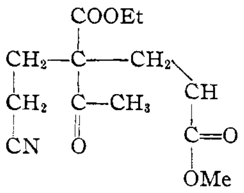
NOTES

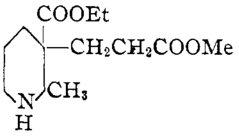
So-called 5-Carbethoxy-9-methyl-2-oxo-1-azabicyclo[3.3.1]nonane. A Correction

By Noel F. Albertson

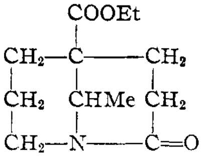
Reduction of ethyl (2-carbomethoxyethyl)-(2-cyanoethyl)-acetoacetate (I) with Raney nickel catalyst has been reported to give ethyl 3-(2-carbomethoxyethyl)-2-methylnipecotate (II) and 5-carbethoxy-9-methyl-2-oxo-1-azabicyclo[3.3.1]-nonane (III).[1] Structure III was assigned largely on the basis of the fact that a sample of II, on standing, partially crystallized with formation of more of this solid material. In a review article[2] on Bredt's rule, Fawcett pointed out that compound III was the first reported example of a bridgehead amide.[3] This fact, together with the "low" hydrogen analysis[4] obtained for the solid product, suggested that this compound should be re-examined. An ultraviolet absorption spectrum showed that conjugated unsaturation was present. The compound was found to absorb bromine readily and to absorb two moles of hydrogen in the presence of a palladium or platinum catalyst. These facts suggested that the solid was actually 4a-carbethoxy-1,2,3,4,4a,5,6,7-octahydro-7-quinolone (IV).



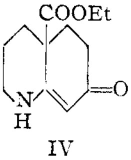
I



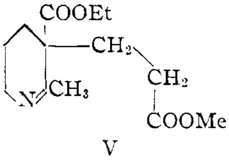
II



III



IV



V

Such a product could not arise from a sample of II unless II contained V as an impurity.[5,6] Other work in this Laboratory has shown that there is a tendency to form unsaturated piperidines by Raney nickel reduction of certain 5-oxonitriles.[7]

The infrared spectrum showed the presence of an ester group, and failed to disclose any evidence of a hydroxyl. On the basis of the evidence cited, it is apparent that reduction of I has led to ring closure between the methyl and ester groups to give IV rather than between the amine and ester groups to give III.

Although these data permit only one interpretation for the carbon–nitrogen skeleton of the reduction product, caution (after one mistake) led to additional experiments to confirm structure IV.

When IV was refluxed with methanolic potassium hydroxide and the resulting potassium salt acidified, carbon dioxide was evolved from the cold solution as was expected from the vinylog of a β-oxo ester. Heating the resulting octahydro-7-quinolone with sulfur gave 7-quinolinol the identity of which was confirmed by melting point, color test with ferric chloride and ultraviolet absorption spectrum. Incidentally, the same quinolone was obtained as one product of the reduction of benzyl (2-carbomethoxyethyl)-(2-cyanoethyl)-acetoacetate.

As anticipated for the vinylog of an amide, IV did not give a 2,4-dinitrophenylhydrazone or a semicarbazone under the usual reaction conditions.

An examination of structure IV indicates that reduction of the 8,8a double bond would lead to a Mannich base type. Thus, reduction under different conditions should lead to different results. Such was found to be the case. Reduction of IV with a palladium catalyst in acetic acid solution gave 4a-carbethoxy-decahydro-7-quinolinol. This reacted with thionyl chloride to give 4a-carbethoxydecahydro-7-chloroquinoline hydrochloride.

Reduction of IV using Raney nickel catalyst in ethanol at 110° proved to be very exothermic and the temperature rose rapidly to 155°.[8] The product, $C_{12}H_{21}NO_2$, was neutral and water soluble indicating that amide formation between the amine and ester functions had occurred. Since the product contained two more carbon atoms than had been expected, these must have come from the solvent. Confirmatory evidence was obtained by

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(1) N. F. Albertson, This Journal, **72**, 2594 (1950).

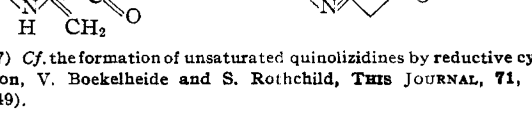
(2) F. S. Fawcett, *Chem. Revs.*, **47**, 259 (1950).

(3) G. M. Badger, J. W. Cook and T. Walker (*J. Chem. Soc.*, 1141 (1949)) postulated the existence of 5-phenyl-1-azabicyclo[3.3.1]nonan-2-one as an intermediate. This compound was not isolated, however, a compound containing a carbonyl joined to a bridgehead nitrogen, namely, 5-ethyl-1,3-diaza-2,4,9-trioxobicyclo[3.3.1]nonane, has recently been reported by J. Baumler, E. Sorkin and H. Erlenmeyer in *Helv. Chim. Acta*, **34**, 459 (1951). Ring closure to the oxygen to give 1,3-dioxo-8a-ethyl-decahydropyrano[2,3-d]pyrimidine would appear to be an equally plausible explanation for the product.

(4) Actually the published data agree with the correct formula, $C_{12}H_{17}NO_3$, rather than with the assigned structure, III.

(5) It should be noted that although a sample of II had partially crystallized in five months, no further crystallization occurred in several years.

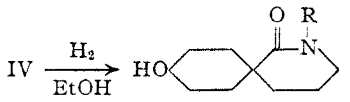
(6) Dr. W. S. Johnson suggested that IV was formed *via* the following:



(7) *Cf.* the formation of unsaturated quinolizidines by reductive cyclization, V. Boekelheide and S. Rothchild, This Journal, **71**, 879 (1949).

(8) The actual temperature may have been even higher than the 155° shown by the thermocouple because of time lag, etc.

carrying out the reduction in methanol. The resulting sirup (VII?) could not be seeded by the solid obtained in ethanol. The properties of the latter product agree with its formulation as 2-ethyl-9-oxy-2-azaspiro[5.5]hendecanone (VI). Its formation from IV involves (a) hydrogenation of the 8,8a-double bond, (b) ethylation of the nitrogen by the solvent, (c) hydrogenolysis of the C–N bond which is β not only to a carbonyl but also to a carbethoxy group, (d) cyclization of the amine and ester groups, and (e) reduction of the keto group.



VI, R = Et
VII, R = Me

Reduction of IV with sodium and 2-methylpentanol-4 gave decahydro-7-quinolinol.

It was originally planned to convert VI or VII to 2-alkyl-2-azaspiro[5.5]hendecane and to compare this with a synthetic specimen. This was later deemed unnecessary. However, the sirup, VII, was reduced with lithium aluminum hydride to a strong base having the properties expected of 2-methyl-2-azaspiro[5.5]hendecan-9-ol. Also, ethyl 1-(2-cyanoethyl)-cyclohexane-2-onecarboxylate ethylene glycol ketal was reduced to 2-azaspiro-[5.5]hendecan-1,7-dione.

In the paper in which the synthesis of IV is described,[1] two other compounds have been identified only by empirical formula. After the paper was submitted for publication, the structure of these two compounds was established by synthesis. The compound, $C_9H_{13}NO_4$, obtained by hydrolysis of ethyl 2-(2-cyanoethyl)-cyclopentanone-2-carboxylate and distillation of the hydrolysis product is 3-(3-carboxypropyl)-glutarimide. The by-product obtained in the preparation of 4a-carbethoxyoctahydro-1-pyridine is 3-(3-carbethoxypropyl)-2-piperidone. Both of these products are readily obtained from cyclopentanone-2-carboxylic esters by treatment with acrylonitrile in alcohol with sodium ethylate as a catalyst. If the temperature is allowed to rise during the addition of acrylonitrile, the cyclopentanone ring is opened and the product is a 2-(2-cyanoethyl)-adipic acid diester.

Experimental[9]

4a-Carbethoxy-1,2,3,4,49,5,6,7-octahydro-7-quinolone (IV).—Reduction of 389 g. of ethyl (2-carbomethoxyethyl)-(2-cyanoethyl)-acetoacetate in 1500 ml. of alcohol at 100° using Raney nickel catalyst required four hours. This was worked up as previously described[1] to give 151 g. of IV after the ether wash and 45 g. more from the distillation residue. This compound gave a definite, though not intense, red color with aqueous or alcoholic ferric chloride. It also absorbed bromine. It showed an absorption maximum at 303 mμ (ε 30,215) and a minimum at 250 mμ (ε 471). The infrared spectrum showed a band at 5.83 μ (ester) and one at 6.15 μ (amide?).[9a] A sample recrystallized from methanol gave the following analytical data. Found: C, 64.53; H, 7.38; N(AP), 6.30. A sample from ethanol–ether gave: C, 64.78, 64.70; H, 7.43, 7.54. Calcd. for $C_{12}H_{17}NO_3$: C, 64.54; H, 7.68; N, 6.27.

4a-Carbethoxydecahydro-7-quinolinol.—A solution of 10 g. of IV in 100 ml. of acetic acid was reduced using 10% palladium-on-carbon catalyst at 50 lb. initial pressure and 50°. Reduction took six hours. Filtration and concentration gave a sirup which was taken up in water. Addition of potassium carbonate gave an oil which was extracted once with ether. The product soon crystallized from the ether. A sample, recrystallized from water, melted at 101.6–104.4° cor. The same compound (2.2 g. crude yield) was obtained by reducing 2.6 g. of IV with Adams platinum oxide catalyst in ethanol at 50°.

Anal. Calcd. for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.20; H, 9.34; N(K), 6.09.

4a-Carbethoxy-7-chlorodecahydroquinoline Hydrochloride.—Treatment of 2 g. of 4a-carbethoxydecahydro-7-quinolinol with 1.0 ml. of thionyl chloride in chloroform gave 2.0 g. of product. A sample, recrystallized twice from isopropyl alcohol–ether, melted at 199.0–199.4° cor.

Anal. Calcd. for $C_{12}H_{20}ClNO_2 \cdot HCl$: Cl, 25.13; N, 4.96. Found: Cl, 25.07; N(D), 4.92.

Octahydro-7-quinolone.—Ten grams of IV was refluxed 13 hours with 5 g. of potassium hydroxide in 40 ml. of methanol. The solvent was removed *in vacuo*, the solid dissolved in water and acidified with hydrochloric acid. The solution was again taken to dryness and extracted with hot isopropyl alcohol. The first crop, 2.5 g., melted at 210–212°. Concentration of the filtrate gave a second crop of 2.0 g. The combined crops were treated with aqueous potassium carbonate to give the base, m.p. 182.2–184.2° cor. from ethyl acetate. No attempt was made to locate the double bond in this quinolone.

Anal. Calcd. for $C_9H_{13}NO$: N, 9.26. Found: N(D), 9.11.

This compound was also prepared (in poor yield) by reduction of 65 g. of benzyl (2-carbomethoxyethyl)-(2-cyanoethyl)-acetoacetate in 100 ml. of methanol with Raney nickel catalyst at 1900 lb. initial pressure and 85°. Reduction took six hours. Removal of the catalyst and solvent gave 42 g. of red brown sirup soluble in dilute hydrochloric acid but insoluble in water and ammonium hydroxide. The sirup was stirred with about 100 ml. of ether and the ether layer decanted. The remaining heavy oil partially crystallized, the crystals being identical with the octahydro-7-quinolone prepared above.

The benzyl (2-carbomethoxyethyl)-(2-cyanoethyl)-acetoacetate was prepared by adding 18 ml. of acrylonitrile to 62 g. of benzyl-(2-carbomethoxyethyl)-acetoacetate to which had been added a ml. of methanolic potassium hydroxide. The reaction product was washed with water and used directly.

Benzyl (2-Carbomethoxyethyl)-acetoacetate.—A mixture of 108 g. of ethyl (2-carbomethoxyethyl)-acetoacetate[10] and 53 ml. of benzyl alcohol was heated in a flask equipped for distillation. When the liquid temperature reached 170°, ethanol distilled over. In less than two hours 62% of the theoretical amount of ethanol was collected. Distillation gave 85.2 g. (61%) of product boiling at 165–168° (1.8 mm.) and 33 g. of recovered starting material. The product gave an intense violet color with alcoholic ferric chloride.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.97; H, 6.73.

7-Quinolinol.—A mixture of 0.63 g. of octahydro-7-quinolone and 0.40 g. of sulfur was immersed in a bath at 135° and heated to 230° over 15 minutes. The temperature of the bath was increased to 240° over the next ten minutes. Long needles sublimed to the upper surface of the flask. These decomposed at 231° after softening at 226°. With ferric chloride in aqueous alcohol a red brown color was observed. The ultraviolet absorption spectrum of a sample recrystallized from aqueous ethanol checked the curve published by Ewing and Steck.[11]

2-Ethyl-9-oxy-2-azaspiro[5.5]hendecanone (VI).—A suspension of 22.3 g. of IV in 130 ml. of ethanol was heated with Raney nickel catalyst to 110° and 980 lb. of hydrogen pressure. Reduction started and the heat was turned off. The temperature rose to 155° after 20 minutes and the reduction was over. Removal of the catalyst and solvent

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(9) N(AP) refers to nitrogen determined by titration with perchloric acid in acetic acid; N(K) refers to Kjeldahl nitrogen; and N(D) refers to Dumas nitrogen.

(9a) A referee has pointed out that the band at 6.15μ (equivalent to 1627 cm.$^{-1}$) actually is characteristic of the vinylog of an amide and supports the assigned structure. *Cf.* N. H. Cromwell, *et al.*, THIS JOURNAL, **71**, 3337 (1949).

(10) N. F. Albertson THIS JOURNAL, **70**, 669 (1948).

(11) G. Ewing and E. Steck, *ibid.*, **68**, 2181 (1946).

left 20.4 g. of crystals. These were extracted with hot benzene to remove the product from 3.9 g. of solid melting above 250°. Concentration of the benzene extracts and addition of Skellysolve B precipitated the product; m.p. 111–114°. It was very soluble in water and neutral to litmus. There was no absorption in the ultraviolet. The infrared spectrum showed the presence of an amide linkage and possibly an OH group. A sample, recrystallized from ethyl acetate, melted at 114–115.5°.

Anal. Calcd. for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63; ethoxyl, none. Found: C, 67.86; H, 10.03; N(D), 6.85; ethoxyl, none.

2-Methyl-2-azaspiro[5.5]hendecan-9-ol.—When an equivalent amount of methanol was substituted for ethanol in the above experiment there was obtained 2.4 g. of by-product melting above 290° and 17.9 g. of sirup which could not be induced to crystallize even on seeding with the product melting at 115°. The crude sirup was reduced with lithium aluminum hydride to give 3 g. of very viscous pale yellow sirup distilling at 110–120° (0.7 mm.).

Anal. Calcd. for $C_{11}H_{21}NO$: N, 7.64. Found: N(AP), 7.54.

Decahydro-7-quinolinol.—Reduction of 45.1 g. of IV with 39.0 g. of sodium and 87.6 g. of 2-methylpentanol-4 in toluene gave 39.8 g. of oil most of which crystallized while still hot. Trituration with ether gave about 12 g. melting at 162–165°. This was a strong base in water and reacted with acetic anhydride to give a viscous oil. A mixed m.p. with the starting material was depressed (m.p. 137–157°). A sample, recrystallized from ethyl acetate, melted at 170.3–171.4° cor.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.65; H, 11.04; N, 9.03. Found: C, 69.60; H, 10.98; N(AP), 8.94.

Ethyl 2-(2-Cyanoethyl)-cyclohexanone-2-carboxylate Ethylene Glycol Ketal.—A mixture of 22.3 g. of ethyl 2-(2-cyanoethyl)-cyclohexanone-2-carboxylate, 38 g. of ethylene glycol, 1.5 g. of toluenesulfonic acid monohydrate and 100 ml. of benzene was refluxed overnight using a water separator. The benzene phase was washed with water, aqueous potassium carbonate and water. The product (22.5 g.) was collected at 110–139° at 0.07 mm., but most boiled at the higher temperature; $n^{25}D$ 1.4818.

Anal. Calcd. for $C_{14}H_{21}NO_4$: N, 5.24. Found: N(K), 5.21.

2-Aza-spiro[5.5]hendecan-1,7-dione.—Reduction of 21 g. of the above ketal in 70 ml. of ethanol with a Raney nickel catalyst at 60° required two hours. It was necessary to distil out some 4a-carbethoxydecahydroquinoline, b.p. 82–84° at 0.09 mm. before the product (11.3 g.) crystallized. After trituration with a small amount of benzene and three recrystallizations from isopropyl alcohol–ether, the product melted at 226.5–228.5°.

Anal. Calcd. for $C_{10}H_{15}NO_2$: N, 7.73. Found: N(K), 7.67.

The picrate of 4a-carbethoxydecahydroquinoline was prepared. It melted at 181.7–183.2° cor., from ethanol.

Anal. Calcd. for $C_{12}H_{21}NO_2 \cdot C_6H_3N_3O_7$: N, 12.72. Found: N(D), 12.82.

Methyl Ethyl 2-(2-Cyanoethyl)-adipate.—To 0.1 g. of sodium in 35 ml. of ethanol was added 38 g. of methyl cyclopentanone-2-carboxylate. Then 20 ml. of acrylonitrile was added slowly at an initial temperature of 30°. The reaction mixture was allowed to heat up to 75° and was then kept from heating up further by cooling as required. After two hours several milliliters of acetic acid was added, the solvent removed and the residue washed with water. Fractionation gave 7.9 g. of starting material and 45.4 g. of product boiling at 137–156° (0.6 mm.). It gave no color with ferric chloride.

Anal. Calcd. for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 60.18; H, 7.73; N, 5.65.

By using 105 g. of ethyl cyclopentanone-2-carboxylate, there was obtained 148 g. of diethyl 2-(2-cyanoethyl)-adipate; b.p. 158–162° at 0.2 mm.; $n^{25}D$ 1.4442.

Anal. Calcd. for $C_{13}H_{21}NO_4$: N, 5.49. Found: N(K), 5.45.

3-(3-Carbethoxypropyl)-2-piperidone.—Reduction of 90.5 g. of methyl ethyl-2-(2-cyanoethyladipate) in 500 ml. of methanol with Raney nickel catalyst at 80° and 700 lb. initial hydrogen pressure required five hours. Removal of the catalyst and solvent left 76 g. of oil which crystallized in several hours. Recrystallization from ether gave a solid melting at 54–56°. The same compound was obtained by reduction of 132 g. of diethyl 2-(2-cyanoethyladipate) in ethanol, and was shown by means of mixed melting point to be identical with the by-product previously reported.[1]

Anal. Calcd. for $C_{11}H_{19}NO_3$: N, 6.57. Found: N(K), 6.56.

3-(3-Carboxypropyl)-glutarimide.—A mixture of 4 g. of methyl ethyl-2-(2-cyanoethyl)-adipate, 4 g. of sodium carbonate and 36 ml. of water was refluxed for six hours, acidified to congo paper with hydrochloric acid and extracted with ethyl acetate. Concentration gave 2.9 g. of sirup which was dried over phosphorus pentoxide–potassium hydroxide. Some of the sirup was warmed in a test-tube for several minutes over a free flame to effect cyclization. Upon cooling and addition of water white crystals readily formed in good yield; m.p. 149–151.5° after recrystallization from water. The m.p. was not depressed on admixture with the $C_9H_{13}NO_4$ compound previously reported[1] to result from hydrolysis of ethyl 2-(2-cyanoethyl)-cyclopentanone-2-carboxylate, followed by distillation of the intermediate.

Acknowledgment.—We are happy to have had the opportunity of discussing this problem with Dr. W. S. Johnson. We are indebted to Mrs. C. Diacetis for technical assistance, to Mr. Morris Auerbach and Kenneth Fleischer and staff for analytical results, and to Dr. Frederick Nachod, Miss Catherine Martini and Mrs. M. Becker for measuring and interpreting absorption spectra.

STERLING-WINTHROP RESEARCH INSTITUTE
RENSSELAER, N. Y. RECEIVED JULY 16, 1951

The Separation of Mixtures of *cis*- and *trans*-Estradiols

BY NORMAN BARSEL

Estrone on reduction with Raney nickel in aqueous potassium hydroxide, forms a mixture of estradiol-17-β, m.p. 178° (85–90%) and estradiol-17-α, m.p. 223° (10–15%). Recrystallization from aqueous ethanol usually removes the 17-β and leaves a residue in solution that is enriched in estradiol-17-α. Originally, a separation of the 17-beta compound as its slightly soluble digitonide[1] was suggested. Later, an insoluble urea complex was used to separate this same epimer.[2]

We have found that sharp separations may be more easily accomplished through the dipropionates of this mixture.[3] The 17-β dipropionate crystallizes from hot methanol before the 17-α dipropionate which melts at 76–77°, $[\alpha]^{25}D + 36$, 1% in dioxane. *Anal.* Calcd. for $C_{24}H_{32}O_4$: C, 74.95; H, 8.40. Found: C, 75.04; 8.50. The latter separates as an oil only after the solution had been concentrated.

We further noted that propionation of such a mixture of diols in pyridine below 95° forms the 17-monopropionates whereas above 105° the dipropionates are produced.

Saponification of the dipropionates in methanolic potassium hydroxide yields the pure diols.

RESEARCH DEPT., INTERNATIONAL HORMONES, INC.
BROOKLYN, NEW YORK RECEIVED SEPTEMBER 17, 1951

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(1) O. Wintersteiner, THIS JOURNAL, **59**, 765 (1937).

(2) H. Priewe, U. S. Patent 2,300,134 (1942).

(3) K. Miescher and C. R. Scholz, *Helv. Chim. Acta*, **20**, 268 (1937).