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Naphtho[2,3-a]quinolizinium Derivatives

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The alkylation of 2-acetonylpyridines with β-phenylethyl bromides leads to ketones which may be cyclized to 1-methyl-2-(2-pyridyl)-3,4-dihydronaphthalenes. Aromatization of the dihydronaphthalenes followed by quaternization with chloroacetaldoxime affords salts which may be cyclized to yield the title compounds.

Benz[a]anthracene (I) has attracted particular interest since certain of its alkyl derivatives are carcinogenic (1). Interesting congeners are the azonia (2) benz[a]anthracenes in which a carbon at a bridgehead position has been replaced by a quaternary nitrogen atom. To date, of the six such azonialogs of benz[a]anthracene possible, only three, the 6a- (3), 7a- (4) and 11a-azoniabenz[a]anthracenes (4) have been prepared. The present communication describes the first synthesis of 4a-azoniabenz[a]anthracene or naphtho[2,3-a]quinolizinium derivatives (II). No commonly used naphthalene synthesis appeared promising for the preparation of the required 1-methyl-2-(2-pyridyl)naphthalene (VI), and the method devised was based upon the observation of Rapson and Robinson (5) that 4-phenyl-2-pentanone could be cyclized in sulfuric acid to yield 1-methyl-3,4-dihydronaphthalene.

The alkylation of the methylene group of 2-acetonyl- (6) or 3-methyl-2-acetonylpyridine (III) (7) by 2-phenyl-1-bromoethane, or 2-phenyl-1-bromopropane was carried out in benzene-dimethylformamide solution using hydride ion as the base. The new ketones (IV) did not form crystalline derivatives with the usual carbonyl reagents, but were easily identifiable as ketones by the infrared spectra. The ketones (IV) when treated with sulfuric acid (5) appeared to undergo sulfonation, but were cyclized in good yield by heating on the steam bath with polyphosphoric acid. The resulting 3,4-dihydronaphthalenes (V) were dehydrogenated over palladium-charcoal to afford the naphthalenes (VII).

The conversion of the 2-(2-pyridyl)naphthalenes to naphtho[2,3-a]quinolizinium derivatives (VIII) involved the procedure developed by Kimber and Parham (8). Both the quaternization with chloroacetaldoxime (yielding VII) and the cyclization in concentrated hydrochloric acid worked well. The yields and spectral data for the new naphtho[2,3-a]quinolizinium perchlorates are reported in Table I.

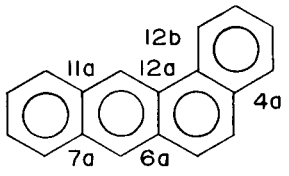
The simplest derivative, the 13-methylnaphtho-[2,3-a]quinolizinium cation (VIIIa) is an azonialog (2) of the carcinogenic (9) 12-methylbenz[a]anthracene. The higher homolog VIIIb is an azonialog of 7,12-dimethylbenz[a]anthracene, one of the most widely studied synthetic carcinogens (10). The 1,13-dimethylnaphtho[2,3-a]quinolizinium system (VIIIc) is of special interest, not only because the hydrocarbon counterpart proved so difficult to synthesize (11) but because it is the first example of a quinolizinium derivative which should have optical asymmetry due to the mutual out-of-plane displacement of the two methyl groups. Unfortunately our preliminary attempts at making a diastereoisomeric salt were thwarted by the insolubility of the perchlorate salt of VIIIc.

While 13-methylnaphtho[2,3-a]quinolizinium perchlorate (VIIIa) proved too insoluble in the solvents available to permit the measurement of the proton magnetic resonance, the two higher homologs were sufficiently soluble in trifluoroacetic acid to permit measurements. Resonance due to the protons of the methyl groups was observed at 7.04 and 7.76 τ in the case of the 8,13-dimethylnaphtho[2,3-a]-quinolizinium cation and at 7.10 and 7.31 τ in the case of the 1,13-isomer.

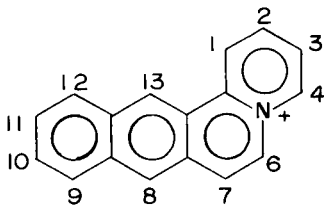
TABLE I

Naphtho[2,3-a]quinolizinium Perchlorates (VIII)

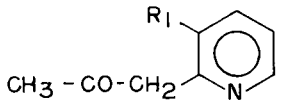
R_1	R_2	Yield %	λ max, mμ (log ε)
-	-	76	240 (4.42), 260 (4.36), 297sh, 308 (4.84), 372 (3.77), 388 (3.77), 420sh.
-	CH_3	82	244 (4.32), 267 (4.19), 303sh, 314 (4.83), 377 (3.69), 395 (3.69), 420 (3.60).
CH_3	-	48	245 (4.39), 263 (4.40), 312sh, 320 (4.74), 383 (4.80), 400 (3.82), 435sh.



I

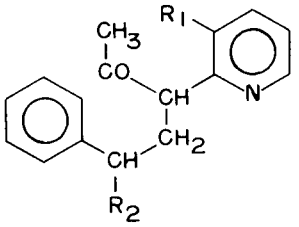


II



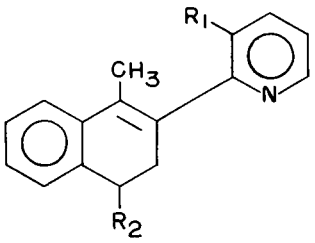
III

1. NaH
2. C_6H_5 / CH-R_2 / CH_2Br



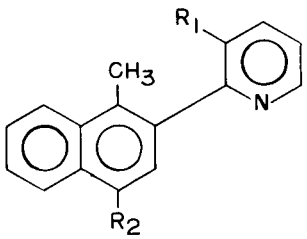
IV

PPA



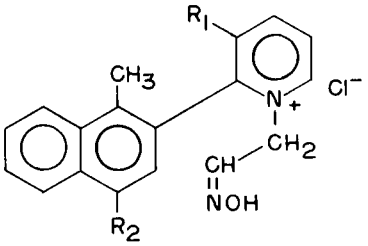
V

Pd-C

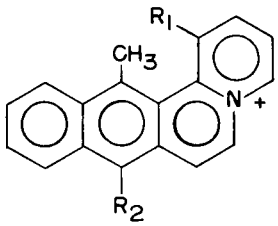


VI

$ClCH_2CH{=}NOH$



VII



VIII

a, $R_1 = R_2 = H$

b, $R_1 = H$, $R_2 = CH_3$

c, $R_1 = CH_3$, $R_2 = H$

TABLE II

Experimental Data

Derivative	M.p. (a)	Yield %	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
IV, Ketones									
a base	115-130 (0.5mm)	45	$C_{16}H_{17}NO$	80.30 (b)	79.78	7.16	6.84	5.85	6.10
b base	115-130 (0.5mm)	25	$C_{17}H_{19}NO$	80.59	80.10	7.56	7.87	5.53	5.61
c base	110-124 (0.5mm)	31 (b)							
V, 3,4-Dihydronaphthalenes									
a base	120 (0.5mm)	92	$C_{16}H_{15}N$	86.84	87.09	6.83	6.36	6.33	6.39
a picrate	254-255	--	$C_{22}H_{18}N_4O_7$	58.66	58.68	4.03	3.78	12.44	12.62
b base	110 (0.5mm)	90	$C_{17}H_{17}N$	86.70	86.56	7.28	7.34	5.95	5.96
b picrate	185.5-186.5	--	$C_{23}H_{20}N_4O_7$	59.48	59.67	4.34	4.53	12.06	12.19
c base	140 (0.5mm)	98 (b)							
c picrate	170-172	--	$C_{23}H_{20}N_4O_7$	59.48	59.47	4.34	4.20	12.06	12.25
VI, Naphthalenes									
a base	97-98	63	$C_{16}H_{13}N$	87.64	87.80	5.97	6.04	6.39	6.42
b base	130 (0.5mm)	62.5	$C_{17}H_{15}N$	87.40	87.57	6.49	6.53	6.00	6.16
b picrate	226.5-227.5	--	$C_{23}H_{18}N_4O_7$	59.74	59.61	3.92	3.63	12.12	12.16
c base	125 (0.5mm)	83 (b)							
c picrate	217-219	--	$C_{23}H_{18}N_4O_7$	59.74	59.78	3.92	3.97	12.12	12.34
VII, 1-(2-Isonitrosoethyl)pyridinium Salts									
a chloride	211-213	88 (c)	$C_{18}H_{17}ClN_2O$	69.11	69.22	5.48	5.57	8.96	9.13
b chloride	159-161	72 (d)	$C_{19}H_{19}ClN_2O\cdot{}^3/_4H_2O$	67.05	66.64	6.07	5.69	8.23	8.26
c chloride	214-215	90 (e)	$C_{19}H_{19}ClN_2O\cdot{}^1/_4H_2O$	68.87	69.11	5.93	5.79	8.46	8.54
VIII, Naphtho[2,3-a]quinolizinium Perchlorates									
a perchlorate	272-274	76 (f)	$C_{18}H_{14}ClNO_4$	62.89	62.72	4.10	3.99	4.08	4.27
a picrate	229	-- (f)	$C_{24}H_{16}N_4O_7$	61.02	61.09	3.41	3.80	11.86	12.04
b perchlorate	240-241	82 (g)	$C_{19}H_{16}ClNO_4$	63.78	63.79	4.51	4.30	3.92	4.21
b picrate	214-214.5	-- (g)	$C_{25}H_{18}N_4O_7$	61.73	61.52	3.73	3.57	11.52	11.68
c perchlorate	237-239	48 (h)	$C_{19}H_{16}ClNO_4$	63.78	63.81	4.51	4.49	3.92	4.11

(a) Where pressures have been cited, the data are boiling points of liquids. (b) Liquid could not be purified satisfactorily. (c) Colorless prisms. (d) Colorless rosettes. (e) Colorless plates. (f) Yellow needles. (g) Orange needles. (h) Orange rosettes.

EXPERIMENTAL

Elemental analyses were by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, Germany. Melting points were determined in capillaries using a Laboratory Devices Mel-Temp block. The ultraviolet absorption data were obtained with a Cary Model 14 Spectrophotometer using 1 cm. silica cells and 95% ethanol as the solvent. The proton magnetic resonance data were obtained with a Varian Associates A-60 Spectrometer.

Preparation of 5-Phenyl-2-(2-pyridyl)-2-pentanone (IV) and Its Homologs.

A mechanically stirred suspension of 2.57 g. of sodium hydride (12) in a mixture of 50 ml. of dry benzene (13) and 50 ml. of dry dimethylformamide was cooled to 0° and 0.1 mole of 2-acetonylpyridine (6), or 2-acetonyl-3-methylpyridine (7) was added slowly. Cooling and stirring were continued for 0.5 hour when 0.1 mole of 2-phenyl-1-bromoethane or 2-phenyl-1-bromopropane was added and the cooling bath removed. After the mixture had been stirred for two hours at room temperature, it was refluxed on the steam bath for 3 hours, cooled and poured into water. The ether extract of the aqueous suspension was extracted in turn with 6 *N* hydrochloric acid and the acid extract neutralized with an excess of solid sodium bicarbonate. The resulting oil was extracted with ether and the ether solution dried and concentrated. The residue was distilled through a spinning band column. Thin-layer chromatography of the distillate, using Dragendorff's reagent (14) or iodine vapor to render the spots visible, showed that a small amount of the acetonylpyridine was present. In two cases (IVa and b), analytical samples were obtained by chromatographing the liquid on a silica gel column followed by distillation in a bulb tube (15). Experimental data may be found in Table II.

1-Methyl-2-(2-pyridyl)-3,4-dihydronaphthalenes (V).

The crude ketones (1 g.) were heated with 15 g. of polyphoric acid for 3 hours with stirring on a steam bath. Ice was then added to the cooled solution with stirring. The turbidity of the resulting solution was removed by one extraction with ether. Neutralization of the acid solution was effected by addition of solid sodium bicarbonate and concentrated ammonia solution and the resulting oil extracted with ether. The ethereal solution was dried (magnesium sulfate), concentrated, and the residue distilled under reduced pressure in a bulb tube, affording a colorless oil. This procedure proved satisfactory on an 8 g. scale.

The picrates were crystallized from ethanol. In two cases (Va and b), analytical samples of the free bases were prepared by decomposing about 200 mg. of the picrate by use of sodium carbonate solution, extracting the oil with ether, removing the ether from the dried solution and distilling the residue in a bulb tube. Experimental data may be found in Table II.

1-Methyl-2-(2-pyridyl)naphthalenes (VI).

The dihydronaphthalenes (V) (3 g.) were heated at 230° for 4 hours with 1 g. of 30% palladium-on-carbon catalyst (16). The cooled mixture was extracted with boiling methanol, filtered, and the filtrate concentrated. Distillation of the naphthalenes under reduced pressure and purification of analytical samples were carried out as in the case of the dihydronaphthalenes (V). Experimental data will be found in Table II.

1-(2-Isonitrosoethyl)-2-(1-methyl-2-naphthyl)pyridinium Chlorides (VII).

The 2-(2-pyridyl)naphthalenes (0.01 mole) and chloroacetaldoxime (8) (0.011 mole) were dissolved in 3 ml. of tetramethylene sulfone and allowed to stand in the dark in a stoppered flask until the mixture solidified (3-7 days). The solid was triturated with acetone and collected. The product was recrystallized from methanol-ethyl acetate (Table II).

Naphtho[2,3-a]quinolizinium Perchlorates.

The 1-(2-isonitrosoethyl)pyridinium salt (VII, 1 g.) was refluxed for 8 hours in 10 ml. of concentrated hydrochloric acid. The solution was concentrated under vacuum in a rotary evaporator, the residual oil taken up in water, and 72% perchloric acid added dropwise to the solution. The perchlorate was collected and recrystallized from methanol (charcoal).

To prepare the picrate instead of the perchlorate, the oil left after removing the concentrated hydrochloric acid was dissolved in ethanol and treated with ethanolic picric acid. Experimental data will be found in Tables I and II.

Acknowledgment.

This investigation was supported by Public Health Service Research Grant No. CA-05509 of the National Cancer Institute.

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Received September 27, 1965 Durham, North Carolina 27706