Stereochemical Aspects of Antihistamine Action. 4.[1] Absolute Configuration of Carbinoxamine Antipodes[2a]

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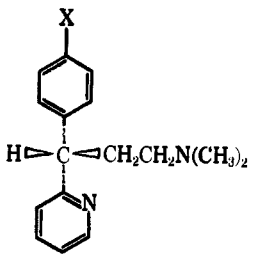
The antihistaminically more active (−)-antipode of carbinoxamine (I) has the *S* configuration and is stereochemically superimposable upon the antihistaminically more active (*S*)-(+)-antipodes of the pheniramines (II). The salient features of the scheme used to establish the configuration of (−)-I involve its conversion into a pure diastereoisomer of the piperidine analog, (+)-IIIb, the new endocyclic center of asymmetry of which was maintained intact while the original exocyclic center was destroyed in the final step, oxidation of the carbinol, (+)-Vb, to the ketone, (*R*)-(−)-VI. The relative configuration of the 2 centers of asymmetry in (+)-Vb was assigned on the basis of the *J* values for the benzylic protons of (+)-Vb and authentic racemic erythro and threo compounds (Vb and VIIb). While biological data suggest that the carbinoxamines I and the pheniramines II may bind differently to the same receptor, the disparity is not such as to invert the configurational requirements for antihistaminic activity.

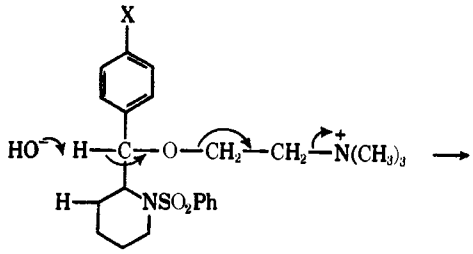
The O atom joining the asymmetric center and the aliphatic amine side chain in analogs of carbinoxamine I marks the only structural difference between them and the pheniramines II. However, in studies con-



II

ducted using the IV histamine challenge, the facts that the antipodal potency ratios of the Cl analogs differ significantly, 37:1[3] and 95:1,[4] respectively, and that para substituents do not accord the same increments in potency[4,5] in both series, suggest that I and II may not bind to the receptor in the same manner.[6] Divergence in receptor binding and its reflection in inversion of configurational requirements of receptors are of considerable contemporary interest.[7] These considerations and the possibility that I, like II,[1c] could be converted into a benzoylpiperidine (VI) of known abs config[1c] provided the impetus for determining the abs configns of the carbinoxamine (I) antipodes, the first of the antihistaminic diarylmethyl ethanolamine ethers to be so studied.

The sequence of the reactions shown in Scheme I was dictated by several considerations. Since II does racemize in base,[1c] redn of the Pyr ring precedes the Hofmann elimination. While Pd-catalyzed redn of an aromatic halide is a facile process at the level of I or III,[1c] this redn was initially delayed until after hydrolysis of the enol ether IV to the Ph carbinol V. Thus, if the benzylic OH resisted hydrogenolysis, the chances of isolating a pure diastereoisomer (III, IV, or V) could be increased by adding further derivatives with which to operate. The Hofmann elim could lead either to IV or, by classical fragmentation, directly to VI, CH_2CH_2, and Me_3N. Thus, initial redn of the Pyr ring, while it favors formation of IV,



VI + $CH_2{=}CH_2$ + $N(CH_3)_3$

still offered a less pedestrian route to VI. Complete racemization of VI might be obviated by decompn of III·MeI in an apolar solv.[1c] However, the fragmentation pathway is more confining in that a pure diastereoisomer must be isolated prior to this step. Adequate precedents exist for the oxidn of α-asym secondary carbinols to ketones without racemization using a two-phase acid–dichromate system[8] and for the survival of benzylic OH under the mild acidic conditions required to cleave enol ethers. Finally, a blocking group was needed to direct the Hofmann process toward the side chain. The nature of the blocking group was dictated by the struct of (*R*)-(−)-VI. The chemistry of these conversions was initially investigated with (±)-I·bimaleate.

The diastereoisomeric mixt of free amines obtd after PtO_2 redn of the Pyr ring of (±)-I·bimaleate was an oil which resisted all attempts to fractionally cryst pure, diastereoisomeric salts. The diastereoisomeric mixt of solid benzenesulfonamides formed under Schotten–Baumann conditions could not be

(1) (a) Paper 1: A. Shafi'ee and G. Hite, *J. Pharm. Sci.*, **56**, 1041 (1967); (b) paper 2: *ibid.*, **56**, 1689 (1967); (c) paper 3: *J. Med. Chem.*, **12**, 266 (1969).

(2) (a) Supported in part by Grant NB-03593 from the U. S. Public Health Service, Bethesda, Md.; (b) undergraduate research participants; Recipients, Lunsford-Richardson Award, 1968, First Prize, Northeast Regional Competition.

(3) A. P. Roszkowski and W. M. Govier, *Pharmacologist*, **1**, 60 (1959); calculated on a molar basis.

(4) (a) F. E. Roth, *Chemotherapia*, **3**, 120 (1961); (b) F. E. Roth and W. M. Govier, *J. Pharmacol. Exp. Ther.*, **124**, 347 (1958).

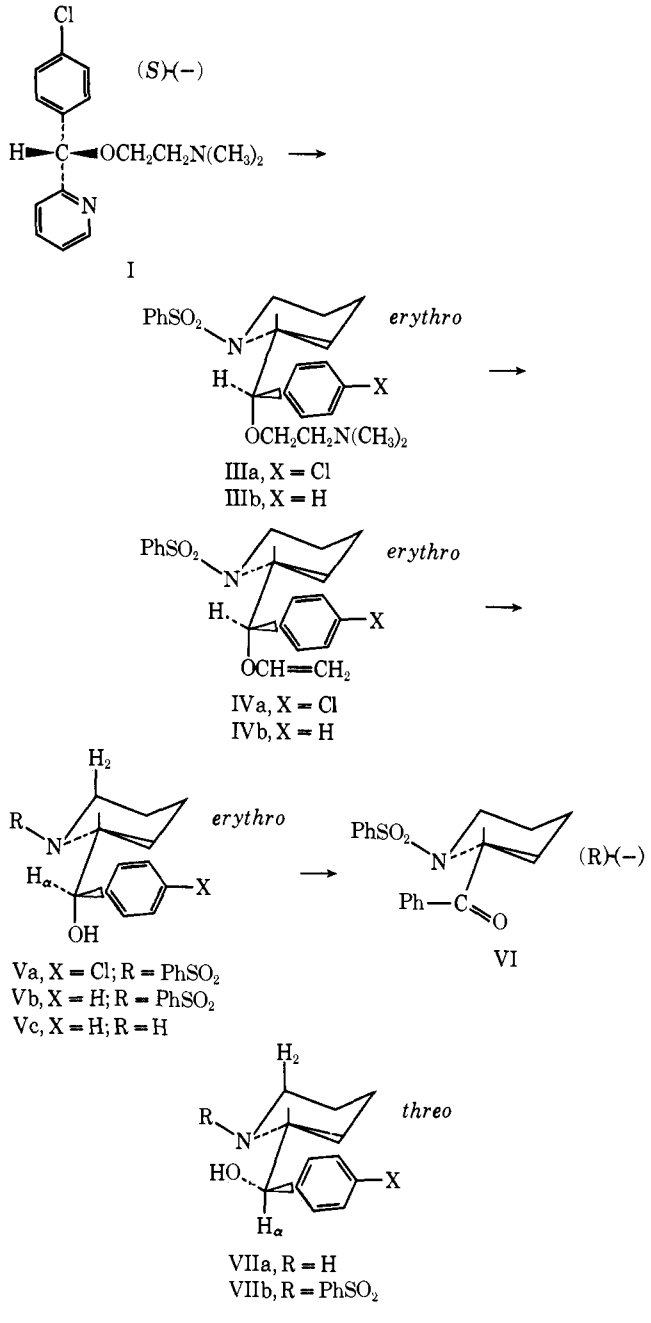
(5) A. Labelle and R. Tislow, *ibid.*, **113**, 72 (1954).

(6) It is less likely, in the view of the authors, that these observations can be entirely and satisfyingly explained on the basis of non-receptor-related events since studies on isolated guinea pig ileum, also used as a measure of antihistaminic potency, provide even higher antipodal potency ratios[4a] than tests run on intact animals.

(7) B. Belleau and J. Puranen, *J. Med. Chem.*, **6**, 325 (1963); P. S. Portoghese, *ibid.*, **8**, 609 (1965).

(8) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).

SCHEME I



resolved, but a sharply melting *p*-TsOH salt of (±)-IIIa, was obtd. Subjection of this to the conditions of the Hofmann elim afforded (±)-IVa in excellent yield. No ketonic product could be identified. Hydrolysis of (±)-IVa proceeded smoothly and Pd-catalyzed redn of (±)-Va afforded (±)-Vb identical in all respects with the material formed by benzenesulfonation of authentic[9] (±)-*erythro*-2-(α-hydroxybenzyl)piperidine, (±)-Vc.

The (+)-salt of (+)-tartaric acid with (−)-I, the antihistaminically more active antipode, on exhaustive redn in the presence of Pt and then in the presence of Pd, afforded a mixture of free amines and subsequently, a sharp melting sulfonamide, (+)-IIIb, and its methiodide. Hofmann elimination of (+)-IIIb·methiodide followed by hydrolysis of the enol ether IVb gave (+)-Vb which was oxidized[8] to (*R*)-(−)-VI.[1c]

The ir and nmr spectra of (+)-Vb were identical with those of authentic (±)-Vb and differed from those of the threo diastereoisomer (±)-VIIb. The spectral evidence corroborates previous stereochemical assignments.[9b] The more stable rotational isomers of Vb and VIIb about the C_2–C_α bonds are those shown in which the largest (Ph, $PhSO_2N$) units are trans or approx so as reqd for minimization of nonbonded repulsions. Both the character and positions of the ir OH absorptions support this. The former exhibits a strong, sharp band at 3610 cm^{-1} indicative of non-H-bonded OH while the latter exhibits a strong, broad absorption at 3540 cm^{-1} suggesting H bonding to the neg charged O of the SO_2N moiety. This, and the higher J value for VIIb (d, $J_{2,\alpha}$ = 10 Hz, H, OCH) clearly establishes the latter as the threo isomer and Vb (d, $J_{2,\alpha}$ = 7 Hz, H, OCH) as the erythro isomer according to the Karplus[10] relationship between the magnitude of J and the dihedral angle separating vicinal protons. Thus, since (+)-Vb is erythro and 2*R*, the exocyclic center must be α*S*. Tracing this back through the sequence, (−)-I is seen to have the *S* configuration which is superimposable upon the antihistaminically more active (+)-antipodes of the pheniramines (II).

Whatever differences in mode of binding may exist, these are insufficient to bring about inversion of the configurational requirements for antihistaminic action.

Experimental Section[11]

(±)-*erythro*-1-Benzenesulfonyl-2-{*p*-chloro-α-[2'-(*N*,*N*-dimethylamino)ethoxy]benzyl}piperidine [(±)-IIIa] *p*-Toluenesulfonate.—To 0.6 g of PtO_2 in 200 ml of H_2O was added 20 g of (±)-I·hydrogen maleate, mp 118–120°. To complete the redn, an addnl 0.3 g of cat was reqd at about 70% theor H_2 uptake. The mixt was filtd, alkald with NaOH, and extd with Et_2O. The ext was dried, clarified, filtd, and evapd to give an oil: ir (neat) 3607 sharp, 3410 cm^{-1} broad (NH). This was shaken for 2 hr with 100 ml of 10% NaOH and 17.6 g of $PhSO_2Cl$. The mixt was extd with Et_2O and the ext was dried, clarified, filtd, and evapd to give 21 g of oil (±)-IIIa: ir (neat) NH absent. This was redissolved in 200 ml of Et_2O and treated with 8.27 g of *p*-$MePhSO_3H$. The resulting gum solidified when tritd with dry Me_2CO and the solid was recrystd from H_2O–EtOH to give 20 g (65%) of (±)-IIIa·Ts, mp 135–136°. *Anal.* ($C_{29}H_{37}ClN_2O_6S_2 \cdot H_2O$) C, H, N, S.

(9) (a) K. E. Crook and S. M. McElvain, *J. Amer. Chem. Soc.*, **52**, 4006 (1930); (b) A. Dudas and I. Weisz, *Chem. Ber.*, **94**, 414 (1961).

(10) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(11) Mp's were measured in a Thomas-Hoover Uni-Melt app and are uncor. $[\alpha]^t_D$ Values were measured with a Perkin-Elmer Model 141 photoelectric polarimeter. Ir spectra were determined with a Perkin-Elmer Model 421 spectrophotometer. Assignments of absorption bands, believed accurate to within ±5 cm^{-1}, were made by analogy with reported values.[12] Nmr spectra were run on D_2O-treated samples and were detd in $CDCl_3$ (TMS) using a Varian A-60A spectrometer. Assignments of absorption bands, believed accurate to within 1 Hz, are made by analogy with reported values.[13] Anal. for elements indicated by symbols were performed by Weiler and Strauss, Oxford, England, and were within ±0.4% of the theor values. Acid and base washings of nonpolar solvs were conducted with 1 *N* HCl and satd $NaHCO_3$, respectively. Drying and clarification of nonpolar solns were carried out simultaneously with anhyd Na_2SO_4 and Norit, resp. After filtn through Celite pads in sintered glass funnels, the solvs were removed under red press. Cat redns were carried out in a Parr Model 3921 shaker at 40–60 psig. Detns of $[\alpha]^t_D$ and ir and nmr spectra and cat redns were conducted at ambient temp.

(12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1964.

(13) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates Analytical Instrument Division, Palo Alto, Calif., Vol. 1, 1962; N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, *ibid.*, Vol. II, 1963.

(±)-*erythro*-**1-Benzenesulfonyl-2-(*p*-chloro-α-vinyloxybenzyl)piperidine** [(±)-**IVa**].—Treatment of 15 g of (±)-IIIa in Et_2O with 9 g of MeI afforded a quant yield methiodide which was dissolved in warm H_2O and treated with freshly prepd AgOH (from 17 g of $AgNO_3$). When the supernatant failed to give a pos I^- test ($NaNO_2$–H^+–starch) the mixt was filt and the H_2O was evapd. To the residue was added 800 ml of C_6H_6. This was slowly distd off as fresh dry C_6H_6 was added, until only a dry scum remained of the original residue. The C_6H_6 soln was evapd, and the residue was crystd from heptane to give 9.8 g (78%) of (±)-IVa: mp 132–133°; ir ($CHCl_3$) 1615 and 1635 cm^{-1} d (CH=CH_2). *Anal.* ($C_{20}H_{22}ClNO_3S$) C, H, N.

(±)-*erythro*-**1-Benzenesulfonyl-2-(*p*-chloro-α-hydroxybenzyl)piperidine** [(±)-**Va**].—To 7.84 g of (±)-IVa dissolved in 60 ml of warm 80% EtOH was added 2 ml of 12 *N* HCl. After 12 hr the solv was evapd, and the residue was crystd from heptane to give 5.5 g (75%) of (±)-Va: mp 116–117°; ir ($CHCl_3$) 3610 cm^{-1} (OH). *Anal.* ($C_{18}H_{20}ClNO_3S$) C, H, N.

(±)-*erythro*-**1-Benzenesulfonyl-2-(α-hydroxybenzyl)piperidine** [(±)-**Vb**]. **A.**—Redn of 3.66 g of (±)-Va in 50 ml of EtOH in the presence of 3 g of 10% Pd/C gave 2.64 g (80%) of (±)-Vb after removal of the cat and solv and recrystn of the residue from heptane: mp 121–122°; ir ($CHCl_3$) 3610 cm^{-1} (OH); nmr ($CDCl_3$) δ 7.65–7.25 (m, 10 H, Ph and $PhSO_2$), 5.07 (d, $J_{\alpha,2}$ = 7 Hz, H, OCH), 4.21 (unres 3-line m, *J* = 7 Hz, H, NCH), 3.9–3.1 (m, 2 H, NCH_2), 2.0–1.2 ppm (m, 6 H, $CH_2CH_2CH_2$). *Anal.* ($C_{18}H_{21}NO_3S$) C, H, N.

B.—To 0.95 g of (±)-*erythro*-2-(α-hydroxybenzyl)piperidine [(±)-Vc], prepd as descrd by Crook and McElvain,[9a] mp 141–142°, in 25 ml of Pyr was added dropwise over 1 hr, 0.88 g of $PhSO_2Cl$. The solv was evapd, and the residue was mixed with $CHCl_3$. The soln was washed with acid and with base, dried, filtd, and evapd to give an authentic sample of (±)-Vb from heptane–Et_2O: 0.5 g (30%); mp 122–123°; mmp with (±)-Vb obtd from (±)-Va, 121–122°; ir ($CHCl_3$) and nmr ($CDCl_3$) superimposable upon spectra of (±)-Vb obtd from (±)-Va. *Anal.* ($C_{18}H_{21}NO_3S$) C, H, N.

(±)-*threo*-**1-Benzenesulfonyl-2-(α-hydroxybenzyl)piperidine** [(±)-**VIIb**].—When 0.48 g of (±)-*threo*-2-(α-hydroxybenzyl)-piperidine [(±)-VIIa], mp 171–172°, obtd as descrd by Crook and McElvain,[9a] mp 171–173°, was treated as in the prepn and work-up of (±)-Vb, there was obtd from heptane 0.33 g (40%) of (±)-VIIb: mp 94–95°; ir ($CHCl_3$) 3540 cm^{-1} (OH); nmr ($CDCl_3$) δ 8.2–7.2 (m, 10 H, Ph and $PhSO_2$), 4.91 (d, $J_{2\alpha}$ = 10 Hz, H, OCH), 4.3–2.9 (complex, 3 H, NCH_2 and NCH), 1.8–0.8 ppm (m, 6 H, $CH_2CH_2CH_2$). *Anal.* ($C_{18}H_{21}NO_3S$) C, H, N.

(2*R*,α*S*)-(+)-*erythro*-**1-Benzenesulfonyl-2-{α-[2'-(*N*,*N*-dimethylamino)ethoxy]benzyl}piperidine** [(2*R*:α*S*)-(+)-**IIIb**] **Methiodide.**—After 55 g of the (−)-tartaric acid salt of (*S*)-(−)-Ia [(*S*)-(+)-carbinoxamine·bitartrate], mp 135–137° softens, clear liquid 181–182.5°, $[\alpha]_D$ (MeOH) +33.5 ± 1.5° (*c* 3.56) in 500 ml of 75% EtOH was redd as descrd for (±)-I, the cat was removed and replaced with 8 g of 10% Pd/C. Redn was contd until the free amine, isolable from the reaction mixt. was halogen free (Na fusion). The free amine was treated as descd in the prepn of (±)-IIIa to give 20 g (40%) of (2*R*,α*S*)-(+)-IIIb from Et_2O–pet ether (30–60°): mp 98–99°; $[\alpha]_D$ (MeOH) +61 ± 1.5° (*c* 1.89). *Anal.* ($C_{22}H_{30}N_2O_3S$) C, H, N.

The methiodide was obtained in quant yield in Et_2O and was recrystd from EtOH: mp 187–188°; $[\alpha]_D$ (MeOH) +43.4 ± 1.5° (*c* 2.19). *Anal.* ($C_{23}H_{33}IN_2O_3S$) C, H, N.

(2*R*,α*S*)-(+)-*erythro*-**1-Benzenesulfonyl-2-(α-hydroxybenzyl)piperidine** [(2*R*:α*S*)-(+)-**Vb**].—Subjection of 10.9 g of (2*R*:α*S*)-(+)-IIIb·methiodide to the conditions of the Hofmann elim descrd in the prepn of (±)-IVa afforded 3.6 g (50%) of opt act (2*R*,α*S*)-IVb: mp 102–103°; ir ($CHCl_3$) 1613 and 1633 cm^{-1}, d (CH=CH_2). *Anal.* ($C_{20}H_{23}NO_3S$) C, H, N. When subjected to the condns empld for the hydrol of (±)-IVa, 3.6 g of (2*R*,α*S*)-IVb afforded 2.0 g (60%) of (2*R*:α*S*)-(+)-Vb: mp 142–143°; $[\alpha]_D$ (EtOH) +45 ± 2° (*c* 0.82); ir ($CHCl_3$) and nmr ($CDCl_3$) identical with that of (±)-Vb. *Anal.* ($C_{18}H_{21}NO_3S$) C, H, N.

(*R*)-(−)-**1-Benzenesulfonyl-2-benzoylpiperidine** (**VI**).—To 0.1 g of (2*R*,α*S*)-(+)-Vb in 20 ml of Et_2O was added 1.5 ml of oxid soln prepd from 5 g of $Na_2Cr_2O_7 \cdot 2H_2O$, 3.75 ml of concd H_2SO_4 and H_2O to make 25 ml of soln. After stirring for 3 hr, the Et_2O was sepd, washed with H_2O and base, dried, clarified, filtd, and evapd to give a residue. This was crystd from heptane to afford 67 mg of (*R*)-(−)-VI: mp 103–103.5°, $[\alpha]_D$ (THF) −18 ± 3° (*c* 0.85); lit.[1c] mp 103°, $[\alpha]_D$ (THF) −20 ± 1°.

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Some Aryloxyalkylamines, *N*-Arylethylenediamines, and Related Compounds as Anorectic Agents

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The anorectic and stimulant properties of some 2-phenoxytriethylamines and related compounds have been compared. The effect of phenyl-ring substitution differs from that in the amphetamine series. A *p*-CN group is particularly effective in producing anorectic activity without stimulant effects.

Most anorectic drugs have associated undesirable properties such as CNS stimulation, euphoria, addictiveness, and hypertension.

A considerable number of modifications have been made to the amphetamine structure with a view to reducing its stimulant properties while retaining anorexigenic activity.[1] The most successful compound of this type is the *N*-ethyl-*m*-trifluoromethyl derivative, fenfluramine.[2] Some 1-phenoxy-2-propylamine derivatives are also claimed to have a favorable ratio of anorexigenic to stimulant activity.[3] We have observed anorexigenic activity in some tertiary phenoxyalkylamines (Table I) and find that substitution in this series has different effects on anorexigenic and central stimulant

(1) (a) "Amphetamines and Related Compounds," S. Garattini and E. Costa, Ed., Raven Press, New York, N. Y., 1969; (b) D. L. Marsh and D. A. Herring, *J. Pharmacol.*, **100**, 298 (1950); (c) G. F. Holland, C. J. Buck, and A. Weissman, *J. Med. Chem.*, **6**, 519 (1963).

(2) J. C. Le Douarec and H. Schmitt, *Therapie*, **19**, 831 (1964).

(3) Boehringer, Ingelheim, French Patent 1,529,480 (1967); *Chem. Abstr.*, **71**, 12806 (1969).