and heated under reflux for 22 hr. The solvent was removed to give 19 g. (32%), m.p. 150–154°. Recrystallization (ethanol) gave m.p. 158–159°.

Anal. Calcd. for $C_{14}H_{16}BrNO$: C, 57.2; H, 5.5; N, 4.8. Found: C, 57.4; H, 5.7; N, 5.1.

1-Phenethyl-2-piperidinemethanol hydrobromide. A mixture of 14 g. (0.048 mol.) of 2-hydroxymethyl-1-phenethylpyridinium bromide in 250 ml. of ethanol and 1.3 g. of 5% rhodium on carbon afforded complete uptake of hydrogen[1] after 3 hr. The catalyst was removed and the filtrate concentrated to dryness. Crystallization (ethanol-ether) gave 10 g., m.p. 153–154° and recrystallization (ethanol-ether) gave m.p. 157–158°.

Anal. Calcd. for $C_{14}H_{22}BrNO$: C, 56.0; H, 7.4; N, 4.7. Found: C, 56.3; H, 7.1; N, 4.9.

3-(3-Dimethylaminopropoxy)-1-ethylpiperidine (Compound 7). Sodium hydride (3.1 g., 0.13 mol.) was stirred under 50 ml. of dry toluene while a solution of 15.4 g. (0.12 mol.) of 1-ethyl-3-piperidinol in 50 ml. of toluene was added over 40 min. Stirring was continued at 20° for 2 hr. and then under reflux for 2 hr. This solution was treated over 1 hr. with the filtered solution prepared from 38.4 g. (0.24 mol.) of 3-dimethylaminopropyl chloride hydrochloride dissolved in water, made basic with 40% sodium hydroxide, extracted with 150 ml. of toluene and dried (magnesium sulfate). Reflux was continued for 6 hr. When cool, the mixture was filtered and the residue distilled to yield 9.8 g. (38%) of product, b.p. 116–118° (6 mm.).

3-(3-Dimethylaminopropoxy)-1-ethyl-1-methylpiperidinium iodide methiodide (Compound 8). Addition of 3.2 g. (0.015 mol.) of 3-(3-dimethylaminopropoxy)-1-ethylpiperidine in 10 ml. of acetonitrile to a cooled solution of 4.7 g. (0.033 mol.) of methyl iodide in 15 ml. of acetonitrile caused an immediate exothermic reaction. After 20 hr. the precipitated product (4.7 g.) was separated.

Acknowledgment. The authors wish to thank Dr. G. Ungar and his staff for the pharmacological results of the screening of the compounds and Mrs. T. Ast for technical assistance.

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6-Alkylacridizinium Derivatives[1]

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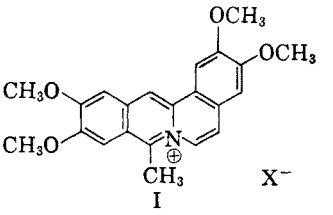
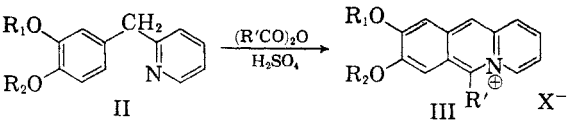
Probably the first reported compound containing the fully aromatic quinolizinium[2] nucleus was the Coralyn (I) of Schneider and Schroeter,[3,4] described in 1920. Coralyn, an 8-methyl-2,3,10,11-tetramethoxybenz[a]acridizinium salt was obtained in 90% yield by the action of sulfoacetic acid (acetic anhydride containing a small amount of sulfuric acid) on papaverine.



I

It seemed likely that 2-(3,4-dialkoxybenzyl)-pyridines (II) might be made to undergo a similar acylative cyclization, affording the first simple 6-alkylacridizinium salts III.



II III

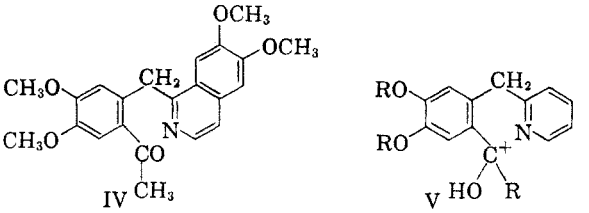
The requisite benzylpyridines (II) were prepared by reaction of 2-pyridyllithium with the appropriate aldehyde, followed by reduction of the crude carbinol. The acylative cyclization was carried out at 100° by means of sulfuric acid in a large excess of the appropriate anhydride, and the results are summarized in Table I.

TABLE I

6-ALKYL-8,9-ALKOXYACRIDIZINIUM SALTS (III)

R_1	R_2	R′	% Yield (as)	Ultraviolet Absorption Maxima, mμ (Perchlorate)		
CH_3	CH_3	CH_3	—[a]	368	382	401
C_2H_5	C_2H_5	CH_3	74[b](ClO_4)	370	384	404
C_2H_5	C_2H_5	C_2H_5	48[c]	370	385	405
—CH_2—		CH_3	25(Pic.)[d]			

[a] A 31% yield of sulfoacetate, m.p. 255–262° (dec.), was recorded, but this salt was never obtained in a state of analytical purity. [b] Product melting at 252–256° (dec.). [c] A part of the yield (25%) was obtained as the perchlorate m.p. 260–264° (dec.), the remainder (23%) as picrate, m.p. 188–192°. [d] No perchlorate of this compound was prepared.



IV V

Schneider and Schroeter[3] adduced evidence to show that the acetylative cyclization of papaverine occurred *via* acetopapaverine (IV). Probably the acylative cyclization of the 2-(3,4-dialkoxybenzyl)pyridine likewise occurs *via* a carbonyl derivative, or more exactly, *via* the conjugate acid V. The Coralyn synthesis can be regarded not only as the prototype of the Woodward synthesis of

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(2) *Chemical Abstracts* nomenclature.

(3) W. Schneider and K. Schroeter, *Ber.* **53B**, 1459 (1920).

(4) W. Schneider and O. Boger, *Ber.*, **54B**, 2021 (1921).

TABLE II

6-ALKYLACRIDIZINIUM SALTS, III

R_1	R_2	R′	M.P., °C.	Formula	C Calcd.	C Obsd.	H Calcd.	H Obsd.	N Calcd.	N Obsd.
				Picrates						
CH_3	CH_3	CH_3	239–241 (dec.)[a]	$C_{22}H_{18}N_4O_9$	54.80	55.02	3.76	3.91	11.62	12.04
C_2H_5	C_2H_5	CH_3	205–206[b]	$C_{24}H_{22}N_4O_9 \cdot {}^1/_2H_2O$	55.00	54.81	4.46	4.72	10.79	10.65
C_2H_5	C_2H_5	C_2H_5	197–199[c]	$C_{25}H_{24}N_4O_9$	57.25	57.43	4.62	4.92	10.69	10.50
—CH_2—		CH_3	235–236[d]	$C_{21}H_{14}N_4O_9$	54.09	54.03	3.03	3.19	12.01	11.99
				Perchlorates						
CH_3	CH_3	CH_3	288–291[e]	$C_{16}H_{16}ClNO_6$	54.10	54.39	4.57	4.59	3.86	4.32
C_2H_5	C_2H_5	CH_3	272–274[f]	$C_{18}H_{20}ClNO_6 \cdot 3/2H_2O$	52.98	53.13	5.67	5.72	3.44	3.68
C_2H_5	C_2H_5	C_2H_5	269–270[g]	$C_{19}H_{22}ClNO_6$	57.69	57.31	5.56	5.66	3.56	3.75

[a] Needles from acetone. [b] Well formed needles from acetone-ethanol. [c] Flakes from acetone-ethanol. [d] Granules from ethanol. [e] All of the perchlorates formed needles which melted with decomposition. [f] From acetone-water. [g] From acetone-ethanol.

quinolizinium derivatives,[5–8] but also a further example of aromatic cyclodehydration,[9] one involving electrophilic attack on aromatic nitrogen rather than the usual carbon.

EXPERIMENTAL[10]

2-(3′,4′-Methylenedioxybenzyl)pyridine (II) (R_1 — R_2 = —O—CH_2O—) was prepared essentially as in the case of the known 2-(3,4-dimethoxybenzyl)pyridine[11] (II, R_1 = R_2 = OCH_3). To a solution of butyllithium prepared from 30.5 g. of *n*-butyl chloride, and maintained at a temperature of −50°, 40 g. of 2-bromopyridine was added in dry ether. The reaction mixture was stirred for 15 min., and then 42.7 g. of piperonal in dry ether was added. The temperature of the mixture was maintained at 0° for 1 hr. longer, and then allowed to come to room temperature. The reaction mixture was poured into dilute acid, the acid layer separated and made basic, and the resulting oil taken up in ether. The ethereal solution was washed, dried and concentrated and the crude residue was used directly for the reduction. A solution of the residue in 300 ml. of benzene was cooled and treated with 38 g. of thionyl chloride, the temperature being kept below 25°. After the mixture had stood for an additional hour, it was made basic with sodium hydroxide solution. The benzene layer was separated, wahed, dried and concentrated. The residue was dissolved in 250 ml. of glacial acetic acid and while this was heated on the steam bath during a 6 hr. period, 36 g. of zinc powder was added in small portions. The excess zinc was removed by filtration, the acetic acid was evaporated under reduced pressure, and the residue made alkaline with sodium hydroxide. The oil which separated was taken up in ether, and the ethereal extract washed, dried and concentrated. The residue was fractionated yielding 13.2 g. (28%) of an oil, b.p. 185–196° (3 mm.).

A *picrate* was prepared for analysis as fine yellow granules from ethanol, m.p. 143–145°.

Anal. Calcd. for $C_{19}H_{13}N_4O_9$: C, 51.70; H, 2.97; N, 12.70. Found: C, 52.00; H, 3.59; N, 12.66.

2-(3′,4′-Diethoxybenzyl)pyridine (II, R_1 = R_2 = OC_2H_5). Essentially the same procedure was used except that the aldehyde was 3,4-diethoxybenzaldehyde. The yield of 2-(3′,4′-diethoxybenzyl) pyridine, b.p. 170–180°(3 mm.) was 12.5%.

The *picrate*, prepared for analysis, crystallized from ethanol as bright yellow clusters, m.p. 157–158°.

Anal. Calcd. for $C_{22}H_{22}N_4O_9$: C, 54.40; H, 4.56; N, 11.51. Found: C, 54.36; H, 4.84; N, 11.79.

Acetylative cyclization of the benzylpyridine derivatives. One gram of the benzylpyridine derivative (II) was dissolved in 20 ml. of acetic or propionic anhydride containing 0.8 ml. of concentrated sulfuric acid. The mixture was heated on the steam bath for 2 hr., after which it was cooled, and the salt precipitated by addition of ether. The organic solvents were separated from the salt either by filtration or decantation. The crude sulfoacetate salt was dissolved in water, and perchloric acid added to precipitate the product as a *perchlorate* salt which was crystallized from an acetone-ethanol mixture.

The *picrate* was prepared by addition of an alcoholic solution of picric acid to an aqueous solution containing the crude sulfoacetate salt. The results are summarized in Table II.

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(8) A. Richards and T. S. Stevens, *J. Chem. Soc.*, 3067 (1958).

(9) *Cf.*, C. K. Bradsher, *Chem. Revs.*, **38**, 447 (1946).

(10) All melting points were taken on a Fisher-Johns hot stage and are uncorrected. All analyses were by Micro Tech Laboratories, Skokie, Illinois.

(11) N. Sugiomoto, *J. Pharm. Soc. Japan*, **76**, 1045 (1956).

Benzo[*b*]quinolizidine Derivatives[1]

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It was shown earlier[2] that benzo[*b*]quinolizidine derivatives (I, R = H) can be produced by the catalylic reduction of the acridizinium nucleus. As part of a study of the relation between structure

(1) This investigation was supported by a research grant (H-2170) from the National Heart Institute of the National Institutes of Health.

(2) C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **77**, 4812 (1955).