Reduction of 2,4-Dinitrophenyl *p*-Toluenesulfonate.—Hydriodic acid (const. boiling, 1.5 cc.) was added to a solution of 2,4-dinitrophenyl *p*-toluenesulfonate (0.5 g.) in 7.5 cc. of acetic acid containing 1 g. of red phosphorus, and the mixture heated under reflux during ninety minutes. The phosphorus was then filtered off and washed with a little hot acetic acid. A small volume of aqueous sodium bisulfite was added to the filtrate, followed by saturated sodium hydroxide until the solution was alkaline. The resulting precipitate was filtered off (0.3 g., m. p. 112–117°) and purified by dissolving in acid, reprecipitating with alkali, and recrystallizing from dilute ethyl alcohol. It then had m. p. 121–123°. On acetylation it gave a diacetate which, after recrystallizing from absolute ethanol, had m. p. 166°. (Ullmann and Nádai[7] gave m. p. 167°.)

Reduction of *p*-Tolyl 2,4-Dinitrophenyl Sulfone.—On adding a solution of 2.25 g. of stannous chloride in 3 cc. of absolute ethanol to the sulfone (0.5 g.) there was a violent reaction. Concentrated hydrochloric acid (3 cc.) was added, the solution evaporated to half its volume, made alkaline with sodium hydroxide solution, and the crude amine filtered off. It was purified by dissolving in acid, reprecipitating with alkali, and recrystallizing from alcohol. It had m. p. 187° (191°, cor.) and on admixture with starting material melted at 160°.

Anal. Calcd. for $C_{13}H_{14}O_2N_2S$: C, 59.50; H, 5.38. Found: C, 59.66; H, 5.54.

Summary

A solution of sodium iodide in acetone is devoid of action on phenyl *p*-toluenesulfonate or monotosyl apocupreine, in a sealed tube at 100° during two hours. Under the same conditions, 2,4-dinitrophenyl *p*-toluenesulfonate gives rise to an equimolecular mixture of *p*-tolyl 2,4-dinitrophenyl sulfone, sodium 2,4-dinitrophenate, sodium *p*-toluenesulfonate, and free iodine.

Reduction of the sulfone with stannous chloride yields *p*-tolyl 2,4-diaminophenyl sulfone.

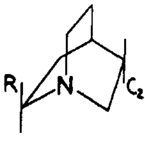
PITTSBURGH 13, PA. RECEIVED AUGUST 19, 1944

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

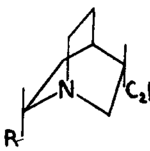
The *cis*- and *trans*-Forms of *dl*-3,4-Diethylpiperidine[1]

BY C. F. KOELSCH AND CHARLES H. STRATTON

Twenty-two years ago, certain ingenious deductions led Kenner[2] to the conclusion that quinine and cinchonidine corresponded sterically to structure I, quinidine and cinchonine to structure II.



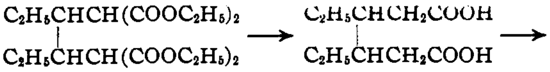
I



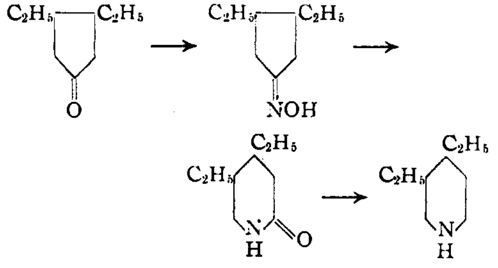
II

Some time ago it appeared desirable to establish these structures more directly, and some experiments were undertaken in this Laboratory with that end in view. However, the recent work of Prelog and Zalán[3] has amply confirmed Kenner's conclusion, and our investigation has now been discontinued. One result of our investigation of some general interest is described in the present paper. The synthesis of the two forms of *dl*-3,4-diethylpiperidine has been carried out through the reactions outlined below, and it has been possible to identify the *cis* and the *trans* forms of the base by determining the respective *meso* or *dl* configuration of the intermediate *β*,*γ*-diethyladipic acid.

$C_2H_5CH{=}C(COOC_2H_5)_2 \longrightarrow$



$$\begin{array}{l} C_2H_5CHCH(COOC_2H_5)_2 \\ | \\ C_2H_5CHCH(COOC_2H_5)_2 \end{array} \longrightarrow \begin{array}{l} C_2H_5CHCH_2COOH \\ | \\ C_2H_5CHCH_2COOH \end{array} \longrightarrow$$



Experimental

Reduction of ethyl propylidenemalonate with sodium amalgam according to the procedure used for the ethylidene analog[4] was unsatisfactory. Even though the reaction mixture was never allowed to become basic, large amounts of ketonic material were formed. Reduction with aluminum amalgam, the reagent used by Vogel[5] for a similar purpose, likewise gave a mixture containing ketonic material. But hydrolysis of this latter mixture under special conditions, followed by decarboxylation furnished the desired two forms of *β*,*γ*-diethyladipic acid. The following experiment is representative of eleven similar ones.

Ten grams of 0.001 in. aluminum foil was pressed into a 500 ml. flask and covered with 10% sodium hydroxide. When the evolution of hydrogen became brisk, the solution was decanted, and the metal was washed with water, alcohol, and ether. A mixture of 200 ml. of ether, 100 g. of ethyl propylidenemalonate and 3 g. of mercuric chloride was poured into the flask, and the whole was shaken vigorously until amalgamation appeared complete. Water (30 ml.) was then added and the flask was left under a reflux condenser for ten hours. Sodium sulfate was then added, the mixture was filtered, and the insoluble materials were washed well with ether. Distillation of the ether solution gave 34.5 g. of ethyl propyl- and propylidenemalonate, b. p. 105–115° at 12 mm., and 52 g. of dimeric reduction products, b. p. 184–188° at 3 mm. Redistillation of the latter at 6 mm. (b. p. 190°) led to no useful

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[1] From the Ph.D. Thesis of Charles H. Stratton, September, 1943.

[2] Kenner, *Ann. Rep. Chem. Soc.*, **19**, 156 (1922).

[3] Prelog and Zalán, *Helv. Chim. Acta*, **27**, 535 (1944).

[4] Higgenbotham and Lapworth, *J. Chem. Soc.*, **123**, 1618 (1923).

[5] Vogel, *ibid.*, 1985 (1927); 1013 (1928).

separation, although a middle fraction had $n^{20}D$ 1.4569 and an end fraction $n^{20}D$ 1.4298. The distillate gave a strong ferric chloride reaction, as did an undistilled sample, and analysis and behavior on hydrolysis indicated that the material was a mixture of **ethyl α,δ-dicarbethoxy-β,γ-diethyladipate** and **2,2,5-tricarbethoxy-3,4-diethylcyclopentanone.** Quite remarkably the cyclized product appeared to represent largely the *dl*-, and the acyclic product the *meso*, form of the tetrabasic ester.

Anal. Calcd. for $C_{20}H_{34}O_8$: C, 59.7; H, 8.5. Calcd. for $C_{18}H_{28}O_7$: C, 60.6; H, 7.9. Found: C, 60.2; H, 7.9.

Basic Hydrolysis of the Dimeric Reduction Product.—The dimeric reduction product (77.5 g.) was dribbled into a stirred and boiling solution of 100 g. of sodium hydroxide in 300 ml. of methanol. After it had boiled for five hours, the solution was mixed with 500 ml. of water and distilled to 99°. The residue was acidified to congo red and extracted with eight 200-ml. portions of ether. Distillation gave 5.3 g. of ketonic material,[6] b. p. 85° at 12 mm., and 29.2 g. of crude mixed *dl*- and *meso*-β,γ-diethyladipic acids, b. p. 140–190° at 3 mm. Crystallization of 64.3 g. of the crude mixed acids from benzene-ligroin gave 45 g. of a mixture of the two acids, m. p. 84–94°. No useful separation could be effected by crystallizing the mixed acids from ligroin–dioxane, nitromethane, dilute acetic acid, water, or constant boiling hydrochloric acid, even though well-formed large crystals were frequently obtained. Attempts to separate the acids by crystallization of the sodium, magnesium, calcium, or aniline salts from several solvents were likewise fruitless. The cinchonine salt of the *dl*-acid, a "diastereo compound"[7] is an oil, whereas the **cinchonine salt of *meso*-β,γ-diethyladipic acid** separates from alcohol–acetone in the form of cubes that slowly change to needles, m. p. 170–172°.

Anal. Calcd. for $C_{10}H_{18}O_4 + C_{19}H_{22}N_2O$: C, 70.1; H, 8.1. Found: C, 70.1; H, 8.3.

The mixed acids were separated through these salts and finally purified by crystallization from benzene. From 33 g. of mixed acids, there were obtained 6 g. of ***dl*-β,γ-diethyladipic acid**, m. p. 133–134°, and 7.5 g. of ***meso*-β,γ-diethyladipic acid**, m. p. 101–102°. The *meso* acid was more readily obtained in quantity by acid hydrolysis of the dimeric reduction product as described below.

Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.3; H, 9.0. Found: (*dl*) C, 59.5; H, 8.9; (*meso*) C, 59.1; H, 9.0.

A solution of 2 g. of the *dl* acid and 4.6 g. of brucine tetrahydrate in 6 ml. of hot ethanol and 24 ml. of water deposited 1.74 g. of the **brucine salt of *d*-β,γ-diethyladipic acid,** crystals from alcohol that melted partly at 120–122°, then resolidified and melted again at 178°.

Anal. Calcd. for $C_{10}H_{18}O_4 + 2C_{23}H_{26}N_2O_4$: C, 67.9; H, 7.1. Found: C, 67.5; H, 7.0.

***d*-β,γ-Diethyladipic acid** separated from benzene in the form of coarse needles, m. p. 114–114.5°, $[\alpha]^{37}D$ +10.4° in absolute ethanol (c = 5.54).

Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.3; H, 9.0. Found: C, 59.4; H, 9.0.

One gram of *dl*-β,γ-diethyladipic acid was boiled for two hours with excess acetic anhydride, the solution was then distilled to dryness under reduced pressure, and the residue was pyrolyzed at 210° under atmospheric pressure. There was obtained 0.61 g. (88%) of crude *trans*-3,4-diethylcyclopentanone (obtained in quantity by acid hydrolysis of the dimeric reduction product as described below) which furnished 0.6 g. (70%) of its semicarbazone, m. p. 203–206° with decomposition.

meso-β,γ-Diethyladipic acid (1.3 g.) similarly treated, gave 0.49 g. (54%) of *cis*-3,4-diethylcyclopentanone; pyrolysis of the *meso* acid (14 g.) at 270° in the presence of 1 g. of barium carbonate gave 6.6 g. (69%) of pure ***cis*-3,4-diethylcyclopentanone,** b. p. 100° at 27 mm.

Anal. Calcd. for $C_9H_{16}O$: C, 77.1; H, 11.5. Found: C, 77.2; H, 11.5.

The **semicarbazone** of *cis*-3,4-diethylcyclopentanone formed plates from alcohol, m. p. 185–186.5° with decomposition.

Anal. Calcd. for $C_{10}H_{19}N_3O$: C, 60.9; H, 9.7. Found: C, 61.0; H, 9.5.

The **oxime** of *cis*-3,4-diethylcyclopentanone, b. p. 147° at 27 mm., was obtained in a yield of 91%. It sintered at 30° and melted at 38–39°.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.6; H, 11.1 Found: C, 69.7; H, 10.8.

Acid Hydrolysis of the Dimeric Reduction Product.—A mixture of 114 g. of the dimeric reduction product with 300 ml. of 20% hydrochloric acid was boiled for twenty hours under a partial reflux, about 100 ml. of distillate being collected each hour and the distillate being replaced with hydrochloric acid. The residue was then cooled, and the substance which separated was distilled at 3 mm. and crystallized from benzene–ligroin, giving 18.3 g. (33%) of *meso*-β,γ-diethyladipic acid, m. p. 101–102°. The ketonic material obtained by extracting the distillate from the acid hydrolysis, was nearly exclusively *trans*-3,4-diethylcyclopentanone, b. p. 95° at 17 mm. It furnished a **semicarbazone** (yield, 80%) that separated from alcohol in the form of elongated plates that melted at 202.5–206° with decomposition.

Anal. Calcd. for $C_{10}H_{19}N_3O$: C, 60.9; H, 9.7. Found: C, 60.7; H, 9.6.

The **oxime** of *trans*-3,4-diethylcyclopentanone, b. p. 110° at 4 mm., was obtained in a yield of 92%. It was crystallized from ligroin, m. p. 59.5–62°.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.6; H, 11.1 Found: C, 69.9; H, 10.8.

The **2,5-dipiperonal derivative** of *trans*-3,4-diethylcyclopentanone separated from chloroform-alcohol in the form of yellow prisms, m. p. 167–169°.

Anal. Calcd. for $C_{25}H_{24}O_5$: C, 74.2; H, 6.0. Found: C, 74.3; H, 6.0.

***cis*-4,5-Diethylpiperidone-2.**—A mixture of 3.7 g. of *cis*-3,4-diethylcyclopentanone oxime with 8 ml. of 85% sulfuric acid was warmed to 120°, whereupon an exothermic reaction started, and the temperature rose to 170°. The mixture was cooled and neutralized below 10° with 30% potassium hydroxide, and the product was extracted with chloroform. It was obtained in a yield of 86%; b. p. 141° at 3 mm., m. p. 51–57°.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.6; H, 11.1. Found: C, 69.9; H, 10.7.

***cis*-3,4-Diethylpiperidine.**—A solution of the *cis* piperidone (2.9 g.) in 50 ml. of dry butyl alcohol was treated with 4.4 g. of sodium. The basic product boiled at 125° at 115 mm.; yield 86%. The **chloroplatinate** formed pale orange nodules from alcohol that sintered at 158° and melted at 160–162° with decomposition.

Anal. Calcd. for $2C_9H_{19}N + 2HCl + PtCl_4$: C, 31.2; H, 5.8; Pt, 28.2. Found: C, 31.7; H, 5.8; Pt, 28.6.

The **picrate** formed yellow prisms from methanol, m. p. 130–132°.

Anal. Calcd. for $C_9H_{19}N + C_6H_3N_3O_7$: C, 48.7; H, 5.4. Found: C, 48.9; H, 5.8.

***trans*-4,5-Diethylpiperidone-2** was obtained from *trans*-3,4-diethylcyclopentanone oxime in a yield of 88%. It boiled at 148° at 5 mm. and melted at 70–71° after it had been crystallized from ligroin.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.6; H, 11.1. Found: C, 69.4; H, 11.1.

***trans*-3,4-Diethylpiperidine** was obtained in a yield of 78% from 6.6 g. of the *trans*-piperidone. It boiled at 115–120° at 90 mm., yielded a chloroplatinate that melted at 158–159°, and a picrate that melted at 106.5–107.5°.

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(6) This material (Calcd. for $C_9H_{16}O$: C, 77.1; H, 11.5. Found: C, 77.3; H, 11.3) was approximately 90% *trans*-3,4-diethylcyclopentanone, and 10% the *cis* isomer, separable by conversion into semicarbazones and fractional crystallization of these.

(7) Shriner, Adams, and Marvel, in Gilman's "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, p. 189.

These compounds were not analyzed since they appear to be identical with the 3,4-diethylpiperidine (b. p. 193° at 720 mm.) and its derivatives (chloroplatinate, m. p. 159–160°; picrate, m. p. 107–108°) previously prepared by Koenigs and Bernhart.[8]

Summary

The reduction of ethyl propylidenemalonate with aluminum amalgam yields a mixture of substances from which there can be obtained the *dl* and the *meso* forms of β,γ-diethyladipic acid. These acids have been characterized and converted into the corresponding forms of 3,4-diethylcyclopentanone, 3,4-diethylcyclopentanone oxime, 4,5-diethylpiperidone-2, and 3,4-diethylpiperidine.

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[8] Koenigs, *Ber.*, **37**, 3248 (1904); Koenigs and Bernhart, *ibid.*, **38**, 3049 (1905).

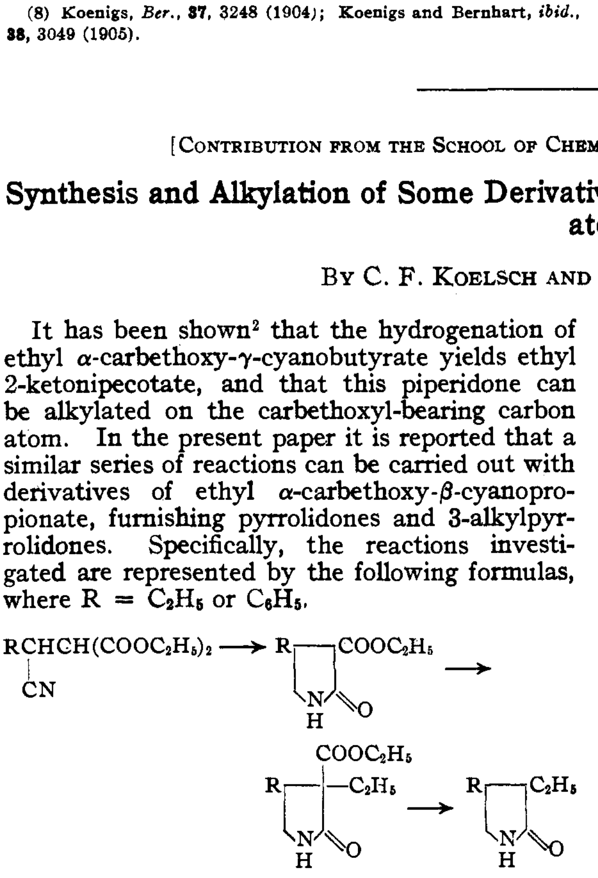
MINNEAPOLIS, MINNESOTA RECEIVED AUGUST 28, 1944

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Synthesis and Alkylation of Some Derivatives of Ethyl 2-Ketopyrrolidine-3-carboxylate[1]

BY C. F. KOELSCH AND CHARLES H. STRATTON

It has been shown[2] that the hydrogenation of ethyl α-carbethoxy-γ-cyanobutyrate yields ethyl 2-ketonipecotate, and that this piperidone can be alkylated on the carbethoxyl-bearing carbon atom. In the present paper it is reported that a similar series of reactions can be carried out with derivatives of ethyl α-carbethoxy-β-cyanopropionate, furnishing pyrrolidones and 3-alkylpyrrolidones. Specifically, the reactions investigated are represented by the following formulas, where R = C_2H_5 or C_6H_5.



Sodium and butyl alcohol converts the products into pyrrolidines, but the yields obtainable are much inferior to those realized in the reduction of analogous piperidones.[3]

Experimental

Ethyl α-Carbethoxy-β-cyanovalerate.—A solution of 59 g. of sodium cyanide in 150 ml. of water and 300 ml. of alcohol was treated at below 10° with 66 g. of acetic acid and then added with stirring to 200 g. of ethyl propylidenemalonate. After it had been stirred for one hour, the mixture was diluted with water, acidified, and extracted with ether. Distillation gave 141 g. (62%) of product with b. p. 130–140° at 2.5 mm.

Anal. Calcd. for $C_{11}H_{17}NO_4$: C, 58.2; H, 7.5. Found: C, 58.3; H, 7.8.

Reduction of 13.1 g. of the cyanoester in 150 ml. of alcohol at 175° using Raney nickel and hydrogen at 100 atmospheres took place in less than one hour, and gave 5.2 g. (80%) of **4-ethylpyrrolidone-2**, b. p. 104–106° at 5 mm., m. p. 39–41°. This substance has been reported previously[4] as a liquid, b. p. 117–118° at 13 mm.

Anal. Calcd. for $C_6H_{11}NO$: C, 63.7; H, 9.7. Found: C, 63.2; H, 9.8.

Reduction of 35 g. of the cyanoester in 125 ml. of alcohol in the same way but at 100° gave 24.3 g. (85%) of **ethyl 4-ethyl-2-ketopyrrolidine-3-carboxylate,** colorless coarse needles from benzene–ligroin, m. p. 83–84.5°.

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.4; H, 8.0. Found: C, 58.6; H, 8.1.

Saponification of the pyrrolidone-ester with alcoholic potassium hydroxide and distillation of the resulting acid gave 4-ethylpyrrolidone-2 in a yield of 64%. Reduction of 3.8 g. of this pyrrolidone in 95 ml. of dry butyl alcohol with 7.7 g. of sodium gave 0.75 g. (22%) of **3-ethylpyrrolidine,** b. p. 122–132°, analyzed in the form of its **picrate,** yellow needles from alcohol, m. p. 102.5–103°.

Anal. Calcd. for $C_6H_{13}N + C_6H_3N_3O_7$: C, 43.9; H, 4.9. Found: C, 44.0; H, 5.2.

A solution of 0.3 mole of sodium ethoxide, 47.2 g. of ethyl 4-ethyl-2-ketopyrrolidine-3-carboxylate, and 47.5 g. of ethyl iodide in 200 ml. of absolute alcohol was boiled for one and one-half hours, and then most of the alcohol was distilled. The residue was diluted to 600 ml. with 20% aqueous calcium chloride and extracted with fifteen 100-ml. portions of ether. Distillation at 11 mm. gave 36 g. of product, b. p. 165–185°, and crystallization of the distillate from benzene–ligroin gave 20.3 g. (38%) of **ethyl 3,4-diethyl-2-ketopyrrolidine-3-carboxylate,** m. p. 76.5–77°.

Anal. Calcd. for $C_{11}H_{19}NO_3$: C, 62.0; H, 9.0. Found: C, 62.2; H, 9.2.

Saponification of 29.8 g. of the ester with alcoholic potassium hydroxide followed by distillation of the resulting acid gave 18 g. (91%) of **3,4-diethylpyrrolidone-2,** b. p. 138–142° at 10 mm., m. p. 16–18°.

Anal. Calcd. for $C_8H_{15}NO$: C, 68.0; H, 10.7. Found: C, 68.0; H, 10.8.

Reduction of 18 g. of 3,4-diethylpyrrolidone-2 in 300 ml. of dry butyl alcohol with 23 g. of sodium gave 1.6 g. (12%) of **3,4-diethylpyrrolidine,** b. p. 57° at 12 mm., analyzed in the form of its **picrate,** flat yellow needles from benzene, m. p. 116.5–117°.

Anal. Calcd. for $C_8H_{17}N + C_6H_3N_3O_7$: C, 47.2; H, 5.7. Found: C, 47.1; H, 6.0.

Ethyl α-Carbethoxy-β-cyano-β-phenylpropionate, m. p. 48° (reported[5] 48.5°) was obtained in yields of 90–94% when a solution of 20.2 g. of sodium cyanide and 23 g. of

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[1] From the Ph.D. Thesis of Charles H. Stratton, September, 1943.

[2] Koelsch, THIS JOURNAL, **65**, 2458 (1943).

[3] Koelsch, *ibid.*, **65**, 2460 (1943).

[4] Guha-Sircar, *J. Indian Chem. Soc.*, **5**, 549 (1928).

[5] Bredt and Kallen, *Ann.*, **293**, 342 (1896).