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Stereochemical Studies on Medicinal Agents. II. Absolute Configuration of (−)-Phenampromide

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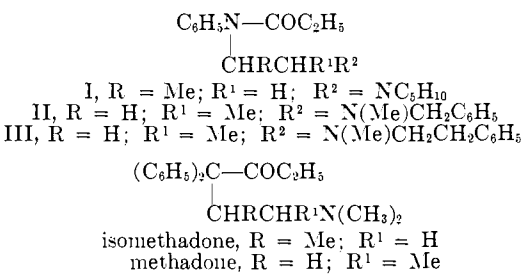
(−)-Phenampromide has been related to (*R*)-N-phenylalanine whose configuration was established by observing the steric course of displacement reactions of aniline on (*S*)-2-bromopropionate at different aniline concentrations.

Phenampromide (I)[1] is a relatively new, potent analgetic which may be considered structurally related to isomethadone. As in the case of (−)-isomethadone (XVII),[2] (−)-phenampromide[3] has greater analgetic potency than its (+)-enantiomer.[1]

We recently have determined[4] the configuration of certain basic anilide analgetics (II and III)[5,6] which bear somewhat of a structural similarity to methadone. Our results were quite unexpected as, unlike the methadone analgetics,[7] the more active enantiomers of II and III are related to (*S*)-alanine.

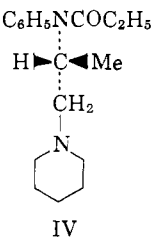
These results have prompted us to determine the configuration of (−)-phenampromide to see whether this analgetic is stereochemically related to (*S*)-isomethadone (XVII). We wish to report the chemical transformations which permit assignment of this structure as (*R*)-N-(1-methyl-2-piperidinoethyl)propionanilide (IV).[8]



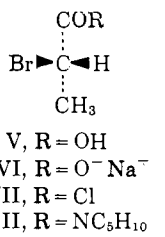
I, R = Me; R^1 = H; R^2 = NC_5H_{10}
II, R = H; R^1 = Me; R^2 = $N(Me)CH_2C_6H_5$
III, R = H; R^1 = Me; R^2 = $N(Me)CH_2CH_2C_6H_5$

isomethadone, R = Me; R^1 = H
methadone, R = H; R^1 = Me

Our first approach involved the preparation of the (*S*)-bromoamide VIII, which we hoped to transform into the anilino derivative XIII, *via* an S_N2 displacement reaction with aniline. Since our starting material, (*S*)-2-bromopropionic acid (V),[9] is optically labile, we prepared the acid chloride VII by treating the sodium salt VI with oxalyl chloride at 0°. This then was converted *in situ* to VIII, $[\alpha]_D$ +81.6°, which subsequently was transformed, under various conditions, to the anilino amide XIII. As the stereochemical course of similar reactions is known to proceed with inversion[10] of configuration, the anilino compound should be in the (*R*) series. In these experiments, however, the low rotation, $[\alpha]_D$ −2°,[11] of the product XIII suggested that a substantial amount of racemization had occurred during this inversion step. We turned, therefore, to an alternate route which would afford XIII in a high degree of optical purity.



IV



V, R = OH
VI, R = O^-Na^+
VII, R = Cl
VIII, R = NC_5H_{10}

A compound which can be transformed into phenampromide is N-phenylalanine (IX).[12] We have prepared IX from 2-chloropropionic acid and aniline. The spectral characteristics of this amino acid are of interest. An infrared spectrum of IX in absolute ethanol shows a band at 5.75 μ, indicating the presence of an un-ionized carboxyl group. The fact that the ultraviolet spectrum of IX is superimposable with that of its methyl ester XV also supports the presence of an un-ionized species in solution. If the zwitterionic form of IX had been present, it should have shown a hypsochromic shift[13] when compared to XV. Interestingly, a solid state (mull) infrared spectrum displays an ab-

(1) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Org. Chem.*, **26**, 476 (1961).

(2) D. G. Leimbach and N. B. Eddy, *J. Pharmacol. Exptl. Therap.*, **110**, 135 (1954).

(3) Both the base and the corresponding hydrochloride salt are levorotatory.

(4) P. S. Portoghese and D. L. Larson, *J. Pharm. Sci.*, **53**, 302 (1964).

(5) W. B. Wright, Jr., and R. A. Hardy, Jr., *J. Med. Chem.*, **6**, 128 (1963).

(6) W. B. Wright, Jr., H. J. Brabander, and R. A. Hardy, Jr., *J. Org. Chem.*, **26**, 485 (1961).

(7) A. H. Beckett in "Progress in Drug Research," Vol.1, E. Jucker, Ed., Birkhauser Verlag, Basel, 1959, p. 455.

(8) For a preliminary report on this work see, P. S. Portoghese, *Chem. Ind.* (London), 582 (1964).

(9) S. J. Fu, S. M. Birnbaum, and J. P. Greenstein, *J. Am. Chem. Soc.*, **76**, 6054 (1954).

(10) W. A. Cowdry, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 1208 (1937).

(11) This represents the maximum rotation obtained.

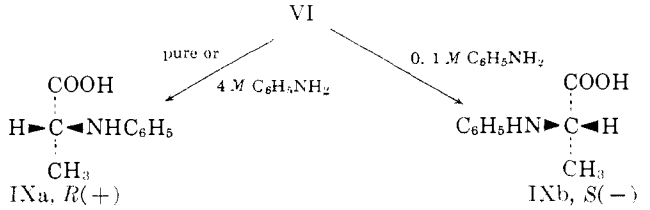
(12) H. Tiemann, *Ber.*, **15**, 2034 (1882).

(13) W. D. Kumler and L. A. Strait, *J. Am. Chem. Soc.*, **65**, 2349 (1943).

sorption at 6.30 μ which corresponds to carboxylate anion. This indicates that only in the crystalline state is IX present as the zwitterion.

Although most resolution procedures have employed N-acylated amino acids to promote salt formation with optically active bases,[14] the preceding spectral data suggested that the negatively substituted nitrogen of IX would not be basic enough to prevent salt formation with a basic resolving agent.

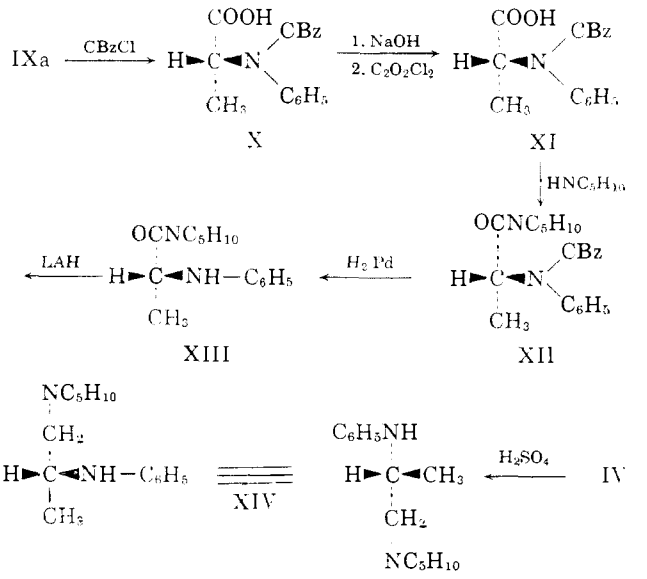
The deracemization of IX was accomplished by fractional crystallization of its quinine salt from methanol–acetone. On the first crystallization, the salt crystallized in the form of large triclinic crystals. Recrystallization altered neither the optical rotation nor the melting point of the material. Regeneration of the amino acid from the quinine salt afforded (+)-N-phenylalanine (IXa), $[\alpha]D$ +71°.



Our configurational assignment[15] of (+)-N-phenylalanine (IXa) is based upon the conclusions of Cowdrey, *et al.*, who have rigorously established the mechanism and steric course of displacement reactions on optically active sodium 2-bromopropionate (VI). When VI was heated in pure aniline, partially racemic IXa, $[\alpha]D$ +28.5°, was produced. Carrying out the reaction of 0.1 *M* VI in 4 *M* methanolic aniline likewise afforded IXa, $[\alpha]D$ +7.0°. When the concentration of aniline was reduced to 0.1 *M*, the partially racemic enantiomeric product IXb, $[\alpha]D$ −9.0°, was formed.

The aforementioned results are consistent with the established stereochemical course of displacement reactions on VI.[10] In both pure or 4 *M* aniline the net effect is inversion due to S$_N$2 attack by aniline. However, in 0.1 *M* aniline there is net retention of configuration due to neighboring carboxylate anion participation. Since VI is known to have the (*S*) configuration,[9] an S$_N$2 displacement by aniline should afford a product in the (*R*) series. Thus, (+)-N-phenylalanine is represented by formula IXa and possesses the (*R*) configuration. The configuration of (−)-phenampromide (IV) was established by transforming *R*(+)-N-phenylalanine (IXa) to the diamine XIV, obtained from the hydrolysis of IV.

In preliminary experiments, we found that piperidinolysis of the racemic ester XV produced a small quantity of racemic XIII only on prolonged heating at 100°. Since a substantial amount of racemization could occur under such conditions, we employed a less direct route to ensure the optical purity of XIII. Stirring a mixture of (*R*)-N-phenylalanine and benzyl chloroformate in aqueous sodium bicarbonate solution for 15 hr. afforded the carbobenzoxy derivative X, $[\alpha]D$ −36.8°, which was converted to its sodium salt by titration with methanolic sodium methoxide. Addition of an equivalent quantity of oxalyl chloride to a cooled suspension of the sodium salt in ether afforded the acid chloride XI, which was then treated *in situ* with 2 equiv. of piperidine. Chromatographic purification of the crude product yielded XII, $[\alpha]D$ −60°. The infrared spectrum of XII is identical with that of the racemic compound which was prepared by treating racemic XIII with benzyl chloroformate.



During the chromatographic purification of XII, an oily fraction was isolated which displayed infrared absorption bands at 5.40, 5.60, and 5.85 μ. The spectral data are consistent with structure XVI, which can arise by the interaction of the sodium salt of X with the acid chloride XI. Little if any anhydride XVI was detected in preliminary experiments with racemic material. We attribute this to the difference in solubility between the racemic and optically active sodium salts of X, the latter having greater solubility in ether due to the presence of impurities.

Catalytic hydrogenolysis of XII afforded XIII, $[\alpha]D$ −13°, whose infrared spectrum is identical with that of the racemic compound.[1] The (−) rotation of XIII corroborates our configurational assignment of (+)-N-phenylalanine. Assuming XIII to be optically pure, the partially racemic XIII, $[\alpha]D$ −2°, arising from the S$_N$2 reaction of VIII with aniline, possesses approximately 15% optical activity.

Reduction of XIII with lithium aluminum hydride produced the diamine XIV, which was directly converted to its dipicrate salt, m.p. 134–135°, $[\alpha]D$ −60°. The infrared spectrum of XIV dipicrate is identical with that of the diamine dipicrate, $[\alpha]D$ −53°, m.p. 134–135°, derived from the sulfuric acid hydrolysis of (−)-phenampromide.[3]

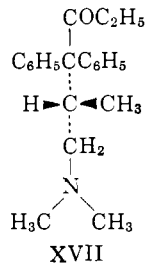
The fact that (*R*)-phenampromide (IV), (*S*)-isomethadone (XVII),[16] and (2*S*:3*R*)-propoxyphene (XVIII)[17] are stereochemically related and all possess

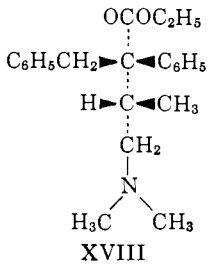
(14) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1961, p. 515.

(15) For a preliminary report on this work see, P. S. Portoghese, *J. Pharm. Sci.*, **53**, 228 (1964).

(16) A. H. Beckett, G. Kirk, and R. Thomas, *J. Chem. Soc.*, 1386 (1962).

(17) H. R. Sullivan, J. R. Beck, and A. Pohland, *J. Org. Chem.*, **28**, 2381 (1963).


XVII


XVIII

greater analgetic activity[1,2,18] than their enantiomers suggests that these analgetics are exerting their activity through a stereoselective combination with a common analgetic receptor. (*S*)-Isomethadone is 40 times as potent as its enantiomorph,[2] and (2*S*:3*R*)-propoxyphene has been reported[18] to possess all the activity in the racemate. This is in contrast to phenampromide[1] where the potency of the (*R*) is only 4 times greater than the (*S*) compound. The differences in the enantiomeric potency ratios may be due, in part, to differences in the ability of enantiomorphs to combine with an analgetic receptor in a pharmacologically productive conformation.[7] It is conceivable that the planar nature of the amide moiety in phenampromide is a contributing factor in lowering the receptor's discrimination between enantiomers.

Experimental[19]

(*S*)-2-Bromopropionpiperidide (VIII).—A stirred solution of 16.1 g. (0.11 mole) of (*S*)-2-bromopropionic acid in 30 ml. of methanol, maintained at −15°, was titrated to a phenolphthalein end point with 1 *M* methanolic NaOH. The solvent was removed *in vacuo* and the sodium salt VI was dried at 25° (0.1 mm.) for 36 hr. The salt was pulverized and again dried at 65° (0.1 mm.) for 30 min. To a stirred suspension of 17.6 g. (0.10 mole) of VI in 100 ml. of ether maintained at 0° was added dropwise 13.0 g. (0.10 mole) of oxalyl chloride. After the evolution of gas had stopped (15 min.), the mixture was maintined below 5° while a solution of 17.0 g. (0.20 mole) of piperidine in 30 ml. of ether was added with stirring. After standing at 0° for an additional 50 min., the mixture was filtered and the organic phase was washed with dilute HCl then with water. The ether solution was dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo*. The yield of VIII, $[\alpha]^{29}D$ +81.6° (5% in chloroform), was 17.1 g. An infrared spectrum of this amide was identical with that of racemic VIII.[1]

Reactions of Aniline with (*S*)-2-Bromopropionpiperidide (VIII).—A solution of 17.1 g. (0.08 mole) of VIII and 14.5 g. (0.16 mole) of aniline in 50 ml. of benzene was refluxed for 6 hr. The mixture was filtered and the solvent was removed *in vacuo*. The remaining oil crystallized from 45 ml. of ethanol to yield 8.03 g. of XIII, m.p. 88–89.5°, $[\alpha]^{23}D$ −2.4° (5% in ethanol). The infrared spectrum was identical with that of the totally racemic[1] material.

In a subsequent experiment 3.35 g. (0.015 mole) of VIII, 1.40 g. (0.015 mole) of aniline, 1.6 g. (0.015 mole) of Na_2CO_3, and 4.0 g. of Drierite were refluxed in 12 ml. of benzene for 12 hr. The product XIII, obtained in a yield of 0.85 g., was totally racemic.

In another experiment 13.0 g. (0.055 mole) of VIII was stirred with 10.2 g. (0.11 mole) of aniline at room temperature. After 2 hr., the mixture was mixed with 40 ml. of benzene and filtered. The solvent was removed *in vacuo* and the residual oil was crystallized from 25 ml. of ethanol. The yield of XIII, $[\alpha]^{20}D$ −1.2° (5% in ethanol), was 6.22 g.

(±)-N-Phenylalanine[12] (IX).—A mixture of 54.3 g. (0.50 mole) of 2-chloropropionic acid, 140 g. (1.50 moles) of aniline, and 100 ml. of ethanol were heated on a steam bath for 4.5 hr. The solvent was removed *in vacuo*, 200 ml. of 5 *N* NaOH was added, and the mixture was extracted twice with ethyl acetate. The aqueous solution was acidified with concentrated H_2SO_4 to pH 4 and the product was filtered, washed with water, and dried. The yield of crude product, m.p. 156–160°, was 55.5 g. (67%). After recrystallization from methanol, the melting point was 158–160°. A solid-state, infrared spectrum (mull) showed a band at 6.30 μ (carboxylate anion). In absolute ethanol the 6.30-μ band was absent and an absorption at 5.73 μ was observed; λ_{max}^{alc} 242 mμ (ε 10,300) and 291 mμ (ε 1900).

Methyl (±)-N-Phenylalaninate (XV).—Dry HCl was bubbled into a solution of 4.95 g. (0.03 mole) of IX in 50 ml. of methanol to saturation. The methanol was removed *in vacuo*, and the crude hydrochloride was recrystallized from methanol–ether. The yield of XV hydrochloride, m.p. 176°, was 5.9 g.

To an aqueous solution containing 4.96 g. (0.023 mole) of the hydrochloride, enough 1 *N* NaOH was added to make the solution distinctly alkaline. The free base was extracted into ether, dried over Drierite, and the solvent was removed *in vacuo*. The yield of XV, m.p. 46–48°, was 3.9 g. It showed no change in melting point when recrystallized from Skellysolve B; λ_{max}^{alc} 242 mμ (ε 10,000) and 291 mμ (ε 1900).

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.03; H, 7.33; N, 7.83. Found: C, 67.44; H, 7.35; N, 8.00.

(+)-N-Phenylalanine (IXa).—(±)-N-Phenylalanine (74.3 g., 0.45 mole) was dissolved in 675 ml. of acetone and combined with a solution consisting of 145.8 g. (0.45 mole) of quinine dissolved in 135 ml. of methanol and 315 ml. of acetone. After 24 hr. at room temperature, there was obtained 59.5 g. of quinine salt, m.p. 199–201°, $[\alpha]^{22}D$ −126° (2% in ethanol), in the form of large prisms. Two subsequent recrystallizations did not alter the melting point or specific rotation.

Anal. Calcd. for $C_{29}H_{35}N_3O_2$: C, 71.20; H, 7.22; N, 8.58. Found: C, 71.11; H, 7.33; N, 8.90.

The quinine salt (50.0 g., 0.10 mole) was shaken in a separatory funnel with 150 ml. of *M* NaOH and 100 ml. of chloroform. The organic phase was drawn off and the aqueous phase was washed with a portion of chloroform. The aqueous phase was then acidified to pH 4, and the product was filtered, washed with water, and dried *in vacuo*. The yield of IXa, m.p. 149–150°, $[\alpha]^{23}D$ +71° (2% in ethanol), was 13.1 g. The infrared spectrum (mull) was very similar to racemic IX.

Reactions of Sodium (*S*)-2-Brompropionate (VI) with Aniline.—A mixture of 0.53 g. (0.003 mole) of VI and 1 ml. of aniline was heated on a steam bath for 20 min. After addition of 6 ml. of 1 *M* NaOH, the mixture was extracted with ether. The aqueous solution was acidified to pH 4 and the precipitate was washed and dried. The yield of IXa, m.p. 150–155°, $[\alpha]^{22}D$ +28.5° (4% in ethanol), was 0.20 g.

A solution of 1.75 g. (0.01 mole) of VI and 14.9 g. (0.16 mole) of aniline in 40 ml. of methanol was refluxed for 45 min. The solution was cooled, acidified with 500 ml. of 0.1 *N* H_2SO_4, filtered, and extracted with ethyl acetate. The organic phase was dried and the solvent was removed. The solid residue was washed with ether, then dried. The yield of IXa, m.p. 158–160°, $[\alpha]^{22}D$ +7.0° (4% in ethanol), was 0.46 g.

A solution of 1.75 g. (0.01 mole) of VI and 0.93 g. (0.01 mole) of aniline in 100 ml. of methanol was refluxed for 5 hr. After this period, 30 ml. 6 *N* HCl was added to the solution and the methanol was removed *in vacuo*. The solution was extracted with ethyl acetate, and the organic phase was dried over Na_2SO_4. The ethyl acetate was removed, and the solid residue was filtered, washed with ether, and dried. The yield of IXb, m.p. 157–159°, $[\alpha]^{23}D$ −9.0° (4% in ethanol), was 0.16 g.

Attempted Piperidinolysis of Methyl (±)-N-Phenylalaninate (XV).—A mixture of 0.90 g. (0.005 mole) of ester and 4 ml. of piperidine was heated on a steam bath for 4 hr. An infrared spectrum and thin layer chromatography indicated that only a small quantity of the amide was formed.

(−)-N-Carbobenzoxy-N-phenylalanine (X).—To a 70-ml. aqueous solution containing 8.4 g. (0.10 mole) of $NaHCO_3$ and 6.6 g. (0.04 mole) of IXa, $[\alpha]^{23}D$ +71°, was added 7.5 ml. of benzyl chloroformate. The mixture was stirred vigorously for 15 hr. and extracted with ether. The aqueous solution was acidified to pH 4 with HCl and extracted with chloroform. The chloroform layer was washed with 1 *M* HCl and dried over Na_2SO_4, and the solvent was removed *in vacuo*. The yield of X, an oil, $[\alpha]D$ −36.8° (3% in ethanol), was 4.05 g. When the reaction was carried out with racemic N-phenylalanine following the same procedure, a crystalline product, m.p. 93.5–94.5°, was isolated which had an infrared spectrum identical with that of the optically active material.

(18) A. Pohland and H. R. Sullivan, *J. Am. Chem. Soc.*, **77**, 3400 (1955).
(19) All melting points are corrected.

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.25; H, 5.75; N, 4.69. Found: C, 68.34; H, 5.80; N, 4.69.

(−)-2-(N-Carbobenzoxyanilino)propionpiperidide (XII).—A cooled solution of 4 g. (0.013 mole) of X in 10 ml. of methanol was titrated with 1 *M* methanolic NaOH or NaOMe to a phenolphthalein end point. The methanol was removed and replaced with a mixture of ether–Skellysolve B. After the material was collected and dried at 65° (0.1 mm.) for 36 hr., there was obtained 3.16 g. of sodium salt. This salt, partially soluble in ether, was placed in 20 ml. of ether and cooled to about 0°. To the stirred mixture was added dropwise, 1.4 g. (0.011 mole) of oxalyl chloride in 10 ml. of ether. After all the gas had evolved (15 min.), 1.87 g. (0.02 mole) of piperidine was added to the cooled, stirred mixture over a 15-min. period. The mixture was allowed to stand for 0.5 hr. and filtered. The ether solution was washed with 1 *M* HCl, then with 1 *M* $NaHCO_3$, dried over Drierite, and the ether was removed *in vacuo*. There was obtained 2.41 g. of an oil which was chromatographed on a silicic acid–chloroform column. The first fraction (0.42 g.) consisted mainly of XVI, an oil; λ_{max} 5.40, 5.60 (anhydride), and 5.86 μ (carbamate). The second fraction (1.54 g.), which contained the desired product, was recrystallized several times from ethyl acetate–Skellysolve B to afford 0.50 g. of XII, m.p. 74–76°, $[\alpha]^{23}D$ −60° (2% in ethanol), λ_{max} 5.88 (carbamate) and 6.03 μ (amide).

Anal. Calcd. for $C_{22}H_{26}N_2O_3$: C, 72.21; H, 7.15; N, 7.65. Found: C, 71.96; H, 7.07; N, 7.32.

The infrared spectrum of the above compound was identical with that of racemic XII, m.p. 93–95°, prepared by treating 2.32 g. (0.01 mole) of racemic XIII with 2 g. (0.022 mole) of benzyl chloroformate in a mixture of 15 ml. each of 1.5 *M* $NaHCO_3$ and $CHCl_3$. The mixture was stirred vigorously for 6 hr. and the chloroform layer was separated from the aqueous phase. After washing the organic phase with 1 *M* HCl, it was dried over Drierite and the solvent was removed. The oil (2.24 g.) solidified on standing and was recrystallized from ethyl acetate–Skellysolve B.

(−)-2-Anilinopropionpiperidide (XIII).—Intermediate XII (0.47 g., 0.001 mole) in 10 ml. of methanol was shaken for 17 min. with 0.1 g. of palladium on carbon under hydrogen at 1.76 kg./cm.^{2} (25 p.s.i.). The mixture was filtered and the catalyst was washed with methanol. The solvent was removed *in vacuo* to afford 0.26 g. of XIII, m.p. 63–65°, $[\alpha]^{23}D$ −13° (1% in ethanol). The infrared spectrum of XIII was identical with that of the racemic compound.[1]

(−)-N^1-Pentamethylene-N^2-phenyl-1,2-propanediamine Dipicrate.—To a stirred mixture of 0.082 g. (0.002 mole) of $LiAlH_4$ in 2 ml. of tetrahydrofuran was dropped 0.25 g. (0.001 mole) of XIII in 2 ml. of tetrahydrofuran. The mixture was refluxed for 5 hr., then treated successively with 0.1 ml. of water, 0.2 ml. of 15% NaOH, and 0.1 ml. of water, and filtered. The solvent was removed *in vacuo* and the residue was dissolved in 1 ml. of ethanol. Enough saturated ethanolic picric acid was added to produce complete precipitation. The yield of XIV dipicrate, m.p. 132.5–134.5°, was 0.56 g. Recrystallization from ethanol afforded 0.40 g. of the salt, m.p. 134–135.5°, $[\alpha]^{23}D$ −60° (2% in acetone).

Anal. Calcd. for $C_{26}H_{28}N_8O_{14}$: C, 46.25; H, 4.23; N, 16.61. Found: C, 46.31; H, 4.41; N, 16.51.

Hydrolysis of (−)-Phenampromide (IV).—A mixture of 3 ml. of concentrated H_2SO_4, 3 ml. of water, and 1.37 g. (0.005 mole) of (−)-phenampromide[3] was heated on a steam bath for 15 hr. The solution was made basic with 4 *N* NaOH and extracted with ether. The organic phase was dried, and the solvent was removed *in vacuo*. To the residue was added 4 ml. of ethanol and enough saturated alcoholic picric acid to ensure complete precipitation. The yield of XIV dipicrate, m.p. 133.5–135.5°, was 1.74 g. Recrystallization from ethanol afforded 1.48 g., m.p. 134–136°, $[\alpha]^{23}D$ −53° (2% in acetone), of XIV dipicrate. No melting point depression was observed when the salt was mixed with the dipicrate of the diamine XIV obtained from IXa. The infrared ($CHCl_3$) spectra of the dipicrates obtained by different routes were identical.

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Substituent Constants for Aliphatic Functions Obtained from Partition Coefficients

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From the partition coefficients between 1-octanol and water of a variety of derivatives of the type $C_6H_5(CH_2)_nX$, the partition constants (π) for the aliphatic functions X have been determined. The practical value of the additive character of π for the correlation of biological activity with chemical structure is illustrated with data on the narcotic action of alcohols, esters, ketones, and ether on tadpoles. The relation of π to ΔR_M (a chromatographically determined substituent constant) is shown.

Recently we have shown that substituent constants can be useful in the quantitative correlation of biological activity with chemical structure.[3] In particular, we have found that using electronic parameters such as the Hammett σ-constant, pK_a values, or electron densities obtained from molecular orbital calculations with a substituent constant π (π = log P_X − log P_H) obtained from partition coefficients, mathematical expressions could be found for correlation in a wide variety of structure–activity problems. π is a free-energy-related constant for a functional group and is similar to σ. For example, π for the CH_3 group is found by subtracting the logarithm of the partition coefficient for benzene (P_H) from that of toluene (P_X). We have used 1-octanol–water for the solvent system. In evaluating π from partition coefficients obtained with over 200 aromatic compounds, we have observed that π for a given function remains approximately constant in much the same fashion as does σ as long as no strong group interactions occur.[4]

We now report values for functional groups not attached to an aromatic nucleus. These too appear to be approximately constant when strong group interactions are absent.

Table I gives the logarithm of the partition coefficients for a variety of compounds of the type $C_6H_5(CH_2)_nX$. The phenyl group was included for analytical con-

(1) On leave from Okayama University, Okayama, Japan.

(2) On leave from Kyoto University, Kyoto, Japan.

(3) (a) C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964); (b) C. Hansch and A. R. Steward, *J. Med. Chem.*, **7**, 691 (1964); (c) C. Hansch, A. R. Steward, and J. Iwasa, unpublished results.

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