For further characterization of *dl*-α-methylglutamic acid, the diethyl ester and the dinitrobenzoyl derivative of the diethyl ester were prepared.

Experimental

γ-Cyano-γ-valerolactone (I).—A solution of 86.5 g. (0.6 mole) of ethyl levulinate in 100 ml. of ether was added dropwise to a vigorously stirred solution of 40 g. (0.75 mole) of ammonium chloride in 120 ml. of water cooled to 5–10°. Then a solution of 32 g. (0.65 mole) of sodium cyanide in 70 ml. of water was added with stirring. The mixture was stirred for an additional hour at 10° and then allowed to stand at room temperature overnight. The ether layer was separated and the aqueous layer extracted with ether. The ether extracts were combined, washed with 2 *N* HCl, then with water, dried and distilled after the addition of 2 drops of 85% phosphoric acid. Fifteen grams of ethyl levulinate, b.p. 96° (16 mm.), was recovered and 32 g. (51%) of γ-cyano-γ-valerolactone (I), b.p. 142–145° (16 mm.), m.p. 29–30°, was obtained; reported[4] m.p. 29–30°.

γ-Cyano-γ-valerolactam (II).—A solution of 20 g. of γ-cyano-γ-valerolactone (I) in 200 ml. of methanol was saturated at 0° with anhydrous ammonia gas and then allowed to stand overnight at room temperature. The excess ammonia and the methyl alcohol was removed under diminished pressure. The precipitate was recrystallized from water to give 13 g. (65%) of γ-cyano-γ-valerolactam (II), m.p. 143–144°. The lactam (II) is soluble in water, alcohol, acetone and only slightly soluble in benzene and ether. A 10% aqueous solution of II has a *p*H of 7.2–7.4.

Anal. Calcd. for $C_6H_8ON_2$: N, 22.57. Found: N, 22.37, 22.42.

γ-Cyano-γ-valerolactam (II) **Directly from Ethyl Levulinate.**—A solution of 100 g. (0.69 mole) of ethyl levulinate in 350 ml. of ethanol was added to a solution of 55 g. (1.03 mole) of ammonium chloride and 67 g. (1.03 mole) of potassium cyanide in 550 ml. of water and the mixture was allowed to stand at room temperature for 24 hours. Then 400 ml. of 28% ammonium hydroxide was added and the solution was allowed to stand for an additional 24 hours. The mixture was concentrated to dryness under diminished pressure. The residue was crystallized twice from water and once from methanol to yield 63 g. (73%) of II, m.p. 143–144°.

***dl*-α-Methylglutamic Acid** (III).—A solution of 10 g. of γ-cyano-γ-valerolactam (II) in 150 ml. of 38% hydrobromic acid was refluxed for 2 hours. The solution was then concentrated to dryness under reduced pressure. The residue was dissolved in 20 ml. of hot water and *p*H adjusted to 3.2–3.5 with 6 *N* ammonium hydroxide. After the addition of 100 ml. of ethanol, the mixture was allowed to stand overnight. A yield of 11 g. (85%) of *dl*-α-methylglutamic acid (III), m.p. 167–169°, was filtered from the mixture. Recrystallization from 70 ml. of water gave 10 g. of product, m.p. 168–170° dec. (uncor.); reported[2] m.p. 168–170° dec. A 10% aqueous solution has a *p*H 3.1–3.3.

Anal. Calcd. for $C_6H_{11}O_4N$: N, 8.69. Found: N, 8.42, 8.44.

Diethyl *dl*-α-Methylglutamate.—A suspension of 1.6 g. (0.01 mole) of *dl*-α-methylglutamic acid in 50 ml. of abs. ethanol was saturated with anhydrous hydrogen chloride and the mixture refluxed for 3 hours. The resulting solution was concentrated under reduced pressure. The residue was dissolved in water and the aqueous solution was made alkaline with potassium carbonate solution. The oil was separated from the aqueous layer which was extracted several times with ether. The oil and the ether extracts were combined, dried and distilled. The yield of diethyl *dl*-α-methylglutamate, b.p. 94–96° (2 mm.), $n^{21}D$ 1.4506, was 0.75 g. (32%).

Anal. Calcd. for $C_{10}H_{19}O_4N$: N, 6.45. Found: N, 6.49, 6.52.

Diethyl N-(3,5-Dinitrobenzoyl)-*dl*-α-methylglutamate.—3,5-Dinitrobenzoyl chloride, 0.6 g. (0.0026 mole), was added to a solution of 0.5 g. (0.002 mole) of diethyl *dl*-α-methylglutamate in 10 ml. of anhydrous pyridine and the mixture was heated at 70° for 3 hours. The cold solution was poured into water and extracted several times with ether. The combined ether extract was washed once with 0.5 *N* sodium hydroxide solution and once with 0.5 *N* hydrochloric acid solution. After distilling the ether, the residue was recrystallized from ethanol until the m.p. was constant at 111–112°. The yield of diethyl N-(3,5-dinitrobenzoyl)-*dl*-α-methylglutamate was 0.4 g. (38%).

Anal. Calcd. for $C_{17}H_{21}O_9N_3$: N, 10.22. Found: N, 10.03, 10.04.

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(4) A. J. Ultée, *Rec. trav. chim.*, **28**, 22 (1909).

The Base Strengths of *cis*- and *trans*-1,2-Amino-alcohols

BY T. A. GEISSMAN, BURTON D. WILSON AND ROBERT B. MEDZ

RECEIVED MARCH 22, 1954

In a recent note, Smith and Hartung[1] reported the basic dissociation constants of tropine (pK_B 2.98) and pseudotropine (pK_B 3.67), and expressed the opinion that the weaker base strength of pseudotropine is consistent with its *cis*-configuration of the N–CH_3 and OH groups, a configuration that has been established by the acyl migration experiments of Fodor and Nador.[2]

Before the time of Fodor and Nador's first report[3] of their findings we had carried out base-strength determinations on the tropanols and a number of other amino alcohols. Our results (Table I) are in substantial agreement with Smith and Hartung's findings as to the difference between

TABLE I[4]

Compound	10^3 × ionic strength	pK_B	No. of runs	Range
Tropine	0.7	3.67	7	3.60–3.72
	5–10	3.50	6	3.41–3.55
	100	3.37	4	3.31–3.45
Tropine·HCl	10	3.45	3	3.42–3.46
	100	3.39	2	3.36–3.41
Pseudotropine	0.6	4.14	10	3.96–4.22
	5–10	3.99	5	3.97–4.02
	100	3.89	1	.....
Pseudotropine·HCl	10	3.96	4	3.94–4.07
	100	3.90	2	3.89–3.91
Piperidine[5]	30	2.82	6	2.78–2.85

the strengths of the two tropanols (although the absolute values differ somewhat from theirs).[6] The values in Table I show that tropine is a stronger base than pseudotropine by about 0.50 pK unit. At that time it was our provisional conclusion that these pK values indicated the opposite configurations for the tropanols from what they now appear

(1) P. F. Smith and W. H. Hartung, THIS JOURNAL, **75**, 3859 (1953).

(2) G. Fodor and K. Nador, *J. Chem. Soc.*, 721 (1953).

(3) G. Fodor and K. Nador, *Nature*, **169**, 462 (1952).

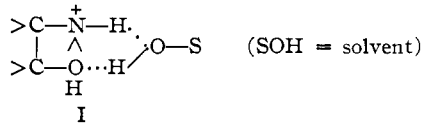
(4) All measurements at 25°.

(5) I. M. Kolthoff, *Biochem. Z.*, **162**, 289 (1925), reports pK_B 2.80 at 25°. W. F. K. Wynne-Jones and G. Salomon, *Trans. Faraday Soc.*, **34**, 1321 (1938), report pK_B 2.89 (25°) at u = 0.1 and 2.94 (25°) at u = 0 (extrapolated).

(6) When this manuscript was originally submitted, the Referee questioned the discrepancy between the absolute values for the pK's found by us and by Smith, *et al.* We have carried out repeated measurements on the carefully purified free bases and their hydrochlorides. Our new values are in substantial agreement with those we first obtained. Control determinations on piperidine gave values in excellent agreement with the reported pK.

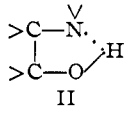
to be. In view of Fodor and Nador's result, it was our opinion that the base strengths of the tropanols do not represent what would be expected, but are actually anomalous in comparison with the behavior of analogously constituted systems; that is, the *a priori* interpretation of the base strengths would, on logical grounds, lead to the conclusion opposite to what is now known to be the correct one; their interpretation in terms of the known structures rests upon *post hoc* arguments.

Prelog and Häfliger[7] showed that there exist distinct differences in the pK values of pairs of 1,2-aminoalcohols, the *cis*-oid isomer being the stronger base. Prelog and Häfliger attributed this difference to the fact that hydrogen bonding stabilized the *cis*-oid conjugate acid (I) and thus made the *cis*-oid base appear the stronger (its conjugate acid the weaker) of such a *threo–erythro* pair. While it



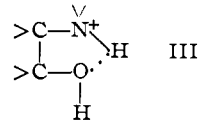
I

may be argued *a priori*, as Smith and Hartung appear to have done, that hydrogen bonding could stabilize the base with respect to protonation (II), making the *cis*-oid member the weaker base, and thus direct the argument to the opposite conclusion,



II

Prelog and Häfliger's results in the case of the ephedrine–pseudoephedrine series, interpreted in the light of structure assignments arrived at in other ways,[8] lead to the conclusion that the possibility of hydrogen bonding between the amino and hydroxyl groups increases base strength. Pauling[9] and Trotman-Dickenson[10] have discussed hydrogen-bonded solvation of amines and ammonium ions and have concluded that hydrogen bonding is more effective in the ions than in the free bases.[11] From these considerations it is reasonable to conclude that if a structure such as II is regarded as possible, the sterically equivalent III would be equally likely, and thus the stabilization of the ion III should contribute to increasing the strength of the base, as Prelog and Häfliger conclude.



III

In order to examine this question further, pK values were determined for four amines, *dl-cis*- and *trans*-2-aminocyclohexanol and *dl-cis*- and *trans*-2-aminocyclopentanol.[12] The results (Table II) are entirely in accord with the conclusions of Prelog and Häfliger. The *cis*- and *trans*-aminocyclohexanols and the *cis*-aminocyclopentanol are of about equal strength as bases and are stronger (by about 0.4 pK unit) than *trans*-aminocyclopentanol.

TABLE II

dl-1,2-Aminocycloalkanol	pK_A
cis-6	9.72
cis-5	9.70
trans-6	9.63
trans-5	9.28

In view of the foregoing evidence it would appear to be the logical conclusion that tropine, the stronger base, has the *cis* configuration and that pseudotropine is *trans*. Fodor and Nador[2] have shown, however, that the reverse is true.

It can be concluded that a sound interpretation of the differences between the base strengths of tropine and pseudotropine cannot be based upon a consideration only of the configuration of the hydroxyl group. Still unresolved effects of the conformations of these substances in solution may be of importance, possibly with respect to inter- rather than intramolecular interactions. It is possible that the strain imposed upon the ring system by the ethylene bridge is affected by the position of the hydroxyl group with respect to the bridge, and thus the tendency for the nitrogen atom to assume the tetrahedral form by ionization is affected by the configuration of the hydroxyl group. These questions cannot be answered without further study of suitably constituted models. This work is in prospect.

Experimental

Samples of tropine and pseudotropine were prepared by known methods. The compounds were rigorously purified by distillation and recrystallization. The pure substances had m.p. 63–64° (tropine) and 110–110.5° (pseudotropine).

Piperidine was redistilled; a middle, constant-boiling (107.2–107.3° (760.1 mm.)) fraction was used.

Titrations were carried out under nitrogen. Precautions were taken to exclude access of air to the purified bases. The standard acid and base used in the titrations were carefully standardized.

Calculation of the half-neutralization point from the weight of sample used, or by selecting the mid-point of the completed titration curve always gave values that agreed to within less than the differences between successive runs, and usually within 0.01 pK unit. In Table I no attempt has been made to define the statistical limits of error, but it is probable that the average values given are correct to ± 0.05 pK unit.

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(7) V. Prelog and O. Häfliger, *Helv. Chim. Acta*, **33**, 2021 (1950).

(8) W. J. Close, *J. Org. Chem.*, **15**, 1131 (1950).

(9) L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1949.

(10) A. F. Trotman-Dickenson, *J. Chem. Soc.*, 1293 (1949).

(11) See also, G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, p. 229.

(12) We are indebted to Dr. W. E. McCasland for his generosity in furnishing us with samples of these four compounds.

Stereochemical Specificity of Enzymatic Cleavage of β-Phenylserine

BY JAMES B. GILBERT

RECEIVED APRIL 28, 1954

The enzymatic cleavage of several β-hydroxy-α-amino acids,[1] including β-phenyl-DL-serine,[2] of unspecified configuration, to glycine and an aldehyde has been described. However, the rate of splitting

(1) A. E. Braunshtein and G. Ia. Vilenkina, *Doklady Akad. Nauk S.S.S.R.*, **66**, 243 (1949).

(2) G. Ia. Vilenkina, *ibid.*, **69**, 385 (1949).