Simple Procedure for Determining Octanol–Aqueous Partition, Distribution, and Ionization Coefficients by Reversed-Phase High-Pressure Liquid Chromatography

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Received November 14, 1977, from the *Institute of Organic Chemistry, Syntex Research, Palo Alto, CA 94304.* Accepted for publication January 30, 1978.

Abstract □ The described simple, accurate, and precise reversed-phase high-pressure liquid chromatographic procedure is in excellent agreement with 1-octanol shake-flask partition or distribution coefficients over a 3.5 log range. A chemically bonded octadecylsilane support is persilated and coated with 1-octanol. With 1-octanol-saturated buffers as mobile phases, a stable baseline (compared to 1-octanol adsorbed on silica) is obtained rapidly, and the log relative retention times are highly correlated with unit slope to log distribution or partition coefficients obtained from the classical shake-flask procedures. Only relatively basic, unhindered pyridines deviate, probably because of binding with residual silinol sites. In addition, if the apparent pKa or pKa^b of an ionizable compound lies within the pH operating range of the column support, the apparent pKa or pKa^b usually can be determined simultaneously with log P by measuring the log distribution coefficient at several pH values. The procedure gives rapid results, requires little material, and can tolerate impurities.

Keyphrases □ Partition coefficients—various compounds, high-pressure liquid chromatographic determination □ Distribution coefficients—various compounds, high-pressure liquid chromatographic determination □ Ionization coefficients—various compounds, high-pressure liquid chromatographic determination □ High-pressure liquid chromatography—determination, partition, distribution, and ionization coefficients for various compounds

There is considerable interest in determining octanol–aqueous partition coefficients in the emerging area of rational drug design (1). Therefore, a reversed-phase high-pressure liquid chromatographic (HPLC) procedure was sought that would be accurate *vis á vis* standard shake-flask octanol–aqueous partition coefficients; precise, *i.e.*, reproducible from day to day; rapidly set up, *i.e.*, baseline rapidly established; and not especially temperature sensitive.

BACKGROUND

The shake-flask procedure (2) is considered the standard reference procedure, but it suffers from several problems. It is time consuming and subject to purity, stability, and mass balance problems. Moreover, it requires handling relatively large quantities of odiferous 1-octanol.

A reversed-phase TLC procedure was described (3), which is more suitable to determining large numbers of analogs. However, the preparation of standardized plates and the necessity of running several dilution series of mobile phases—to detect hydrogen-bonding effects—detract from this procedure. Procedures were reported that used reversed-phase HPLC to measure lipophilicity (4, 5). These procedures (acetonitrile-buffer solutions on octadecylsilane bonded packings) are fast and accurate and avoid purity and stability problems, but octadecylsilane is more like an alkane than an alcohol phase. Therefore, the differential effects of hydrogen bonding limit use of these procedures to close analogs (6).

Hulshoff and Perrin (7) compared reversed-phase HPLC and TLC procedures and also investigated oleyl alcohol supported on Porasil C[1] as an HPLC procedure to measure the lipophilicities of a series of benzodiazepines. Likewise, Mirrlees *et al.* (8) used 1-octanol supported on Hyflo supercel[2] and compared some of the earlier work on reversed-phase TLC and HPLC. Henry *et al.* (9) compared various HPLC techniques such as C-18 Corasil[1] and 1-octanol and squalene on Corasil II and Porasil A. These procedures (8, 9), using 1-octanol physically adsorbed on a solid support, would be close to ideal (a physically bonded "octanol"-like alcohol with the hydroxyl end free). However, attempts to obtain a stable baseline were unsuccessful in this laboratory and others[3].

Since 1-octanol itself is very lipophilic [log $P_{octanol}$ = 3.15 (1)], it should bond strongly to octadecylsilane and give a stable column with minimal free silinol sites (5). Providing that the aqueous mobile phase is saturated with octanol, a system much like that of the octanol–aqueous shake-flask system should result.

EXPERIMENTAL

C-18 Corasil, 37–50 μm, was persilated by the method of McCall (5) and dry packed in stainless steel tubing (2 mm i.d.) in lengths of ~3, 10, and 50 cm. A precolumn of silica gel (70–230 mesh) with dimensions of 9 mm i.d. × 8.5 cm also was prepared. Both columns were loaded with 99.97% (certified) 1-octanol by injecting directly into the column under pressure until droplets appeared. The columns were mounted on a high-pressure liquid chromatograph and flushed with octanol-saturated water (or buffer, 0.01 *M*) until the eluate appeared clear. The analytical column was then attached to the 254-nm UV detector, and elution was continued until a stable baseline was obtained (~30–45 min). All solutions were first filtered[4] to reduce contamination or column clogging.

Samples were dissolved in octanol-saturated buffer and/or a minimal amount of methanol, and a 25-μl injection loop was used. Elution times, t_x, were measured with a stopwatch; methanol in octanol-saturated buffer served as a suitable nonretained compound to define t_0, the dead volume; pyridine *N*-oxide or formamide also can be used. Then, $k' = (t_x - t_0)/t_0$. Sample concentrations were adjusted so that relative peak areas remained approximately constant. Column length and flow rate (~1–2 ml/min) were selected for analytical convenience.

In other respects, the procedure follows published methods (5, 8, 9). The same octadecylsilane columns were used with 25% (w/w) methanol–buffer as the mobile phase to demonstrate the effects of octanol[5]. All experiments were performed at ambient temperature (25 ± 1°). The pH of the eluate was determined using aqueous buffers; addition of octanol at saturation had no effect on pH.

Log D or log P (distribution or partition) coefficients for unknowns were determined by interpolation from the standard regression line between shake-flask log D or log P and log k'. Daily standards were highly correlated with each other; different column lengths were correlated with a slope close to 1.0 but with a significant intercept because of a constant increase in log k' with column length.

Shake-flask measurements were made with the same solutions as used in HPLC following the general procedure of Fujita *et al.* (2). Hexaldehyde was measured by vapor phase chromatography at two dilutions because of poor UV absorption.

RESULTS AND DISCUSSION

The effects of ionization and the differential effects of hydrogen bonding are unfortunately ignored in many new methods for determining partition coefficients. If one is cognizant of the effects of ionization, one can simply use the distribution coefficient D in place of the partition

[1] Waters Associates.
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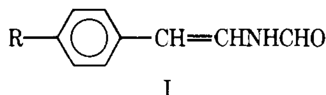

coefficient P (10); however, one must correct:

$$P = [\text{octanol}]/[\text{aqueous}]\ (1 - \alpha) = D/(1 - \alpha) \qquad \text{(Eq. 1)}$$

for relative differences in hydrogen-bonding effects when comparing different experimental procedures (6).

This correction is demonstrated in Fig. 1 where log k' determined on octadecylsilane–25% (w/w) methanol–pH 7.00 phosphate buffer is plotted *versus* log P determined by the new HPLC procedure on the same columns for some tuberin [N-(β-styryl)formamide] analogs (I)[5]. The neutral substituents are highly linear between the two systems; however, the hydrogen-bonding substituents fall off of this line. Therefore, octadecylsilane–25% (w/w) methanol does *not* correctly represent the partitioning behavior of these compounds *vis á vis* an octanol–aqueous system. On the other hand, the excellent agreement between log P determined by octanol-coated octadecylsilane using HPLC and the classical shake-flask values in the identical solvents is shown in Table I.

A comparison of a large number of standards is given in Table II. Several shake-flask values were redetermined in the same solvent system as used in HPLC to have an accurate comparison. Since pH 7.00 (0.01 M) buffer was used, some compounds (*e.g.*, p-nitrophenol) were ionized and some were not. Therefore, since linear correlation was obtained, this procedure is sensitive to distribution as well as partition effects.

The wide range of substituent groups, both hydrogen-bond donors and acceptors, clearly demonstrates the excellent modeling of the shake-flask procedure. Of all classes of compounds studied thus far, only two gave poor agreement between the two methods. The relatively unhindered basic pyridines (pyridine, 3-picoline, 4-picoline, and 2-amino-4-picoline) deviated considerably and were retained on the column much longer than expected. This result can probably be attributed to bonding with residual

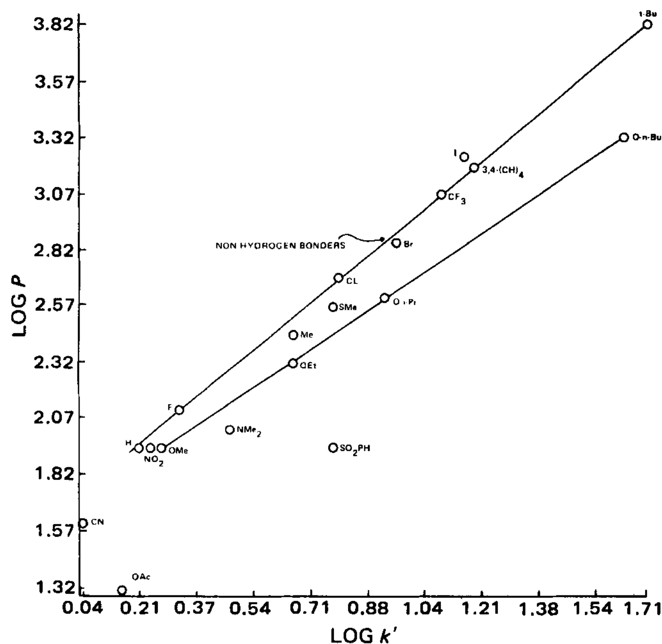

Figure 1—*Partitioning behavior of tuberins in two HPLC systems. The vertical axis gives log* P *determined on octanol-coated octadecylsilyl-bonded support with octanol saturated pH 7.00 (0.01* M*) phosphate buffer as the mobile phase. The horizontal axis gives log* k′ *determined on the same octadecylsilyl-bonded support but with 25% (w/w) methanol in pH 7.00 (0.001* M*) phosphate buffer and no octanol. Note the deviation of hydrogen-bonded substituents between the two systems. Key (R in Structure I): t-Bu, tert-butyl; O-n-Bu, butoxy; I, iodo; 3,4-(CH)$_4$, 3,4-benzo (the β-naphthyl analog); CF$_3$, trifluoromethyl; Br, bromo, CL, chloro; O-i-Pr, isopropoxy; SMe, methylthio; Me, methyl; OEt, ethoxy; SO$_2$PH, phenylsulfono; F, fluoro; NMe$_2$, dimethylamino; H, unsubstituted; NO$_2$, nitro; OMe, methoxy; CN, cyano; and OAc, acetoxy.*

Table I—Agreement between Shake-Flask and HPLC Log P Values in Tuberin Series and for Naproxen [a]

R (Structure I)	Log $P_{\text{shake flask}}$	Log P_{HPLC}
Unsubstituted	1.93 ± 0.01	1.95[b]
Methoxy	1.92 ± 0.02	1.94[b]
Cyano	1.58 ± 0.01	1.62[b]
Acetoxy	1.40 ± 0.01	1.32[b]
Naproxen[c]	3.18[d]	3.20 ± 0.01

[a] With pH 7.00 (0.01 M) phosphate buffer; ambient temperature. [b] The standard deviation of regression between log P and log k' for standards is 0.03, omitting tuberins. [c] (+)-6-Methoxy-α-methylnaphthaleneacetic acid. [d] See Table II, footnote b.

silinol sites. For example, different batches of persilated octadecylsilane gave somewhat different log D values for these compounds, while all other compounds behaved as expected.

The other class of deviants, also recognized by Mirrlees *et al.* (8), are the very lipophilic acids or bases, which can still have significant partitioning of the ionized species. Generally, very poor peak shapes were obtained with such compounds. The solution to this problem would be to work at more propitious pH values to drive the ionization completely in one direction. If peak shape is not a problem, however, and the apparent pKa is between 2 and 8 (the pH operating range of octadecylsilyl-bonded supports), then both log P and pKa can be determined simultaneously by measuring log D at several pH values. Horváth *et al.* (11) reported a similar procedure using standard octadecylsilane columns. Since $P = D\,[(K_a/H) + 1]$ for acids and $P = D\,[(H/K_a{}^b) + 1]$ for bases, then for acids:

$$D = P + K_a(-D/H) \qquad \text{(Eq. 2}a\text{)}$$

and for bases:

$$D = P + (1/K_a{}^b)\,(-DH) \qquad \text{(Eq. 2}b\text{)}$$

where the distribution coefficient D (from interpolation using standards) is correlated *versus* $(-D/H)$ or $(-DH)$ by ordinary least squares. To determine the intercept P and the slope K_a (or $1/K_a{}^b$) most accurately, measurements should be taken near pH 2 and approximately the pKa for acids and near pH 8 and the pKa^b for bases. Since D appears on both sides of Eqs. $2a$ and $2b$, propagation of errors in D make the standard

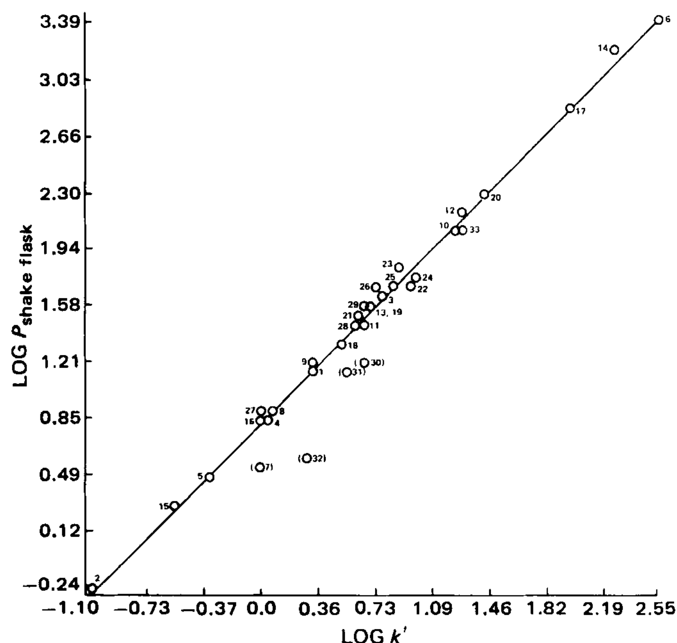

Figure 2—*Comparison of log* P$_{shake\ flask}$ *with log* k′ *determined by octanol-coated octadecylsilyl-bonded support with octanol-saturated pH 7.00 (0.01* M*) phosphate buffer as the mobile phase. Compounds are numbered as in Table II. Note the excellent agreement over 3.5 log* P *units, except for unhindered pyridines, which can be attributed to specific binding to residual silinol sites. Correlation is for Eq. 4.*

Table II—Shake-Flask and HPLC Partition and Distribution Coefficients at pH 7.00 for Standard Compounds

Number	Name	Log $P^{a,b}$	Log $k'^{a,c}$
1	Acetanilide	1.16 ± 0.02 (3)	0.322 ± 0.001 (2)
2	Acetone	−0.24 (1)	−1.097 (1)
3	Acetophenone	1.66 ± 0.08 (3)	0.782 ± 0.02 (3)
4	2-Acetylpyridine	0.85 ± 0.03 (4)[d]	0.047 (1)
5	4-Acetylpyridine	0.48 ± 0.01 (4)[d]	−0.328 (1)
6	Acridine	3.39 (1)	2.554 (1)
7	2-Amino-4-picoline	0.56 ± 0.03 (6)[d]	−0.0127 (1)
8	Aniline	0.93 ± 0.05 (3)	0.0614 (1)
9	*o*-Anisidine	1.23 ± 0.04 (4)[d]	0.335 ± 0.005 (2)
10	Anisole	2.08 ± 0.04 (3)	1.250 (1)
11	Benzaldehyde	1.45 ± 0.03 (2)	0.656 ± 0.007 (4)
12	Benzene	2.15 ± 0.01 (3)	1.262 ± 0.01 (2)
13	Benzonitrile	1.56 ± 0.00 (2)	0.688 (1)
14	Benzophenone	3.18 (1)	2.272 (1)
15	2-Butanone	0.28 ± 0.02 (2)	−0.540 ± 0.008 (2)
16	Catechol	0.86 ± 0.02 (2)	−0.006 ± 0.02 (3)
17	Chlorobenzene	2.84 (1)	1.966 (1)
18	2-Chloropyridine	1.34 ± 0.02 (4)[d]	0.515 (1)
19	4-Cyanophenol	1.58 ± 0.04 (2)	0.667 (1)
20	*N,N*-Dimethylaniline	2.30 ± 0.01 (3)	1.430 (1)
21	*m*-Dinitrobenzene	1.49 ± 0.00 (2)	0.614 ± 0.006 (2)
22	2-Ethylpyridine	1.69 ± 0.08 (5)[d]	0.962 ± 0.09 (3)
23	4-Fluorophenol	1.79 ± 0.03 (2)	0.888 (1)
24	Hexaldehyde	1.78 (2)[d]	0.984 (1)
25	2,6-Lutidine	1.68 ± 0.15 (4)[d]	0.842 ± 0.1 (3)
26	4-Nitrophenol	1.68 ± 0.01 (3)	0.741 (1)
27	2-Pentanone	0.91 ± 0.03 (4)[d]	−0.0105 (1)
28	Phenol	1.48 ± 0.02 (5)	0.609 ± 0.009 (3)
29	Phenylacetonitrile	1.56 (1)	0.654 ± 0.03 (2)
30	3-Picoline	1.20 ± 0.02 (3)	0.654 (1)
31	4-Picoline	1.18 (1)	0.533 (1)
32	Pyridine	0.63 ± 0.02 (4)	0.301 (1)
33	Quinoline	2.04 ± 0.02 (4)	1.290 (1)

[a] Average ± *SD* (number of determinations or dilutions). [b] Values from Pomona College Medicinal Chemistry Project (Claremont, Calif.), unless otherwise indicated. Corrected for ionization using pKa corrected to 25° (A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N.Y., 1962). [c] Octadecylsilane coated with octanol, using octanol-saturated pH 7.00 (0.01 *M*) phosphate buffer as the mobile phase; ambient temperature. Each point is the average of at least two injections. Number in parentheses is the number of independent determinations on different columns. All data were related back to a single set of conditions by simple linear regression using overlapping series of compounds. [d] This work; same solutions and temperatures (25 ± 1°) as HPLC work.

least-squares estimates of errors in P and K somewhat biased (the estimates of P and K are correct). However, in practice, fitting experimental data to the nonlinear form $\log D = \log P - \log [1 + (K_a/H)]$, where the error analysis is correct, gives virtually identical errors as found in the linearized Eqs. 2*a* and 2*b*. Therefore, propagation of error does not appear to be serious. [Note that $s_{\log y} = (0.4343 s_y)/y$, where s is the standard deviation (12)]. Furthermore, for any two pH values, the following equations can be derived:

$$K_a = H_1H_2(D_1 - D_2)/(H_1D_2 - H_2D_1) \quad \text{(Eq. 3a)}$$

$$s_{K_a} = [1/(H_1D_2 - H_2D_1)^2][(D_1 - D_2)^2(H_2^4D_1^2s_{H_1}^2 + H_1^4D_2^2s_{H_2}^2) + H_1^2H_2^2(H_1 - H_2)^2(D_2^2s_{D_1}^2 + D_1^2s_{D_2}^2)]^{1/2} \quad \text{(Eq. 3b)}$$

$$K_a{}^b = (D_1 - D_2)/(H_1D_1 - H_2D_2) \quad \text{(Eq. 3c)}$$

$$s_{K_a{}^b} = [1/(H_1D_1 - H_2D_2)^2][(D_1 - D_2)^2(D_1^2s_{H_1}^2 + D_2^2s_{H_2}^2) + (H_1 - H_2)^2(D_2^2s_{D_1}^2 + D_1^2s_{D_2}^2)]^{1/2} \quad \text{(Eq. 3d)}$$

and the standard deviation in K_a can be estimated by propagation of error. The results also agree closely with those of ordinary least squares near the pKa.

Some comparisons of pKa values determined by the reversed-phase HPLC and other procedures are given in Table III. The procedure is clearly sufficiently accurate for quantitative structure–activity studies and requires only a small amount of material, which can be impure if the impurity separates from the main peak. To increase the degrees of freedom, each observation (injection) can be used instead of averages. Errors for pKa are slightly larger than those for log P by the HPLC procedure, but they are comparable to other methods. Furthermore, this result is not always found in other series of compounds.

The overall correlation between $\log P_{\text{shake flask}}$ and $\log k'$, including all points (Fig. 2), is given by:

Table III—Comparison of Log *P* and Apparent pKa$^{\text{Octanol/Water}}$ Determined Simultaneously by HPLC with Literature Values

Compound	HPLC[a] pKa	HPLC[a] Log *P*	Literature[b] pKa	Literature[b] Log *P*
Naproxen	4.28 ± 0.02[c]	3.21 ± 0.01[c]	4.53 ± 0.06[c,d]	3.18
	4.21 ± 0.02[e]	3.20 ± 0.01[e]	4.39 ± 0.02[d,e]	
			4.15[f]	
			4.57[c,g]	
			4.6	
Benzoic acid	4.33 ± 0.02[c]	1.78 ± 0.01[c]	4.20[c]	1.87
	4.38 ± 0.03[e]	1.77 ± 0.01[e]	4.18	
Salicylic acid	3.52 ± 0.03[c]	2.00 ± 0.01[c]	3.00	2.23 ± 0.03[h]
	3.29 ± 0.03[e]	2.18 ± 0.01[e]		
p-Toluic acid	4.30 ± 0.09[c]	2.22 ± 0.02[c]	4.37	2.27
	4.41 ± 0.01[e]	2.26 ± 0.01[e]		

[a] Three or four injections at each of two to four pH values at indicated ionic strength; each injection was converted to log *D* (then *D*) by use of standards and used to fit Eq. 1*a*. [b] See Table II, footnote *b*. The pKa values corrected to 25° from Albert and Serjeant or G. Kortüm, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solution," Butterworths, London, England, 1961, unless otherwise indicated. [c] $n = 0.1$. [d] Spectrophotometric. [e] $\mu = 0.01$. [f] Titration in water; 25°. [g] Titration in ethanol, extrapolated to 0% ethanol. [h] Average of three literature values.

$$\log P = 1.025\ (0.061) \log k' + 0.797\ (0.061) \quad \text{(Eq. 4)}$$

$$n = 33 \quad s = 0.127 \quad r = 0.987 \quad F_{1,31} = 1167$$

where F is the overall F test for the regression, and the 95% confidence limits on the regression coefficients are given in parentheses. Omitting the relatively unhindered pyridine, 3- and 4-picolines, and 2-amino-4-picoline yields:

$$\log P = 1.002\ (0.025) \log k' + 0.853\ (0.026) \quad \text{(Eq. 5)}$$

$$n = 29 \quad s = 0.051 \quad r = 0.998 \quad F_{1,27} = 6643$$

The compounds 2-ethylpyridine and quinoline deviate by 2.48 and 2.07 *SD*, respectively, from calculated values. These compounds are slightly more hindered and weaker bases than pyridine and the picolines. Omitting these two compounds yields:

$$\log P = 1.008\ (0.020) \log k' + 0.857\ (0.021) \quad \text{(Eq. 6)}$$

$$n = 27 \quad s = 0.040 \quad r = 0.999 \quad F_{1,25} = 10{,}533$$

All points are now less than 2 *SD* from calculated values using Eq. 6, and hindered, weakly basic pyridines such as 2,6-lutidine and acridine are easily accommodated by this equation. Thus, essentially perfect agreement between shake-flask and reversed-phase HPLC procedures using octanol over a log *D* range of 3.5 units is obtained. Only small, basic, unhindered pyridines deviate, presumably because of binding to residual silinol sites. Since most drugs are considerably larger, this deviation should not pose a practical limitation. Furthermore, it seems only prudent that at least one member of a potentially suspect series should be determined by classical procedures and the agreement with the reversed-phase HPLC values established. Finally, other reversed-phase packing materials from other sources were not investigated; presumably, they would differ in the extent of free silinol sites after persilation (5).

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ACKNOWLEDGMENTS

The authors thank Dr. David Johnson, Dr. Richard Runkel, and Dr. David Robertson for permission to cite their pKa determinations on naproxen and Dr. Richard Jones for access to his NLNMRQ modification of Metzler's (Upjohn) NONLIN program.
This paper is contribution 500 from the Syntex Institute of Organic Chemistry.

Substituted Tetralins VI: Tentative Assignment of Absolute Stereochemistry of 1-Methyl-1-phenyl-1,2,3,4-tetrahydro-3-naphthoic Acid and *N,N*,1-Trimethyl-1-phenyl-1,2,3,4-tetrahydro-3-naphthylamine Isomers

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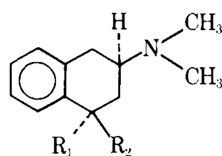
Abstract ☐ The absolute configurations of the enantiomers of *N,N*,1-trimethyl-*cis*- and *trans*-1-phenyl-1,2,3,4-tetrahydro-3-naphthylamines (I*a* and I*b*) were assigned tentatively from the circular dichroism spectrum of a bridged ketone derived by cyclization of optically active 1-methyl-*cis*-1-phenyl-1,2,3,4-tetrahydro-3-naphthoic acid (II*a*). Thus, (−)-II*a* and the corresponding amine, (−)-I*a*, were assigned the (2*S*, 4*R*)-configuration. Epimerization of (−)-II*a* through its methyl ester yielded the *trans*-acid, (−)-II*b*, which established the absolute configuration of (−)-II*b* and the corresponding amine, (−)-I*b*, as (2*R*, 4*R*).

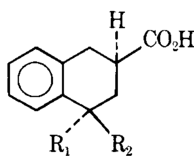
Keyphrases ☐ Tetralins, substituted—absolute configurations of enantiomers of 1-methyl-1-phenyl-1,2,3,4-tetrahydro-3-naphthoic acid and *N,N*,1-trimethyl-1-phenyl-1,2,3,4-tetrahydro-3-naphthylamine assigned ☐ Naphthoic acids and naphthylamines, substituted—absolute configurations of enantiomers assigned ☐ Stereochemistry—substituted naphthoic acids and naphthylamines, absolute configurations assigned

Previous publications described the synthesis of racemic *N,N*,1-trimethyl - 1 - phenyl-1,2,3,4-tetrahydro-3-naphthylamine diastereoisomers (I*a* and I*b*) (1) and the precursors 1-methyl-1-phenyl-1,2,3,4-tetrahydro-3-naphthoic acids (II*a* and II*b*) (2). Since various aminotetralin structures (1) exhibit analgesic (3–5) and/or analgesic antagonist (6) properties in animals, it was desirable to resolve some of the more active racemic compounds and to establish the absolute configuration of the enantiomers. Moreover, the precursor acids are potentially stereoselective anti-inflammatory analgesics.

This report describes the resolution of the diastereoisomeric acids (±)-II*a* and (±)-II*b*, the stereospecific conversion of each enantiomer to the corresponding *N,N*-dimethylamino derivatives, and the tentative assignment of absolute stereochemistry of the acids and amines.



I*a*: $R_1 = CH_3$, $R_2 = C_6H_5$
I*b*: $R_1 = C_6H_5$, $R_2 = CH_3$



II*a*: $R_1 = CH_3$, $R_2 = C_6H_5$
II*b*: $R_1 = C_6H_5$, $R_2 = CH_3$

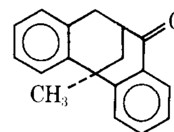
DISCUSSION

Stereochemical relationships among stereoisomers I*a*–I*b* and II*a*–II*b* were elucidated by resolution of the acids and stereospecific conversion of II*a* and II*b* to the corresponding amines. Thus, racemic II*a* and II*b* were resolved by fractional recrystallization of their (+)-dehydroabietylamine salts. Each enantiomer was converted to the corresponding primary amine *via* the Curtius reaction. Subsequent Eschweiler–Clarke methylation afforded the tertiary amines. In this manner, (−)-I*a* was obtained from (−)-II*a*, (−)-I*b* was obtained from (−)-II*b*, *etc.*

The absolute configurations of the enantiomeric *cis*-acids, (−)-II*a* and (+)-II*a*, were determined by investigating the spectral properties of the bridged ketone (+)-7,12-dihydro-12-methyl-6,12-methanodibenzo[*a,d*]cycloocten-5(6*H*)-one [(+)-III], prepared by cyclization of (−)-II*a* in anhydrous hydrogen fluoride. This cyclization previously was employed to assign the relative stereochemistry of racemic II*a* and II*b* (2).

The absolute configuration of (+)-III was determined from its circular dichroism spectrum (Fig. 1), which exhibited a strong positive Cotton effect for the carbonyl $n \rightarrow \pi^*$ transition. The assignment was made on the basis of the octant rule for aryl ketones developed by Snatzke (7). The aryl ketone chirality rule is an extension of the chirality rules for conjugated enones (7, 8), wherein conjugation of the π-bonds of the aromatic ring with the carbonyl group is formally considered to comprise a combination of both *cisoid*- and *transoid*-enone contributions. In aryl ketones, the *cisoid*- and *transoid*-enone contributions predict the same sign of their Cotton effects and thus reinforce each other.

The aryl ketone chirality rule was employed to predict successfully the sign of the $n \rightarrow \pi^*$ Cotton effect for a wide variety of aryl ketones for which absolute configurations were established independently by chemical synthesis and/or X-ray crystallography. The rule was shown to hold for flavanones (9, 10), α-tetralones (11, 12), respirones and related 9,9′-spirobifluorenone derivatives (13), 1-oxo[2.2]*p*-cyclophanes (14), and 1-oxo[2.2]*m*-cyclophanes (15). In fact, a literature search through August 1977 revealed only one partial exception to the rule, a series of 6-bromo-7-oxoditerpenoids containing an aromatic C-ring (16) for which



III

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