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

Some Attempts to Prepare Derivatives of Benz[*f*]isoquinoline and a Synthesis of Benz[*h*]isoquinoline[1]

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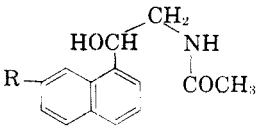
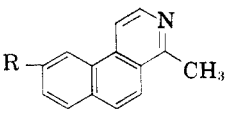
New syntheses of N-acetyl-β-hydroxy-1-naphthaleneethylamine and of its 7-acetamido derivative are described. Conversion of these compounds to substituted benz[*f*]isoquinolines by Bischler-Napieralski cyclization could not be accomplished. Enlargement of the five-membered ring in ethylbenz[*c*]phthalimidoacetate gave both benz[*f*]- and benz[*h*]-isoquinoline derivatives, in a ratio of about 1:7. The latter derivative was converted into the new heterocyclic compound, benz[*h*]isoquinoline.

In an investigation of possible synthetic routes to morphine, derivatives of benz[*f*]isoquinoline were needed. Attempts were made to cyclize 7-acetamido-N-acetyl-β-hydroxy-1-naphthaleneethylamine (I) to II, but only amorphous or tarry products were obtained. Since Pictet and Manevitch[2] had reported successful cyclization of a simpler compound, Ia to IIa, we tried to repeat their experiments. Here again, however, we obtained only tarry products.[3]

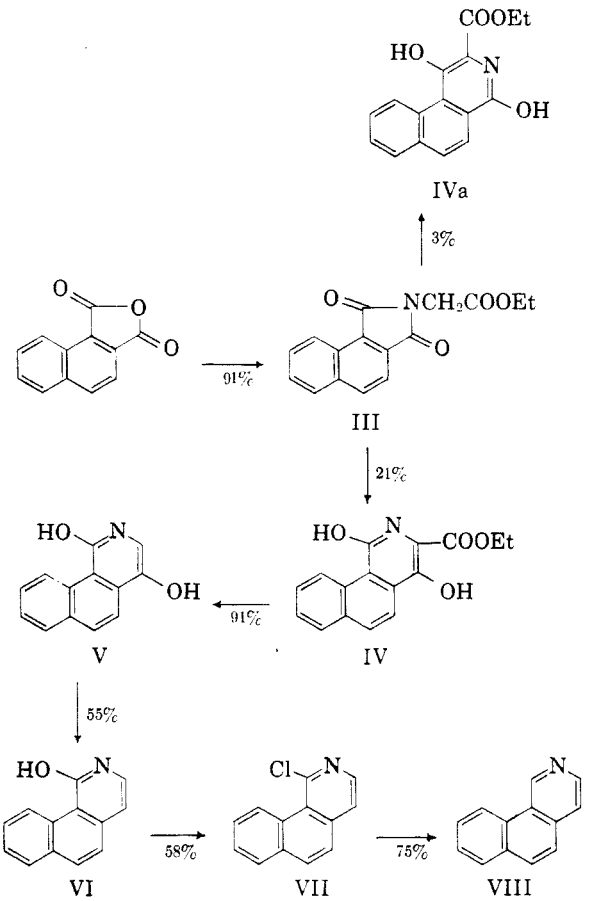


I, R = NHCOCH$_3$
Ia, R = H



II, R = NHCOCH$_3$
IIa, R = H

A new benzisoquinoline synthesis, outlined in the chart below, then was devised and carried out. Unfortunately for our purposes, the synthesis yielded mainly a benz[*h*]isoquinoline derivative (IV) rather than the desired benz[*f*]-compound (IV-a). The preponderance of IV is a consequence of the differing reactivities of the two imide carbonyl groups in III, that of the β one being greater because of steric effects and because of the comparatively high electron density at the α-position of the attached naphthalene nucleus.



That the main product had the benz[*h*] structure (IV) was demonstrated by converting it by standard methods shown in the chart, into the parent heterocycle, benz[*h*]isoquinoline (VIII). Although this compound was new, its tetrahydro derivative is known. Hydrogenation of VIII gave a substance whose derivatives corresponded to those of the known tetrahydro compound. The minor product (IV-a) was characterized by analysis, and its structure therefore is based only on analogy.

(1) From the Ph.D. Thesis of Robert Marion Lindquist, December, 1950.

(2) Pictet and Manevitch, *Arch. sci. phys. nat.*, **35**, 46 (1913).

(3) The properties reported by Pictet and Manevitch for their 4-methylbenz[*f*]isoquinoline are those which might properly belong to such a compound, judging by analogy with known relatives. It is probable that their reaction succeeded because of fortuitous circumstances which neither we nor Dey and Rajagopalan [*Arch. Pharm.*, **277**, 359 (1939)] in our re-investigations were able to discover. A promising subject for future work is the quality of phosphorus pentoxide or phosphorus oxychloride used, for we now know from the work of Snyder and Weber [*J. Am. Chem. Soc.*, **72**, 2963 (1950)] that polyphosphoric acid will bring about Bischler-Napieralsky reactions where classical reagents fail.

EXPERIMENTAL

SYNTHESIS OF I

7-Acetamido-1-acetonaphthone was obtained by adding 84 ml. (1.25 moles) of acetyl chloride during one hour to a stirred and cooled mixture of 185 g. (1 mole) of 2-acetamidonaphthalene and 670 g. (5 moles) of aluminum chloride in two liters of carbon bisulfide. The mixture was kept at room temperature for eight hours and then was boiled for one hour. This procedure gave a somewhat better yield (128 g., 56%) than that of Brown and co-workers.[4] The orientation of the product has been demonstrated by Leonard and Hyson,[5] and we confirmed this orientation in two ways: (a) by converting the substance into known 7-acetamido-1-naphthoic acid with pyridine and iodine; and (b) by converting the substance into the known 1,7-diacetamidonaphthalene (yield 50%) by oximation and Beckmann rearrangement with hydrogen chloride in acetic anhydride.

A similar acylation of 2-acetamidonaphthalene (18.5 g.) in 250 ml. of carbon bisulfide with aluminum chloride (67 g.) and chloroacetyl chloride (10 ml.) gave only a poor yield of a mixture of isomeric nuclear chloroacetyl derivatives separated in part by fractional crystallization from alcohol. The least soluble of these, 1.9 g., m.p. 222–223°, was *2-acetamido-x-chloroacetylnaphthalene.*

Anal. Calc'd for $C_{14}H_{12}ClNO_2$: C, 64.3; H, 4.6. Found: C, 64.3; H, 4.5.

When it was warmed with pyridine and then with aqueous sodium hydroxide, this isomer gave *2-acetamido-x-naphthoic acid,* colorless needles from dilute acetic acid, m.p. 275° with gas evolution.

Anal. Calc'd for $C_{13}H_{11}NO_3$: C, 68.1; H, 4.8. Found: C, 68.0; H, 4.9.

The more soluble isomers were separated by manual sorting of crystals. There was obtained 1.2 g. of *2-acetamido-6-chloroacetylnaphthalene,* cream-colored micro needles, m.p. 160.5–161°.

Anal. Calc'd for $C_{14}H_{12}ClNO_2$: C, 64.3; H, 4.6. Found: C, 64.2; H, 4.8.

With pyridine and sodium hydroxide, this chloro ketone gave 6-acetamido-2-naphthoic acid, m.p. 223–227°, reported[6] 230–232°.

The manual separation also gave 2 g. of *7-acetamido-1-chloroacetylnaphthalene,* bright yellow prisms, m.p. 141.5–142°.

Anal. Calc'd for $C_{14}H_{12}ClNO_2$: C, 64.3; H, 4.6. Found: C, 64.0; H, 4.6.

With pyridine and sodium hydroxide, the latter gave 7-acetamido-1-naphthoic acid, m.p. 232–233° alone or mixed with a known sample.

7-Acetamido-1-bromoacetylnaphthalene was obtained by adding one drop of hydrochloric acid and then 48 g. of bromine to a stirred solution of 61.5 g. of 7-acetamido-1-acetonaphthone in 600 ml. of methanol at 45°. (In other apparently more suitable solvents, only tarry substances were obtained). The product was precipitated with water (m.p. 142–146°) and recrystallized from chloroform and ligroin, giving bright yellow needles (54 g., 63%), m.p. 153.5–154°.

Anal. Calc'd for $C_{14}H_{12}BrNO_2$: C, 54.9; H, 4.0. Found: C, 54.9; H, 4.3.

With pyridine and then aqueous sodium hydroxide, 1.3 g. of the bromo ketone gave 0.6 g. of 7-acetamido-1-naphthoic acid, m.p. 232–233°.

When a solution of 50 g. of the bromo ketone in 600 ml. of hot isopropyl alcohol was treated with aluminum isopropoxide, (from 22 g. of aluminum) boiled for 20 minutes, and then poured into iced hydrochloric acid, it gave 33.7 g. of *7-acetamido-β-hydroxy-1-naphthaleneethyl bromide,* tan cubes from benzene, m.p. 150–151°. This bromohydrin, however, did not react satisfactorily with potassium phthalimide.

Anal. Calc'd for $C_{14}H_{14}BrNO_2$: C, 54.6; H, 4.6. Found: C, 54.9; H, 4.6.

7-Acetamido-1-phthalimidoacetylnaphthalene was obtained by boiling a stirred mixture of 71 g. of 7-acetamido-1-bromoacetylnaphthalene and 46.5 g. of potassium phthalimide in 750 ml. of xylene for two hours. The resulting suspension was cooled and filtered, and the solid was washed with water, methanol, and acetone. The residue (72.6 g., 84%, m.p. 220–223°) was sufficiently pure for use in the next step; a portion recrystallized from methanol formed small pale yellow needles, m.p. 225–226°.

Anal. Calc'd for $C_{22}H_{16}N_2O_4$: C, 71.0; H, 4.3. Found: C, 70.7; H, 4.6.

7-Acetamido-β-hydroxy-N-phthalyl-1-naphthaleneethylamine was obtained by adding 46 g. of the preceding phthalimido ketone in 3–5 g. portions at 10–20 minute intervals to a boiling solution of aluminum isopropoxide (from 11 g. of aluminum in 400 ml. of isopropyl alcohol). The mixture was boiled and stirred for 30 minutes after the addition was complete, and then it was poured into iced hydrochloric acid. The product was triturated with acetic acid yielding 37 g. (80%), m.p. 224–226°; a portion recrystallized from methanol formed white needles, m.p. 225.5–226.5° (a mixture with the ketone had m.p. 200–213°).

Anal. Calc'd for $C_{22}H_{18}N_2O_4$: C, 70.6; H, 4.9. Found: C, 70.6; H, 5.1.

A suspension of 11 g. of the phthalimido alcohol containing 20 ml. of 85% hydrazine hydrate was warmed on a steam-bath until the solid dissolved and phthalhydrazide began to separate, or about five minutes. The mixture then was cooled and filtered, and the filtrate was evaporated under reduced pressure. The basic product was extracted with dilute hydrochloric acid and then was precipitated with caustic, giving 5.9 g. of free amine, m.p. 186–189° dec; no suitable solvent for recrystallization was found. A solution of the crude amine in 25 ml. of water containing 2 ml. of hydrochloric acid was treated with 5 ml. of acetic anhydride and then with 5 g. of sodium carbonate. The crude product, 6.35 g. (76%), m.p. 197–198°, was crystallized from dioxane and ligroin giving *7-acetamido-N-acetyl-β-hydroxy-1-naphthaleneethylamine* (I), colorless needles, m.p. 199–199.5°.

Anal. Calc'd for $C_{16}H_{18}N_2O_3$: C, 67.1; H, 6.4. Found: C, 67.2; H, 6.6.

SYNTHESIS OF I-A

A solution of 170 g. of 1-acetonaphthone in 650 ml. of dry ether was cooled and stirred while 160 g. of bromine was added dropwise. The solution then was washed with water, dried over sodium carbonate, and evaporated under reduced pressure. The residue was mixed with 1400 ml. of xylene and 193 g. of potassium phthalimide. The mixture was boiled and stirred for two hours, and then was filtered hot. The filtrate deposited 215 g. of crude product when it was cooled. Two crystallizations from xylene gave 171 g. (54%) of nearly pure *1-phthalimidoacetylnaphthalene,* m.p. 160–164°; further crystallization from alcohol gave cream-colored needles, m.p. 171.5–172°.

Anal. Calc'd for $C_{20}H_{13}NO_3$: C, 76.2; H, 4.2. Found: C, 76.0; H, 4.4.

The phthalimido ketone was reduced by adding 85 g. of it in portions during four hours to a stirred boiling solution of aluminum isopropoxide (from 27 g. of aluminum and 750 ml. of isopropyl alcohol). The crude yellow product (83.5 g.) had m.p. 135–150°. Recrystallization from benzene gave 27 g. of colorless *β-hydroxy-N-phthalyl-1-naphthaleneethylamine,* m.p. 162–166°. A portion crystallized again from alcohol had m.p. 171–172° (146–157° when mixed with the parent ketone).

(4) Brown, Jacobs, Winstein, Levy, Mors, and Ott, *J. Org. Chem.,* **11,** 163 (1946).

(5) Leonard and Hyson, *J. Org. Chem.,* **13,** 164 (1948).

(6) Dziewonski, Schoemowna, and Waldmann, *Ber.,* **58,** 1217 (1925).

Anal. Calc'd for $C_{20}H_{15}NO_3$: C, 75.7; H, 4.8. Found: C, 75.7; H, 5.0.

A suspension of 27 g. of the phthalimido alcohol in 100 ml. of methanol containing 15 ml. of hydrazine hydrate was boiled for 30 minutes. Phthalhydrazide then was removed by filtration, and methanol by distillation under reduced pressure. The residue was extracted with dilute hydrochloric acid, and the extract was treated with excess acetic anhydride and sodium carbonate. The resulting crude *N-acetyl-β-hydroxy-1-naphthaleneethylamine* (14 g., 72%) had m.p. 147–148°. Crystallization from alcohol gave colorless microneedles, m.p. 149–150°; reported 145–146°[1], 150–151°.[7]

Anal. Calc'd for $C_{14}H_{15}NO_2$: C, 73.3; H, 6.6. Found: C, 73.2; H, 6.9.

N-Acetyl-β-acetoxy-1-naphthaleneethylamine, from the preceding compound with acetic anhydride in pyridine, formed colorless needles from methanol, m.p. 118–119°.

Anal. Calc'd for $C_{16}H_{17}NO_3$: C, 70.8; H, 6.3. Found: C, 70.9; H, 6.5.

SYNTHESIS OF VIII

Ethyl benz[c]phthalimidoacetate (III). Benz[c]phthalic anhydride (75 g.)[8] and glycine (30 g.) were ground together and then were heated for 30 minutes with intermittent stirring in a vessel immersed in an oil-bath at 200–210°. The vessel then was evacuated to remove water, and the contents were removed, pulverized, and then reheated in the same way for another 30 minutes. A small portion of the resulting *benz[c]phthalimidoacetic acid* was crystallized from alcohol and then from acetone, giving yellow needles, m.p. 239–240°.

Anal. Calc'd for $C_{14}H_9NO_4$: C, 65.9; H, 3.6. Found: C, 65.9; H, 3.8.

To the remainder of the acid was added 1200 ml. of absolute alcohol. The mixture was boiled and hydrogen chloride was passed in until complete solution occurred. It then was kept at room temperature for eight hours, and the resulting crystalline product was removed and washed with alcohol. There was obtained 98 g. of III, yellow needles, m.p. 138–139°. Recrystallization from alcohol gave yellow needles, m.p. 139–140°.

Anal. Calc'd for $C_{16}H_{13}NO_4$: C, 67.8; H, 4.6. Found: C, 68.1; H, 4.9.

Sodium (5 g.) was dissolved in 200 ml. of absolute alcohol, and the resulting solution together with 30 g. of III was placed in a pressure bottle and heated in a boiling water-bath for three hours. The resulting suspension was poured into two liters of water. Insoluble material was removed and the solution was treated with 18 g. of ammonium chloride. The resulting precipitate was washed with water and dried. The total product from five such experiments (44 g.) was heated on a steam-bath with 100 ml. of acetic acid. The undissolved part (4.9 g., m.p. 220–225°) was nearly pure *2-carbethoxy-1,4-dihydroxybenz[f]isoquinoline* (IV-a), which formed bright yellow needles from acetic acid, m.p. 232–233°

Anal. Calc'd for $C_{16}H_{13}NO_4$: C, 67.8; H, 4.6. Found: C, 67.6; H, 4.9.

When it was cooled, the acetic acid filtrate deposited 32 g. of crude *3-carbethoxy-1,4-dihydroxybenz[h]isoquinoline* (IV) m.p. 175–190°. Recrystallization from a large volume of alcohol gave fine pale tan needles, m.p. 214–214.5°.

Anal. Calc'd for $C_{16}H_{13}NO_4$: C, 67.8; H, 4.6. Found: C, 67.7; H, 4.8.

A suspension of 32 g. of IV in 800 ml. of 1:1 sulfuric acid was boiled for 90 minutes, then cooled and poured into one liter of water. The resulting *1,4-dihydroxybenz[h]isoquinoline* (V) formed faintly purple prisms from acetic acid; yield 22 g., m.p. 285–286° (block preheated to 280°). The compound was soluble in aqueous sodium hydroxide.

Anal. Calc'd for $C_{13}H_9NO_2$: C, 73.9; H, 4.3. Found: C, 73.6; H, 4.4.

A mixture of 5.5 g. of V, 1 g. of red phosphorus, and 25 ml. of 48% hydriodic acid was heated in a sealed tube at 190° for three hours. The product was separated by filtration and then was recrystallized from dilute alcohol. The combined material from four such experiments (11.3 g., m.p. 180–190°) was crystallized from alcohol and then from benzene, giving tan needles of *1-hydroxybenz[h]isoquinoline* (VI), m.p. 200–201°, that were insoluble in aqueous sodium hydroxide.

Anal. Calc'd for $C_{13}H_9NO$: C, 80.0; H, 4.7. Found: C, 80.1; H, 4.8.

A suspension of 10 g. of VI in 30 ml. of phosphorus oxychloride was boiled for 30 minutes and then poured on 400 g. of ice. The resulting green gum was triturated with 5% sodium carbonate until it solidified. The product then was dissolved in 130 ml. of benzene and decolorized with 6 g. of alumina. Crystallization from dilute alcohol gave 6.4 g. of *1-chlorobenz[h]isoquinoline* (VII), faintly yellow plates, m.p. 97–98°.

Anal. Calc'd for $C_{13}H_8ClN$: C, 73.1; H, 3.8. Found: C, 72.9; H, 4.1.

To a solution of 1.4 g. of potassium hydroxide in 100 ml. of alcohol was added 4.3 g. of VII and 1.5 g. of Raney nickel. The mixture was shaken under hydrogen at room temperature and atmospheric pressure for six hours. The total *benz[h]isoquinoline* (VIII) from two such experiments (5.6 g.) had b.p. 195–196° at 16 mm. and m.p. 46–47°.

Anal. Calc'd for $C_{13}H_9N$: C, 87.1; H, 5.1. Found: C, 87.4; H, 5.3.

The *picrate* formed a yellow crystalline powder from alcohol, m.p. 216–217°.

Anal. Calc'd for $C_{19}H_{12}N_4O_7$: C, 55.9; H, 3.0. Found: C, 56.0; H, 3.3.

A mixture of 1 g. of VIII, 3.5 g. of tin, and 50 ml. of conc'd hydrochloric acid was boiled for five hours, heated on a steam-bath for eight hours and then cooled. The tin complex was removed by filtration and decomposed with alkali. The oily base was taken up in ether and extracted with 5% hydrochloric acid. Addition of excess sodium nitrite gave *N-nitroso-1,2,3,4-tetrahydrobenz[h]isoquinoline*, colorless plates from dilute acetic acid, m.p. 103–104°, reported[9] 105°.

Anal. Calc'd for $C_{13}H_{12}N_2O$: C, 73.6; H, 5.7. Found: C, 73.7; H, 5.8.

The nitroso derivative was decomposed with cuprous chloride and hydrochloric acid[10] and the resulting 1,2,3,4-tetrahydrobenz[h]isoquinoline was converted into its *picrate*, m.p. 223.5–224.5°, reported[9] 225–226°, and into its *o-nitrobenzoyl derivative*, m.p. 242–243°, reported[9] 240°.

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(7) Dey and Rajagopalan, *Arch. Pharm.*, **277**, 359 (1939).
(8) Hershberg and Fieser, *Org. Syntheses*, Coll. Vol. **2**, 423 (1943).
(9) Mayer and Schnecko, *Ber.*, **56**, 1408 (1923).
(10) Jones and Kenner, *J. Chem. Soc.*, 711 (1932).