yldiazomethane with dimethyl fumarate, 10.0 g. (55.5 millimoles) of *cis*-stilbene was heated to 180° under nitrogen. Ethyl diazoacetate (6.35 g., 55.5 millimoles) was added dropwise at such a rate as to maintain the temperature between 180 and 200°. During the addition, the mixture turned deep brown and 1310 ml. (53 millimoles) of nitrogen was collected. The reaction mixture was then hydrolyzed by refluxing for 6.5 hours with 100 ml. of 5% ethanolic sodium hydroxide. The ethanol was removed *in vacuo* and the residue treated with hot water and filtered. No solid remained on the filter paper. The filtrate was extracted with chloroform to give a light yellow $CHCl_3$ layer and a deep red aqueous layer. The chloroform layer was dried and distilled to give 5.85 g. of unreacted *cis*-stilbene. There was virtually no residue from the distillation indicating the absence of *trans*-stilbene. The aqueous layer was acidified with concd. HCl to give a deep brown oil. This was separated and dissolved in 10 ml. of hot 10% NaOH; 10 ml. of hot water was added and the mixture was cooled in the refrigerator. Filtration gave no solid material. In view of the insolubility of the sodium salt of VIIa (less than 0.30 g. of acid saturates 20 ml. of cold 5% NaOH) the reaction apparently led to, at most, 6% of the *trans*-ester, and probably much less.

The filtered aqueous solution was then diluted to 150 ml. and 5% HCl was added slowly with vigorous stirring until the deep red color had disappeared and a light brown solution remained. The aqueous layer was separated by decantation from the almost black oil which had separated and then acidified to *p*H 1. The mixture was extracted with benzene, dried and the benzene removed *in vacuo* to give 3.2 g. of light brown, very viscous oil. This oil was refluxed for 1 hr. with an excess of $SOCl_2$, cooled and poured into rapidly stirred ice and ammonium hydroxide. The brown precipitate was filtered, dried and extracted in a Soxhlet for two days with benzene. The benzene was removed and the residual solid washed with a little cold benzene to give 0.97 g. (18% yield) of the amide of the *cis*-acid VIIIa, m.p. 193–204°. Recrystallization from ethanol–water gave the pure colorless amide, m.p. 213.5–215.5°, reported[6] m.p. 212–215°. The infrared spectra of the impure and the recrystallized materials were virtually superimposable.

The amide was converted to its corresponding acid VIIIa in the following way: To a mixture of 0.5 g. of the crude amide in 10 ml. of acetic acid was added a fourfold excess of sodium nitrite followed by 20 drops of concentrated HCl. After the initial evolution of gas had subsided (*ca.* 2 min.) the mixture was warmed on a steam-cone until no more gas evolved, after which it was poured into 50 ml. of water. Filtration followed by recrystallization from ethanol–water gave 0.2 g. of colorless solid, m.p. 145–147°. Several recrystallizations from ethanol–water gave the colorless acid, m.p. 152.5–154.5°; admixture with the *trans*-acid VIIa, m.p. 122–138°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.73; H, 5.99.

GAINESVILLE, FLA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

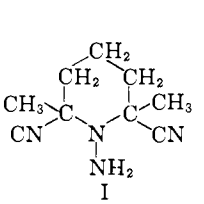
Azo Compounds. XXX.[1] Decomposition Products Obtained from the Oxidation of 1-Amino-2,6-dicyano-2,4,6-trimethylpiperidine. The Abnormal Oxidation

BY C. G. OVERBERGER, GEORGE KESSLIN AND PAO-TUNG HUANG[2]

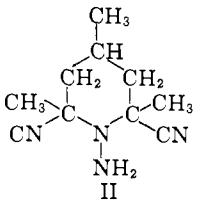
RECEIVED NOVEMBER 22, 1958

Oxidation of 1-amino-2,6-dicyano-2,4,6-trimethylpiperidine yielded two products. One product was shown to be *cis*-1,2-dicyano-1,2,4-trimethylcyclopentane by conversion to a bicyclic derivative, 3-imino-3a,5,6a-trimethylcyclopenta(c)pyrrolidine-1-one. The second product was demonstrated to be 2,6-dicyano-4-methylheptene-2. Conformational considerations are consistent with a concerted nitrogen elimination mechanism for the formation of the cyclic oxidation product as has been proposed previously for related oxidations.

A previous paper in this series[3] has described the isolation and proof of structure of the oxidation products of 3,7-dicyano-3,7-dimethylhomopiperidazine, subsequently shown to be instead, 1-amino-2,6-dicyano-2,6-dimethylpiperidine (I).[4]



I



II

Three products were isolated. Two of these were shown to be *cis*- and *trans*-1,2-dicyano-1,2-dimethylcyclopentanes, isolated in 16–26 and 3.9% yields, respectively. The third product, isolated in 28–38%, yield, was demonstrated to be 2,6-dicyanoheptene-2. This paper describes the isolation and proof of structure of the oxidation products of the homologous 1-amino-2,6-dicyano-2,4,6-trimethylpiperidine (II) and correlates the previous results.

Discussion

Besides the physical and chemical evidence available in support of the structure of its homolog I,[4] additional experimental confirmation of structure II has been obtained. Deamination of II resulted in the quantitative evolution of nitrogen and the isolation of 2,6-dicyano-2,4,6-trimethylpiperidine (III). The infrared spectrum of III indicated the loss of one of the twin NH stretching frequencies in the 3μ region, and of the NH_2 bending frequency at 6.07 μ, exhibited by II.

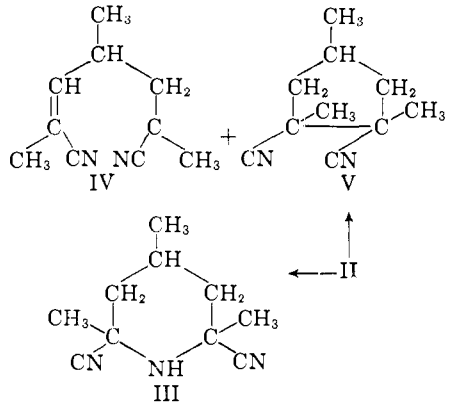
Oxidation of II with bromine at 0–5° gave two isomeric products (IV) and V). Quantitative hydrogenation of the crude oxidation mixture indicated the presence of 80% of the linear unsaturated isomer IV. Its isolation was achieved in 11% yield by crystallization or in 41.9% yield as mono- and diamide derivatives from the alkaline hydrogen peroxide hydrolysis of the crude oxidation mixture. The saturated cyclic isomer V could not be isolated directly from the crude oxidation mixture by distillation, sublimation or chromatography. Since

(1) This is the 30th in a series of papers concerned with the preparation and reactions of azo and diazo compounds. For the previous paper in this series, see C. G. Overberger and A. V. DiGiulio, THIS JOURNAL, **81**, 2154 (1959).

(2) A portion of a thesis submitted by Pao-tung Huang in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the Polytechnic Institute of Brooklyn.

(3) C. G. Overberger, P. Huang and T. B. Gibbs, Jr., THIS JOURNAL, **75**, 2082 (1953).

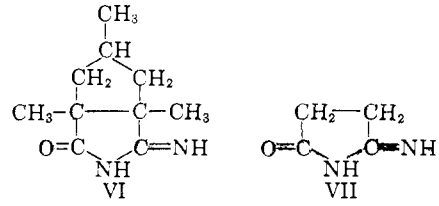
(4) C. G. Overberger and B. S. Marks, *ibid.*, **77**, 4097 (1955).



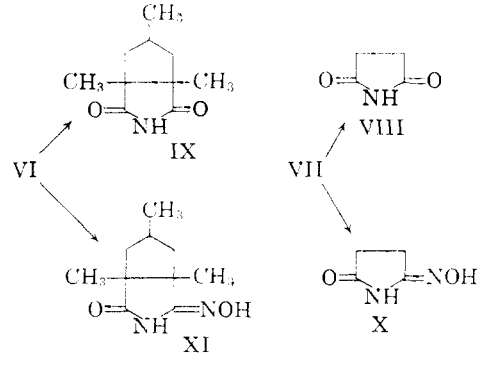
direct methods of separation of V proved unsuccessful, a number of indirect approaches were made. Attempts to add diethyl malonate or benzyl mercaptan under basic catalysis to the olefinic moiety in the mixture failed. The presence of 20% of V in the crude oxidation mixture was finally demonstrated by formation and characterization of its bicyclic derivative VI from the alkaline hydrogen peroxide hydrolysis of the crude oxidation mixture.

The structure of IV was determined in the following way. Its analysis and molecular weight conformed to the formula $C_{10}H_{14}N_2$. Its infrared spectrum revealed the presence of a double bond (6.15 μ) and both α,β-unsaturated nitrile (2225 cm.$^{-1}$) and saturated nitrile (2250 cm.$^{-1}$) groups, in agreement with the entensive study of nitriles by Kiston and Griffith.[5] The position of the double bond was located by permanganate oxidation of IV and identification of the products. Oxidation yielded no carbon dioxide, and γ-cyano-α-methyl-*n*-valeric acid, a hitherto unreported acid, was obtained in 51–87% yield. The latter was hydrolyzed to a diacid conforming in analysis and neutralization equivalent to α,α'-dimethylglutaric acid and was a mixture of *meso*- and *dl*-isomers of α,α'-dimethylglutaric acid previously characterized by Auwers.[6] Separation of the isomers by the method of Auwers gave the high melting *dl*-form.

The structure of V was determined in the following way. Since V could not be directly isolated, evidence for the assignment of structure was obtained for its high melting solid derivative VI isolated from the alkaline hydrogen peroxide hydrolysis of the crude oxidation mixture. Analysis and molecular weight for VI corresponded to the formula $C_{10}H_{16}N_2O$, indicative of a monoamide of one of the isomeric dinitriles IV or V. Its infrared spectrum showed no evidence of a nitrile frequency in the 4.5 μ region, nor for the typical primary amide which generally has two bands for NH stretching in the 3.0 μ region, a doublet in the 6.0–6.2 μ region and a band at 7.05–7.15 μ. Instead were found single strong bands at 3.04, 6.0 and 6.52 μ, which corresponded more closely with a monosubstituted amide structure. Attempted quantitative hydrogenation resulted in no absorption of hydrogen. These data suggested the formulation of VI as a bicyclic compound isomeric with the monoamide of the cyclic dinitrile



Additional evidence for structure VI was obtained from its striking similarities in physical and chemical properties with the recently reported analogous structure VII.[7] The ultraviolet spectrum of VII showed λ_{max} 227 mμ and ϵ 22,000; structure VI, λ_{max} 227 mμ and ϵ 18,400. Hydrolysis of VII produced succinimide (VIII) which showed λ_{max} 240 mμ and $\epsilon \not> 200$. The infrared spectrum of VIII exhibited frequencies at 3.18, 5.65 and 5.90 μ characteristic of ring type diacylimides possessing the group –CO–NH–CO–.[8] Hydrolysis of VI with both 50% sulfuric acid and aqueous alcoholic sodium hydroxide resulted in the formation of IX; structure IX showed λ_{max} 247 mμ and ϵ 215. The infrared spectrum of IX exhibited frequencies at 3.15, 5.62 and 5.87 μ. Finally, in direct analogy with the work of Elvidge and Linstead who prepared the monooxime X from VII, similar monoöxime XI formation from VI was observed. Oxime XI showed

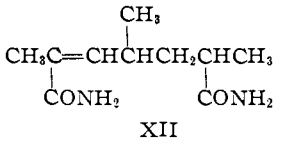


λ_{max} 226 mμ and ϵ 12,000; oxime XI had λ_{max} 222 mμ and ϵ 9,860. On this basis, it is reasonable to assign the structure of VI as 3-imino-3a,5,6a-trimethylcyclopenta(c)pyrrolidine-1-one. The formation of this bicyclic compound during the alkaline peroxide hydrolysis requires that the parent dinitrile be *cis*-1,2-dicyano-1,2,4-trimethylcyclopentane. The mild conditions of hydrolysis excludes the possibility of any stereo change during this reaction. As far as is known, this is the first recorded instance of this type of cyclization from the alkaline peroxide hydrolysis of a nitrile.[9]

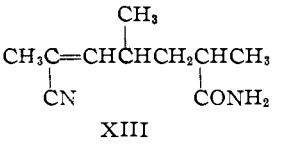
Only two other products were isolated from the alkaline peroxide hydrolysis of the crude oxidation mixture XII and XIII, both of which were shown to be derivatives of the same linear unsaturated

(5) R. E. Kiston and T. H. Griffith, *Anal. Chem.*, **24**, 334 (1952).
(6) K. Auwers, *Ann.*, **285**, 241 (1895).
(7) J. A. Elvidge and R. P. Linstead, *J. Chem. Soc.*, 442 (1954).
(8) H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1949, p. 14.
(9) Br. Radziszewski, *Ber.*, **18**, 355 (1885).

isomer (IV) isolated by crystallization at Dry Ice temperatures. A mixture melting point of XII with the diamide prepared from the pure linear



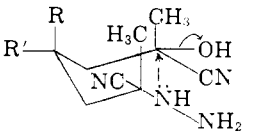
XII



XIII

isomer showed no depression, while XIII could be converted to XII by further hydrolysis with alkaline peroxide. Quantitative hydrogenation of both XII and XIII resulted in the theoretical uptake of hydrogen, and in the case of XIII resulted in a shift in the nitrile frequency from 2210 (4.52 μ) to 2245 cm.$^{-1}$ (4.45 μ), consistent with the presence of an α,β-unsaturated nitrile grouping.[5]

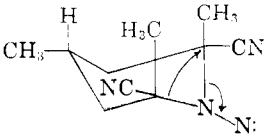
An attempt to resolve the deaminated 1-aminopiperidine (III) by means of its dibenzoyl-*d*-tartaric acid salt, a technique used successfully in a similar case, failed to give anything but amorphous salts. The configuration of the parent 1-aminopiperidine (II) thus remains indeterminate, although consistent with a possible *cis* configuration. Assuming a displacement mechanism for ring closure, conformational examination of the probably intermediate cyanohydrin at the moment of cyclization to form the piperidine ring results in the observation that cyclization could proceed through a transition state or intermediate in which the two linear cyano groups or the two methyl groups, or one cyano and one methyl group, are in the eclipsed position. It is not possible to decide this point on the evidence presented here. Because of dipole–dipole repulsion, we prefer a representation in which the methyl groups are axial. It will be recalled that the *cis*-cyclopentane derivative is the only one obtained on oxidation. A similar



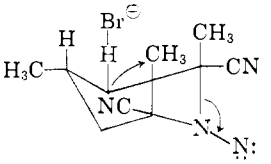
R = H, R′ = CH_3
R = CH_3, R′ = H

argument has been used by Wendler,[10] in a related problem, to distinguish between the diastereomers of 3-acetamido-1,3-diphenylpropan-1-ol. He suggests that the one isomer which undergoes N–O acetyl migration is that which suffers the least serious 1,3-*cis*-axial non-bonded interactions in the proposed cyclic mechanism.

The above considerations concerning the possible 1,3-*cis*-dicyano configuration of the 1-aminopiperidine starting product are consistent with the concerted stereospecific nitrogen elimination mechanism previously proposed[11] for the formation of coupling products in such oxidations, in view of the present demonstration that the only coupling product isolated from the oxidation had a *cis*-dicyano configuration. It will also be recalled that only a small amount of the coupled product in the previously reported homologous case (3.9%)[3] was *trans*. The high proportion of unsaturated



linear product may result from an elimination mechanism of the following type, the reaction being



facilitated by the strong electron withdrawing properties of the nitrile group. This scheme differs from that proposed for the linear isomer in the N-aminodiphenylpiperidine series[11] where ionization of a similar intermediate provides a reasonable explanation since the phenyl groups can easily stabilize the positive charge.

The smaller yield of coupled product in the case reported here as compared with N-amino-2,6 diphenylpiperidine may be due to the fact that ring closure is occurring at a tertiary carbon instead of a secondary carbon.

Experimental[12]

Preparation of 4-Methylheptanedione-2,6-dioxime.—The 4-methylheptanedione-2,6-dioxime was prepared by the method of Shaw[13,14] as modified.[15] From freshly distilled collidine (b.p. 170.6–170.8°) yields of 34.6% of crude product and 29.8% of distilled product (b.p. 145–150° (1 mm.)) were obtained.

Preparation of 1-Amino-2,6-dicyano-2,4,6-trimethylpiperidine.—The 1-amino-2,6-dicyano-2,4,6-trimethylpiperidine preparation was based on the general method of Thiele and Heuser[16] for preparing linear cyano hydrazines as modified.[17]

To a solution of 128 g. (0.745 mole) of distilled dioxime in 525 ml. of 10% sulfuric acid was added, with stirring, 107.5 g. (1.56 moles) of sodium nitrite over a period of two hours at a reaction temperature of −5 to 5°. After all the sodium nitrite was added, 6.5 g. of barium carbonate was added to make the solution neutral. The precipitated barium sulfate was filtered off with the aid of Super-Cel (filter-aid), and the filter cake was washed well with water. The combined filtrate and washings totaled 1700 ml. To 107 g. of hydrazine sulfate (0.823 mole) in 3870 ml. of water and 81.2 g. (1.66 moles) of sodium cyanide in 387 ml. of water was added the 1700 ml. of solution containing the diketone. This mixture was agitated at room temperature for a period of 60 hours. At the end of the time, the precipitated 1-aminopiperidine was collected on a filter, washed with water and dried in the oven at 100°, 40.8 g. (28.6%), m.p. 129.5–130.5°.

Only an orange colored viscous mass was obtained upon evaporation of a methylene chloride extract of the mother liquor.

In another experiment, a 28% yield of product was obtained from the use of undistilled, crude dioxime.

Preparation of 2,6-Dicyano-2,4,6-trimethylpiperidine (III).—This procedure was based on that reported by Overberger and Marks[4] for the deamination of 1-amino-2,6-dimethylpiperidine. 1-Amino-2,6-dicyano-2,4,6-trimethylpiperidine (5 g., 0.026 mole) was dissolved in 35 ml. of glacial

(10) L. J. Wendler, *Experientia*, **9**, 416 (1953).

(11) C. G. Overberger, J. G. Lombardino and R. G. Hiskey, THIS JOURNAL, **79**, 6430 (1957).

(12) All melting points are corrected. Analyses by Drs. Weiler and Strauss, Oxford, England.

(13) B. D. Shaw, *J. Chem. Soc.*, **127**, 213 (1925).

(14) B. D. Shaw, *ibid.*, 300 (1937).

(15) A. C. Cope, H. L. Dryden, Jr., C. G. Overberger and A. A. D'Addico, THIS JOURNAL, **73**, 3416 (1951).

(16) J. Thiele and K. Heuser, *Ann.*, **290**, 1 (1896).

(17) C. G. Overberger, T. B. Gibbs, Jr., S. Chibnik, P. Huang and J. J. Monagle, THIS JOURNAL, **74**, 3290 (1952).

acetic acid and cooled to 15°. To this solution was added dropwise, with stirring, over a period of one hour, 2.31 g. (0.033 mole) of 98.5% sodium nitrite dissolved in 15 ml. of water. The temperature was not allowed to exceed 15°; 87% of the theoretical nitrogen was evolved. The reaction mixture was cooled to 0–5° and neutralized by the gradual addition of 40 g. of 85% potassium hydroxide pellets, 75 ml. of water was added and the mixture filtered. The yellow solid on the filter, on drying at 90°, weighed 3.05 g., m.p. 118–131°. Recrystallization of the yellow solid from ethanol gave yellow crystals, m.p. 124–131°.

The yellow solid, 3.0 g., m.p. 118–131°, was dissolved in 35 ml. of benzene and 10 ml. of petroleum ether (30–60°) and the mixture was added to a 1" diameter column containing 75 g. of activated alumina suspended in 1:9 benzene–petroleum ether. The chromatogram was developed with 100 ml. of 1:9 benzene–petroleum ether and then eluted successively with 100 ml. of 2:8 benzene–petroleum ether, 100 ml. of 1:1 benzene–petroleum ether, 100 ml. of 9:1 benzene–petroleum ether, 100 ml. of benzene, 100 ml. of 1:9 ether–benzene and 450 ml. of ether; 50-ml. fractions were collected. On evaporation, fractions 9–14 yielded a yellow solid of wide melting point range. Fractions 15–23 yielded 1.193 g. (26.3%) of a white crystalline solid, m.p. 137.4–142.5°. After two recrystallizations from ether, the solid melted at 141.6–142.5°. The infrared spectrum showed bands at 3.01 (NH), 4.48 (CN) and none at 6.07 μ (NH_2).

Anal. Calcd. for $C_{10}H_{15}N_3$: C, 67.76; H, 8.53; N, 23.71. Found: C, 67.71; H, 8.53; N, 23.60.

Oxidation of 1-Amino-2,6-dicyano-2,4,6-trimethylpiperidine and Isolation of the Oxidation Products.—To a suspension of 10 g. (0.052 mole) of 1-amino-2,6-dicyano-2,4,6-trimethylpiperidine in 100 ml. of anhydrous ethanol, cooled to 1°, was added dropwise 8.4 g. (0.052 mole) of bromine accompanied by almost quantitative nitrogen evolution. The temperature was maintained below 4° during the addition. The clear yellow solution was evaporated free of solvent under vacuum at room temperature. The residue was dissolved in 50 ml. of methylene chloride and neutralized by washing with 5% sodium carbonate solution. The neutralized methylene chloride solution containing the oxidation products was washed with 50 ml. of water, dried over magnesium sulfate, and then evaporated free of methylene chloride. The residue was a yellow oil weighing 8.59 g. (101.9%).

Isolation of Solid, Linear, Unsaturated Dinitrile IV.—The residue, 8.59 g., from the evaporation was dissolved in 9 ml. of methylene chloride and cooled to Dry Ice temperatures. The crystallized product was rapidly filtered and weighed 1.36 g. (16.1%) after drying. Recrystallization from petroleum ether yielded 0.933 g. (11.1%) of linear unsaturated isomer, m.p. 51.4–52.0°.

Anal. Calcd. for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 73.95; H, 8.42; N, 17.91.

Isolation of Liquid Fraction.—The filtrate from the linear unsaturated isomer isolation was evaporated free of methylene chloride leaving a residue of 6.45 g. (76.5%). Quantitative hydrogenation of a sample of this residue in alcohol, with 5% palladium-on-charcoal as the catalyst, resulted in the uptake of 70% of the theoretical hydrogen for the linear unsaturated dinitrile. The remaining residue, 6.35 g., was chromatographed on alumina.

This residue was dissolved in 10 ml. of petroleum ether (30–60°) and 5 ml. of methylene chloride and added to a column of 60 g. of alumina (1.5 cm. × 34 cm.) suspended in petroleum ether. The chromatogram was developed and eluted with the following succession of solvents: 100 ml. of 8:2 petroleum ether–methylene chloride, 100 ml. of methylene chloride, 100 ml. of 1:1 methylene chloride–methanol and 150 ml. of methanol; 50-ml. fractions were collected. On evaporation, fractions 1–4 weighed 5.46 g. (65.8% based on the original 1-aminopiperidine) and represents the liquid fraction taken for alkaline peroxide hydrolysis, as subsequently described. The only other fraction of significant weight, fraction 6, weighed 0.489 g. and consisted of a reddish-brown tacky solid which could not be identified. Combined fractions 1–4 indicated 69.9% as unsaturated linear isomer by quantitative hydrogenation.

Permanganate Oxidation of the Linear Unsaturated Isomer.—To a suspension of 1.62 g. (0.01 mole) of the solid isomer in 50 ml. of water was added a saturated solution of 3.16 g. (0.02 mole) of potassium permanganate at room temperature. The addition was completed in two hours and the temperature of the solution, raised as the reaction continued, was kept below 20°. When carried out in a closed system, no carbon dioxide was collected in a buret and lime water at the outlet did not give turbidity. After the addition was completed, the solution was stirred for another hour and allowed to stand overnight. The solution was warmed on a steam-bath and the manganese dioxide was removed by suction and washed with water.

The filtrate was made more alkaline by addition of 10 ml. of 10% sodium hydroxide and the alkaline solution was extracted seven times with ether. The ether extract, after drying with anhydrous magnesium sulfate, on removal of solvent gave 0.23 g. of residue which could not be characterized.

The alkaline solution from the ether extraction was acidified with dilute sulfuric acid, saturated with ammonium sulfate and extracted eight times with ether. From the ether extract was obtained 1.2 g. of crude γ-cyano-α-methyl-*n*-valeric acid, a yellowish liquid with a sharp acid odor. Hydrolysis was effected with 30 ml. of 40% sulfuric acid by refluxing at 130° for three hours. After cooling, the acidic solution was poured onto 200 g. of chopped ice. To the solution was added 100 g. of ammonium sulfate and the solution was extracted ten times with ether. From the ether extract, there was obtained 1.30 g. of crude solid, α,α'-methylglutaric acid.

To purify the diacid, it was dissolved in ether and boiled with decolorizing carbon. The filtrate was evaporated to a small volume and petroleum ether (b.p. 30–60°) was added. The solid precipitated was collected, washed with petroleum ether, and dried in a vacuum, 1.1 g. (80.8%), 100–117°, neut. equiv. 81.7 (calculated for α,α'-dimethylglutaric acid, 80.0). Separation of the isomers by recrystallization was unsuccessful. When 0.28 g. of the solid, m.p. 100–117°, was fractionally crystallized by first dissolving it in a mixture of petroleum ether (b.p. 90–100°) and methylene chloride and then cooled in a Dry Ice-box for three hours, 0.17 g. of crystalline solid was obtained, m.p. 107–125°. The fact that this fraction was a mixture of the pure isomers was shown by analysis.

Anal. Calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.58; H, 7.37.

Concentration of the filtrate gave 0.07 g. of a second fraction, m.p. 104–107°. Sublimation at 85° at 1 mm. changed the m.p. of the solid to 100–105°.

Anal. Calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.87; H, 7.42.

Attempted separation of the isomers by the method of Auwers[6] gave the high-melting *dl*-form, m.p. 138–140° (140–141°[6]).

In one experiment, the γ-cyano-α-methyl-*n*-valeric acid was purified by distillation and identified by analysis, 87%, b.p. 114° (0.9 mm.), $n^{25}D$ 1.4408, d^{27}_4 1.0818.

Anal. Calcd. for $C_7H_{11}O_2N$: C, 59.55; H, 7.86; N, 9.92. Found: C, 59.60; H, 8.03; N, 9.99.

Alkaline Hydrogen Peroxide Hydrolysis of the Linear Unsaturated Isomer.—The procedure used was essentially the Mooradian and Cloke[18] modification of the Radziszewski reaction.[9] Pure solid linear unsaturated isomer, m.p. 51.4–52.0° (0.213 g., 0.00132 mole), was dissolved in 3 ml. of 10% hydrogen peroxide and 3.5 ml. of acetone. The mixture was cooled to 0° and 0.47 ml. of 10% sodium hydroxide solution was added. The mixture was then allowed to stand at −12° for 24 hours. No precipitation of solids occurred; the acetone was then evaporated at room temperature under vacuum and the residual aqueous solution saturated with ammonium sulfate. The saturated aqueous solution was then extracted with four portions of 5 ml. each of ether. The combined ether extracts were dried over magnesium sulfate and allowed to stand 24 hours at −12°. At the end of this time the white precipitate was collected by filtration and dried to give 0.042 g. (16.2%) of crude diamide, m.p. 129–130°. Sublimation of 0.03 g. at 115–120° (0.6 mm.) yielded two fractions: 1, 0.009 g., m.p. 133.5–139°; 2, 0.015 g., m.p. 138.8–141.0°. An analytical sample was prepared by recrystallization from ether, m.p. 140.7–141.4°.

(18) A. Mooradian and J. B. Cloke. THIS JOURNAL, **68**, 785 (1946).

Anal. Calcd. for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.1. Found: C, 60.52; H, 9.02; N, 14.0.

Alkaline Hydrogen Peroxide Hydrolysis of the Liquid Fraction from the Oxidation. Isolation of Solids VI, XII and XIII.—The liquid fraction isolated by chromatography, 2.346 g., assaying 69.9% as unsaturated linear isomer, was dissolved in 30 ml. of 10% hydrogen peroxide and 35 ml. of acetone. To this mixture at 0° was added 4.7 ml. of 10% sodium hydroxide and the combined solution allowed to stand at −12° for 24 hours. The precipitated white solid was filtered and washed with 6 ml. of 30% aqueous acetone. Upon drying in the oven at 105°, there was obtained 0.471 g. (18.1%) of crude solid VI, 3-imino-3a,5,6a-trimethylcyclopenta(c)pyrollidine-1-one, m.p. 292.3–295.3°. The filtrate was evaporated free of acetone and saturated with ammonium sulfate. Further precipitation of VI occurred. Filtration and drying yielded a second crop of 0.27 g. (10.3%) of crude VI, m.p. 286.3–290.3°, for a combined yield of 0.741 g. (28.4%). Recrystallization from methanol yielded pure solid VI, m.p. 295.4–296.2°. The infrared spectrum showed bands at 3.04, 6.0 and 6.52 μ and the ultraviolet absorption showed λ_{max} 227 mμ, ϵ 18,400.

Anal. Calcd. for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.5. Found: C, 66.44; H, 8.74; N, 15.6.

The filtrate from the filtration of the second crop of VI was extracted with four portions of 50 ml. of ether; after drying over magnesium sulfate and standing for 24 hours at room temperature there was deposited a "cottony," white solid. Filtration and drying yielded 0.368 g. (12.8%) of crude XII, 2,6-dicyano-4-methyl heptene-2-diamide, m.p. 127.4–128.9°. Recrystallization from ether yielded pure diamide, m.p. 140.7–141.4°. The infrared spectrum showed bands at 3.03, 3.15, 6.0, 6.08 and 7.08 μ.

A mixture melting point with the diamide obtained from the alkaline peroxide hydrolysis of pure linear unsaturated isomer, m.p. 138.8–141.0°, gave a m.p. 139.0–141.2°. Hence, the diamide isolated in this experiment is derived from the same linear unsaturated dinitrile which was isolated as a solid by freezing the oxidation mixture to Dry Ice temperatures.

The ether filtrate from the filtration of XII was evaporated free of ether leaving a residue of 1.584 g. of viscous liquid. This was chromatographed on alumina. The 1.584 g. of viscous liquid was dissolved in 4 ml. of benzene and 3 ml. of petroleum ether (30–60°) and added to a column of 50 g. of alumina (1.5 cm. × 29.5 cm.) suspended in petroleum ether. The container was rinsed with 2 ml. of benzene and 3 ml. of petroleum ether. The chromatogram was developed and eluted with the following succession of solvents: 100 ml. of petroleum ether, 150 ml. of 1:1 petroleum ether–benzene, 200 ml. of benzene, 200 ml. of 1:1 benzene–methanol, and 180 ml. of methanol; 50-ml. fractions were collected. Fraction 10, after evaporation, weighed 0.146 g., m.p. 55–69°. Recrystallization from ether gave 0.041 g. of solid XIII, the monoamide of the linear unsaturated dinitrile, m.p. 75.5–77.2°. Fraction 11, 0.794 g., upon recrystallization from 20 ml. of ether and 2 ml. of benzene (9 days at −12°) yielded 0.317 g. of amorphous, white solid, m.p. 85.8–100°. Sublimation of the 0.317 g. of solid at 85–90° (0.4 mm.) yielded a sublimate of 0.083 g. of XIII, m.p. 70–75°. The sublimation residue upon repeated recrystallization from ether yielded 0.025 g. of XII, the diamide of the linear isomer. The filtrate from the recrystallization of fraction 11, after evaporation, yielded 0.407 g. of tacky solid, m.p. 50–63°, from which was obtained, by recrystallization from benzene–petroleum ether followed by sublimation at 60–65° (0.4 mm.), a further 0.166 g. of XIII, m.p. 72.5–76.5°. The total weight of crude XIII was 0.290 g. (11.1%). An analytical sample prepared by recrystallization of crude XIII from ether had a m.p. 76.8–77.6°. The infrared spectrum showed bands at 2.96, 3.15, 4.52, 6.03, 6.12 and 7.07 μ.

Anal. Calcd. for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.5. Found: C, 66.85; H, 8.91; N, 15.2.

In another bromine oxidation, the oxidation products as obtained from 10.0 g. of 1-aminopiperidine, after solvent evaporation and neutralization, were chromatographed directly on alumina without any attempt to isolate pure linear isomer at Dry Ice temperatures. The oxidation residue was thus dissolved in 5 ml. of methylene chloride and 10 ml. of petroleum ether (30–60°) and added to a column of 75 g. of alumina (2.8 cm. × 12 cm.) suspended in petroleum ether. The chromatogram was developed and eluted with the following succession of solvents: 100 ml. of 8:2 petroleum ether–methylene chloride, 150 ml. of methylene chloride, and 150 ml. of 1:1 methylene chloride–methanol; 50-ml. fractions were collected. Fractions 1–5 weighed 7.58 g. (90%) after evaporation, and consisted of a light yellow oil assaying 80% of the theoretical linear unsaturated isomer by quantitative hydrogenation.

Alkaline peroxide hydrolysis of the 7.58 g. of chromatographed oxidation mixture, by the same procedure previously employed, yielded 1.965 g. (21.0% of the theoretical bicyclic derivative) of crude VI, m.p. 290–296°. Crude XII, m.p. 130–130.6°, 1.338 g., was isolated as before and upon sublimation of an aliquot was shown to contain at least 1.202 g. (11.7% of the theoretical diamide) of XII, m.p. 136–139°. Crude XIII was again isolated by chromatography of the evaporated filtrate obtained in the recrystallization of XII. Sublimation and resublimation of an aliquot of two chromatogram fractions gave 2.83 g. (30.2% of the theoretical monoamide) of XIII, m.p. 70.2–73°.

Alkaline Hydrogen Peroxide Hydrolysis of the Linear Unsaturated Monoamide.—Solid XIII, m.p. 70–73°, 0.50 g., was dissolved in 5 ml. of 10% hydrogen peroxide and 2 ml. of acetone. After cooling to 0° and adding 1 ml. of 10% sodium hydroxide, the mixture was allowed to stand three days at −12°. Upon evaporation of the acetone, precipitation occurred, 5 ml. of water was added and the solution was then saturated with ammonium sulfate. The suspension of solids was agitated with 30 ml. of ether and removed by filtration. After washing the filter cake with 10 ml. of water, and drying, 0.306 g. (55.7% of the theoretical diamide) of XII was obtained, m.p. 140.4–141.6°.

A mixture melting point with diamide from pure unsaturated linear isomer previously prepared, m.p. 138.8–141.0°, gave m.p. 140.8–141.5°.

Alkaline Hydrolysis of the Bicyclic Derivative VI.—Solid VI, m.p. 295.4–296.2°, 0.500 g., was refluxed for 12 hours with 1 g. of sodium hydroxide in 20 ml. of methanol and 5 ml. water. To this, 40 ml. of water was then added and the methanol removed by distillation. The aqueous solution was treated with carbon and then acidified with concentrated sulfuric acid. The mixture was cooled to room temperature and a crop of white crystals was collected by filtration, and dried. The weight of the first crop crystals was 0.321 g., m.p. 149.0–150.0°. By saturation of the filtrate with ammonium sulfate and filtration, a second crop of crystals, 0.053 g., m.p. 144.0–149.0°, was obtained. The total weight of 1,2,4-trimethylcyclopentane-1,2-dicarboximide amounted to 0.374 g. (74.5%).

Recrystallization by slow evaporation from a solution in 10 ml. of petroleum ether (30–60°) and 10 ml. of ether yielded 0.195 g., m.p. 149.4–150.0°. The infrared spectrum showed bands at 3.15, 5.62 and 5.87 μ and the ultraviolet absorption showed λ_{max} 247 mμ, ϵ 215.

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.45; H, 8.04; N, 7.85.

Acid Hydrolysis of the Bicyclic Derivative VI.—Solid VI, m.p. 292.3–295.3°, 0.402 g., was heated at 160° (oil-bath temperature) with 10 ml. of 50% sulfuric acid and 0.2 g. of sodium chloride for 1 hour. The mixture was cooled and quenched on crushed ice, the aqueous solution was extracted with four portions of 30 ml. each of ether, the ether extracts dried over magnesium sulfate and then evaporated free of ether. The residue, m.p. 140–146°, weighed 0.114 g.; two sublimations at 120° (0.5 mm.) yielded 0.085 g. of dicarboximide, m.p. 145.2–147.2°. A mixture melting point with the solid obtained by alkaline hydrolysis of VI, m.p. 149.0–150.0°, gave a m.p. 145.4–148.5°. Thus the solids formed by alkaline and acid hydrolysis of VI are identical.

Oximation of the Bicyclic Derivative VI.—Solid VI, m.p. 295.4–296.2°, 0.30 g., was refluxed 14 hours with 0.30 g. of hydroxylamine hydrochloride[7] in 20 ml. of anhydrous ethanol. The mixture was cooled overnight at −12° to crystallize the product. The dry, white solid oxime weighed 0.21 g. (64.2%), m.p. 231.0–232.0° (gas evolution). An analytical sample was recrystallized from ethanol, m.p. 231.0−232.0°. The ultraviolet absorption showed λ_{max} 222 mμ, ϵ 9860.

Anal. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 61.25; H, 7.92; N, 14.5.

Quantitative Hydrogenation.—The procedure in these experiments was based on the method described by Ogg and

Cooper.[19] A 5% palladium-on-activated-charcoal was used as a catalyst. In all cases the quantity of reagents used was approximately a 0.1-g. sample, 0.12 g. of 5% palladium-on-charcoal and 10 ml. of anhydrous alcohol. Reactions were carried out at room temperature and atmospheric pressure.

Solid VI, m.p. 295.4–296.2°, 0.0945 g., was hydrogenated in 10 ml. of ethanol in the presence of 0.12 g. of 5% palladium-on-charcoal catalyst. No uptake of hydrogen was noted over a period of one hour. After standing in the hydrogenator overnight, the solution was filtered free of catalyst and evaporated to dryness. The solid residue weighed 0.086 g., m.p. 285–290°.

A mixture melting point with pure VI gave m.p. 290.8–293.5°. Hence, VI contains no carbon–carbon unsaturation.

Solid XII, linear diamide, 0.0967 g., was hydrogenated in 10 ml. of ethanol over 0.12 g. of palladium-on-charcoal. The hydrogen uptake amounted to 11.14 ml. (in 15 minutes) and corresponded to 101.8% of the theoretical linear diamide. Filtration of the catalyst, and evaporation of solvent left behind 0.09 g. of solid residue. Recrystallization from 5 ml. of methanol gave 0.055 g. of white crystalline solid, m.p. 220–224°. The infrared absorption spectrum showed bands at 2.98, 3.15, 6.0, 6.07 and 7.05 μ.

Solid XIII, m.p. 76.8–77.6°, 0.871 g., was hydrogenated in 10 ml. of anhydrous ethanol over 0.12 g. of 5% palladium-on-charcoal. The hydrogen uptake amounted to 10.98 ml. (in 15 minutes) and corresponded to 101.3% of the theoretical linear monoamide. The filtered and evaporated solution yielded 0.088 g. of white solid residue of wide melting point range, m.p. 109–120°. The infrared spectrum was examined particularly for the position of the nitrile frequency as compared to the unhydrogenated XIII. The infrared absorption showed bands at 2.96, 3.13, 4.45, 6.01, 6.1 and 7.05 μ. The shift in the nitrile frequency on hydrogenation from 2210 (4.52 μ) to 2245 cm.$^{-1}$ (4.45 μ) supports the presence of an α,β-unsaturated cyano grouping in the linear unsaturated monoamide, solid XIII.

(19) C. L. Ogg and E. J. Cooper, *Anal. Chem.*, **21**, 1400 (1949).

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Strong Analgesics. The Preparation of Some Ethyl 1-Anilinoalkyl-4-Phenylpiperidine-4-Carboxylates

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A series of ethyl 1-(ω-arylaminoalkyl)-4-phenylpiperidine-4-carboxylates has been prepared and evaluated for analgesic activity by the rat thermal stimulus method. The most effective groups were the 2-aminoanilinoethyl and the unsubstituted anilinoethyl.

In an earlier paper[2] we reported that the N-methyl group of meperidine, ethyl 1-methyl-4-phenylpiperidine - 4 - carboxylate hydrochloride, could be replaced by an N-cinnamyl group to give a compound having enhanced analgesic activity. When the cinnamyl group bore an amino substituent in the 4-position the activity fell to about one-third of the unsubstituted compound. This is in contrast to the 4-aminophenethyl derivative which was more active than the unsubstituted phenethyl derivative. It was of interest to us to investigate the effect of inserting the amino group between the aryl and alkyl portions of the aralkyl substituent on the meperidine nitrogen. The resulting substituted anilinoalkyl derivatives of nor-meperidine are the subject of this paper.

In the preparation of the ethyl 1-anilinoalkyl-4-phenylpiperidine-4-carboxylates it was found that several methods could be used. When the appropriate anilinoalkyl bromide could be readily obtained it was condensed with ethyl 4-phenylpiperidine-4-carboxylate (method A). It was found that ethyl 1-(ω-chloroalkyl)-4-phenylpiperidine-4-carboxylate hydrochloride could be condensed with various substituted anilines in the presence of aqueous sodium carbonate (method B), sodamide in dry toluene (method C) or in Cellosolve (method D). Method D is generally the easiest to carry out and gives the best yields.

The ethyl 1-(ω-chloralkyl)-4-phenylpiperidine-4-carboxylates were obtained by refluxing the corresponding hydroxyalkyl compounds with thionyl chloride. The hydroxyalkyl compounds were obtained by treating ethyl 4-phenylpiperidine-4-carboxylate with ethylene oxide or trimethylene chlorohydrin to give ethyl 1-(2-hydroxyethyl)-4-phenylpiperidine-4-carboxylate or ethyl 1-(3-hydroxypropyl)-4-phenylpiperidine-4-carboxylate, respectively.

The anilinoalkyl bromides were obtained by treating the corresponding alcohols with hydrobromic acid using the procedure of Pearlman,[3] or by adding phosphorus tribromide to the corresponding alcohol.

The nitro compounds were reduced following the procedure of Furst and Balcom.[4]

The pharmacological evaluation of these compounds for analgesic potency was done by the Bass, Vander Brook[5a] modification of the D'Amour, Smith[5b] rat thermal stimulus method. The results are given in Table I and will be discussed in detail elsewhere.

Experimental[6]

The following intermediates were prepared by methods reported in the literature: 2-(4-methylanilino)-ethanol, 3-(2-nitroanilino)-1-propanol, 2-(2-nitroanilino)-ethanol, 2-(2-nitroanilino)-ethyl chloride.

3-(2,6-Dimethylanilino)-propanol Hydrobromide.—2,6-Dimethylaniline (12.1 g., 0.1 mole) and trimethylene bromohydrin (13.9 g., 0.1 mole) were heated on a steam-bath 4 hours. After cooling and standing, the oil crystallized. It was recrystallized from absolute alcohol and washed with ether; yield 23.4 g. (90%), m.p. 195–197°.

Anal. Calcd. for $C_{11}H_{18}BrNO$: Br, 30.71. Found: Br, 30.58.

(1) Cutter Laboratories, Berkeley, Calif.

(2) B. Elpern, L. Gardner and L. Grumbach, THIS JOURNAL, **79**, 1951 (1957).

(3) W. M. Pearlman, *ibid.*, **70**, 871 (1948).

(4) D. Balcom and A. Furst, *ibid.*, **75**, 4334 (1953).

(5) (a) W. B. Bass and M. J. Vander Brook, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 569 (1952); (b) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exptl. Therap.*, **72**, 74 (1941).

(6) All melting points corrected.