[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS]

# Synthesis of Some Cycloalkylpyridines

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The synthesis of 3-cyclopentylpyridine and 4-cyclopentylpyridine has shown that two $C_{10}H_{13}N$ bases from petroleum were incorrectly identified as 3-cyclopentylpyridine and 4-cyclopentylpyridine. 2-Cyclopentylpyridine has been successfully alkylated on the cyclopentane ring with methyl iodide in an ammonia solution of sodamide to form 2-(1-methylcyclopentyl)-pyridine. The action of cyclopentyl chloride on the three picolines in an ammonia solution of sodamide has yielded the three isomeric (cyclopentylmethyl)-pyridines as well as 2-(dicyclopentylmethyl)-pyridine and 4-(dicyclopentylmethyl)-pyridine.

In an endeavor to elucidate the structure of several unidentified bases which were isolated from petroleum, the synthesis of a number of cycloalkylpyridines was undertaken. An earlier communication[2] described the synthesis of eight of these cycloalkylpyridines. It was believed that one or more of the $C_{11}H_{15}N$ bases of Table I might be cycloalkylpyridines. This hypothesis was based primarily on the isolation of two $C_{10}H_{13}N$ bases by Thomas[3,4] and their identification by Truitt[4,5] as 3-cyclopentylpyridine and 4-cyclopentylpyridine. However, the synthesis of the three isomeric cylopentylpyridines during this investigation has shown conclusively that neither of the $C_{10}H_{13}N$ petroleum bases is a cyclopentylpyridine.

TABLE I

A. $C_{11}H_{15}N$ BASES ISOLATED FROM PETROLEUM

| Isolated by | Picrate m.p., °C. | $n_D$ | B.p., °C. |
|---|---|---|---|
| Garland[a] | 144–145 | 1.5121(20°) | 230 |
| Pickard[b] | 117 | 1.5090(35°)[c] | 225 |
| Pickard | 134 | 1.5052(35°)[c] | 228 |
| Pickard | 146 | 1.5162(35°)[c] | 228 |
| Pickard | 154 | 1.5150(35°)[c] | 228 |
| Pickard | 181 | 1.5070(35°)[c] | 224 |
| Pickard | 182.5 | 1.5056(35°)[c] | 228 |
| Crouch[c] | 154 | 1.5165(20°)[d] | 234 |
| Hackmann and Wibaut[e] | 145–147 | 1.5340(20°) | 258 |

B. $C_{10}H_{13}N$ BASES ISOLATED FROM PETROLEUM

| Isolated by | Picrate m.p., °C. | $n^{20}D$ | B.p., °C. | Mm. |
|---|---|---|---|---|
| Thomas[f] | 117.5 | 1.5172 | 215.5 | 747 |
| Thomas | 145–146 | 1.5167 | 218 | 744 |

[a] F. M. Garland, Ph.D. Dissertation, University of Texas, 1939. [b] P. L. Pickard, Ph.D. Dissertation, University of Texas, 1947. [c] Refractive index and boiling point of base mixture from which the solid picrates were obtained. [d] W. W. Crouch, Ph.D. Dissertation, University of Texas, 1942. [e] J. T. Hackmann and J. P. Wibaut, *Rec. trav. chim.*, 62, 229 (1943). [f] E. D. Thomas, M.A. Thesis, University of Texas, 1943; H. L. Lochte, E. D. Thomas and Price Truitt, THIS JOURNAL 66, 550 (1944).

The synthesis of 3-cyclopentylpyridine and 3-cyclohexylpyridine from 3-bromopyridine was accomplished. The reaction of its Grignard complex with cyclopentanone and cyclohexanone gives 3-pyridyl alcohols which are analogous to the 2-pyridyl alcohols obtained by the Emmert reaction.[2] Dehydration of the alcohol and hydrogenation of the resulting olefin yields the cycloalkylpyridine.

The Grignard complex of the 3-bromopyridine was prepared according to the procedure of Anderson and Seegers[6] which in turn was patterned after the original procedure of Overhoff and Proost[7] for the Grignard reaction of 2-bromopyridine. Although Wibaut and Van der Voort[8] claimed an improved procedure, the results obtained by following their method were poor when cyclopentanone was used to react with the Grignard complex.

The 3-cyclopentylpyridine which was prepared from 3-bromopyridine and cyclopentanone by the method outlined above did not agree in physical constants with the $C_{10}H_{13}N$ petroleum base which had been identified by Lochte and Truitt[4] as 3-cyclopentylpyridine. The melting point of the picrate was different, and the melting point of a mixture of a sample of the original $C_{10}H_{13}N$ petroleum base picrate with the picrate of 3-cyclopentylpyridine was lower than the melting point of either picrate.

Since the identification of one of the $C_{10}H_{13}N$ petroleum bases as 3-cyclopentylpyridine appeared to be in error, the synthesis of 4-cyclopentylpyridine was undertaken to verify or disprove the identification of the other $C_{10}H_{13}N$ petroleum base as 4-cyclopentylpyridine. The synthesis was accomplished by two separate routes. A small quantity of 4-(1-cyclopentenyl)-pyridine was isolated as the picrate from the higher boiling Emmert reaction products of pyridine and cyclopentanone[3] after the higher boiling materials had been treated with sulfuric acid, basified and distilled. Hydrogenation of the 4-(1-cyclopentenyl)-pyridine yielded 4-cyclopentylpyridine.

Inasmuch as the above preparation yielded only a very small quantity of 4-cyclopentylpyridine as the picrate, a separate synthesis was undertaken to obtain several grams of the pure base from which to obtain accurate physical constants. The glutarimide synthesis of Crouch and Lochte[9,10] was chosen since Truitt[4,5] had also used that method. Truitt prepared β-cyclopentylglutaric acid by condensing cyclopentanecarboxaldehyde with two molar equivalents of cyanoacetamide and hydrolyzing the resulting product. In the present investigation the β-

(1) From the Ph.D. Dissertation of Edward N. Wheeler, University of Texas (1953). Union Carbide and Carbon Fellow, 1952–1953.

(2) H. L. Lochte, Paul F. Kruse, Jr., and E. N. Wheeler, THIS JOURNAL, **75**, 4477 (1953).

(3) E. D. Thomas, M.A. Thesis, University of Texas, 1943.

(4) H. L. Lochte, E. D. Thomas and Price Truitt, THIS JOURNAL, **66**, 550 (1944).

(5) Price Truitt, Ph.D. Dissertation, University of Texas, 1944.

(6) L. C. Anderson and N. V. Seegers, THIS JOURNAL, **71**, 345 (1949).

(7) J. Overhoff and W. Proost, *Rec. trav. chim.*, **57**, 179 (1938).

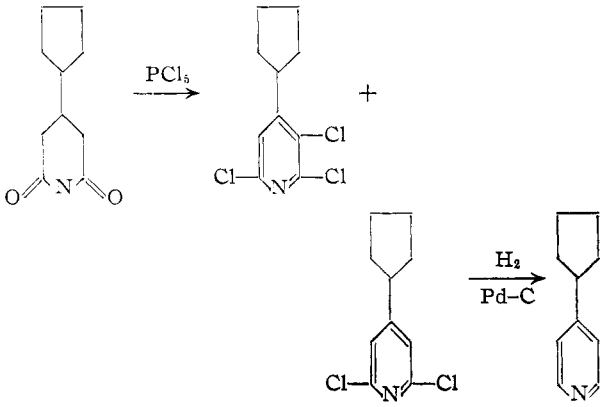
(8) J. P. Wibaut and H. G. P. Van der Voort, *ibid.*, **71**, 798 (1952).

(9) W. W. Crouch and H. L. Lochte, THIS JOURNAL, **65**, 270 (1943).

(10) H. J. den Hertog and E. Farenhorst, *Rec. trav. chim.*, **67**, 280 (1948).

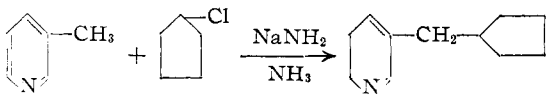
cyclopentylglutaric acid was prepared by reducing ethyl cyclopentylmalonate to 2-cyclopentyl-1,3-propanediol with lithium aluminum hydride. The glycol was converted to the dibromide which was allowed to react with potassium cyanide to give β-cyclopentylglutaronitrile. Hydrolysis of the dinitrile with concentrated hydrochloric acid yielded β-cyclopentylglutarimide instead of the expected acid.

The action of phosphorus pentachloride on β-cyclopentylglutarimide converted it to a mixture of 2,3,6-trichloro-4-cyclopentylpyridine and 2,6-dichloro-4-cyclopentylpyridine in 63% yield. Hydrogenolysis of the mixture of chloropyridines produced 4-cyclopentylpyridine in about 80% yield based on unrecovered starting material.

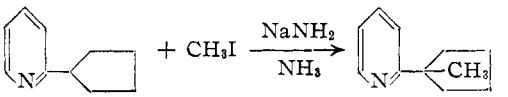



A mixture of the picrates of 4-cyclopentylpyridine from the glutarimide synthesis and from the Emmert reaction showed no depression in melting point. A mixture melting point with the picrate of the $C_{10}H_{13}N$ petroleum base which had been identified as 4-cyclopentylpyridine gave a large depression in melting point. In retrospect it may readily be seen that the identification of the two $C_{10}H_{13}N$ petroleum bases as 3- and 4-cyclopentylpyridine violated the empirical rule that pyridines with a hydrocarbon substituent in the 3- and 4-position have a higher boiling point (10 to 25° higher) and a higher refractive index than pyridines with the same hydrocarbon substituent in the 2-position.

The alkylation procedure of Brown and Murphey[11] was found to be extremely useful in the synthesis of cycloalkylpyridines. The novel discovery by Brown and Murphey that the hydrogens on the methyl group of 3-picoline may be replaced by alkyl groups made possible the synthesis of 3-(cyclopentylmethyl)-pyridine from 3-picoline. Following their procedure all three of the isomeric (cyclopentylmethyl)-pyridines were synthesized by the action of cyclopentyl chloride on the corresponding picoline dissolved in a solution of sodamide in liquid ammonia. A fourth cycloalkylpyridine was




prepared by the reaction of methyl iodide with 2-cyclopentylpyridine in the above manner to yield 2-(1-methylcyclopentyl)-pyridine. 3-Cyclopentylpyridine failed to react under the same conditions




although a large excess of methyl iodide and sodamide was used. In the reaction of cyclopentyl chloride with 2-picoline and 4-picoline the dialkylated products, 2-(dicyclopentylmethyl)-pyridine and 4-(dicyclopentylmethyl)-pyridine, were also isolated. The attempted synthesis of 4-cyclopentylpyridine by the reaction of 1,4-dichlorobutane with 4-picoline yielded only polymeric materials and some 4-(di-3-butenylmethyl)-pyridine.

## Experimental

**3-(1-Cyclohexenyl)-pyridine.**—Sulfuric acid (188 g., 1.9 moles) was added slowly to 85 g. of 1-(3-pyridyl)-cyclohexanol (0.48 mole) in the same manner as described for the dehydration of 2-pyridyl alcohols.[2] After basification, extraction and distillation, 71.5 g. (94% yield) of 3-(1-cyclohexenyl)-pyridine was obtained.

**3-Cyclohexylpyridine.**—Sixty-four grams of 3-(1-cyclohexenyl)-pyridine (0.4 mole) was hydrogenated at one atmosphere pressure for seven hours, using 1 g. of Adams catalyst and ethanol as solvent. After filtering off the catalyst, 110 g. of picric acid was added to the filtrate. The picrate was recrystallized twice, and the total yield obtained melting 130–131° was 132 g. or an 85% yield based on the 3-(1-cyclohexenyl)-pyridine. Liberation of the base with ammonium hydroxide, extraction with benzene and distillation yielded the pure base.

**3-Cyclopentylpyridine.**—Forty grams of 3-(1-cyclopentenyl)-pyridine which was prepared in the same manner as 3-(1-cyclohexenyl)-pyridine was hydrogenated using 1 g. of Adams catalyst in about 60 ml. of glacial acetic acid for six hours. The 3-cyclopentylpyridine which was purified *via* the picrate had the following properties: b.p. 125° (19 mm.), $n^{26}D$ 1.5298; mol. refraction calcd., 45.72; found, 45.65.

The picrate melted 128–128.7°. Truitt[4,5] reported a m.p. of 116° for the picrate of synthetic 3-cyclopentylpyridine. Recrystallization of a sample of the picrate of the $C_{10}H_{13}N$ base which was left by Thomas[3,4] and identified as 3-cyclopentylpyridine by Truitt gave a sharp m.p. of 116–117°. A mixture of the picrate of 3-cyclopentylpyridine and the $C_{10}H_{13}N$ picrate melted 101–114°. The picrates were thus shown to be different compounds.

**2-(Cyclopentylmethyl)-pyridine.**—Following the method used by Brown and Murphey,[11] one mole of sodamide was prepared in liquid ammonia by the method of Vaughn, Vogt and Nieuwland[12] and treated with 2-picoline (0.33 mole, 124 g.). Cyclopentyl chloride (105 g., 1 mole) was then added. The ammonia was allowed to evaporate, and water was then cautiously added. The reaction mixture was extracted with benzene, dried over sodium hydroxide pellets, and fractionated. The products consisted of 50 g. of unchanged 2-picoline, 98 g. of 2-(cyclopentylmethyl)-pyridine (61% yield on cyclopentyl chloride) boiling 134° at 31 mm., and 7 g. of 2-(dicyclopentylmethyl)-pyridine boiling 193–195° at 31 mm.

**2-(1-Methylcyclopentyl)-pyridine.**—The same procedure as for the preparation of 2-cyclopentylpyridine was followed using 23 g. of sodium (1 mole), 73.5 g. of 2-cyclopentylpyridine[2] (0.5 mole), and 142 g. of methyl iodide. The products were extremely difficult to separate by fractional distillation, but non-aqueous titration of the basic nitrogen showed that about 65% conversion had been attained. To circumvent the difficult separation, the mixture was recycled through the alkylation step using about a 400% excess of methyl iodide and sodamide. A near quantitative conversion was thus attained with fractions of the same refractive index being obtained upon fractional distillation. By purification through the picrate the pure base was obtained boiling 119° (27 mm.).

(11) H. C. Brown and W. A. Murphey, THIS JOURNAL, **73**, 3308 (1951).

(12) T. H. Vaughn, R. R. Vogt and J. A. Nieuwland, *ibid.*, **56**, 2120 (1934).

TABLE II

A. THE GRIGNARD REACTION OF CYCLOPENTANONE AND CYCLOHEXANONE WITH 3-BROMOPYRIDINE

| Reactant | Product | Yield,[a] % | M.p., °C. | B.p. °C. | B.p. Mm. | Formula | Nitrogen, % [b] Calcd. | Found |
|---|---|---|---|---|---|---|---|---|
| Cyclohexanone | 1-(3-Pyridyl)-cyclohexanol | 60 | 91[c] | 168 | 3 | $C_{11}H_{15}NO$ | 7.91 | 7.90 |
| Cyclopentanone | 1-(3-Pyridyl)-cyclopentanol | 35 | .. | 135 | 2 | $C_{10}H_{13}NO$ | 8.59 | 8.59 |

B. CYCLOALKENYLPYRIDINES

| Pyridine | B.p. °C. | Mm. | $n^{20}D$ | $d^{20}_4$ | Formula | Nitrogen, % [b] Calcd. | Found |
|---|---|---|---|---|---|---|---|
| 3-(1-Cyclohexenyl) | 161 | 31 | 1.5717 | 1.040 | $C_{11}H_{13}N$ | 8.80 | 8.82 |
| 3-(1-Cyclopentenyl) | 139 | 21 | 1.5800 | 1.047 | $C_{10}H_{11}N$ | 9.65 | 9.64 |

[a] Yield based on unrecovered 3-bromopyridine. [b] Nitrogen analyses by non-aqueous titration of basic nitrogen using method of Fritz, *Anal. Chem.*, **22**, 1028 (1950). [c] H. E. French and Kern Sears, THIS JOURNAL, **73**, 469 (1951); m.p. of 1-(3-pyridyl)-cyclohexanol 89–90°.

TABLE III

CYCLOALKYLPYRIDINES FROM ALKYLATION IN LIQUID AMMONIA

| Pyridine | Moles | Sodamide, moles | Halide | Moles | Product | Conversion to product, % |
|---|---|---|---|---|---|---|
| 2-Methyl | 1.3 | 1.0 | Cyclopentyl chloride | 1.0 | 2-(Cyclopentylmethyl)-pyridine | 61 |
| 3-Methyl | 1.2 | 1.0 | Cyclopentyl chloride | 1.0 | 3-(Cyclopentylmethyl)-pyridine | 16 |
| 4-Methyl | 0.5 | 0.5 | Cyclopentyl chloride | 0.5 | 4-(Cyclopentylmethyl)-pyridine | 47 |
| 4-Methyl | 0.5 | 1.2 | 1,4-Dichlorobutane | 0.5 | ..... | 0 |
| 2-Cyclopentyl | 0.5 | 1.0 | Methyl iodide | 1.0 | 2-(1-Methylcyclopentyl)-pyridine | 65 |
| 3-Cyclopentyl | 0.14 | 1.0 | Methyl iodide | 1.0 | ..... | 0 |

TABLE IV

CYCLOALKYLPYRIDINES

| Pyridine | B.p.[a] °C. | Mm. | $n^{20}D$ | $d^{20}_4$ | Formula | Nitrogen, % [b] Calcd. | Found |
|---|---|---|---|---|---|---|---|
| 3-Cyclopentyl | 245–246 | 749 | 1.5324 | 1.005 | $C_{10}H_{13}N$ | 9.52 | 9.46 |
| 4-Cyclopentyl | 245–246 | 738 | 1.5306 | 1.002 | $C_{10}H_{13}N$ | 9.52 | 9.45 |
| 3-Cyclohexyl | 262–263 | 746 | 1.5297 | 0.998 | $C_{11}H_{15}N$ | 8.70 | 8.71 |
| 2-(Cyclopentylmethyl)[c] | 240.5–241.5 | 747 | 1.5178 | .973 | $C_{11}H_{15}N$ | 8.70 | 8.65 |
| 3-(Cyclopentylmethyl) | 256–257 | 746 | 1.5209 | .981 | $C_{11}H_{15}N$ | 8.70 | 8.64 |
| 4-(Cyclopentylmethyl) | 258–259 | 746 | 1.5209 | .981 | $C_{11}H_{15}N$ | 8.70 | 8.66 |
| 2-(1-Methylcyclopentyl) | 227–228 | 752 | 1.5227 | .983 | $C_{11}H_{15}N$ | 8.70 | 8.69 |
| 2-(Dicyclopentylmethyl) | 198 | 32 | 1.5298 | .997 | $C_{16}H_{23}N$ | 6.11 | 6.12 |
| 4-(Dicyclopentylmethyl) | 205–215 | 27 | .... | ... | $C_{16}H_{23}N$ | 6.11 | 6.16 |

[a] Atmospheric boiling points corrected. [b] All nitrogen analyses by non-aqueous titration of basic nitrogen, using method of Fritz, *Anal. Chem.*, 22, 1028 (1950). [c] W. W. Crouch, Ph.D. Dissertation, University of Texas, 1943; b.p., 241–242 (742 mm.), $n^{20}D$ 1.5177, $d^{20}_4$ 0.9718; A. E. Chichibabin, *Bull. soc. chim.*, [5] **5**, 435 (1938).

Preparation of the picrate was somewhat unusual in that the picrate did not form readily as a crystalline solid, but tended to be a liquid. Equimolar quantities of picric acid and the 2-(1-methylcyclopentyl)-pyridine were weighed out several times and crystallization was attempted from both ethanol and 60% acetic acid in water. Upon standing for several days, about a third of the oily precipitate crystallized. Upon recrystallization a picrate was obtained melting 108.4–109.8°. Analysis disclosed the apparent difficulty as arising from insufficient picric acid being added to form the stable picrate which contained more than the 1:1 ratio of picric acid to base.

*Anal.* Calcd. for $C_{11}H_{15}N \cdot 1.5C_6H_3N_3O_7$: N, 15.26. Found: N, 15.47, 15.23.

When picric acid and the base were weighed out on a 1.5:1 molar base, a near quantitative yield of the picrate was obtained from ethanol. This anomaly was not observed with the styphnate and trinitro-*m*-cresolate derivatives which were prepared in the usual manner.

**4-(Di-3-butenylmethyl)-pyridine.**—4-Picoline (46.6 g., 0.5 mole) and 63.5 g. of 1,4-dichlorobutane (0.5 mole) were added simultaneously to a mole of sodamide in about 800 ml. of ammonia in an attempt to synthesize 4-cyclopentylpyridine. Distillation of the product yielded only 2 g. of material boiling 80–180° (39 mm.) and 5 g. of 4-(di-3-butenylmethyl)-pyridine ($n^{28.3}D$ 1.5270) boiling 184–188° (39 mm.). Most of the product was a tarry residue.

*Anal.* Calcd. for $C_{14}H_{19}N$: N, 6.96. Found: N, 6.94.

**Picrate of 4-(1-Cyclopentenyl)-pyridine.**—The higher boiling material from the Emmert reaction of cyclopentanone and pyridine[2] was combined with the residues from the mother liquors which were obtained in purifying the 1-(2-pyridyl)-cyclopentanol. Upon fractionation there was obtained 8 g. of material boiling 180–205° (35 mm.), which, after dehydration with sulfuric acid, basification, extraction and distillation, yielded about 3 g. of material boiling at 160–190° (35 mm.). Picric acid in ethanol was added, and the resulting picrate was recrystallized, yielding 0.9 g. of picrate melting 180–182° (with decomposition).

*Anal.* Calcd. for $C_{11}H_{13}N \cdot C_6H_3N_3O_7$: N, 14.97. Found: N, 15.13.

**Picrate of 4-Cyclopentylpyridine.**—Excess ammonium hydroxide was added to 0.70 g. of the picrate of 4-(1-cyclopentenyl)-pyridine (1.86 mmoles), and the liberated base was very carefully extracted several times with ether. The ether was evaporated in a small hydrogenation flask, 71 mg. of Adams catalyst was added, and 10 ml. of glacial acetic acid was used as a solvent. After absorbing 1.89 millimoles of hydrogen, the catalyst was filtered from the solvent, and 0.415 g. of picric acid was added. The picrate melted at 130–131° after two recrystallizations.

*Anal.* Calcd. for $C_{11}H_{15}N \cdot C_6H_3N_3O_7$: N, 15.14. Found: N, 14.89.

**2-Cyclopentyl-1,3-propanediol.**—The procedure of Nystrom and Brown[13] was followed, using 73 g. of lithium aluminum hydride (1.92 moles, 57% excess), 274 g. of ethyl cyclopentylmalonate (1.20 moles), and 1.8 liters of ether.

(13) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 1197 (1947).

TABLE V

A. PICRATE MELTING POINTS AND ANALYSES

| Picrate of | M.p.,[a] °C. | Formula | Nitrogen, % [b] Calcd. | Found |
|---|---|---|---|---|
| 1-(3-Pyridyl)-cyclohexanol | 169–169.5 | $C_{11}H_{15}NO \cdot C_6H_3N_3O_7$ | 13.79 | 13.92 |
| 1-(3-Pyridyl)-cyclopentanol | 132.8–133.2 | $C_{10}H_{13}NO \cdot C_6H_3N_3O_7$ | 14.28 | 14.32 |
| 3-(1-Cyclohexenyl)-pyridine | 175.5–176.5 | $C_{11}H_{13}N \cdot C_6H_3N_3O_7$ | 14.41 | 14.42 |
| 3-(1-Cyclopentenyl)-pyridine | 170.8–171.5 | $C_{10}H_{11}N \cdot C_6H_3N_3O_7$ | 14.97 | 14.99 |
| 3-Cyclohexylpyridine | 130–131 | $C_{11}H_{15}N \cdot C_6H_3N_3O_7$ | 14.36 | 14.34 |
| 3-Cyclopentylpyridine | 128–128.7 | $C_{10}H_{13}N \cdot C_6H_3N_3O_7$ | 14.89 | 15.07 |
| 2-(Cyclopentylmethyl)-pyridine | 123.8–124.4[c] | $C_{11}H_{15}N \cdot C_6H_3N_3O_7$ | 14.36 | 14.49 |
| 3-(Cyclopentylmethyl)-pyridine | 120–121.4 | $C_{11}H_{15}N \cdot C_6H_3N_3O_7$ | 14.36 | 14.52 |
| 4-(Cyclopentylmethyl)-pyridine | 150.5–151.5 | $C_{11}H_{15}N \cdot C_6H_3N_3O_7$ | 14.36 | 14.45 |
| 2-(Dicyclopentylmethyl)-pyridine | 108–109.5 | $C_{16}H_{23}N \cdot C_6H_3N_3O_7$ | 12.25 | 12.34 |
| 2-(1-Methylcyclopentyl)-pyridine | 108.4–109.8 | $C_{11}H_{15}N \cdot 1^1/_2C_6H_3N_3O_7$ | 15.26 | 15.23, 15.47 |
| 4-Cyclopentylpyridine | 131–132 | $C_{10}H_{13}N \cdot C_6H_3N_3O_7$ | 14.89 | 15.14 |
| 4-(Di-3-butenylmethyl)-pyridine | 112.5–113 | $C_{14}H_{19}N \cdot C_6H_3N_3O_7$ | 13.02 | 12.60, 12.84 |

B. STYPHNATES AND TRINITRO-*m*-CRESOLATES

| Pyridine | Styphnate M.p.,[a] °C. | Styphnate Formula | Styphnate Nitrogen, % [b] Calcd. | Styphnate Found | Trinitro-*m*-cresolate M.p.,[a] °C. | Trinitro-*m*-cresolate Formula | Trinitro-*m*-cresolate Nitrogen, % [b] Calcd. | Found |
|---|---|---|---|---|---|---|---|---|
| 3-Cyclopentyl | 155 | $C_{10}H_{13}N \cdot C_6H_3N_3O_8$ | 14.28 | 14.43 | 164 | $C_{10}H_{13}N \cdot C_7H_5N_3O_7$ | 14.36 | 14.33 |
| 4-Cyclopentyl | 151 | $C_{10}H_{13}N \cdot C_6H_3N_3O_8$ | 14.28 | 14.26 | 145 | $C_{10}H_{13}N \cdot C_7H_5N_3O_7$ | 14.36 | 14.29 |
| 3-Cyclohexyl | 172*d.* | $C_{11}H_{15}N \cdot C_6H_3N_3O_8$ | 13.79 | 13.94 | 165 | $C_{11}H_{15}N \cdot C_7H_5N_3O_7$ | 13.86 | 14.16 |
| 2-(Cyclopentylmethyl) | 122 | $C_{11}H_{15}N \cdot C_6H_3N_3O_8$ | 13.79 | 13.87 | 147 | $C_{11}H_{15}N \cdot C_7H_5N_3O_7$ | 13.86 | 14.11 |
| 3-(Cyclopentylmethyl) | 148.5*d.* | $C_{11}H_{15}N \cdot C_6H_3N_3O_8$ | 13.79 | 13.78<br>13.88 | 139 | $C_{11}H_{15}N \cdot C_7H_5N_3O_7$ | 13.86 | 13.82 |
| 4-(Cyclopentylmethyl) | 118.5 | $C_{11}H_{15}N \cdot C_6H_3N_3O_8$ | 13.79 | 13.86 | 148*d.* | $C_{11}H_{15}N \cdot C_7H_5N_3O_7$ | 13.86 | 13.78 |
| 2-(1-Methylcyclopentyl) | 117.4 | $C_{11}H_{15}N \cdot C_6H_3N_3O_8$ | 13.79 | 13.81 | 122 | $C_{11}H_{15}N \cdot C_7H_5N_3O_7$ | 13.86 | 13.75 |

[a] All melting points corrected; melting point ranges were usually one degree or less with the highest temperature being recorded. [b] All analyses by the Analytical Laboratory of the Biochemical Institute of The University of Texas; most of the analyses by Miss M. A. Smith and Joe Ireland. [c] W. W. Crouch, Ph.D. Dissertation, University of Texas, 1943; m.p. of picrate 124–125°.

The ester was added slowly over a four-hour period to an ether slurry of the lithium aluminum hydride, and the mixture was refluxed for an additional three hours. Ethyl acetate was then added (44 g., 0.5 mole), followed by the addition of ethanol and then water. The slurry was diluted with more ether and poured into a 4-l. erlenmeyer flask in which there was 400 ml. of concentrated sulfuric acid and a large amount of cracked ice. The sulfuric acid layer was separated and extracted eight times with 100-ml. portions of ether. The last two extractions yielded only 1.1 g. of crude glycol.

The ether extract was evaporated and the crude glycol was dried by azeotroping the water off with benzene. The residue was recrystallized from a 10% solution of benzene in petroleum ether, yielding 153.5 g. of 2-cyclopentyl-1,3-propanediol (89% theoretical). The recrystallized 2-cyclopentyl-1,3-propanediol had the following properties: m.p. 68–69° and b.p. 164–165° (17 mm.).

*Anal.* Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.29. Found: C, 66.58; H, 11.16.

**β-Cyclopentylglutaronitrile.**—2-Cyclopentyl-1,3-propanediol (153 g., 1.06 moles) was treated with 454 g. of 48% hydrobromic acid (2.69 moles, 27% excess) and 145 g. of 96% sulfuric acid following the general procedure in "Organic Syntheses."[14] After refluxing the glycol for six hours with the sulfuric–hydrobromic acid mixture in a one-liter round-bottom flask, the reaction product was poured onto ice. The lower layer was separated and washed with ammonium hydroxide solution, and the upper water layer was extracted with benzene. The combined organic layers were dried over a small amount of calcium chloride and distilled, yielding 194 g. of 1,3-dibromo-2-cyclopentylpropane (68% yield) boiling 135–138° (18 mm.), $n^{20}D$ 1.5249. The crude 1,3-dibromo-2-cyclopentylpropane (193 g., 0.71 mole) was treated with 137 g. of 95% potassium cyanide (2 moles), 100 ml. of water and 300 ml. of ethanol following the "Organic Syntheses"[15] procedure for the preparation for glutaronitrile. After refluxing the mixture for 24 hours, the solution was poured onto cracked ice and extracted with benzene. The solution was very dark and had to be filtered to remove a black suspension before suitable separation could be achieved of the two phases obtained during the benzene extraction. Upon distillation of the benzene extract, there was obtained 75 g. of β-cyclopentylglutaronitrile (65% yield) boiling 137–140° (1–1.3 mm.) and having an index of refraction of 1.4788 ($n^{20}D$).

*Anal.* Calcd. for $C_{10}H_{14}N_2$: N, 17.27. Found: N, 17.10.

**β-Cyclopentylglutarimide.**—The procedure in "Organic Syntheses"[16] for the preparation of glutaric acid was followed. β-Cyclopentylglutaronitrile (73 g., 0.45 mole) was added to 190 ml. of concentrated hydrochloric acid and kept at steam-bath temperature for 4.5 hours. When the mixture was cooled, it turned almost completely solid. After filtering, washing with a little cold water, and drying, there was obtained about 80 g. of the crude glutarimide (97% yield). At this point the solid was believed to be β-cyclopentylglutaric acid, and an attempt to recrystallize it from ethanol and water turned the majority of the product into an oil. However, 17 g. of the imide was recovered and recrystallized from a 10% solution of benzene in petroleum ether. The pure β-cyclopentylglutarimide melted 147–148°.

*Anal.* Calcd. for $C_{10}H_{15}NO_2$: N, 7.73. Found: N, 7.90.

**β-Cyclopentylglutarimide from β-Cyclopentylglutaric Acid.**—β-Cyclopentylglutaric acid (50 g., 0.25 mole, m.p. 112.4–112.9°) was placed in a 250-ml. erlenmeyer flask and saturated with anhydrous ammonia. The material was fused, and ammonia was passed in until again saturated. The flask was then heated up to 220°, and ammonia was passed in while cooling down to the solidification point. This process was repeated, and the product was recrystallized from petroleum ether and benzene, giving 42 g. of β-cyclopentylglutarimide (93% yield) melting 147–148°.

**2,6-Dichloro-4-cyclopentylpyridine and 2,3,6-Trichloro-4-cyclopentylpyridine.**—β-Cyclopentylglutarimide (43 g.) was warmed with 150 g. of phosphorus pentachloride in a 250-ml. Claisen flask until liquefaction had taken place. After

(14) "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., p. 25.

(15) Reference 14, p. 536.

(16) Reference 14, p. 289.

standing for one hour, the phosphorus chlorides were distilled off under vacuum. The residue was poured over cracked ice and concentrated sodium hydroxide was added. The benzene extract was evaporated and distilled yielding 33 g. of material boiling 175–180° (6 mm.). The liquid had the following properties: $n^{20}D$ 1.5684 and $d^{20}_4$ 1.311.

*Anal.* Found: C, 51.6, 52.1; H, 4.73, 4.72.

The liquid was undoubtedly a mixture of the dichloro- and trichloropyridine compounds. The calculated analytical data for a mixture which is 60% dichloro and 40% trichloro are: C, 52.2; H, 4.65. The molecular refraction figured on this same basis is: calcd.: 57.40; found, 57.26.

**4-Cyclopentylpyridine.**—The mixture of chloropyridines (36 g.) was shaken with hydrogen at 30 pounds pressure, using 8 g. of 5% palladium on charcoal as catalyst and 200 ml. of ethanol as solvent. After 36 hours, the catalyst was filtered off and washed with absolute ethanol. The ethanol solution was evaporated, and the residue was distributed between dilute hydrochloric acid and benzene. The water layer was basified and extracted with ether, and the combined ether extracts were evaporated. Distillation of the residue gave 4.3 g. of 4-cyclopentylpyridine. Distillation of the neutral benzene extract yielded 27.5 g. of the starting material. The yield of 4-cyclopentylpyridine on unrecovered starting material was 79%. The 4-cyclopentylpyridine was purified through the picrate, which melted 131–132°. Truitt reported m.p. 146°. The purified base had the properties: b.p. 129° (23 mm.), $n^{20}D$ 1.5306, and $d^{20}_4$ 1.002.

*Anal.* Calcd. for $C_{10}H_{13}N$: N, 9.52. Found: N, 9.45.

A mixture melting point with the 4-cyclopentylpyridine picrate obtained from the Emmert synthesis showed no depression in melting point.

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# NOTES

## Poly-L-proline

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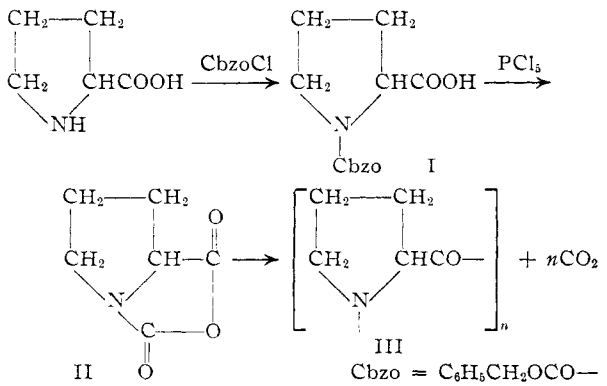
A high molecular weight peptide composed exclusively of proline residues may serve as a useful model in physicochemical and biological studies of proteins, such as collagen, gelatin, casein and zein, which contain a high percentage of proline. The attempts of Astbury, *et al.*,[1] to synthesize polyproline by the polymerization of the corresponding N-carboxyamino acid anhydride were unsuccessful, probably due to the difficulties involved in the preparation and purification of N-carboxyproline anhydride.[2] The successful synthesis of N-carboxy-L-proline anhydride II enabled us to prepare poly-L-proline III according to the scheme




Carbobenzoxy-L-proline (I), obtained from L-proline and benzyl chloroformate in the usual way, was converted into N-carboxy-L-proline anhydride (II) by means of phosphorus pentachloride. II was purified by molecular distillation; it yielded on polymerization in bulk or in dioxane solution poly-L-proline (III). In the latter case diethylamine was used to initiate polymerization.

The chemical constitution of the products of polymerization of II was ascertained by elementary analysis and by the quantitative recovery of proline after acid hydrolysis. The specific rotation of the proline recovered from the hydrolyzate of III, proved that the polyproline synthesized from L-proline consists entirely of L-proline residues. Poly-L-proline shows a remarkably high levorotation in water and in formic acid. The specific rotation in water was practically independent of temperature (between 0° and 80°) and of *p*H (between *p*H 3 and 11). Since no gelation occurred on cooling aqueous polyproline solutions, the above observations seem to support the widely accepted view that the mutarotation of gelatin[3] is associated with gel formation.[4]

As it has been found that the polyproline preparations obtained either by bulk polymerization or by polymerization in solution, using an amine as a polymerization initiator, contain as terminal groups only carboxyl groups and no free imino groups, it seems likely that a termination reaction of the type discussed recently by Sela and Berger[5] took place in both cases. Such a termination reaction should lead to polymers containing one carboxyl group for each peptide chain in the case of amine initiated polymers and two carboxyl groups per peptide chain in the case of polymers prepared by bulk polymerization. Based on this assumption average chain lengths, $n$ = 35 to 42 and $n$ = 67 to 133, were

(1) W. T. Astbury, C. E. Dalgliesh, S. E. Darmon and G. B. B. M. Sutherland, *Nature*, **162**, 596 (1948).

(2) E. M. Petri and A. J. Staverman, *Rec. Trav. Chim.*, **71**, 385 (1952).

(3) C. R. Smith, THIS JOURNAL, **41**, 135 (1919).

(4) J. D. Ferry, *Advances in Protein Chem.*, **4**, 1 (1948).

(5) M. Sela and A. Berger, THIS JOURNAL, **75**, 6350 (1953).