theory is based on the widely quoted explanation of Duvoisin *et al.* (22) for their finding that pyridoxine reduces or abolishes the antiparkinsonian effect of levodopa. They suggested that pyridoxine, in the form of pyridoxal phosphate, increases decarboxylase activity so that more levodopa is converted to dopamine in the periphery and less is available to penetrate into the central nervous system. However, this mechanism was refuted by Johnson *et al.* (23), who found no evidence of decarboxylase facilitation in levodopa-treated Parkinsonian patients receiving pyridoxine. These investigators offered the formation of a Schiff's base complex between pyridoxal phosphate and dopamine (24, 25) and other mechanisms (26) as alternative explanations.

Harris *et al.* (13) suggested that pyridoxine hydrochloride directly inhibits prolactin release and that dopamine involvement is unlikely. The present results may support the concept of direct prolactin inhibition by pyridoxine hydrochloride since pyridoxal hydrochloride also can be readily metabolized to the active form of the vitamin that serves as the coenzyme in the conversion of dopa to dopamine. In addition, although studies with radioactive tracers showed that an equilibrium between all active vitamin B_6 forms is established in the mammalian organism, this equilibrium does not result when large doses are given (27, 28). Even though the effects of pyridoxal hydrochloride on chlorpromazine hydrochloride-induced prolactin secretion were tested at two different time intervals, a different sampling time may reveal a prolactin-suppressant effect for this form of the vitamin.

Clarification of the mechanism(s) by which pyridoxine hydrochloride partially inhibits prolactin secretion requires further study.

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Resolution of (±)-Propranolol

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Abstract □ Two improvements in propranolol resolution were developed. Both the (+)- and (−)-di-(*p*-toluoyl)tartaric acids were used as the resolving agents. This procedure reduced the number of crystallizations needed to obtain a pure product. Furthermore, synthesis of the resolving agent was improved.

Keyphrases □ Propranolol—racemic mixtures, resolution of enantiomers, (+)- and (−)-di-(*p*-toluoyl)tartaric acids used as resolving agents □ Enantiomers—propranolol, resolving agents

Propranolol (I) [1-isopropylamino-3-(1-naphthoxy)-2-propanol], the principal commercially available β-adrenergic blocking agent, is usually supplied as the racemic compound[1]. The (−)-isomer has as much as 60 times greater β-blocking activity than the (+)-isomer (1). Not only can there be significant differences in the pharmacological activity of the enantiomers, but, as has been shown for other drugs, there also can be significant metabolic differences (2, 3).

DISCUSSION

There is only one preliminary report on the metabolism of propranolol enantiomers (4). In preparation for a metabolic study in humans, two improvements in the overall procedure for resolution of these enantiomers were made. First, preparation of the resolving agent [di-(*p*-toluoyl)tartaric acid (II)] was modified. In contrast to the original report (5), the agent was found to be insoluble in pure benzene. Moreover, the customary spectral data were not reported and are included here.

Second, in the original report on racemic propranolol resolution (1), only the (−)-di-(*p*-toluoyl)tartaric acid was used to resolve both enan-

[1] Available as (±)-propranolol hydrochloride (Inderal).

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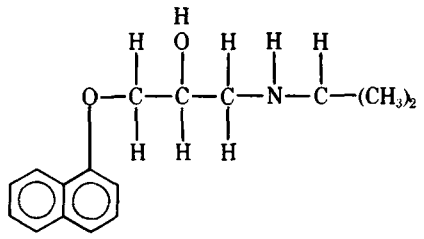

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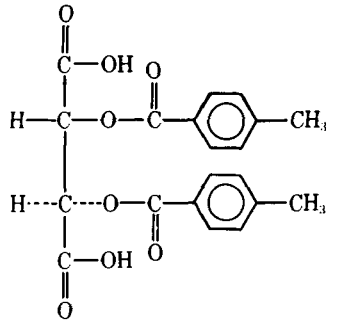

II

tiomers. In the present work, (−)- and (+)-di-(*p*-toluoyl)tartaric acids were employed in the resolution. This procedure required fewer recrystallizations to achieve optical purity. In particular, the (−)-propranolol was best isolated with (+)-di-(*p*-toluoyl)tartaric acid. Pure compounds were obtained after only one to five recrystallizations; in the original study, pure compounds were obtained "by a tedious fractional crystallization" (1).

In the original study (1), the optical rotations of propranolol enantiomers were reported to be +10.6 and −10.2°, with a melting point of 72°. The values obtained here are +8.34 and −8.32°, with a melting point of 72°. Despite the discrepancy between these rotations and those previously reported, the present values are apparently correct since the optical rotations of the respective hydrochloride derivatives obtained here (−23.82 and +22.85°) agree well with those reported (−22.7 and +22.2°). Furthermore, a sample of the (−)-enantiomer hydrochloride[2] gave a specific rotation of −23.80°. The metabolic studies will be published elsewhere.

EXPERIMENTAL

(−)-Di-(*p*-toluoyl)tartaric Acid (II)—(+)-Tartaric acid (31.6 g, 0.21 mole) and *p*-toluoyl chloride (108 g, 0.699 mole) were heated in an oil bath until the reaction mixture solidified (140°); it was then kept at that temperature for 2 hr. The cooled solid was triturated with benzene (70 ml), collected by filtration, and washed with benzene. The material was dissolved in refluxing toluene (480 ml), the mixture was filtered hot, and the filtrate was cooled to 18° to yield the II anhydride (65 g, 84%). It was recrystallized from refluxing ethyl acetate (500 ml), mp 206°, $[\alpha]_D^{18}$ +183° (c, 0.33 in acetone) and −135°, after a 1% mixture was heated in 95% ethanol; IR: ν_{max} (KBr) OH, none, 1890, 1810, 1740, and 1710 (C=O) cm^{-1} [lit. (5) mp 198° and [α] +195° (c, 0.5 in acetone)].

The anhydride (44 g, 0.12 mole) was refluxed for 2 hr in 5% aqueous acetone (250 ml). The solvent was removed, and the residue was recrystallized from a solution of 5% acetone in benzene (130 ml) to yield II (36 g, 78%), mp 173°, $[\alpha]_D^{18}$ −136.5° (c, 0.33 in ethanol); UV: λ_{max} (in ethanol) 240 (ε 28,200) nm; IR: λ_{max} (KBr) 3400–2500 (OH) and 1730 (C=O) cm^{-1} [lit. (4) mp 172° and $[\alpha]_D^{18}$ −140° (c, 1.0 in ethanol)].

Racemic Propranolol Resolution—(+)-Di-(*p*-toluoyl)tartaric acid (5.79 g, 15.0 mmoles), prepared from (−)-tartaric acid as just described, and (±)-propranolol (3.88 g, 15.0 mmoles) were dissolved in methanol (55 ml). The solution volume was reduced to 40 ml by boiling and then allowed to cool to 18°.

The resulting first crop of crystals (6 g) was redissolved in boiling methanol (70 ml). The procedure was repeated until the salt gave a constant optical rotation, $[\alpha]_D^{18}$ +63.06°.

To obtain the free base, the tartarate was decomposed with 0.5 *N* NaOH and the precipitated product was extracted with ether. The organic phase was dried (magnesium sulfate), the ether was evaporated off, and the residue was recrystallized from cyclohexane to yield (−)-propranolol, mp 72°, $[\alpha]_D^{18}$ −8.32° (c, 1.0 in ethanol); UV: λ_{max} (in 95% ethanol) 293 (ε 6000) nm [lit. (1) mp 72° and [α] −10.2° (c, 1.02)].

Treatment of (−)-propranolol (1.7 g) in ether (100 ml) with dry hydrogen chloride yielded (−)-propranolol hydrochloride, mp 196°, $[\alpha]_D^{18}$ −23.82° (c, 1.0 in ethanol) [lit. (1) mp 192° and [α] −22.7°]. An aliquot was recrystallized by suspending the material in hot benzene and then adding dropwise anhydrous ethanol to clear the suspension, mp 196°, [α] −23.45° (c, 1.0 in ethanol).

(+)-Propranolol was obtained by the identical procedure but with II as the resolving agent. In one series, after five recrystallizations the tartarate salt had an optical rotation of −63.27°. Table I shows a sequence of typical experiments beginning with equimolar amounts (15 mmoles) of racemic propranolol and the resolving agent in methanol (70 ml).

(+)-Propranolol was then isolated as described for its enantiomer, mp 72°, $[\alpha]_D^{18}$ +8.34° (c, 1.0 ethanol) [lit. (1) mp 73° and [α] +10.6°]. The (+)-propranolol hydrochloride had a melting point of 196°, $[\alpha]_D^{18}$ +22.97° (c, 1.0 in ethanol) [lit. (1) mp 192° and [α] +22.2°].

In another experiment, partially resolved propranolol, [α] +3.67° (4.00 g, 15.4 mmoles), was complexed with II (4.28 g, 11.0 mmoles), *i.e.*, an amount equivalent to the percent of the (+)-isomer. After two crystallizations from boiling methanol (55 ml), the optically pure complex was obtained (2.80 g), mp 163–165°, [α] −64.64°. It gave the free base, $[\alpha]_D^{18}$ +7.82° (c, 1.0 ethanol), which with hydrochloric acid gave (+)-propranolol hydrochloride, $[\alpha]_D^{18}$ +22.85° (c, 1.0 ethanol).

Propranolol hydrochloride for use in humans was not recrystallized from benzene. It was assayed for the presence of di-(*p*-toluoyl)tartaric acid spectrophotometrically as follows. The ratio of ε at λ_{max} (in ethanol) 290 (ε 5950) and of ε at λ_{min} 245 (ε 760) of racemic propranolol hydrochloride prepared from propranolol, which had not been treated with the resolving agent, was compared with the ratio of $\epsilon\lambda_{max}/\epsilon\lambda_{min}$ of resolved propranolol hydrochloride. Since (+)- and (−)-di-(*p*-toluoyl)tartaric acids have an ε of 25,000 at 245 nm, even a 0.1% contamination would cause a detectable alteration in the absorbance ratio at 290 and 245 nm. No contamination was detected in either propranolol enantiomer.

Table I—Fractional Crystallization of Salt of Equimolar Amounts of Racemic Propranolol and (−)-Di-(*p*-toluoyl)tartaric Acid in 70 ml of Methanol

Step	Methanol, ml	Yield of Complex: Millimoles	Yield of Complex: Percent Theoretical[a]	Melting Point	$[\alpha]_D^{18}$
1	70	8.79	117	156–164°	−68.2°
2	70	6.20	83	160–165°	−65.4°
3	65	4.96	66	162–165°	−64.4°
4	60	3.25	43	162–165°	−63.6°
5	55	2.94	39	163–165°	−62.9°

[a] Given as percent of maximal yield (7.5 mmoles).

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