crystallized. It was rich in the B racemate. Two more recrystallizations from EtOH afforded pure B racemate: yield, 8.2 g (31%); mp 178–179.5°. *Anal.* ($C_{17}H_{26}N_2O_2 \cdot C_2H_2O_4$) C, H, N.

This oxalate salt was converted to the free base. The formyl group was removed by the technique described in method F. The usual work-up gave the B racemate (**63**) of 2-(*o*-aminophenethyl)-5-ethyl-1-methylpiperidine (5.5 g, 98%) as an oil which was pure enough for use as an intermediate.

The mother liquor from the preparation of the oxalate salt was evaporated. The residue was recrystallized from *i*-PrOH. A solid (1.8 g) was obtained which tlc indicated to be a mixture of A and B racemates. The solid was discarded. Evaporation of the mother liquor gave a crystalline residue rich in the A racemate. It was converted to 6.7 g of free base. The formyl group was removed by the technique described in method F to give a crystalline dihydrochloride. Recrystallization from *i*-PrOH and then EtOH–*i*-Pr_2O gave material which was approximately 90% A and 10% B (tlc, silica gel, EtOH + trace NH_4OH). *Anal.* ($C_{16}H_{26}N_2 \cdot 2HCl$) H, N; C: calcd, 60.18; found, 57.86. This salt was converted to 3.3 g (19%) of free base. It was pure enough for use as an intermediate.

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β-Adrenergic Blocking Agents. 14. Microbiological Reduction of Isopropylaminomethyl 2-Naphthyl Ketone to (*R*)-(−)-2-Isopropylamino-1-(2-naphthyl)ethanol and Related Reductions

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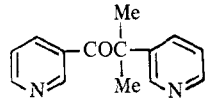
Isopropylaminomethyl 2-naphthyl ketone (**3**) is reduced by *B. theobromae* to (*R*)-(−)-2-isopropylamino-1-(2-naphthyl)ethanol (**4**) of optical purity 89% in low (6.5%) yield. The major metabolic pathway is *via* 2-naphthylglyoxal (**9**), which leads to the isolable products (*R*)-(−)-2-naphthylglycolic acid (**6**) and (*S*)-(+)-(2-naphthyl)ethane-1,2-diol (**5**), both of optical purity >95%.

It has been shown previously that 2-methyl-1,2-di(3-pyridyl)-1-propanone (**1**) (metyrapone, SU-4885) is reduced with ~99% stereospecificity by the organism *Botryodiplodia theobromae Pat.* to give (−)-2-methyl-1,2-di(3-pyridyl)-1-propanol (**2**) in good yield.[1] The absolute configuration of the product is not known. It was of interest to find out whether this organism would convert isopropylaminomethyl 2-naphthyl ketone (**3**)[2] to an optically active form of the β-adrenergic blocking agent 2-isopropylamino-1-(2-naphthyl)ethanol (**4**)[2] (pronethalol). The pharmacologically active (−) isomer of pronethalol has the *R* configuration.[3]



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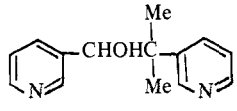

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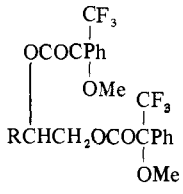
The ketone **3** was incubated with the organism in shake flasks. Fermentation was stopped after 2 days when samples monitored by tlc showed the absence of substrate. Extraction of the fermentation and separation of the products gave one basic, one neutral, and one acidic metabolite. The basic metabolite, which proved to be pronethalol **4**, gave a hydrochloride, $[\alpha]^{21}D$ −46.8°. Optically pure (−)-pronethalol hydrochloride has $[\alpha]^{21}D$ −52.6°,[3] and so the material produced by the organism had an optical purity of 89%,[4] *i.e.*, an *R*-(−) isomer content of 94%. The yield was low (6.5%). The neutral metabolite was (+)-1-(2-naphthyl)ethane-1,2-diol (**5**), $[\alpha]^{21}D$ +32.4°, of uncertain optical purity. The acid metabolite (≃16% yield) was (−)-2-naphthylglycolic acid (**6**), $[\alpha]^{21}D$ −142.2°, also of uncertain optical purity. In a separate experiment 2-naphthoic acid (**7**) was identified as a minor metabolite. The two acidic metabolites are produced from pronethalol by the guinea pig, rabbit, and rat.[5] Diols are known to be metabolites of 1-aryl-2-aminoethanols such as epinephrine.[6]

Comparison of the optical data for the diol **5** and the glycolic acid **6** with data for the phenyl analogs, 1-phenylethane-1,2-diol (**5**, R = phenyl) and mandelic acid (**6**, R = phenyl), showed that the diol and the acid differed in absolute configuration. (*R*)-(−)-Mandelic acid, $[\alpha]^{24}D$ −152.3°, is reduced by $LiAlH_4$ to (*R*)-(−)-1-phenylethane-1,2-diol, $[\alpha]^{25}D$ −39.7°, without racemization.[7] The fermentation glycolic acid **6** and the fermentation diol **5** differ in sign of rotation. That they differ in absolute configuration was confirmed by converting the acid **6**, $[\alpha]^{21}D$ −142.2°, to its methyl ester, $[\alpha]^{21}D$ −133.1°, which by $LiAlH_4$ reduction gave the chemically produced diol **5**, $[\alpha]^{21}D$ −33.7°. Although the optical data were not all measured in the same solvent, the sign and magnitude of the optical rotations and the considerable shift in the same direction for the change acid → diol strongly suggest that (−)-2-naphthylglycolic acid and (−)-1-(2-naphthyl)ethane-1,2-diol have the *R* con-

figuration.[8] Therefore, the fermentation (+)-diol **5** has the *S* configuration and it appears to arise predominantly by a route which does not involve (*R*)-(−)-pronethalol (**4**) and by which the stereochemistry is fixed at the new chiral center in the opposite sense to that fixed by an isopropylaminomethyl substituent.

The optical purity of (*S*)-(+)-diol **5** ($[\alpha]^{21}D$ +32.2°) has been estimated by nmr. Racemic **5** was converted to a mixture of two diastereoisomeric diesters **8**[7] from which



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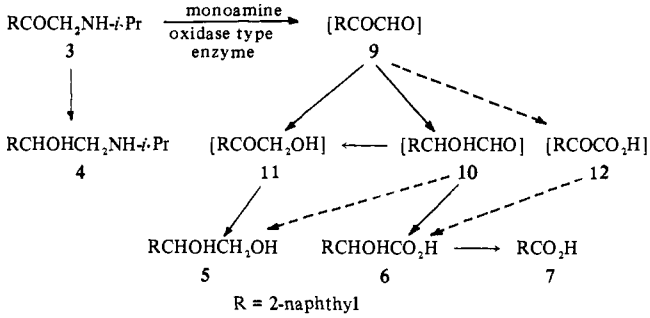
contaminants were removed by preparative tlc. The mixture, which was not otherwise separated, showed two four-line patterns centered at τ 3.63 and 3.98. (*S*)-(+)-**5**, treated in the same way, showed only one four-line pattern centered at τ 3.98. By comparison of the τ 3.63 region with the ^{13}C satellite peaks of the τ 3.98 signals in a slow-scan spectrum, the material is estimated to be >95% optically pure. Thus, the (*R*)-(−)-glycolic acid **6** of $[\alpha]^{21}D$ −142.2° is also >95% optically pure.

Various possible pathways from the ketone **3** to the diol **5** and the acid **6** which do not involve pronethalol **4** are shown in Scheme I.

Scheme I



Fermentation of 2-naphthylglyoxal (**9**) gave (*R*)-(−)-2-naphthylglycolic acid (**6**), $[\alpha]^{21}D$ −141°, and (*S*)-(+)-1-(2-naphthyl)ethane-1,2-diol (**5**), $[\alpha]^{21}D$ +32.2°, and therefore they do not both arise directly from the glycolaldehyde **10**. Tlc and glc monitoring confirmed that the hydroxymethyl ketone **11** was an intermediate.

Fermentation of 2-naphthylglyoxylic acid **12**[9] gave only traces of diol **5** and glycolic acid **6** by tlc, which were too small to isolate, and therefore the assumption was made that this acid is not on a major metabolic pathway. This experiment is not further reported. Fermentation of the hydroxymethyl ketone **11** gave the (*S*)-(+)-diol **5**, $[\alpha]^{21}D$ +30.2°, in good yield and neither 2-naphthylglycolic acid (**6**) nor 2-naphthoic acid was detected. The acetate of **11** gave the diol **5**, $[\alpha]^{21}D$ +2.3°, in good yield, and again no trace of **6** or **7** was seen. Thus, the diol **5** is not converted to the glycolic acid **6** or naphthoic acid **7**, and **11** is not oxidized to **9** or rearranged to **10**.

Aminomethyl ketones are known to hydrolyze under weakly acid conditions.[10] Thus, under fermentation conditions at pH 5.5, the ketone **3** could give the glycolaldehyde **10** and thence **9**, **6**, and **7** by air oxidation or **11** by acid-catalyzed rearrangement.† A control experiment carried out in culture medium at pH 5.5 but without organism showed that traces of 2-naphthylglyoxal **9** were produced during 48 hr. Quantitative estimation was difficult because of contamination with medium constituents, and the experiment is not further reported. Another control experiment in aqueous solution at pH 5.5 was carried out, this time followed by reduction with borohydride to facilitate isolation of products. Amino ketones are known to self condense under alkaline conditions.[11] The amount of pronethalol isolated proved that 91% of **3** was present at the end of the control experiment. The amount of diol **5** isolated (~6%) was a measure of the 2-naphthylglyoxal (**9**) which had been present. The acid fraction (1.5%) was negligible. Thus, nonenzymic hydrolytic removal of the isopropylamino group of **3** can occur, but it is unlikely to account for more than 10% of the products.

The facts collected so far can be explained if the pathways shown by full lines in Scheme I operate, except that from **10** to **11** which is discussed later. The isopropylaminomethyl substituent of **3** and the formyl substituent of **9** are considered to direct the stereochemistry at the adjacent new chiral center in the *R* sense to give (*R*)-(−)-pronethalol (**4**) and (*R*)-glycolaldehyde (**10**, not isolated), respectively, and the hydroxymethyl substituent of **11** is considered to direct it in the *S* sense to give (*S*)-(+)-diol **5**. The similar rotations of (*S*)-diol **5** produced from **3**, **9**, and particularly **11** suggest that little or no **5** arises directly from (*R*)-glycolaldehyde (**10**). The diol **5** of low positive rotation (+2.3°) obtained from the acetate of **11** probably arises in part by hydrolysis of the acetate of **11** and reduction thereof in the *S* sense and in part by direct reduction of the acetate in the *R* sense, followed by hydrolysis.

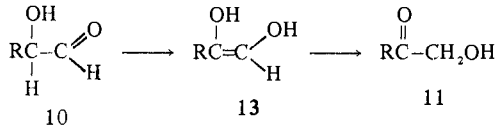
The metabolism of (*R*)-(−)-pronethalol (**4**), (*S*)-(+)-pronethalol, and racemic pronethalol by *B. theobromae* was studied to check that the (*R*)-(−)-**4** obtained from **3** was produced by a stereospecific reduction and not by selective metabolic removal of (*S*)-(+)-**4** produced by a nonspecific reduction. All three compounds proved to be poor substrates; they were slowly metabolized during 7 days and there was no selectivity for one isomer. Thus, the reduction of **3** is stereospecific and by implication the major pathway to **5**, **6**, and **7** is not *via* **4**. In contrast, **3** was completely metabolized in less than 40 hr and **9** and **11** within a few hours.

The expected pronethalol metabolites **5**, **6**, and **7** were formed but did not accumulate despite attempts in several experiments, suggesting that the initial attack on pronethalol was rate determining. Recovered pronethalol samples had the same rotation as the substrate indicating that neither nonselective oxidation to **3**, and some reduction thereof in the *R* sense to (*R*)-(−)-**4**, nor selective oxidation to **3** had occurred. In support of this view, no sign of **3** was seen by tlc monitoring of the fermentations.

It was not possible to isolate any pure glycolic acid **6** from these experiments because there was so little present. (*S*)-(+)-Pronethalol gave (*S*)-(+)-diol ($[\alpha]^{21}D$ +30.5°) as expected, but surprisingly (*R*)-(−)-pronethalol and racemic pronethalol also gave (*S*)-(+)-diol ($[\alpha]^{21}D$ +32.9 and +31.6°). The amounts were very small. The change in absolute configuration when (*R*)-(−)-pronethalol is metabolized to (*S*)-(+)-diol is best accounted for by considering that the *R* form of the glycolaldehyde **10** (and maybe the *S* form as well) can be isomerized to **11**, a change which involves loss

† Kindly pointed out by a referee.

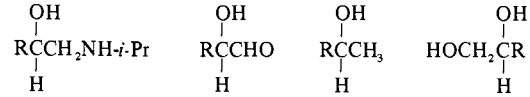
of chirality. Reduction of **11** would give (*S*)-(+)-diol. The conversion of **10** to **11** requires an enolization step to **13** followed by deenolization in a different sense, and there is good chemical precedent for it when R = Ph.[12]



10 **13** **11**

The metabolism of **3** by *B. theobromae* can be summarized as follows. The major pathway is *via* the glyoxal **9**. Reduction of the aldehyde carbonyl group of **9** gives **11** which is reduced to (*S*)-(+)-**5**. There is no evidence that **11** is oxidized to **9** or rearranged to **10**. Reduction of the ketone carbonyl group of **9** gives (*R*)-**10** (not isolated) which is oxidized to (*R*)-(−)-**6** and then to **7**. The evidence suggests that (*R*)-**10** is not reduced to (*R*)-(−)-**5**. The metabolism of **3** to (*R*)-(−)-**4** is a minor pathway as judged by the low yield and the fact that (*R*)-(−)-**4** is a poor substrate. Experiments on the metabolism of (*R*)-(−)-**4** and (*S*)-(+)-**4** suggest that (*R*)-**10** can be isomerized to **11**. The optical purity of the products (*R*)-(−)-**4**, (*S*)-(+)-**5**, and (*R*)-(−)-**6**, in which chirality was introduced by reduction of a carbonyl group to a secondary alcohol group, is 89% or greater.

Finally, the microbiological reduction of methyl 2-naphthyl ketone (**14**) to 1-(2-naphthyl)ethanol (**15**) was examined to see how a methyl group directs reduction at the adjacent prochiral center and to compare with Siewinski's[13] results. The latter reported that *Rhodotorula mucilaginosa* reduces **14** to (*S*)-(−)-**15**, [α]D −38°. *B. theobromae* metabolized **14** slowly and incompletely to give (*S*)-(−)-**15**, [α]D −13.7°, corresponding to material of ~30% optical purity, based on [α]D −44.9° for the pure enantiomer.[14] Siewinski deliberately tried to enhance enantiomeric homogeneity by fractional crystallization, whereas we have deliberately tried not to in order to assess the capabilities of the organism. The small nonpolar methyl group directs much less stereospecifically than the larger and more polar isopropylaminomethyl, formyl, and hydroxymethyl groups. It should be noted that although (−)-**15** has the *S* configuration, hydrogen has been added to the carbonyl group of **14** from the same side of the molecule as for **3** and **9** which gave products **4** and **10** of *R* configuration. The *S* configuration of **15** is a consequence of the sequence rule.[15] Hydrogen *is* added from the opposite side when **11** is converted to (*S*)-**5**.



(*R*)-**4** (*R*)-**10** (*S*)-**15** (*S*)-**5**

Experimental Section

Tlc was carried out using SiO_2 gel GF-254 plates developed in one of the solvent systems: (a) EtOH–NH_4OH, 99:1; (b) EtOAc; (c) 40% HCO_2H–EtOAc, 1:99. Products were detected by viewing in uv light (254 and 350 mμ). Optical rotations were carried out in EtOH.

Microbiological Transformation of Isopropylaminomethyl 2-Naphthyl Ketone (3). (a) The organism was grown in a nutrient solution containing Cerelose (dextrose monohydrate, 3%), ammonium tartrate (0.75%), KH_2PO_4 (0.2%), $MgSO_4 \cdot 7H_2O$ (0.05%), minor elements concentrate[16] (0.1%), and yeast extract (0.1%), adjusted to pH 5.5 before sterilization. Flasks containing sterilized nutrient solution (200 ml) were incubated with *B. theobromae Pat.* and then incubated on a rotary shaker at 25°. After 5 days **3**·HBr[2] (100 mg) in MeOH (2.5 ml) was added to each flask. Two days later the contents of 20 flasks were combined, adjusted from pH 5.5 to pH 2.0 with concentrated HCl, and then extracted five times with EtOAc (250 ml each time). The aqueous layer was then adjusted to pH 11 with NaOH (8 *N*) and extracted three times with EtOAc (250 ml each time). The pH 2 extract was separated into an acid fraction (400 mg), soluble in 5% $NaHCO_3$, and a neutral fraction (530 mg). The pH 11 extract was separated into a basic fraction (105 mg), soluble in 1 *N* HCl, and a neutral fraction (820 mg). The basic fraction, **4**, R_f 0.51 (system a), was treated with Et_2O–HCl to give (*R*)-(−)-**4**·HCl: mp 205–207° from MeOH–EtOAc (110 mg, 6.5%); $[\alpha]^{21}D$ −46.8° (*c* 1.06). The neutral fractions consisted of **5**, R_f 0.37 (racemic standard mp 134° prepared by reduction of **9** by $NaBH_4$, lit.[17] mp 134°) and less polar materials, R_f 0.50 and 0.67 (system b). Purification by preparative tlc gave (*S*)-(+)-**5**: mp 127–129° from EtOAc (600 mg, 49%); $[\alpha]^{21}D$ +32.4° (*c* 0.98); *m/e* 188. The acid fraction consisted of **6**, R_f 0.41 (racemic standard[18]), and a trace of less polar material, R_f 0.56, which in this case was not 2-naphthoic acid, R_f 0.63 (system c). Purification by preparative tlc gave (*R*)-(−)-**6**: mp 160–161° from $CHCl_3$ (210 mg, 16%); $[\alpha]^{21}D$ −142.2° (*c* 0.98); *m/e* 202.

(b) In a separate fermentation using **3**·HBr (600 mg) as substrate, the acid fraction (94 mg) consisted of a mixture of 2-naphthylglycolic acid, R_f 0.41, and 2 naphthoic acid, R_f 0.67 (system c). Separation by preparative tlc gave 2-naphthylglycolic acid (15 mg) and 2-naphthoic acid: mmp 181° from EtOAc–petroleum ether (bp 60–80°) (16 mg); *m/e* 172.

Conversion of (*R*)-(−)-2-Naphthylglycolic Acid (6) to (*R*)-(−)-2-Naphthylethane-1,2-diol (5). (*R*)-(−)-**6** (160 mg from the above experiment), treated with Et_2O–CH_2N_2, gave the Me ester as an oil: R_f 0.60 (system c); $[\alpha]^{21}D$ −133.1° (*c* 1.03). A solution of Me ester (155 mg) in Et_2O (10 ml) was added to a stirred suspension of $LiAlH_4$ (100 mg) in Et_2O (30 ml). The mixture was heated under reflux for 4 hr and cooled, and the excess of $LiAlH_4$ decomposed with EtOAc. The mixture was shaken with 2 *N* H_2SO_4 (30 ml) and then the Et_2O layer was separated. The aqueous layer was extracted with Et_2O. The extracts gave (*R*)-(−)-**5**: mp 126–127° from EtOAc–petroleum ether (bp 60–80°); R_f 0.37 (system b); $[\alpha]^{21}D$ −33.7° (*c* 1.2); mmp [with (*S*)-(+)-**5** from previous experiment] 131–132°.

(±)- and (+)-1-(2-Naphthyl)ethane-1,2-diol Di-(*S*)-α-methoxy-α-trifluoromethylphenylacetates (8). Enantiomerically pure distilled (*S*)-(−)-α-methoxy-α-trifluoromethylphenylacetyl chloride (0.253 g, 1.0 mmol) was added to racemic **5** (0.094 g, 0.5 mmol) in dry C_5H_5N (1 ml). The mixture was heated at 50° for 1 hr, kept at room temperature overnight, and then treated with H_2O and Et_2O. The Et_2O extracts were washed (dilute HCl, H_2O, saturated $NaHCO_3$), dried, and evaporated to give an oil (0.3 g). This was purified by preparative tlc (Et_2O–C_6H_{14}, 7:13) and the band of **8**, R_f 0.4–0.5, collected (0.12 g) and analyzed by nmr (CCl_4) (see discussion). In a similar manner (*S*)-(+)-**5** gave the corresponding diester 8.

Microbiological Transformation of 2-Naphthylglyoxal Hydrate (9). Fermentation of 9[2] (2 g) for 2 days gave an EtOAc extract at pH 2.0 which was separated into an acid fraction (477 mg) and a neutral fraction (1.32 g). The acid fraction gave (*R*)-(−)-**6**: mp 160–161° from $CHCl_3$ (95 mg); $[\alpha]^{21}D$ −141.4° (*c* 0.68). The neutral fraction gave (*S*)-(+)-**5**: mp 128–130° from EtOAc–petroleum ether (bp 60–80°) (705 mg); $[\alpha]^{21}D$ +32.2° (*c* 1.0).

Microbiological Transformation of Hydroxymethyl 2-Naphthyl Ketone (11). Fermentation of 11[19] (500 mg) for 24 hr gave acid and neutral products. The negligible acid fraction (12 mg) contained neither 6 nor 7 by tlc. The neutral fraction (340 mg) gave (*S*)-(+)-**5**: mp 131–132° (180 mg); $[\alpha]^{21}D$ +30.3° (*c* 1.01).

Microbiological Transformation of Acetoxymethyl 2-Naphthyl Ketone. Fermentation of the acetate of 11[19] (1.0 g) for 24 hr gave acid and neutral products. The negligible acid fraction (15 mg) contained neither 6 nor 7 by tlc. The neutral fraction (545 mg) gave **5**: mp 134–135° (270 mg); $[\alpha]^{21}D$ +2.3° (*c* 1.03).

Control Nonenzymic Transformation of Isopropylaminomethyl 2-Naphthyl Ketone (3). Five flasks each containing **3**·HBr (100 mg) in H_2O (200 ml) at pH 5.5 (adjusted by adding 1 *N* NaOH) were shaken in air on a rotary shaker at 25°, as in the microbiological transformation experiment. After 2 days, $NaBH_4$ (200 mg), was added to each flask, and 30 min later the contents of the flasks were combined, adjusted to pH 2.0 with concentrated HCl, and extracted with Et_2O. The aqueous layer was then adjusted to pH 11 with NaOH (8 *N*) and extracted with Et_2O. The combined extracts were separated into basic, neutral, and acid fractions. The basic fraction (340 mg, 91%) was pronethalol (4), mmp 105–106°. The neutral fraction (32 mg, ~6%) was diol **5**, R_f 0.37 (system b). The acid

fraction (7 mg, ~1.5%) was a mixture of 2-naphthylglycolic acid **(6)**, R_f 0.41, and 2-naphthoic acid **(7)**, R_f 0.67 (system c).

Microbiological Transformation of Pronethalol (4). (a) Fermentation of racemic pronethalol (5 g) for 7 days gave acid, basic, and neutral products. The basic material (1.09 g) was racemic **4**, which gave 4·HCl: mp 184°; $[\alpha]^{21}D$ 0° (*c* 1.0). The acidic fraction (30 mg) contained 2-naphthylglycolic acid, R_f 0.41, and 2-naphthoic acid R_f 0.63 (system c), but the amounts recovered by preparative tlc were negligible. The neutral fraction (790 mg) gave (*S*)-(+)-**5**: mp 128–130° (17 mg); $[\alpha]^{21}D$ + 31.6° (*c* 0.8); R_f 0.37 (system b) by preparative tlc.

(b) Fermentation of (*R*)-(−)-pronethalol hydrochloride ($[\alpha]^{21}D$ −52.0°, 3 g) was carried out as in (a). The basic material (85 mg) was characterized as (*R*)-(−)-pronethalol hydrochloride: mp 208–209°; $[\alpha]^{21}D$ −52.2° (*c* 0.5). The acid fraction (17 mg) contained 2-naphthylglycolic acid and 2-naphthoic acid in negligible quantity. The neutral fraction (443 mg) gave (*S*)-(+)-**5**: mp 126–127° (27 mg); $[\alpha]^{21}D$ +32.9° (*c* 0.5) by preparative tlc.

(c) Fermentation of (*S*)-(+)-pronethalol hydrochloride ($[\alpha]^{21}D$ +52.9°, 3.5 g) was carried out as in (a). The basic material (133 mg) was characterized as (*S*)-(+)-pronethalol hydrochloride: mp 208–209°; $[\alpha]^{21}D$ +51.6° (*c* 0.5). The acid fraction (76 mg) contained 2-naphthylglycolic acid and 2-naphthoic acid in negligible quantity. The neutral fraction (830 mg) gave (*S*)-(+)-**5**: mp 125–126° (15 mg); $[\alpha]^{21}D$ +30.5° (*c* 0.5) by preparative tlc.

Microbiological Reduction of Methyl 2-Naphthyl Ketone 14. Fermentation of **14** (1 g) was carried out for 2 days. The neutral fraction (477 mg) contained substrate, R_f 0.65, 1-(2-naphthyl)-ethanol **(15)**, R_f 0.55 (C_6H_6-Et_2O, 1:1), and several more polar minor products. (*S*)-(−)-1-(2-naphthyl)ethanol,[13] mp 71° (260 mg), $[\alpha]^{21}D$ −13.7° (*c* 0.83), was isolated by preparative tlc.

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A Study of the Conformational Requirements for Direct Adrenergic Stimulation†

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A group of tetrahydroisoquinoline derivatives was prepared as fixed cisoid and 2-indanamines as fixed transoid analogs of the adrenergic neurotransmitter, norepinephrine. The compounds were evaluated in comparison with their closest, flexible counterparts, epinine and (*R*)- and (*S*)-α-methyldopamine, respectively, for direct α- and β-adrenergic activities *in vivo* and *in vitro*. Results obtained *in vivo* on the cat nictitating membrane indicate that a transoid conformation (**4**) is better than cisoid (**1**) for inducing direct α stimulation but that a cisoid conformation does not preclude direct α activity. No conclusion could be reached with regard to conformational requirements for direct β activity.

One of us has reported that certain tetrahydroisoquinoline derivatives exhibited marked α-adrenergic blocking properties coupled with prolonged, *indirect*, β-adrenergic stimulating activity.[2] Since this combination of pharmacological properties seemed confined to analogs possessing a tetrahydroisoquinoline, which may be considered a fixed cisoid phenethylamine nucleus, we were led to inquire whether there might be distinctive and separable conformational requirements for *direct* α and β agonism. This would imply that one conformation of the neurotransmitter, norepinephrine, interacts with the "α-adrenergic receptor" to induce α agonism and another conformation interacts with the "β-adrenergic receptor" to induce β agonism. Such a finding would have a bearing on the molecular nature of these receptor interactions, speculative pictures of which have been advanced.[3]

It is, of course, recognized that X-ray crystallographic evidence indicates a transoid conformation for molecules of both norepinephrine hydrochloride[4a] and dopamine hydrochloride[4b] (a theoretical calculation[5] suggesting dopamine exists preferentially in a gauche conformation has been shown to be in error[6]). The energy barriers between the various possible conformations of these flexible molecules are very small, however, and the fact that they may prefer a transoid posture says nothing about what conformation they may assume in binding to an adrenergic receptor site where forces of molecular interaction would come into play. Further, although study of conformationally fixed analogs could introduce an inherent complication if flexibility were a prerequisite to agonist activity,[7] a rigid molecule could induce a uniquely appropriate conformational change in a receptor protein, and, in any event, conformationally fixed agents have been shown to have direct adrenergic activity (*e.g.*, certain 1-substituted 6,7-dihydroxytetrahydroisoquinoline derivatives have been reported to be direct β-adrenergic stimulants of utility as bronchodilators.[8] Moreover, the observed β-adrenergic actions of certain agonists,[9] which may be a consequence of actual differences in

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