gave an analytical sample, orange needles, m.p. 201–202° dec.

Behavior Studies.—The effect of compounds on behavior was determined in the following manner. Rats were conditioned on a variable interval (V.I.) positive reinforcement schedule, *i.e.*, bar pressing in a Skinner box at a steady medium rate which was rewarded automatically with food pellets. Faster or slower rates therefore represented less reward for effort and would indicate that behavior was not optimal. Animals were deprived of food and spent 50 min. each day in the test chamber. The mean rate of response during the test period was determined on 5 consecutive days for each individual animal. On the experimental day, the compound was administered intraperitoneally, and the increased (+) or decreased (−) response rates were computed as a percentage of the normal.

Blood Pressure.—Compounds were injected intravenously into anesthetized, whole male dogs 19–21 kg. at 10-min. intervals. Ten minutes after each injection of compound, a 1-mg. dose of serotonin creatinine sulfate was given to determine whether the animals' response remained constant to within 10% of an initial control injection given. Each compound was examined at least three times, either in the same or different animals. Long-term effects which changed the response of the animal to serotonin as anticipated were seen only with reserpine and methylreserpine. Effects of such compounds were either examined on separate dogs or at the end of the test series. Blood pressure changes were measured by means of an arterial cannula attached to a mercury manometer which operates a lever attached to a pen on a kymograph. Responses were recorded and blood pressure changes were measured in the usual manner.

Effect on Smooth Muscle.—Estrus rat uterus suspended in a Tyrode-Ringer solution muscle bath was used. The muscle was standardized to give consistent contractions to the reintroduction of a 10^{-8} *M* solution of serotonin creatinine sulfate. The potency of oxytocic activity was expressed as the molarity of a compound giving the same contraction as a 10^{-8} *M* solution of serotonin creatinine sulfate.

Antagonism to serotonin was measured by introducing the test compound into the muscle bath at concentrations starting at 10^{-6} *M*. This solution is allowed to equilibrate with the muscle for 2 min. at which time serotonin is added directly to the same bath so that it achieves a concentration of 10^{-8} *M*. Compounds reducing the normal muscle contraction of serotonin by at least 50% under these conditions were classified as antagonists.

Serotonin Release from Platelets.—Whole blood was collected by a siliconized syringe ("Monocote" treated needle) and transferred to siliconized centrifuge tubes containing EDTA-saline (1:10 w./v.). All samples were collected from "apparently normal" subjects, either laboratory and medical staff or subjects for pre-employment physicals at the Cleveland Clinic. The whole blood samples were centrifuged at 700 r.p.m. for 20 min. to prepare platelet-rich plasma samples. Platelet counts were made in the platelet-rich plasma by a bulk dilution procedure. Volumes of 2 ml. of platelet-rich plasma were incubated at 37° for 2 hr. (siliconized conical flasks), the compound under test being added in saline solution to a final concentration of 1 γ/ml. of incubation mixture. Controls (without incubation) were set up in each experiment. After incubation, the platelet-rich plasma samples were transferred to centrifuge tubes with ice-cold saline and centrifuged for 20 min. at 2500–3000 r.p.m. Supernatants were poured off, the tubes were drained, and the platelet pellets were resuspended in saline. Water was added to rupture the platelets and the proteins were precipitated with an equal volume of 20% trichloroacetic acid. Serotonin was assayed spectrophotofluorometrically[21] in the acid extract. Concentrations of serotonin were expressed as nanograms/10^{-9} platelets by reference to the platelet-rich plasma platelet count from which the platelet pellet was derived.

Acknowledgment.—The authors wish to thank Mrs. Martha Dattilo, Mrs. Catherine Rice, Mr. Jesse Green, and Mr. Rong An for their technical assistance.

(21) S. Udenfriend, B. Weissbach, and C. T. Cook, *J. Biol. Chem.*, **215**, 337 (1955).

Stereochemistry of *d*-3,4-Dimethyl-2-phenylmorpholine (Phendimetrazine)[1]

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Acid-catalyzed cyclization of *l-erythro*-N-(β-hydroxyethyl)ephedrine to *d-threo*-3,4-dimethyl-2-phenylmorpholine (I) proceeds with inversion of the benzylic carbon atom. Inversion appears to be caused by the relief of nonbonded destabilizing interaction present in the corresponding *erythro* morpholine (II). Accordingly, acid treatment of the *erythro* morpholine (II) caused partial inversion to the *threo* diastereoisomer (I) and was reflected in change of optical rotation and decreased inhibitory effect on liver monoamine oxidase.

A number of central-stimulating appetite-depressing drugs[2] have a common phenethylamine backbone, *e.g.*, amphetamine, ephedrine, α-diethylaminopropiophenone, etc. Compounds in which this "backbone" is part of a ring system appear to retain central-stimulating and appetite-depressing properties, *e.g.*, *dl*-3-methyl-2-phenylmorpholine (phenmetrazine)[3] and its *d*-N-methyl analog (phendimetrazine).[4,5]

d-3,4-Dimethyl-2-phenylmorpholine (phendimetrazine) was first prepared by the acid-catalyzed cyclization of N-(β-hydroxyethyl)-*l*-ephedrine.[6] We have investigated this reaction, established a *threo* configuration for the cyclization product,[1] and have thus substantiated Foltz and Witkop's interpretation[7] of Otto's findings.[6b] In the meantime, similar conclusions were reached by Clarke[8] (in the N-desmethyl series) and by Drefahl, *et al.*,[9] respectively (see Scheme I).

In accordance with Otto,[6b] acid-catalyzed cyclization of N-(β-hydroxyethyl)-*l*-ephedrine gave *d*-3,4-dimethyl-2-phenylmorpholine. The identical dextrorotatory morpholine was obtained when the same procedure was

(1) Presented at the 29th Congress of the Association Canadienne Française pour l'Avancement des Sciences, Oct. 28, 1961, Ottawa, Ontario.

(2) W. Modell, *J. Am. Med. Assoc.*, **173**, 1131 (1960).

(3) O. Thoma and H. Wick, *Arch. Exptl. Pathol. Pharmakol.*, **222**, 540 (1954).

(4) Phendimetrazine, Plegine®.

(5) (a) M. G. Stegen, T. Zsoter, H. Tom, and C. Chappel, *Toxicol. Appl. Pharmacol.*, **2**, 289 (1960); (b) R. E. S. Young, *Current Therap. Res.*, **3**, 350 (1961); (c) C. Ressler and S. Selmeider, *Clin. Pharmacol. Therap.*, **2**, 727 (1961); (d) K. Opitz and A. Loesser, *Gec. Med. Monthly*, **6**, 349 (1961); (e) L. Kersten and W. Klinger, *Arch. intern. Pharmacodyn.*, **138**, 209 (1962).

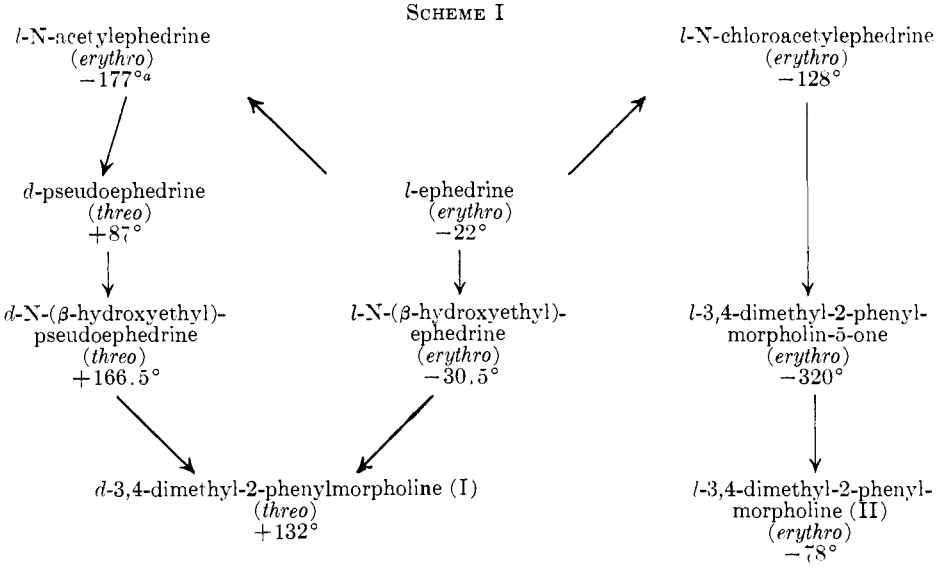
(6) (a) H. Siemer, A. Doppstadt, and M. Pickel, German Patent 1,135,460 (1962); *Chem. Abstr.*, **58**, 532*f* (1963); (b) W. G. Otto, *Angew. Chem.*, **68**, 181 (1956).

(7) C. M. Foltz and B. Witkop, *J. Am. Chem. Soc.*, **79**, 201 (1957).

(8) F. H. Clarke, *J. Org. Chem.*, **27**, 3251 (1962).

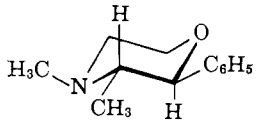
(9) G. Drefahl, M. Hartmann, and A. Skurk, *Chem. Ber.*, **96**, 1011 (1963).

SCHEME I



[a] Molecular rotation; *cf.* P. M. Jones and W. Klyne, *J. Chem. Soc.*, 871 (1960).

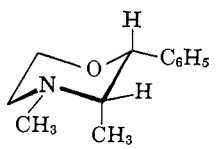
applied to the N-(β-hydroxyethyl) derivative of *d*-pseudoephedrine. Hence, the produced morpholine must have the *threo* configuration. This was corroborated by the n.m.r. spectrum. The coupling constant of 8.8 c.p.s. between the benzylic and its vicinal hydrogens reflects the diaxial conformation expected in a *threo* configuration (I).[10]



I (2*S*: 3*S*)[11]

It is likely that cyclization proceeds *via* a carbonium ion generated in the benzylic position. Destabilizing nonbonded interaction between the phenyl and methyl groups leads to inversion at the benzylic carbon, giving rise to the strain-free cyclized *threo* configuration. If indeed cyclization proceeds *via* a benzyl carbonium ion, treatment with strong acid of the thermodynamically less stable *erythro* isomer should cause inversion to its *threo* diastereoisomer.

To investigate this possibility *l-erythro*-3,4-dimethyl-2-phenylmorpholine was prepared from *l*-ephedrine *via* its *l*-N-chloroacetyl derivative which was cyclized and the resulting *l*-3,4-dimethyl-2-phenylmorpholin-5-one reduced with lithium aluminum hydride. The *erythro* configuration was reflected in the low coupling constant of 2.7 c.p.s. for the benzylic hydrogen as expected for an axial–equatorial conformation (II).[10]



II (2*R*: 3*S*)[11]

The inversion of II by concentrated sulfuric acid to its diastereoisomer I was detected by thin layer chromatography, by examining the resulting mixture with respect to its optical rotation and by its effect on liver monoamine oxidase (MAO) *in vitro*, respectively.

As shown in Table I, the optical rotation of a solution of the thermodynamically less stable *erythro* isomer (II) changed from levo- to dextrorotatory. As expected, the *threo* isomer (I) remained unchanged.

TABLE I

EFFECT OF CONCENTRATED H_2SO_4 ON THE OPTICAL ROTATION OF DIASTEREOISOMERS OF 3,4-DIMETHYL-2-PHENYLMORPHOLINE

	Optical rotation $[\alpha]D$,[a] deg.		
Diastereoisomer	0 hr.[b]	16 hr.[c]	64 hr.[c]
d-threo (I)	32.6	31.6	32.3
l-erythro (II)	−14.1	3.9	7.4[d]

[a] *c* 0.5. [b] In 10% aqueous H_2SO_4. [c] Solution of sample in concentrated H_2SO_4, diluted to 10% aqueous H_2SO_4. [d] About 46% inversion.

The inhibitory effect of *dl*-3-methyl-2-phenylmorpholine on MAO was first mentioned by Thoma and Wick.[3] Prompted by this observation, we have examined the effect of the corresponding N-methyl analogs on guinea pig liver MAO *in vitro*. As shown in Table II *erythro* isomers of ephedrine and of the corresponding morpholine (II) are distinctly more potent inhibitors of liver MAO than their *threo* diastereoisomers. It thus appeared that the inhibitory effect on MAO reflected the configuration of the benzylic carbon. Since this carbon is involved in the acid-catalyzed inversion, it should be possible to detect the inversion by measuring the effect of the equilibrated mixture on liver MAO. As expected (Table III), treatment with strong acid significantly reduced the capacity to inhibit MAO, thus indicating about 80% inversion.

The detected changes in optical rotation and in the inhibitory effect on MAO, respectively, appear to be in accord with the postulated role of the benzyl carbonium ion as intermediate in the acid-catalyzed cyclization of N-(β-hydroxyethyl)derivatives of ephedrine.

Biological Activity.[12]—In contrast to its *d-threo* diastereoisomer (I), in rats, an oral dose of 40 mg./kg. of

(10) (a) *Cf.* L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 86; (b) J. B. Hyne, *Can. J. Chem.*, **39**, 2536 (1961), and references cited therein.

(11) *Cf.* R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

(12) Unpublished results of Drs. Jane Stewart and F. Herr from our Department of Biology.

TABLE II

EFFECT OF CONFIGURATION ON INHIBITION OF GUINEA PIG LIVER MONOAMINE OXIDASE *in Vitro* BY DIASTEREOISOMERS OF EPHEDRINE AND 3,4-DIMETHYL-2-PHENYLMORPHOLINE (PHENDIMETRAZINE)

	% inhibition at final concn.				
Diastereoisomer	1×10^{-2} *M*	3×10^{-3} *M*	1×10^{-3} *M*	3×10^{-4} *M*	1×10^{-4}
d-threo-Pseudoephedrine	53 ± 9[a]	37	12 ± 12		
d-threo-Phendimetrazine	55 ± 3	25 ± 3	3 ± 2		
l-erythro-Ephedrine		64	59		17 ± 2
l-erythro-Phendimetrazine	87	81 ± 11	76 ± 3	62	26 ± 1

[a] Standard error.

TABLE III

EFFECT OF INHIBITION OF GUINEA PIG LIVER MONOAMINE OXIDASE *in Vitro* BY DIASTEREOISOMERS OF 3,4-DIMETHYL-2-PHENYLMORPHOLINE

Diastereoisomer	Compn. of mixture, %[a]						
d-threo (I)	100	95	85	75	50	25	0
l-erythro (II)	0	5	15	25	50	75	100
MAO inhibition, %	2	20	47	55	71	76	80

[a] Final concentration, 1×10^{-3} *M*.

l-erythro-3,4-dimethyl-2-phenylmorpholine (II) did not affect the food intake. No difference in LD_{50} between I[5a] and II was observed.

Experimental[13]

***l-erythro*-N-(β-Hydroxyethyl)ephedrine Acid Oxalate.**—*l*-Ephedrine (16.5 g., 0.1 mole) and 2-iodoethanol (18 g., 0.12 mole), in methanol (60 ml.), were stirred for 16 hr. with anhydrous K_2CO_3 (10 g., 0.73 mole). Methanol was evaporated under reduced pressure, the residue was taken up in water, and the unreacted ephedrine was removed[14] by acetylation according to Welsh.[15] The N-(β-hydroxyethyl) derivative of *l*-ephedrine was isolated as the acid oxalate salt, which after several recrystallizations from methanol, melted at 130–133°, $[\alpha]_D$ −10.2° (water), $[\phi]$ −30.5°.[13]

Anal. Calcd. for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: 55.56; N, 7.06; N, 4.58.

***l-erythro*-N-Acetylephedrine** was prepared from *l*-ephedrine according to Welsh,[15] and had m.p. 85–86°, $[\alpha]_D$ −85.5° ($CHCl_3$), $[\phi]$ −177°.

***d-threo*-Pseudoephedrine** was prepared from *l-erythro*-N-acetylephedrine according to Welsh,[16] and had m.p. 118°, $[\alpha]_D$ 52.7° (alc.), $[\phi]$ 87°.

***d-threo*-N-(β-Hydroxyethyl)pseudoephedrine acid oxalate** was prepared from *d*-pseudoephedrine as described for the *l-erythro* diastereoisomer and had m.p. 143–144°, $[\alpha]_D$ 55.7° (water), $[\phi]$ 166.5°.

Anal. Calcd. for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 56.16; H, 6.98; N, 4.48.

***d-threo*-3,4-Dimethyl-2-phenylmorpholine (I).**—The N-(β-hydroxyethyl) derivative of *l-erythro*-ephedrine or of *d-threo*-pseudoephedrine was dissolved in concentrated H_2SO_4 and left 16 hr. at room temperature. The solution was poured onto ice, rendered alkaline, and the free base was extracted with ether. The residue after removal of ether was dissolved in a hexane–benzene (1:1) mixture and passed through a column of aluminium oxide (activated alumina F 20, Alcoa). The hexane–benzene and benzene eluates were combined, the solvents were evaporated, and the residue was distilled, b.p. 78° (0.35 mm.), $[\alpha]_D$ 69.1° ($CHCl_3$), $[\phi]$ 132°. The hydrochloride salt had m.p. 191°, $[\alpha]_D$ 35.7° (H_2O), $[\phi]$ 112°.

***l-erythro*-N-Chloroacetylephedrine.**—*l*-Ephedrine hydrate (27 g., 0.15 mole) was added to a mixture of dichloromethane (250 ml.) and water (100 ml.) containing NaOH (8.4 g., 0.21 mole). The mixture was stirred and cooled to 0° and chloroacetyl chloride (24.2 g., 0.21 mole) was added dropwise; the cooling bath was removed and stirring was continued at room temperature for 3 hr. The dichloromethane layer was separated, dried (Na_2SO_4), and evaporated under reduced pressure. The oily residue (35 g.) solidified on addition of acetone. Recrystallized from chloroform–acetone it had m.p. 75–76°, $[\alpha]_D$ −53.1° ($CHCl_3$), $[\phi]_D$ −128°.

Anal. Calcd. for $C_{12}H_{16}ClNO_2$: Cl, 14.67; N, 5.80. Found: Cl, 14.50; N, 5.96.

***l-erythro*-3,4-Dimethyl-2-phenylmorpholin-5-one.**—To *l-erythro*-N-chloroacetylephedrine (14.9 g., 62 μmoles) dissolved in ethanol (60 ml.), a solution of potassium hydroxide (4.2 g., 75 μmoles) in ethanol (50 ml.) was gradually added, and the mixture was stirred at room temperature for 16 hr. The bulk of ethanol was evaporated under reduced pressure, and the residue was suspended in water and extracted with $CHCl_3$. The chloroform extract was washed with water and dried (Na_2SO_4), the solvent was evaporated under reduced pressure, and the residue was distilled, b.p. 118–122° (0.35 mm.), $[\alpha]_D$ −155.9° ($CHCl_3$), $[\phi]$ −320°.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.21; H, 7.37; N, 6.82. Found: C, 70.39; H, 7.86; N, 6.41.

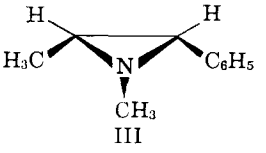
***l-erythro*-3,4-Dimethyl-2-phenylmorpholine (II).**—*l-erythro*-3,4-Dimethyl-2-phenylmorpholin-5-one (11 g., 53.5 μmoles) in ether (50 ml.) was gradually added to a stirred ice-cooled suspension of $LiAlH_4$ (2.5 g.) in ether (50 ml.), and the resulting mixture was stirred overnight at room temperature. Aqueous NaOH (25%) (50 ml.) was added gradually, and the ether layer was separated, washed with water, and extracted with aqueous H_2SO_4 (20%). This was made alkaline, the liberated base was extracted with ether, dried (Na_2SO_4), and treated with HCl, and the precipitated hydrochloride (8.5 g.) was recrystallized from an acetone–methanol–ethyl acetate mixture, m.p. 241–243°, $[\alpha]_D$ −13.6° (H_2O), $[\phi]$ −32° (free base, $[\alpha]_D$ −40.8° ($CHCl_3$), $[\phi]$ −78°).

Anal. Calcd. for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97; Cl, 15.57. Found: C, 63.30; H, 7.84; Cl, 15.48.

Monoamine oxidase activity or inhibition was measured as we have described previously,[17] *i.e.*, by the direct spectrophotometric method of Weissbach, *et al.*[18]

(13) The melting points were determined on a Kofler-like hot stage and are uncorrected. The optical rotations were determined at room temperature in a 10-cm. tube. All microanalyses were done by Mr. W. Turnbull and staff of our Microanalytical laboratory.

(14) Unreacted ephedrine was removed to avoid its conversion to *l*-1,2-dimethyl-3-phenylaziridine (III). Actually, R. Haberl [*Monatsh. Chem.*, **89**, 814 (1958)] has reported on the formation of III as by-product in the preparation of I according to Otto.[6b] We have repeated the preparation and have found (thin layer chromatography with MeOH–benzene, 1:10) that treatment with concentrated H_2SO_4 followed by exposure to strong base indeed produced III as by-product, but only if the unreacted *l*-ephedrine was not removed by acetylation. Unreacted *l*-ephedrine is most likely first inverted to the sulfate ester of *d*-pseudoephedrine [H. Emde, *Helv. Chim. Acta*, **12**, 399 (1929)] which on treatment with base gives the *cis*-*l*-aziridine (III), b.p. 94–98° (23 mm.), $[\alpha]_D$ −127.2° (alc.) [*cf.* K. Tanaka, *J. Pharm. Soc. Japan*, **70**, 212 (1950); *cf. Chem. Abstr.*, **44**, 7273*a* (1950)], $[\phi]$ −187°. *cis* Configuration is reflected in the coupling constant of 5.4 c.p.s. for the benzylic hydrogen. This value is in agreement with the coupling constants for *cis* hydrogens in cyclopropanes (8.0–11.2 c.p.s.) [D. J. Patel, M. E. H. Howden, and J. D. Roberts, *J. Am. Chem. Soc.*, **85**, 3218 (1963)] and in substituted ethylene oxides (4.0–5.2 c.p.s.) [C. A. Reilly and J. D. Swalen, *J. Chem. Phys.*, **32**, 1378 (1960); **35**, 1522 (1961)].



III

(15) (a) L. H. Welsh, *J. Am. Pharm. Assoc.*, **36**, 373 (1947); (b) *ibid.*, **41**, 545 (1952).

(16) L. H. Welsh, *J. Am. Chem. Soc.*, **69**, 128 (1947).

(17) D. Dvornik, M. Kraml, J. Dalac, H. Tom, and T. Zsoter, *Biochem. Pharmacol.*, **12**, 229 (1963).

(18) H. Weissbach, T. E. Smith, J. W. Daly, B. Witkop, and S. Udenfriend, *J. Biol. Chem.*, **235**, 1160 (1960).

Sulfuric Acid Treatment of Phendimetrazine Diastereoisomers.—Samples (50 mg.) of *d-threo-* (I) and *l-erythro*-3,4-dimethyl-2-phenylmorpholine (II) were dissolved in concentrated H_2SO_4 (0.5 ml. each) and left standing at room temperature. After 15 and 64 hr., respectively, the samples were diluted with water to make a 10% solution, and the optical rotation was determined (Table I). The 64-hr. samples (in triplicate) were rendered alkaline, the free bases were extracted with ether, dried (Na_2SO_4), and treated with HCl, and the mixture was evaporated to dryness under reduced pressure. The residue[19] was dissolved in water to make a final concentration of 1×10^{-3} *M*, and the effect on guinea pig liver MAO was determined *in vitro*.[17] The inhibition was 50 ± 4%. Compared to the values listed in Table III, such a degree of inhibition corresponds to a mixture consisting of about 80% of the *threo* diastereoisomer.

Acknowledgment.—We wish to thank Dr. Frank A. L. Anet for the n.m.r. spectra and their interpretation and Jean Dubuc and his group, respectively, for the MAO assays.

(19) Thin layer chromatography [methanol–benzene, 1:10; sprayed with concentrated H_2SO_4 followed by Draggendorf's reagent as modified by Munier and Macheboeuf (*cf.* K. Randerath, "Dünnschichtchromatographie," Verlag Chemie, Weinheim, 1962, p. 128)] indicated a mixture consisting of the unchanged *erythro* (R_f 0.25) and the newly formed *threo* (R_f 0.33) isomers.

The Synthesis of Thyromimetic Substances and Potential Inhibitors of Thyroxine[1]

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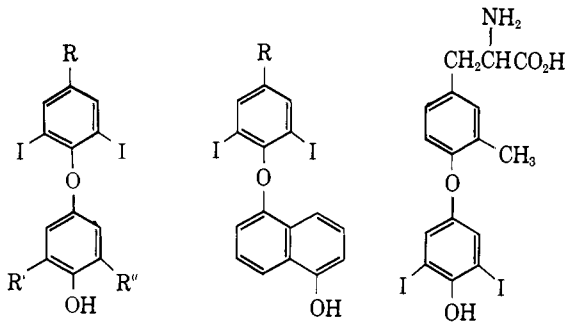
Received January 9, 1965

The syntheses of eight novel analogs of thyroxine are reported. Advantages of using the monobenzoate esters of requisite hydroquinone intermediates in the Glaxo method are described. Preliminary testing data for 3,5-diiodo-3′-methyl-L-thyronine and the corresponding *t*-butyl compound are noted. R_f values for the thyroxine analogs are recorded.

In a previous communication,[3] the basis for our approach to the synthesis of thyroxine analogs and potential inhibitors of thyroxine was summarized. The syntheses of eight novel analogs, Ia–d, IIa–c, and III are now reported; the synthetic scheme for Id was briefly communicated previously.[3]

In view of current theories of thyroxine action and results of testing, the choice of compounds was made on the basis of the postulated relation between activity and presumed ability to form a quinoid structure,[4] the easy oxidation of *t*-butylhydroquinone, the tendency of highly hindered phenols to be converted to cyclohexadienone derivatives, and the thyroxine-like activities of methyl analogs in the tadpole.[3,5] For further references, the monographs of Pitt-Rivers and Tata[6] and the papers of Lissitzky and Bouchilloux[7] are also of direct interest in connection with biochemical activities of substances related to those of the present study.



I II DL-III

Ia, R = L-$CH_2CH(NH_2)COOH$; R′ = CH_3; R″ = H
b, R = L-$CH_2CH(NH_2)COOH$; R′ = *t*-C_4H_9; R″ = H
c, R = CH_2CH_2COOH; R′ = *t*-C_4H_9; R″ = H
d, R = CH_2CH_2COOH; R′ = R″ = *t*-C_4H_9

IIa, R = CH_2COOH
b, R = CH_2CH_2COOH
c, R = L-$CH_2CH(NH_2)COOH$

Pittman, Shida, and Barker[8] found that Ia (the 3′-methyl analog of triiodothyronine) was 44% as active as L-triiodothyronine and twice as active as L-thyroxine in basal metabolic tests in thyroidectomized rats. The testing of two of the analogs prepared in the present study was carried out with Mr. Roy G. Robinson, but only in tadpoles. Using the method for detecting the relative rates of the induced metamorphosis of *Rana catesbeiana* tadpoles developed by Bruice, Winzler, and Kharasch,[5d] it was found that the 3′-methyl analog (Ia), as well as the 3′-*t*-butyl analog (Ib), had activities equivalent to that of L-thyroxine. Thus, the biological effects of these 3′-alkyl analogs as thyronimetic agents appears to be substantiated in these preliminary screenings and is of particular interest in view of earlier considerations on the activities of alkyl-substituted thyronines.[5d,8] It is of special interest to note that a single alkyl group in the prime ring (in place of iodine) exerts a definite positive effect on activity, since it is known

(1) This study was supported in part by Grant A-703 from the National Institutes of Health and in part by supporting grants from the Travenol Laboratories, Skokie, Ill., and the Upjohn Company, Kalamazoo, Mich. An independent synthesis and a rat antigoiter assay of L-3,5-diiodo-4-(3-*t*-butyl-4-hydroxyphenoxy)phenylalanine (Ib) is reported by E. C. Jorgensen and J. A. W. Reid, *J. Med. Chem.*, **8**, 533 (1965).

(2) To whom inquiries should be addressed.

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