TABLE I

YIELDS AND PHYSICAL CONSTANTS OF AMINES AND DERIVATIVES

| Amine | Yield, % | B.p., °C. | $n^{25}D$ | M.p., °C.[a] | Derivative Nitrogen, % Calcd. | Found[b] |
|---|---|---|---|---|---|---|
| | | Alkylphenylthioureas | | | | |
| 2-Aminopentane | 85 | 88–90[c] | 1.4010 | 66–67 | 12.60 | 12.71 |
| 3-Aminopentane | 83 | 88–90[d] | 1.4030 | 88–89 | 12.60 | 12.72 |
| 3-Amino-2-methylbutane | 64 | 82–84[e] | 1.4105 | 92–93 | 12.60 | 12.62 |
| 3-Amino-2,2-dimethylbutane | 70 | 100–102[f] | 1.4105 | 121–122 | 11.85 | 11.66 |
| | | N-Alkylbenzamides | | | | |
| 2-Aminohexane | 63 | 115–117 | 1.4080 | 82–83 | 6.82 | 6.70 |
| 3-Aminohexane | 55 | 115–116 | 1.4093 | 88–89 | 6.82 | 6.79 |
| 2-Aminoheptane | 43 | 140–142[g] | 1.4150 | 71–72 | 6.39 | 6.24 |
| 3-Aminoheptane | 50 | 140–142[g] | 1.4160 | 92–93 | 6.39 | 6.18 |
| 4-Aminoheptane | 55 | 139–141[g] | 1.4160[h] | 109–110 | 6.39 | 6.22 |
| 2-Aminoöctane | 51 | 56–57[i] (13 mm.) | 1.4212 | 77–78 | 6.00 | 5.87 |

[a] All derivatives were crystallized from aqueous methanol. [b] Microanalysis by Galbraith Laboratories, Knoxville, Tenn. [c] A. N. Kost, *et al.*, *Izvest. Akad. Nauk, S. S. S. R., Otdel, Khim. Nauk*, 150 (1951), report 89–91° (*C. A.*, **45**, 10194 (1951)). [d] H. L. Bami, *et al.*, *Current Sci. (India)*, **16**, 253 (1947), report 84–86°. [e] A. Michael and G. Carlson, *J. Org. Chem.*, **4**, 169 (1939), report 85–89°. [f] E. Schwoegler and H. Adkins, THIS JOURNAL, **61**, 3499 (1939), report 102°. [g] E. Rohrmann and H. A. Shonle, ref. 5, report the following values: 2-aminoheptane, b.p. 140–142.5°, $n^{24}D$ 1.4150; 3-aminoheptane, b.p. 139–140°; 4-aminoheptane, b.p. 139–140°, $n^{24}D$ 1.4172. [h] This value obtained for successive fractions in two runs. [i] F. G. Mann and J. W. G. Porter, *J. Chem. Soc.*, 456 (1944), report 58–59° (13 mm.).

Adequate derivatives characterizing these amines have not been described previously. Although amine salts have been prepared for analytical purposes, the melting points admittedly were unsatisfactory for identification purposes.[5] Consequently, alkylphenylurea or N-alkyl benzamide derivatives were prepared in the conventional manner[7] for each amine.

The yields and physical constants of the amines and properties of the derivatives are collected in Table I.

### Experimental

The following procedure describing the preparation of 2-aminohexane is representative and was used to obtain all of the amines indicated in Table I. Fifteen-hundredths of a mole of 2-hexanone oxime was dissolved in 125 ml. of 95% ethyl alcohol containing about 4 g. of Raney nickel catalyst[8] and shaken at room temperature with hydrogen at an initial pressure of three atmospheres in a Parr low pressure hydrogenation apparatus. The apparatus was recharged with hydrogen as needed to maintain the pressure between two and three atmospheres and the shaking was continued usually three to four hours until the theoretical amount of hydrogen was absorbed. With a larger amount of catalyst (five times) the reaction was more rapid but very exothermic. After completion of the reaction, the mixture was filtered, diluted with about 100 ml. of water and acidified with 0.25 equivalent of 20% sulfuric acid. The acid solution was steam distilled until 300–400 ml. of distillate was collected. This distillate was later examined for 2-hexanone. The residue from the steam distillation was treated with 0.3 mole of 25% aqueous sodium hydroxide solution and subjected to further steam distillation and distillate consisting of an aqueous suspension of 2-aminohexane was collected. After cooling, this distillate was extracted with four 50-ml. portions of 35–37° petroleum ether.[9] The combined extracts were dried over anhydrous sodium sulfate and distilled. Several fractions were collected during the distillation and the yield was calculated only on the fractions having constant refractive index. In this manner, 9.50 g. of 2-aminohexane was collected having the properties indicated in Table I.

The 2-aminohexane formed an N-alkylbenzamide when shaken with a mixture of benzoyl chloride and 10% sodium hydroxide and after two crystallizations from aqueous methanol gave the melting point and analysis shown in Table I.

The first steam distillate was repeatedly extracted with 35–37° petroleum ether. The extract was washed with water, dried and concentrated. Distillation of the residue gave 3.0 g. of 2-hexanone, boiling range 132–136°. The 2,4-dinitrophenylhydrazone was prepared, m.p. 106–107°.

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(7) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, pp. 178, 179.

(8) A. A. Pavlic and H. Adkins, THIS JOURNAL, **68**, 1471 (1946).

(9) Before extracting the aminopentanes, the corresponding steam distillate was nearly saturated with potassium carbonate.

## A Synthesis of *dl*-α-Methylglutamic Acid and Some Derivatives

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*dl*-α-Methylglutamic acid has been found to inhibit the enzymatic system concerned with the synthesis and subsequent utilization of glutamine.[1,2] The literature reports only the melting point[2] of *dl*-α-methylglutamic acid. Hence, for the biological studies conducted in our laboratories, it was necessary to devise a synthesis for this compound.

The observation of H. Meyer[3] that lactones derived from acids with a tertiary hydroxyl group form lactams when treated with ammonia suggested the synthesis employed by us which consisted of treating ethyl levulinate with ammonium cyanide in an ether–water medium to form γ-cyano-γ-valerolactone (I). This lactone was then treated with ammonia in an alcohol solution and the γ-cyano-γ-valerolactam (II) obtained was hydrolyzed to *dl*-α-methylglutamic acid (III).

The lactam (II) was also prepared directly by allowing ethyl levulinate to react with ammonium cyanide in an alcohol–water medium and then treating the reaction mixture with ammonium hydroxide.

(1) N. Lichtenstein, H. E. Ross and P. Cohen, *Nature*, **171**, 45 (1953); *J. Biol. Chem.*, **201**, 117 (1953).

(2) P. Ayengar and E. Roberts, *Proc. Soc. Exptl. Biol. Med.*, **79**, 76 (1952).

(3) H. Meyer, *Monatsh.*, **20**, 717 (1899).

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-Aminoalcohols

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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 $pK$.