluent	Diluent: phenol, molal	Alkali-insoluble products: Benzofuran[a] G.	Benzofuran[a] Yield Per pass, %	Benzofuran[a] Yield Ultimate, %	2-Methylbenzofuran[b] G.	2-Methylbenzofuran[b] Yield Per pass, %	2-Methylbenzofuran[b] Yield Ultimate, %	3-Methylbenzofuran[c] G.	3-Methylbenzofuran[c] Yield Per pass, %	3-Methylbenzofuran[c] Yield Ultimate, %	Alkali soluble products Yield, g.: Phenol	*o*-Cresol	*o*-Ethylphenol	*o*-Allylphenol	*o*-Isopropylphenol
Dehydrocyclization of *o*-ethylphenol to benzofuran																
350	None	0	55	16	31	..	..	..	..	..	..	16	0	170	..	..
388	Water	10	174	48	59	..	..	..	..	..	..	25	0	83	..	..
328	Benzene	10	67	21	43	..	..	..	..	..	..	8	2	167	..	..
Dehydrocyclization of *o*-allylphenol to 2-methylbenzofuran																
415	None	0	58	16	16	126	31	32	..	..	..	4	12	0	11	..
389	Water	10	16	5	6	185	48	59	..	..	..	4	6	11	71	..
Dehydrocyclization of *o*-isopropylphenol to 3-methylbenzofuran																
410	None	0	9	2	3	..	..	..	49	12	14	134	6	13	..	48
430	Water	10	13	3	4	..	..	..	232	54	65	12	8	0	..	48
439	Benzene	10	4	1	1	..	..	..	31	7	10	115	1	1	..	112

[a] B.p. 67.5° (20 mm.), $n^{25}D$ 1.5635, d^{25}_4 1.0935, picrate m.p. 103–105°, dibromide m.p. 86–87°. [b] B.p. 192° (744 mm.), $n^{25}D$ 1.5460, d^{25}_4 1.0424, picrate m.p. 76–77°. [c] B.p. 86° (20 mm.), $n^{25}D$ 1.5533, d^{25}_4 1.0568, picrate m.p. 79–80°.

The caustic-extracted ether solution was washed with water, and dried over Drierite. Ether was removed under reduced pressure, and the residue was distilled. The caustic extract together with the water wash was acidified at 0° to *p*H 8 with carbon dioxide. The liberated phenolic material was extracted with ether, the extract was dried and concentrated, and the phenols were distilled.

Procedure B.—The phenol was passed over the catalyst in the presence of ten moles of steam per mole of phenol. After separating the water, the catalysate was worked up as described under A.

Procedure C.—The phenol was passed over the catalyst in the presence of ten moles of benzene per mole of phenol. The catalysate was worked up as described under A except that the solvent for the catalysate was benzene instead of ether.

Acknowledgment.—This work was done under the Monomer Fellowship maintained by Koppers Co., Inc., at Mellon Institute.

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The Separation of Substituted *threo*- and *erythro*-Phenylserines by Paper Chromatography. The Configuration of Arterenol and Epinephrine

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RECEIVED JANUARY 21, 1955

Evidence has been presented recently for the conversion of *threo*-β-(3,4-dihydroxyphenyl)-serine (DOPS) to the natural and pharmacologically active (−)-arterenol.[2] This relationship is the opposite of that proposed by Dalgliesh[3] who suggested that (−)-arterenol is formed enzymatically from the *erythro* diastereoisomer of DOPS. His assignment of the *erythro* configuration to this preparation of DOPS[4] is based on the analogous reaction of 4-nitrobenzaldehyde and glycine ethyl ester to yield the *erythro*-4-nitrophenylserine ethyl ester.[5,6] However, it is now recognized that the Erlenmeyer condensation usually results in a mixture of stereoisomers, the relative ratios of which depend on the conditions employed.[6–10] In addition the isomer obtained may depend to a large extent on the relative solubilities of the two forms.[6] Since *threo*-DOPS is less soluble than the *erythro* form,[10] it would not be surprising if the former were preferentially isolated from a mixture of the two isomers.[11] Bolhofer[10] examined the infrared spectra of the *erythro* and *threo* forms of phenylserine,[12] 3- and 4-hydroxyphenylserines,[10,13] DOPS[10] and threonine. On the basis of the presence of a band at 11.90–11.95 μ in the spectra of the *erythro* isomers and its absence in those of the *threo* compounds, the *erythro* configuration was assigned to the lower-melting, more soluble isomer of DOPS (m.p. 199–200° dec.) and the *threo* to the other isomer (m.p. 220–225° dec.). Bolhofer concluded that the latter isomer is the one which has been synthesized by Rosenmund and Dornsaft[14] and by Dalgliesh and Mann.[4]

In the course of studies on the biogenesis of arterenol, chromatographic methods were investigated for separating possible precursor amino acids from the corresponding amines obtained by enzymatic decarboxylation. With one of these procedures, it has been found possible to separate

(1) This work was done during the tenure of an Established Investigatorship of the American Heart Association. It was aided by grants from the Life Insurance Medical Research Fund (G-51-23) and the Los Angeles County Heart Association to Dr. W. G. Clark.

(2) (a) W. J. Hartman, R. S. Pogrund, W. Drell and W. G. Clark, THIS JOURNAL, **77**, 816 (1955); (b) E. Werle and J. Sell, *Biochem. Z.*, **326**, 110 (1954).

(3) C. E. Dalgliesh, *J. Chem. Soc.*, 3323 (1953).

(4) C. E. Dalgliesh and F. G. Mann, *ibid.*, 657 (1947).

(5) C. E. Dalgliesh, *ibid.*, 90 (1949).

(6) D. O. Holland, P. A. Jenkins and J. H. C. Nayler, *ibid.*, 273 (1953).

(7) E. D. Bergmann, H. Bendas and Ch. Resnick, *ibid.*, 2564 (1953); 1064 (1954).

(8) K. N. F. Shaw and S. W. Fox, THIS JOURNAL, **75**, 3417, 3421 (1953).

(9) M. Viscontini and E. Fuchs, *Helv. Chim. Acta*, **36**, 660 (1953).

(10) W. A. Bolhofer, THIS JOURNAL, **76**, 1322 (1954).

(11) As a demonstration of the ease of isolation of the *threo*-DOPS, it has been possible to isolate unreacted *threo*-DOPS in crystalline form from *in vitro* enzymatic reaction mixtures[2] whereas under similar conditions the *erythro* isomer could not be crystallized.

(12) W. A. Bolhofer, THIS JOURNAL, **74**, 5459 (1952).

(13) W. A. Bolhofer, *ibid.*, **75**, 4469 (1953).

(14) K. W. Rosenmund and H. Dornsaft, *Ber.*, **52**, 1734 (1919)