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.

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

BY WILLIAM DRELL[1]

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)

the diastereoisomers of various phenylserines (see Table I).[15] A sample of the DOPS prepared by Dalgliesh and Mann[4] and kindly furnished by Dr. Mann was compared and found to behave chromatographically identically with the compound designated by Bolhofer[10] as *threo*-DOPS. The correlation observed between R_f value and configuration (R_f *threo* < R_f *erythro*) in all of the examples investigated is supplementary evidence for assigning the *threo* configuration to this compound.

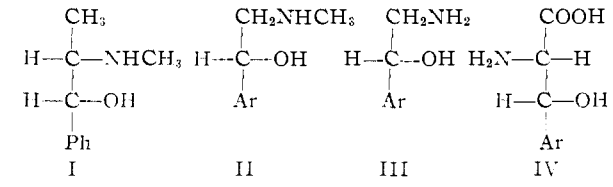
TABLE I

R_f VALUES OF PHENYLSERINES AND THE CORRESPONDING AMINES

Phenylserine	R_f	Amine	R_f
threo-3,4-Dihydroxyphenylserine[a]	0.18	Arterenol	0.51
erythro-3,4-Dihydroxyphenylserine[a]	.25		
3,4-Dihydroxyphenylserine[b]	.18		
threo-3-Hydroxyphenylserine[a]	.31	α-(Aminomethyl)-3-hydroxybenzyl alcohol[h]	.67
erythro-3-Hydroxyphenylserine[a]	.40		
threo-4-Hydroxyphenylserine[a,c]	.30	α-(Aminomethyl)-4-hydroxybenzyl alcohol[h]	.65
erythro-4-Hydroxyphenylserine[a,c]	.37		
threo-4-Nitrophenylserine[d,e]	.47		
erythro-4-Nitrophenylserine[c]	.52		
threo-4-Chlorophenylserine[c]	.56		
erythro-4-Chlorophenylserine[c]	.62		
threo-Phenylserine[f]	.43	α-(Aminomethyl)-benzyl alcohol[h]	.73
erythro-Phenylserine[g]	.49		

[a] Obtained through the courtesy of Drs. J. M. Sprague, K. H. Beyer and W. A. Bolhofer, Sharp & Dohme, Division of Merck and Co., Inc., West Point, Pa. [b] Obtained through the courtesy of Dr. F. G. Mann, University of Cambridge, Eng. [c] Obtained through the courtesy of Dr. D. O. Holland, Beecham Research Labs., Ltd., Betchworth, Surrey, Eng. [d] Obtained through the courtesy of Dr. E. D. Bergmann, Ministry of Defence, Scientific Dept., Tel-Aviv, Israel. [e] Obtained from Dr. Holland as the ethyl ester, which was hydrolyzed in acid. [f] Lack Chemical Co., New York. [g] Synthesized by Dr. R. I. Akawie by the method of Y. Chang and W. H. Hartung, THIS JOURNAL, **75**, 89 (1953). [h] Obtained through the courtesy of Dr. A. M. Lands, Sterling-Winthrop Research Institute, Rensselaer, N. Y.

Freudenberg[17] assigned to (−)-epinephrine the configuration II based on the analogous rotation of (−)-ephedrine (I)[18] the configuration of which has been well established from its relationship to mandelic acid[19,20] and alanine.[20,21] The relationship between (−)-epinephrine and (−)-arterenol seems to be established with a high degree of probability,[3] so that arterenol based on Freudenberg's assignment would be represented by III.



Since the mammalian decarboxylase which converts *threo*- and *erythro*-DOPS to arterenol specifically attacks the L-form,[22] it is possible to assign to natural (−)-arterenol the configuration III[23] based on its formation from *threo*-L-DOPS (IV). This configuration is the opposite of that proposed by Dalgliesh[3] which was based on its formation from the erroneously designated "*erythro*" DOPS. The configurational relationship between arterenol and ephedrine obviates the pharmacological problems raised by Dalgliesh's structure.

Experimental

The most satisfactory solvent mixture was isopropyl alcohol (70 parts), glacial acetic acid (5 parts) and water (25 parts). The descending boundary technique[24] was employed in an all-glass apparatus[25] designed to hold six sheets of 12" by 18" filter paper (Whatman #1). The irrigation time was 14–16 hours. After drying at room temperature the sheets were sprayed with ninhydrin,[26] potassium ferricyanide–hydrochloric acid,[27–29] or N,2,6-trichloro-*p*-benzoquinoneimine[30]–2% borate buffer (*p*H 9.5). The R_f values of the various substituted DL-phenylserines and some of the corresponding DL-amines are listed in Table I.

Acknowledgment.—The author is indebted to Dr. Richard I. Akawie for stimulating and helpful discussions.

ADDED IN PROOF.—G. Erhart and I. Hennig (*Chem. Ber.*, **87**, 892 (1954)) have prepared *threo*-DOPS by a method very similar to that of Bolhofer.[10] A sample graciously supplied by Dr. Erhart has been found to be chromatographically identical with Bolhofer's *threo*-DOPS. Bolhofer has shown that this method produces a mixture of the *threo* and *erythro* forms, which is contrary to the statement of Erhart and Hennig. These workers have also stated that the method of Rosenmund and Dornsaft[14] leads to compounds of the *erythro* series. With respect to DOPS at least, this is not the case since the product prepared by Dalgliesh and Mann[4] by Rosenmund's procedure has been shown in this paper to be the *threo* form. A sample of Dr. Erhart's *erythro*-DOPS (method of synthesis not given) has been found chromatographically to be a mixture of the two

(15) Solvents for separating *threo*- from *erythro*-phenylserine have been reported by Shaw and Fox[8] and Fones.[16] The solvent of Shaw and Fox is unsuited for 4-hydroxy- and dihydroxyphenylserines, since the alkaline conditions involved promote decomposition. Holland, *et al.*,[5] reported a solvent mixture useful for separating *threo*- and *erythro*-4-nitrophenylserines but not the corresponding 4-hydroxyphenylserines. Werle and Sell[2b] recently have reported that the *erythro* forms of the 3- and 4-hydroxy- and 3,4-dihydroxyphenylserines possess higher R_f values than the corresponding *threo* compounds in a solvent system similar to that reported here—isopropyl alcohol (70 parts), glacial acetic acid (20 parts) and water (10 parts).

(16) W. S. Fones, *J. Biol. Chem.*, **204**, 323 (1953).

(17) K. Freudenberg, "Stereochemie," Deuticke, Leipzig, 1932, pp. 697, 720.

(18) The phenyl group is represented by Ph and the 3,4-dihydroxyphenyl group by Ar.

(19) K. Freudenberg, E. Schoeffel and E. Braun, THIS JOURNAL, **54**, 234 (1932).

(20) W. Leithe, *Ber.*, **65**, 660 (1932).

(21) K. Freudenberg and F. Nikolai, *Ann.*, **510**, 223 (1934).

(22) See ref. 3 for discussion and ref. 2 for additional evidence for this specificity.

(23) No further attempt is made to assign "L" or "D" to II or III until the configuration of *threo*-DOPS is unequivocally established. However, it should be pointed out that the footnote on p. 3324 of ref. 3 is in error in that the structure of arterenol as written by Dalgliesh is "L" by the Cahn–Ingold sequence rule while the structure as written above is "D" by this rule.

(24) R. Consden, A. H. Gordon and A. J. P. Martin, *Biochem. J.*, **38**, 224 (1944).

(25) A rectangular Pyrex glass battery jar $15^{11}/_{32}$" by $14^{23}/_{32}$" by $19^{1}/_{4}$" high is available on special order from Corning Glass Works, Corning, N. Y.

(26) 0.5% in pyridine–acetic acid (90:10)—Dr. L. B. Rockland, private communication. The colored areas are more diffuse with this reagent than with the others listed, with correspondingly less accurate R_f values.

(27) W. O. James, *Nature*, **161**, 851 (1948).

(28) M. Goldenberg, M. Faber, E. J. Alston and E. C. Chargaff, *Science*, **109**, 534 (1949).

(29) G. M. Barton, R. S. Evans and J. A. F. Gardner, *Nature*, **170**, 249 (1952).

(30) H. G. Bray, W. V. Thorpe and K. White, *Biochem. J.*, **46**, 271 (1950).

forms. Further evidence for the correct assignment of configuration to *threo*- and *erythro*-DOPS has recently been presented by M. Winitz, S. M. Birnbaum and J. P. Greenstein (THIS JOURNAL, **77**, 3106 (1955)).

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Synthesis of Thiazinethiols

BY J. E. JANSEN AND R. A. MATHES

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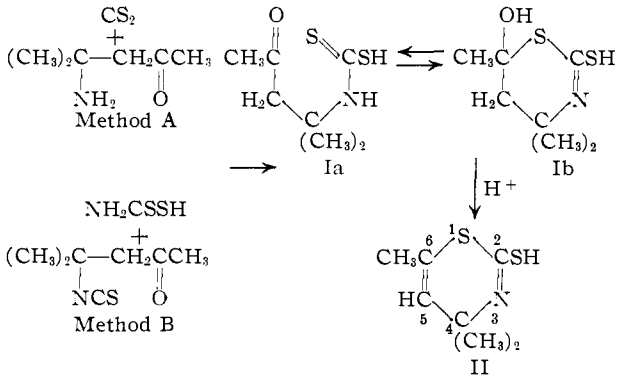
In a previous paper,[1] the synthesis of several alkyl substituted 6H-1,3-thiazine-2-thiols was described. These compounds were prepared by treating α,β-unsaturated ketones with dithiocarbamic acid to form stable intermediates which cyclized to thiazines on treatment with acids. Further investigation has resulted in the discovery of two new synthetic methods for the closely related 4H-1,3-thiazines.

In the first of these methods (method A), diacetoneamine (4-amino-4-methyl-2-pentanone) is treated with carbon bisulfide to give an intermediate, 2-methyl-4-oxopentyldithiocarbamic acid (I).[2] By treatment with sulfuric acid or acetic anhydride, I is converted to 4,4,6-trimethyl-4H-1,3-thiazine-2-thiol (II). It has been further demonstrated that the same sequence of reactions, with the formation of the same compounds, takes place in method B where 2-methyl-2-isothiocyano-4-pentanone and dithiocarbamic acid react together. Although only hydrogen sulfide (contributed by dithiocarbamic acid) is required for this reaction, attempts to prepare I by direct reaction of hydrogen sulfide and 2-methyl-2-isothiocyano-4-pentanone were unsuccessful.



The ring structure Ib is preferred for the intermediate since infrared absorption showed only a weak band at 5.5 to 6 μ which could be attributed to the carbonyl group. In addition, attempts to form a dinitrophenylhydrazone were unsuccessful. A comparison of ultraviolet absorption for I with that for the corresponding dihydrothiazine, 4,4,6-trimethyl-4,5-dihydro-4H-1,3-thiazine-2-thiol (III),[1] shows that they are in fairly close agreement (Table I). This further supports the ring structure Ib.

(1) J. E. Jansen and R. A. Mathes, THIS JOURNAL, **77**, 2866 (1955).
(2) S. Gabriel and T. Posner, *Ber.*, **27**, 1037 (1894).

Experimental[3]

TABLE I

Compound	Spectrum[a] Max.	Min.
I (meth. A)	^{a}285.5 = 60.5	^{a}257.8 = 10.6
	^{a}240.5 = 29.5	
I (meth. B)	^{a}285.5 = 65.1	^{a}257.7 = 12.9
	^{a}240.0 = 33.6	
II	^{a}296.0 = 69.4	
III[b]	^{a}286.5 = 77.6	^{a}258 = 10.2
	^{a}241 = 42.6	

[a] Determinations were made in methanol solution using a Beckman model DK-2 spectrophotometer. [b] Values are at a small variance with those previously reported (reference 1) where a Beckman model DU spectrophotometer was used.

2-Methyl-4-oxopentyldithiocarbamic Acid (I). Method A.—Diacetoneamine[4] (46 g., 0.4 mole), as a 60% aqueous solution, and 31 g. of carbon bisulfide (0.4 mole) were vigorously stirred at room temperature. After about an hour, a yellow, crystalline compound precipitated; agitation was continued for another hour. The solid was filtered, washed and dried to give 63 g. (83%). Purification was effected by recrystallization from acetone. An analytical sample melted at 114° dec.[5] After storage for about three weeks, I decomposed by partially liquefying and evolving hydrogen sulfide and carbon bisulfide.

Anal. Calcd. for $C_7H_{13}NOS_2$: C, 43.93; H, 6.85; N, 7.33. Found: C, 44.08; H, 6.87; N, 7.33.

In a less satisfactory alternative method, the experiment described was repeated using the same weight of reactants, and in addition 17 g. (0.4 mole) of sodium hydroxide. The red-colored solution obtained, which consisted of a solution of the sodium salt of I, was acidified. There was obtained 37 g. (49%) of I as determined by the unchanged melting point of a mixture.

4,4,6-Trimethyl-4H-1,3-thiazine-2-thiol (II).—To 147 g. (0.75 mole) of freshly prepared I, there was added 225 g. of 70% sulfuric acid. This mixture was heated to 85°, and the slurry was added to one liter of ice-water. The solid was filtered, washed free from acid and dried to give 129 g. (96%) of crude product melting at 114–118°. After recrystallization from carbon tetrachloride, an analytical sample melted at 120.5–121.5°.

Anal. Calcd. for $C_7H_{11}NS_2$: C, 48.51; H, 6.40; N, 8.08; S, 37.00; mol. wt., 173. Found: C, 48.81; H, 6.38; N, 7.99; S, 36.57; mol. wt., 177.

An identical compound was obtained by heating I with acetic anhydride to which a drop of sulfuric acid had been added.

2-Methyl-4-oxopentyldithiocarbamic Acid (I). Method B.—A mixture of 31.4 g. (0.2 mole) of 2-methyl-2-isothiocyano-4-pentanone,[6] 18 cc. (0.22 mole) of hydrochloric acid and 50 cc. of 50% ethanol was stirred vigorously while adding 26.5 g. (0.24 mole) of ammonium dithiocarbamate as a 45% aqueous solution. The addition time was about 20 minutes, and cooling was necessary to maintain the reaction mixture at room temperature. The product was present as an insoluble, red liquid and continued stirring for 3 hours converted the liquid to soft pellets. The solid was filtered, washed with water and further washed with petroleum ether which was effective in removing the oiliness. The crude product weighed 27 g. (71%), and melted at 114–114.5° after purification by recrystallization from acetone. This compound was shown to be the same as I prepared by method A by means of ultraviolet absorption spectra which were in good agreement.

Anal. Found: C, 44.23; H, 7.00; N, 7.57.

Since only hydrogen sulfide (contributed by dithiocar-

(3) All melting points are uncorrected.
(4) H. Gilman, Editor, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 196. For the purpose of this work, it was not necessary to prepare the oxalate as described. A water solution of diacetoneamine can be temporarily stored in a refrigerator with little change.
(5) Gabriel and Posner found m.p. 119–120°.
(6) R. A. Mathes, THIS JOURNAL, **75**, 1747 (1953).