The **hydrochloride** was prepared from aqueous hydrochloric acid and was recrystallized from a mixture of methanol and acetone, m.p. 152.5–153.5°.

Anal. Calcd. for $C_{15}H_{22}ClN_5O_2$: C, 53.01; H, 6.53; Cl, 10.43; N, 20.61. Found: C, 53.75; H, 6.20; Cl, 10.34; N, 20.21.

4-Methyl-1,2,5,6-tetrahydrobenzo[*f*]quinolin-3(4H)-one. The Cyclization Product Derived from Methyl 3-[(3,4-Dihydro-2-naphthyl)methylamino]propionate

ZEN-ICHI HORII, CHUZO IWATA, AND YASUMITSU TAMURA

School of Pharmacy, Osaka University, Toneyama, Toyonaka, Osaka, Japan

NORMAN A. NELSON[1] AND GARY H. RASMUSSON

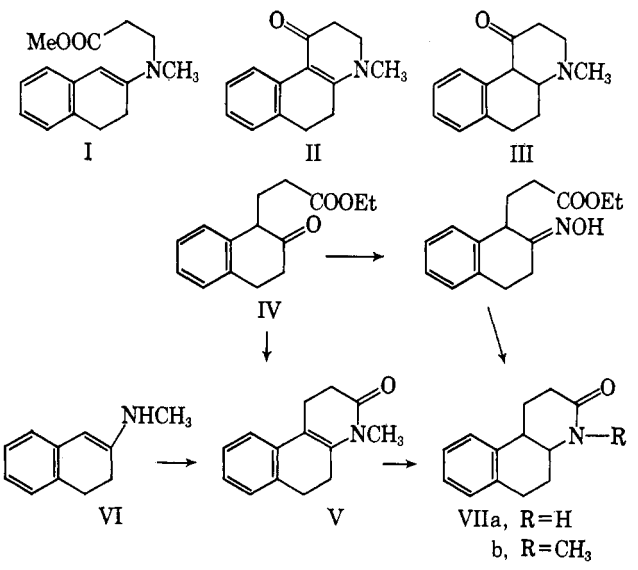
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received March 24, 1964

Several years ago it was reported[2] that the condensation of 2-tetralone and methyl β-methylaminopropionate gives the enamine I which, on heating in ethylene glycol, undergoes an intramolecular acylation reaction[3] to give 4-methyl-3,4,5,6-tetrahydrobenzo[*f*]quinolin-1(2H)-one (II). The structure II was based on the infrared and ultraviolet spectra of the product, the reductive removal of the carbonyl group of the vinylogous amide with lithium aluminum hydride[4] yielding the corresponding enamine, and further chemical transformations consistent with the enamine structure.

More recently, we had occasion to reduce the cyclization product derived from I by catalytic means and obtained a product which has a carbonyl absorption maximum in the infrared at 1620 cm.$^{-1}$ (chloroform). This carbonyl absorption is incompatible with structure III unless such a structure is capable of invoking a nitrogen–carbonyl interaction.[5,6] That this is not the case is indicated by the failure of the hydrogenation product to form a methiodide, picrate, or other stable salts,[7] thus demonstrating the feebly basic character of the product. In a review of this work, Dr. S. Archer suggested that the enamine cyclization product might, in fact, have structure V.[8] Such a structure would explain all of the accumulated physical and chemical data. This paper describes a detailed study which establishes the cyclization product as V and clarifies the step at which the chemical rearrangement occurs.[9] (See Scheme I.)

SCHEME I



Our first indication that the cyclization product has structure V came when we found that a mild treatment of 1-(β-carbethoxyethyl)-2-tetralone (IV) with methylamine gave the same product obtained by heating I in ethylene glycol. The possibility of IV undergoing a reverse Michael reaction and the fragments recombining in a different manner was considered unlikely. However, to further verify that no rearrangement occurred in the conversion of IV to V, the keto ester was converted to the corresponding oxime which in turn was catalytically reduced in the presence of Adams catalyst. The reduction product underwent a spontaneous ring closure to one isomer of the lactam VIIa. N-Methylation of the lactam gave the same product as that derived by catalytic reduction of the cyclization product V. The mutual identity of the products is based on mixture melting point behavior and identical infrared spectra, and thin layer and gas chromatographic results.

In an attempt to determine at what stage rearrangement occurred in the original preparation of V from I, 2-tetralone was treated with methylamine in boiling toluene to generate the intermediate VI and/or the corresponding imino form. The crude mixture was then treated with methyl acrylate to give a complex mixture containing 30–40% of the cyclization product V. When 2-tetralone is treated with methyl β-methylaminopropionate under essentially the same conditions,[2] no cyclization product V could be detected in the crude product I by infrared analysis. Thus, the integrity of structure I appears to be sound.

(1) To whom inquiries should be sent at Department of Chemistry, The Upjohn Company, Kalamazoo, Mich.

(2) N. A. Nelson, J. E. Ladbury, and R. S. P. Hsi, *J. Am. Chem. Soc.*, **80**, 6633 (1958).

(3) The acylation of enamines with reactive carbonyl reagents is well known; see J. Szmuszkovicz, "Advances in Organic Chemistry," Vol. 4, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 1; G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963). While esters are normally unreactive toward enamines, there is no reason to believe that they will not react under more strenuous conditions.

(4) See, for example, N. G. Gaylord, *Experientia*, **10**, 166 (1954); C. F. Koelsch and D. L. Ostercamp, *J. Org. Chem.*, **26**, 1104 (1961). The lithium aluminum hydride reduction of vinylogous amides may also lead to amino alcohols or amino ketones: see J. M. Osbond, *J. Chem. Soc.*, 4711 (1961); K. T. Potts and D. R. Liljegren, *J. Org. Chem.*, **28**, 3202 (1963); G. de Stevens and A. Halamadais, *ibid.*, **26**, 1614 (1961).

(5) See M. R. Bell and S. Archer, *J. Am. Chem. Soc.*, **82**, 151 (1960), and references contained therein for examples of nitrogen–carbonyl interactions.

(6) One isomer of structure III has been prepared by the authors (Osaka group) and it has normal spectral properties.

(7) On treatment with concentrated perchloric acid or anhydrous hydrogen chloride, an ethereal solution of the hydrogenation product gave the corresponding salts as precipitates. However, the salts thus formed are extensively hydrolyzed by water and the free amides can be extracted easily with ether from a dilute aqueous acidic solution.

(8) We are indebted to Dr. Archer for his comments regarding this problem.

(9) This paper has prompted work on the revision of some previously published structures [Z. Horii, C. Iwata, and Y. Tamura, *Chem. Pharm. Bull.* (Tokyo), **10**, 940 (1962)], the results of which will be published in the near future.

It seems reasonable to conclude, therefore, that the rearrangement occurs at the stage in which the enamine I is subjected to the rather strenuous condition of being refluxed in ethylene glycol. The rearrangement can be pictured as a dissociation of I to methyl acrylate and VI followed by a Michael addition of the acrylate to carbon 1 of VI and cyclization. A simpler preparation of V than those discussed thus far consists of heating an ethylene glycol solution of 2-tetralone with methylamine followed by the addition of methyl acrylate. The reaction mixture is composed of at least six compounds, but the product V can be isolated easily.

Experimental

1-(β-Carbethoxyethyl)-2-tetralone (IV).—To a stirred solution of 7 g. of ethyl acrylate and 10 g. of 2-tetralone in 40 ml. of absolute ethanol was added 10 drops of a solution prepared from 500 mg. of sodium and 5 ml. of ethanol. The mixture was cooled to maintain a temperature below 30°, and after being stirred at room temperature for 2 hr. the mixture was poured into cold water and acidified with hydrochloric acid; the product was extracted with ether. The ether extract was washed with sodium bicarbonate solution and water, dried, and distilled giving 4.8 g. of IV, b.p. 165–166° at 4 mm. [lit.[10] b.p. 162.5° at 4 mm.].

1-(β-Carbethoxyethyl)-2-tetralone Oxime.—A mixture of 1.0 g. of the keto ester IV, 0.35 g. of hydroxylamine hydrochloride, 0.41 g. of anhydrous sodium acetate, and 20 ml. of absolute ethanol was refluxed for 6 hr. The reaction mixture was concentrated, diluted with water, and extracted with ether. The ether extract was washed with saturated sodium bicarbonate solution and water, dried, and concentrated. Recrystallization of the residue from aqueous ethanol gave 0.8 g. (78%) of the oxime, m.p. 101–102° raised to 101–103° on further recrystallizations from aqueous ethanol or cyclohexane, $\nu_{max}^{CHCl_3}$ 3546 and 3300 (O–H stretching) and 1718 cm.$^{-1}$ (ester carbonyl).

Anal. Calcd. for $C_{15}H_{19}NO_3 \cdot 0.5H_2O$: C, 66.64; H, 7.46; N, 5.18. Found: C, 66.52, 66.55; H, 7.27, 7.39; N, 5.13, 5.24.

1,2,4a,5,6,10b-Hexahydrobenzo[*f*]quinolin-3(4H)-one (VIIa).—1-(β-Carbethoxyethyl)-2-tetralone oxime (0.4 g.) in 8 ml. of absolute ethanol was shaken under hydrogen in the presence of 0.08 g. of platinum oxide until the theoretical uptake of hydrogen had occurred. Removal of the catalyst and concentration of the filtrate gave a residue which was recrystallized from benzene giving 0.22 g. (70%) of product, m.p. 188–190°. A recrystallized analytical sample had m.p. 191–192°, $\nu_{max}^{CHCl_3}$ 3385 and 3210 (amide N–H) and 1648 cm.$^{-1}$ (amide carbonyl).

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.66; H, 7.33; N, 7.00.

4-Methyl-1,2,4a,5,6,10b-hexahydrobenzo[*f*]quinolin-3(4H)-one (VIIb). A. **From the Lactam V.**—A solution of 400 mg. (0.0019 mole) of 4-methyl-1,2,5,6-tetrahydrobenzo[*f*]quinolin-3(4H)-one[2] in 5 ml. of anhydrous ethanol and 5 ml. of anhydrous dioxane was hydrogenated over 400 mg. of 10% palladium charcoal at 35° and under atmospheric pressure. After 12 hr. the theoretical quantity of hydrogen was consumed. The catalyst was filtered and the solvent was removed by distillation *in vacuo*. The residual solid was recrystallized from ether to yield 270 mg. (68%) of VIIb as colorless crystals, m.p. 135–136°, $\nu_{max}^{CHCl_3}$ 1620 (for a 3% solution) and 1645 cm.$^{-1}$ (for a 0.23% solution, CCl_4).

Anal. Calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.92; H, 8.07; N, 6.33.

B. **From the Lactam VIIa.**—A solution of 0.59 g. of the lactam VIIa in 160 ml. of dry toluene was concentrated to 100 ml. by distillation, then 180 mg. of a 54% suspension of sodium hydride in oil was added. The mixture was refluxed in a nitrogen atmosphere for 2 hr. and cooled, and 9 ml. of methyl iodide was added. The mixture was refluxed for 2 hr., cooled, diluted with water, and extracted with chloroform. The organic extract was washed with water, dried, and concentrated, and the residue was recrystallized two times from ether giving 0.45 g. (72%) of material with m.p. 126–128°. Two additional recrystallizations of the product from ether gave an analytically pure sample of VIIb, m.p. 135–136°. The mixture melting point of this material with that described in part A was not depressed and the two samples had the same infrared spectra and identical behavior on thin layer and gas chromatography.

4-Methyl-1,2,5,6-tetrahydrobenzo[*f*]quinolin-3(4H)-one (V). A. **From 1-(β-Carbethoxyethyl)-2-tetralone.**—A mixture of 1 g. of the keto ester IV and 10 ml. of a 30% solution of methylamine in benzene was kept at room temperature in a sealed flask for 19 hr. Removal of the solvent and trituration of the residue with ether gave 300 mg. of colorless crystals which were recrystallized from aqueous ethanol to give 250 mg. (28%) of V, m.p. 106–107°. Chromatography of the residues on alumina using benzene as eluent afforded an additional 250 mg. of V, m.p. 106–107°. This material did not depress the melting point of the cyclization product derived from I[2] and the infrared spectra of the two samples are identical.

In a different experiment, treatment of the keto ester IV with methylamine as above, but for 84 hr., gave a total of 77% of V, m.p. 105–107°.

B. **From 2-Tetralone.**—A solution of 14.6 g. of 2-tetralone in 175 ml. of ethylene glycol was heated to boiling over a 20-min. period while passing in a stream of gaseous methylamine. When the boiling point was reached, the gas flow was stopped and 50 ml. of distillate was collected. The mixture was cooled somewhat, 8.8 ml. of methyl acrylate was added, and the resulting mixture was refluxed for 8 hr. The solution was cooled, diluted with water, and extracted with ether. The organic extract was washed with water, dried, and concentrated giving 7.1 g. of V, m.p. 103–105°, mixture melting point with authentic V not depressed. The infrared spectra of the two samples are identical. A thin layer chromatogram of the residues using silica gel and 5% methanol in chloroform as developer showed the presence of five other components as well as additional product V.

C. **From 2-Tetralone.**—A mixture of 21.9 g. of 2-tetralone and 300 ml. of toluene was refluxed under a water trap and nitrogen atmosphere while passing in gaseous methylamine for 3 hr. The gas flow was stopped and the solution was refluxed for an additional 2 hr. before collecting 75 ml. of distillate. The mixture was cooled, 13.2 ml. of methyl acrylate was added, and the mixture was refluxed for 4 hr. Removal of the solvent at 80° (0.1 mm.) gave a residue, λ_{infl}^{EtOH} 228 mμ (ε 7,100) and λ_{max}^{EtOH} 307 mμ (ε 10,400). The infrared spectrum ($CHCl_3$) of the residue showed carbonyl absorption bands at 1735, 1720, 1670, and 1640 cm.$^{-1}$ indicating a complex mixture; however, the infrared spectrum and a thin layer chromatogram (when compared with authentic V) clearly established the presence of 30–40% cyclization product V. The residue was refluxed with 200 ml. of ethylene glycol for 8 hr., and work-up of the product as in part B above gave 10.25 g. of V, m.p. 101–104°.

(10) N. P. Shusherina, R. Ya. Levina, and V. I. Zdanovich, *Zh. Obshch. Khim.*, **26**, 2847 (1956).

Some Facile Intramolecular Amide–Lactam–Lactone Interconversions[1]

H. E. ZAUGG AND R. W. DENET

Organic Chemistry Department, Research Division, Abbott Laboratories, North Chicago, Illinois

Received April 23, 1964

When 3-(β-bromoethyl)-3-phenyl-2-benzofuranone (I) was treated with N-benzylcyclohexylamine *at 150°*, the main product formed (*i.e.*, II, R = cyclohexyl, 77% yield) resulted from direct halide displacement.[2] Further treatment of the two amino lactones (II, R = *n*-butyl and cyclohexyl) with cyclohexylamine *at only 100°* effected aminolysis to the corresponding

(1) Part XI: "Neighboring Group Reactions." For Part X see ref. 9.

(2) Compare H. E. Zaugg, F. E. Chadde, and R. J. Michaels, *J. Am. Chem. Soc.*, **84**, 4567 (1962), for alternate routes of reactions of I with secondary amines under various conditions.