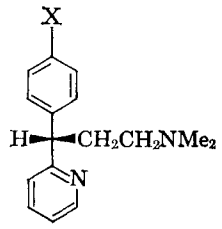
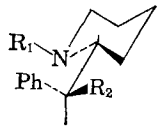
Absolute Configurations of the Enantiomeric Pheniramines, Methylphenidates, and Pipradrols

Sir:

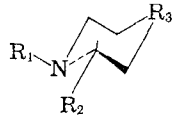
The configurations of biologically active compounds are of interest in studies on the modes of drug action and on the interactions of drugs with receptors (1, 2). Antipodes of the title compounds exhibit significant differences in biological activity (2–6) and speculation regarding the absolute configuration of chlorpheniramine (I*a*) and its receptor exists in the literature (*cf. References 7* and *8*). Since the title compounds are congenerically related, it was possible to develop and exploit a single sequence of reactions leading to the determination of the absolute configurations of all 16 optical isomers of the seven compounds (I*a*, *b*, *c*, threo-VII, XVIII, XIX, XX) of biological interest. Accordingly, the pheniramines (I) were converted to the methylphenidate series (*cf.* VII) in which the relative configuration of the two asymmetric centers is known (6, 9). The endocyclic center of asymmetry introduced in the process was maintained intact while the original exocyclic center was destroyed in the sequence leading to XIII and the pipradrols (XVIII, XIX, XX) the absolute configuration of which was determined by an aufbau sequence[1] involving pipradrol (XVIII) prepared from XIV, (+)-(R)-piperidine-2-carboxylic acid.





I*a* (X = —Cl)
I*b* (X = —Br)
I*c* (X = —H)

II (R₁ = —COPh, R₂ = —$CH_2CH_2NMe_2$)
III (R₁ = —COPh, R₂ = —$CH{=}CH_2$)
IV (R₁ = —COPh, R₂ = —COOH)
V (R₁ = —H, HCl, R₂ = —COOH)
VI (R₁ = —H, R₂ = —$CONH_2$)
VII (R₁ = —H, HCl, R₂ = —CO_2Me)
VIII (R₁ = —SO_2Ph, R₂ = —CO_2Me)
IX (R₁ = —SO_2Ph, R₂ = —CH_2OH)
X (R₁ = —SO_2Ph, R₂ = —CH_2Cl)



XI (R₁ = —SO_2Ph, R₂ = —$CPh{=}CH_2$, R₃ = —CH_2—)
XII (R₁ = —SO_2Ph, R₂ = —COPh, R₃ = —CH_2—)
XIII (R₁ = —SO_2Ph, R₂ = —$COHPh_2$, R₃ = —CH_2—)
XIV (R₁ = —H, R₂ = —COOH, R₃ = —CH_2—)
XV (R₁ = —SO_2Ph, R₂ = —COOH, R₃ = —CH_2—)
XVI (R₁ = —SO_2Ph, R₂ = —CO_2Me, R₃ = —CH_2—)
XVII (R₁ = —H, R₂ = —CO_2Me, R₃ = —CH_2—)
XVIII (R₁ = —H, R₂ = —$COHPh_2$, R₃ = —CH_2—)
XIX (R₁ = —H, R₂ = —$CHPh_2$, R₃ = —CH_2—)
XX (R₁ = —H, R₂ = —$COHPh_2$, R₃ = —S—)

Palladium–hydrogen dehalogenation of both (+) - 3 - (*p* - chlorophenyl) - 3 - (2′ - pyridyl)-1-dimethylaminopropane (I*a*) hydrogen maleate, m.p. 113–114°, $[\alpha]_D^{22}$ + 19°, (c 1.15, water) and the corresponding bromine analog (I*b*), m.p. 106–108°, $[\alpha]_D^{25}$ +34° (c 10.40, dimethylformamide) afforded (+)-3-phenyl-3-(2′-pyridyl)-1-dimethylaminopropane (I*c*) identified as the monohydrobromide salt, m.p. 176–177°. Hydrogenation of I*a*, I*b*, and I*c* with platinum oxide yielded, in each case, an uncrystallizable, dextrorotatory (ethanol) mixture of diastereoisomeric amines. The mixtures were subjected to Schotten-Baumann conditions to convert them to the dextrorotatory *N*-benzoyl derivatives which gave (+)-erythro-3-phenyl-3-(2′-[1′-benzoyl]-piperidyl)-1-dimethylaminopropane (II), m.p. 134–136°, $[\alpha]_D^{30}$ +50.5° (c 6.95, ethanol), by fractional crystallization. Subjection of II to the conditions of the Hofmann elimination yielded (+) - erythro - 3 - phenyl - 3 - (2′ - [1′ - benzoyl]-piperidyl)-1-propene (III), m.p. 125–126°, $[\alpha]_D^{26}$ +121° (c 4.66, carbon tetrachloride). Ozonolysis of III provided (−)-erythro-2-phenyl-2-(2′-[1′-benzoyl]piperidyl)acetic acid (IV), m.p. 221–222°, $[\alpha]_D^{27}$ −51.4° (c 4.71, ethanol), from which (−) - erythro - 2 - phenyl - 2 - (2′ - piperidyl)-acetic acid hydrochloride (V), m.p. 233–235°, $[\alpha]_D^{26}$ −84° (c 1.00, water), was obtained by acid hydrolysis.

An authentic sample of V was prepared from racemic erythro-2-phenyl-2-(2′-piperidyl)acetamide (*cf.* VI), m.p. 174–175°. The (−)-erythro-

[1] We recently learned that Portoghese and Pazdernik also completed the aufbau sequence and reported this at the Fourth Annual Medicinal Chemistry Meeting in Miniature, University of Kansas, Lawrence, Kan., April 4, 1966; (*cf. Reference 2*).

isomer (VI), m.p. 168–169°, $[\alpha]_D^{26}$ −64° (c 1.00, 6:4-ethanol-water), obtained by resolution with (−)-tartaric acid (6) afforded V, m.p. 233–235°, $[\alpha]_D^{26}$ − 81°, (c 1.00, water) upon acid hydrolysis. The mixed melting point of both samples of V was not depressed. Esterification of V yielded the crude levorotatory (water) erythro-ester hydrochloride (VII) which was converted to VIII, (−)-erythro-2-phenyl-2-(2′-[1′-benzenesulfonyl]piperidyl)acetic acid methyl ester, m.p. 154–155°, $[\alpha]_D^{26}$ −49°, (c 1.13, methanol) with benzenesulfonyl chloride in pyridine. Lithium aluminum hydride reduction of VIII yielded (−)-erythro-2-phenyl-2-(2′-[1′-benzenesulfonyl]piperidyl)ethanol (IX), m.p. 105–105.5°, $[\alpha]_D^{20}$ −4.5° (c 4.88, methanol). This was treated with *p*-toluenesulfonyl chloride in pyridine to obtain (+)-erythro-2-phenyl-2-(2′-[1′-benzenesulfonyl]piperidyl)ethyl chloride (X), m.p. 157–158°, $[\alpha]_D^{26}$ +25° (c 2.00, benzene) which was converted to 1-phenyl-1-(2′-[1′-benzenesulfonyl]piperidyl)ethylene (XI), m.p. 87–88°, $[\alpha]_D^{23}$ −66.8°, (c 1.80, benzene), with potassium amide in liquid ammonia. Ozonolysis of XI afforded (−)-1-benzenesulfonyl-2-benzoylpiperidine (XII), m.p. 103–104°, $[\alpha]_D^{26}$ −20° (c 7.00, tetrahydrofuran). Treatment of this ketone with phenyl magnesium bromide yielded XIII, (−)-α-(2′-[1′-benzenesulfonyl]piperidyl)-benzhydrol, m.p. 167–169°, $[\alpha]_D^{20}$ −67°, (c 1.19, tetrahydrofuran), which was also obtained, m.p. and mixed m.p. 167–169°, $[\alpha]_D^{20}$ −64° (c 1.21, tetrahydrofuran), from (R)-(+)-piperidine-2-carboxylic acid (XIV), m.p. 276–277°, $[\alpha]_D^{21}$ +25.5° (c 3.00, water). Following platinum oxide reduction of picolinic acid in the presence of, and resolution with (+)-tartaric acid, XIV was obtained and was treated with benzenesulfonyl chloride in base to give a crude dextrorotatory (benzene) product (XV), 1-benzenesulfonylpiperidine-2-carboxylic acid. Esterification afforded (+)-1-benzenesulfonylpiperidene-2-carboxylic acid methyl ester (XVI), m.p. 61–63°, $[\alpha]_D^{24}$ +54° (c 3.03, benzene). Treatment with phenyl magnesium bromide converted XVI to XIII. Esterification of XIV provided crude, dextrorotatory (ethyl ether) piperidine-2-carboxylic acid methyl ester (XVII) which was converted with phenyl magnesium bromide to (+)-α-(2-piperidyl)-benzhydrol (XVIII), m.p. 98–99°, $[\alpha]_D^{26}$ +58° (c 4.00, methanol), and thence, with benzenesulfonyl chloride in pyridine, to XIII, identical in all respects to that obtained by the other methods described. Birch reduction of XVIII afforded (+)-2-benzhydrylpiperidine (XIX) isolated as the levorotatory hydrochloride salt. The rotatory dispersion curves of the levorotatory hydrochlorides of XVIII, XIX, and XX justify assignment of the same configuration to these compounds.

Accordingly, the absolute configuration of the the more active (2, 5) levorotatory pipradrol hydrochlorides and their dextrorotatory free bases is (R). The absolute configuration of V, VI, and VII is (2S:2′R) while the base-catalyzed epimerization (6) of VI to the (+)-threo-amide and conversion of the latter to the corresponding (+)-threo-acid (*cf.* V) and (+)-threo-ester hydrochloride (*cf.* VII) establishes the latter, the more active analeptic antipode (6) as (2R:2′R). The antihistaminically more active, dextrorotatory pheniramine maleates have the (S) configuration.

The significance of these findings will be discussed in definitive reports to follow (*cf. References 2, 8*).

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