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Derivatives of 10,11-Dihydro-5*H*-dibenzo[*a,d*]cycloheptene and Related Compounds V: Homologous 4-Azaketones and Derivatives

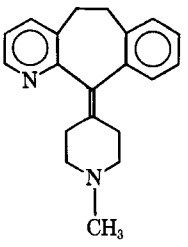
FRANK J. VILLANI, CLAIRE A. ELLIS, and THOMAS A. MANN

Abstract □ 6,7-Benzo-12*H*-5,6,7,12-tetrahydrocycloocta[1,2*b*]pyridine-12-one (III) and 5,6-benzo-5,6,11,12-tetrahydrocycloocta-[1,2*b*]pyridine-11-one (IV) were prepared. Wolff-Kishner reduction gave the corresponding azahydrocarbons (VII*a* and IX). Alkylation of 6,7-benzo-12*H*-5,6,7,12-tetrahydrocycloocta[1,2*b*]pyridine, using potassium amide and liquid ammonia, gave the corresponding 12-dialkylaminoalkyl derivatives (VII*b* and VII*c*). The dehydration of 12 - hydroxy - 12 - (1 - methyl - 4 - piperidyl) - 6,7 - benzo - 12*H*-5,6,7,12-tetrahydrocycloocta[1,2*b*]pyridine (V), prepared by two methods, gave 4-aza-4*b*-(1-methyl-4-piperidyl)-9,10-dihydroindeno-[1,2*a*]indene (VI). The compounds were without significant biological activity.

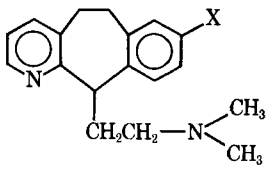
Keyphrases □ 4-Azaketones and derivatives—synthesis, screened for biological activity □ 10,11-Dihydro-5*H*-dibenzo[*a,d*]cycloheptene and related compounds—synthesis of 4-azaketones and derivatives

Compounds I and II have shown very potent antianaphylactic and antihistaminic activities in laboratory animals[1] and in man (1–4). It was of interest to homologate the seven-membered ring to prepare the corresponding amino derivatives from the benzopyridocyclooctanones (III and IV). This report summarizes attempts in this area.

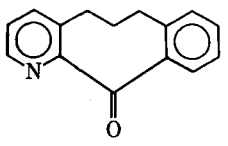
Ketone III was prepared by the intramolecular cyclization of 3-(γ-phenylpropyl)picolinic acid or its corresponding nitrile in a large excess of polyphosphoric acid. Reaction of III with the Grignard reagent, prepared from 1-methyl-4-chloropiperidine, gave the expected tertiary carbinol (V). Reductive alkylation (5), using the disodio derivative of III and 1-methyl-4-chloropiperidine, resulted in a cleaner product in excellent yield.



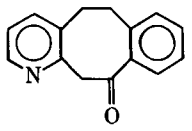
I



II*a*: X = H
II*b*: X = Cl



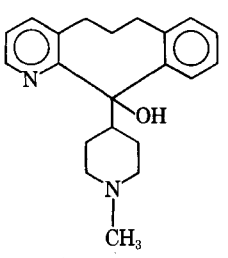
III



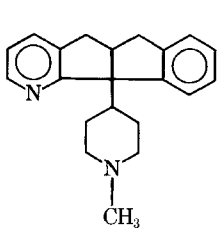
IV

All attempts at the dehydration of V to introduce the exocyclic double bond as in I failed, and the azaindenoindene derivative (VI) was isolated. The structure of VI was established by the usual physical measurements. Of special importance was the weak absorbance in the UV spectrum ($\epsilon_{270\ nm.}$ 6060) compared to that of Compound I ($\epsilon_{239\ nm.}$ 11,000, $\epsilon_{267\ nm.}$ 6100, and $\epsilon_{275\ nm.}$ 5900).

Reduction of III under modified Wolff-Kishner conditions gave the azahydrocarbon VII*a*. Alkylation of VII*a* in the presence of potassium amide gave the

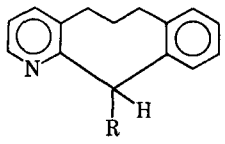


V

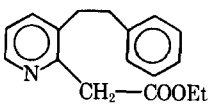


VI

[1] For preliminary communication, see F. J. Villani, P. J. Daniels, C. A. Ellis, T. A. Mann, and K. C. Wang, in "Abstracts of the Division of Medicinal Chemistry," 124th meeting of the American Chemical Society, September 1966. A detailed publication from this laboratory is now in preparation.



VII*a*: R = H
VII*b*: R = $(CH_2)_2N(CH_3)_2$
VII*c*: R = $(CH_2)_3N(CH_3)_2$



VIII

substituted derivatives (VII*b* and VII*c*).

To prepare ketone IV, the lithio derivative of 2-methyl-3-phenethylpyridine was carbonated and converted into the ester VIII. Cyclization of VIII resulted in the isolation of IV, although in low yield due to the ease of decarboxylation of the intermediate pyridyl acetic acid. Considerable amounts of 2-methyl-3-phenethylpyridine were formed during this reaction. Grignard addition to IV was not successful because this compound exists primarily in the enol form.

Reduction of IV under Wolff-Kishner conditions gave the deoxygenated derivative, which resisted all alkylation attempts.

The compounds were screened for antianaphylactic, antihistamine, and antitetrabenazine activity in laboratory animals. The compounds were surprisingly inactive in the antianaphylactic screen at a dose of 10 mg./kg. orally. Antihistaminic potency (*in vitro*) was of a very low order, with a PD_{50} greater than 80 mcg./l. Compound VII*c* showed an ED_{50} of approximately 20 mg./kg. orally in mice against tetrabenazine-induced ptosis, but it was of insufficient potency to warrant further investigation.

EXPERIMENTAL

β-Phenethyl-3-pyridyl Ketone—In a typical preparation, 3-cyanopyridine (20.8 g.) in ether (150 ml.) was added dropwise to a Grignard reagent prepared from β-phenethylbromide (42.5 g.) and magnesium (5.6 g.) in ether (1 l.). The reaction mixture, containing a yellow precipitate, was stirred under reflux (steam bath) for 16 hr. Concentrated hydrochloric acid (200 ml.) was added, and stirring was continued for an additional 6 hr. at room temperature. The ether layer was removed, and the acid solution was heated under reflux with stirring for an additional 4 hr. After cooling, the solution was basified with NH_4OH and extracted with chloroform. The solvent was removed and the product distilled, b.p. 161–170°/1 mm. (yield 20.6 g., 48%), n_D^{26} 1.5814. A small sample was crystallized for analysis from ether–petroleum ether (b.p. 30–60°), m.p. 31–33°.

Anal.—Calc. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.48; H, 6.36; N, 6.66.

A small sample was converted to the hydrochloride, which was recrystallized from ethanol–ether and had a melting point of 136–138°.

Anal.—Calc. for $C_{14}H_{13}NO \cdot HCl$: C, 67.87; H, 5.70; N, 5.66. Found: C, 67.70; H, 5.80; N, 5.65.

3-(γ-Phenylpropyl)pyridine—A mixture of the preceding ketone (189 g.), diethylene glycol (1.2 l.), NaOH (77.5 g.), and 85% hydrazine hydrate (78 ml.) was heated in a flask equipped with a downward condenser until the internal temperature reached 240° and was maintained at this temperature for an additional 4 hr. The cooled reaction mixture was extracted thoroughly (five times) with ether, the extracts were washed with water (five times), the solvent was removed, and the product was distilled to give 152 g. (86%) of a colorless liquid boiling at 130–134°/2 mm., n_D^{26} 1.5610.

3-(γ-Phenylpropyl)pyridine-1-oxide—Hydrogen peroxide (30%, 100 ml.) was added to a cold solution of the 3-(γ-phenylpropyl)-pyridine (166 g.) in glacial acetic acid (250 ml.). The mixture was heated to 60° and so maintained for 20 hr.; then it was poured into ice water (2 l.). The solution was basified (NH_4OH) and extracted with chloroform. The chloroform was removed *in vacuo* on the steam bath, and the residue (171 g., 93%) was recrystallized from benzene–hexane, m.p. 36–37°.

Anal.—Calc. for $C_{14}H_{15}NO \cdot \frac{1}{2} H_2O$: C, 75.65; H, 7.26; N, 6.30. Found: C, 75.41; H, 7.38; N, 6.08.

2-Cyano-3-(γ-phenylpropyl)pyridine—Dimethyl sulfate (64.5 g). was added dropwise to the *N*-oxide (108.5 g.), keeping the temperature between 80 and 85° (6). The mixture was heated on the steam bath for 3 hr., and 200 ml. of water was added. This solution was added under nitrogen and at 0° to a solution of sodium cyanide (76 g.) in water (215 ml.). Stirring was continued at 0° for 4 hr., and the mixture was permitted to warm to room temperature overnight. The product was extracted with chloroform and washed with water, the solvent was removed, and the residue was distilled at 1 mm. The major fraction (b.p. 165–185°/1 mm.) was redistilled to give 64.5 g. (60%) of an oil boiling at 170–175°/1 mm., n_D^{27} 1.5685. This fraction soon solidified, and a small sample was recrystallized from benzene–hexane, m.p. 56–59°.

Anal.—Calc. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.15; H, 6.59; N, 12.66.

The other fractions consisted of the 4- and 6-cyano compounds and were discarded.

3-(γ-Phenylpropyl)picolinic Acid—The nitrile (40.5 g.), sodium hydroxide (40.5 g.), ethanol (300 ml.), and water (75 ml.) were heated under reflux for 30 hr. The solvents were removed *in vacuo*, and the residue was dissolved in water and neutralized with acetic acid. The clear solution was extracted thoroughly with chloroform, and the solvent was removed. The solid residue was dissolved in 15% sodium bicarbonate solution, neutralized with acetic acid, and extracted with chloroform. After removal of the solvent, the residue was triturated with isopropyl ether and air dried to give 38.5 g. (87.5%) of the acid, m.p. 36–39°. The analytical sample was recrystallized from isopropyl ether and had a melting point of 39–40°.

Anal.—Calc. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.09; H, 6.33; N, 5.95.

6,7 - Benzo - 12*H* - 5,6,7,12 - tetrahydrocycloocta[1,2*b*]pyridine-12-one (III)—*Method 1*—3-Phenethylpicolinic acid (50 g.) and polyphosphoric acid (2.5 kg.) were heated with stirring to 190–200° for 3 hr. and poured into ice water. The solution was neutralized with sodium hydroxide (50% solution) and extracted with ether. The ether extracts were concentrated on the steam bath, and the residue was triturated with petroleum ether. The product was recrystallized from benzene–petroleum ether to give 34 g. (73%) of a white solid, m.p. 157–159°.

Anal.—Calc. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 80.16; H, 6.24; N, 6.43.

Method 2—A mixture of nitrile V*b* (42.5 g.) and polyphosphoric acid (2.1 kg.) was heated with stirring at 230–235° for 4 hr., poured into ice water, and processed as in Method 1. A crude product, 27 g. (62.4%), was obtained, m.p. 153–155°.

12 - Hydroxy - (1 - methyl - 4 - piperidyl) - 6,7 - benzo - 12*H*-5,6,7,12-tetrahydrocycloocta[1,2*b*]pyridine (V)—*Grignard Method*—Under nitrogen, the Grignard reagent was prepared from 1-methyl-4-chloropiperidine (13.2 g.) and magnesium (2.4 g.) in tetrahydrofuran (100 ml.), using 1,2-dibromoethane (0.5 ml.) as an initiator. At 10°, ketone III (7 g.) in tetrahydrofuran (250 ml.) was added dropwise, and the mixture was stirred for 45 min. The solvent was removed *in vacuo* on the steam bath; ether (300 ml.) was added, followed by a saturated solution of ammonium chloride. The organic layer was separated and the aqueous layer extracted ($CHCl_3$); the combined extracts concentrated to a residue which resisted crystallization. The material was chromatographed on alumina (250 g.), using 15% ethyl acetate–benzene as the eluant. Seven fractions of 750 ml. each were collected, with the major product being in Fractions 5 and 6. The solvents were removed, and the residues were recrystallized twice from isopropyl ether to give 2 g. (20%) of product, m.p. 120–121°.

Anal.—Calc. for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 78.15; H, 8.20; N, 8.88.

Reductive Alkylation Method—Sodium (2.7 g.) was dissolved in anhydrous ammonia (about 200 ml.). After 20 min., ketone III (13 g.) in tetrahydrofuran (100 ml.) was added dropwise, and stirring was continued for an additional 10 min. 4-Chloro-1-methylpiperidine (7.8 g.) in 25 ml. of tetrahydrofuran was added and the mixture was stirred overnight. Ammonium chloride (5 g.) was added portionwise, and the excess ammonia was allowed

to evaporate. Water (100 ml.) and benzene (100 ml.) were added and the product was extracted with benzene. The benzene solution was evaporated *in vacuo*, and the residue was recrystallized from isopropyl ether. There was obtained 14.2 g. (76%) of V having a melting point of 119–122°.

4 - Aza - 4*b* - (1 - methyl - 4 - piperidyl) - 9,10 - dihydroindeno-[1,2*a*]indene (VI)—Carbinol V (13 g.) and polyphosphoric acid (750 ml.) were heated with stirring at 160° for 18 hr. The warm mixture was poured into ice, made basic with sodium hydroxide, and extracted with chloroform. The residue, after removal of solvent, would not crystallize readily; it was converted to the hydrochloride salt, which was recrystallized twice from ethanol–ether, m.p. 220–224°. The amine base was liberated from the hydrochloride (NH_4OH), and the product was extracted with chloroform. After removal of the solvent, a benzene solution of the residue was chromatographed on 500 g. of alumina, using ether as the eluant and collecting fractions of 300 ml. each. The major portion of the product was eluted in the first five fractions. After removal of the solvent, the residue was recrystallized from petroleum ether, m.p. 95–97° ($\epsilon_{270\ nm.}$ 6060; *m/e* 304).

Anal.—Calc. for $C_{21}H_{24}N_2$: C, 82.85; H, 7.95; N, 9.20. Found: C, 83.00; H, 7.88; N, 9.20.

6,7 - Benzo - 12*H* - 5,6,7,12 - tetrahydrocycloocta[1,2*b*]pyridine (VII*a*)—By using the same procedure as for VI, a mixture of ketone III (44.6 g.), sodium hydroxide (17.5 g.), 99–100% hydrazine hydrate (14.8 g.), water (17.5 ml.), and diethylene glycol (400 ml.) was heated to 240° for 2 hr. and processed as described. It gave 30.5 g. (73%) of product, m.p. 76–78°, from petroleum ether.

Anal.—Calc. for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 86.20; H, 7.24; N, 6.58.

General Alkylation Procedure: Preparation of VII*b* and VII*c*— Potassium metal (2 g.) was added in small portions to liquid ammonia (about 600 ml.), using ferric oxide as the catalyst. After 2 hr., a solution of VII*a* (8.4 g.) in toluene (40 ml.) was added dropwise, followed in 45 min. by the dimethylaminoalkyl chloride (0.045 mole) in toluene (25 ml.). Stirring was continued for an additional 2.5 hr., toluene (150 ml.) was added dropwise, and the ammonia was allowed to evaporate. The reaction mixture was then heated on the steam bath for 6 hr. Water (10 ml.) was added, and the reaction mixture was extracted with chloroform. The solvents were removed, and the residue was dissolved in benzene. Water (10 ml.) was added, and the pH was brought to 4.5–5 by the addition of 1 *N* HCl. The benzene layer, containing unreacted azahydrocarbon, was discarded; the aqueous layer was basified with NH_4OH and extracted with chloroform. The chloroform was removed, and the residue was distilled.

*VII*b—Boiling point 160–167°/1 mm.; yield 27%; n_D^{27} 1.5835. This product soon crystallized and was recrystallized from petroleum ether, m.p. 87–90°.

Anal.—Calc. for $C_{19}H_{24}N_2$: C, 81.38, H, 8.63; N, 9.99. Found: C, 81.51; H, 9.43; N, 9.95.

*VII*b *Maleate*—This compound, m.p. 149–151°, was recrystallized from isopropyl acetate.

Anal.—Calc. for $C_{19}H_{24}N_2 \cdot C_4H_4O_4 \cdot H_2O$: C, 66.64; H, 7.30; N, 6.76. Found: C, 66.27; H, 7.46; N, 6.85.

*VII*c—This compound was obtained (54%) as an amber-colored oil, b.p. 205–210°/1.5 mm.; n_D^{27} 1.5712.

Anal.—Calc. for $C_{20}H_{26}N_2$: C, 81.58; H, 8.90, N, 9.52. Found: C, 81.51; H, 9.00; N, 9.90.

*VII*c *Maleate*—This compound, m.p. 164–166°, was recrystallized from isopropanol.

Anal.—Calc. for $C_{20}H_{26}N_2 \cdot C_4H_4O_4$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.07; H, 7.32; N, 7.23.

Ethyl-3-(β-phenethyl)-2-pyridylacetate—Phenyllithium was prepared from bromobenzene (15.7 g.) and lithium (1.4 g.) in ether (100 ml.). 2-Methyl-3-phenethylpyridine (19.7 g.) in an equal volume of ether was added dropwise and stirred for 30 min. at room temperature. The dark-red solution was poured onto powdered dry ice (75–100 g.), and the dry ice was permitted to evaporate. Ethanol (75 ml.) was added, and the mixture was saturated with anhydrous hydrogen chloride and allowed to stand overnight at room temperature. The solvents were removed *in vacuo* on the steam bath. Water was added to the residue, and the mixture was extracted with chloroform. The chloroform extracts were washed with dilute sodium bicarbonate solution, the solvent was removed, and the residue was distilled. The fraction, b.p. 140–172°/2 mm. (11 g.), was chromatographed on silica gel (350 g.), using finally 50% ether–50% pentane as the eluting agent and collecting fractions of about 200 ml. The solvent was removed from the combined fractions (Fractions 12–20), and the residue was distilled, b.p. 165–170°/1.5 mm.; yield 6.5 g. (24%).

Anal.—Calc. for $C_{17}H_{19}NO_2$: C, 75.81, H, 7.11, N, 5.20. Found: C, 75.70; H, 7.20; N, 5.47.

5,6 - Benzo - 5,6,11,12 - tetrahydrocycloocta[1,2*b*]pyridine - 11-one (IV)—The preceding ester (6.5 g.) and polyphosphoric acid (350 g.) were heated with stirring at 155–160° for 1.5 hr. The warm mixture was poured into ice, basified with ammonia, and extracted with chloroform. The chloroform extracts were washed with water, the solvent was removed, and the residue was recrystallized several times from hexane; yield 1.2 g. (24.5%), m.p. 122–123°.

Anal.—Calc. for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.59; H, 5.92; N, 6.29.

5,6 - Benzo - 5,6,11,12 - tetrahydrocycloocta[1,2*b*]pyridine (IX)—Ketone IV (5.6 g.), 85% hydrazine hydrate (5.3 g.), diethylene glycol (50 ml.), and potassium hydroxide (7.4 g.) were heated at 240° for 3.5 hr., and the product was isolated as previously described to give 2.6 g. (50%) of product, m.p. 86–87°.

Anal.—Calc. for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 85.95; H, 7.30; N, 6.78.

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For Part IV in this series, see F. J. Villani, C. A. Ellis, M. D. Yudis, and J. B. Morton, *J. Org. Chem.*, **36,** 1709(1971).