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Acridizinium Betaines (1)

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The quaternary salts formed by reaction of tolyl sultone (2,1,3H-benzoxathiole-1,1-dioxide) with 2-(1,3-dioxolan-2-yl)- or 2-(2-methyl[1,3]dioxolan-2-yl)pyridine may be cyclized in acid to afford the betaines derived from 7-sulfo- and 7-sulfo-11-methylacridizinium hydroxides. Similarly 1-(1,3-dioxolan-2-yl)isoquinoline may be converted to the betaine of 9-sulfobenzo[a]acridizinium hydroxide.

The sodium salt of 2-(3'-sulfobenzoyl)pyridine may be quaternized with benzyl bromide and the resulting betaine cyclized to afford the betaine of 11-(3'-sulfophenyl)acridizinium hydroxide.

The only reported (2) acridizinium betaine, that of 9-sulfoacridizinium hydroxide, is remarkable for its stability (m.p. 401-402°). This betaine was prepared by cyclization of the compound afforded by the reaction of methyl *p*-(bromomethyl)benzenesulfonate with 2-(1,3-dioxolan-2-yl)pyridine (Ia).

It seemed possible that the use of tolyl sultone II (3) might afford a route to the betaine of 7-sulfoacridizinium hydroxide (IVa). It was found that 2-(1,3-dioxolan-2-yl)pyridine (4) was quaternized in 74% yield by heating it with tolyl sultone (II) on the steam bath, affording the uncyclized betaine (IIIa). Cyclization of IIIa in refluxing 48% hydrobromic acid was accomplished in 53% yield, and the new 7-sulfobetaine resembled closely the 9-isomer. The use of 2-[2-methyl(1,3)dioxolan-2-yl]pyridine (Ib) (4) led to a quaternary salt (IIIb) difficult to cyclize. Only a 26% yield of the sulfobetaine was obtained after heating IIIb for three hours in concentrated sulfuric acid at 100°.

No method was found to cyclize the quaternary salts (IIIc-e) obtained from 2-pyridyl phenyl, *p*-chlorophenyl and benzyl ketones. These salts (IIIc-e) did not appear to cyclize in concentrated sulfuric acid at 100°, while at 170-180° they appeared to undergo sulfonation. 1-(1,3-Dioxolan-2-yl)isoquinoline (5) served as the starting material for a successful preparation of the betaine (V) of 9-sulfobenzo[a]acridizinium hydroxide.

An 11-phenylacridizinium betaine with the sulfo group on the phenyl ring has been prepared starting with 2-benzoylpyridine. The sulfonation of 2-benzoylpyridine is easily carried out in 20% fuming sulfuric acid. The orientation of the sulfonic acid group in the product was demonstrated by quaternization of the sodium salt with methyl iodide, followed by catalytic reduction of the pyridine ring. The reduction product (VII) gave characteristic absorptions indicating the out-of-plane vibrations of three adjacent aromatic hydrogens, convincing evidence that the sulfonation of 2-benzoylpyridine occurs in the *meta* position of the phenyl ring. The sodium salt of 2-(3-sulfobenzoyl)pyridine was quaternized with benzyl bromide and the product cyclized in concentrated sulfuric acid to afford a 75% overall yield (from VI) of the betaine of 11-(3'-sulfophenyl)-acridizinium hydroxide (VIII).

EXPERIMENTAL

All elemental analyses were carried out by Ilse Beetz, Mikroanalytisches Laboratorium, Kronach, Germany, or Janssen Pharmaceutica, Beerse, Belgium. The melting points were determined in capillary tubes using the Mel-Temp apparatus. Ultraviolet absorption spectra were observed in 1 cm silica cells with a Cary Model 14 Spectrophotometer and, except as noted, 95% ethanol was used as a solvent. The infrared data were obtained using a Perkin-Elmer Model 237 Spectrophotometer by the potassium bromide pellet method.

Quaternization of Pyridyl Derivatives by Tolylsultone (II) (3).

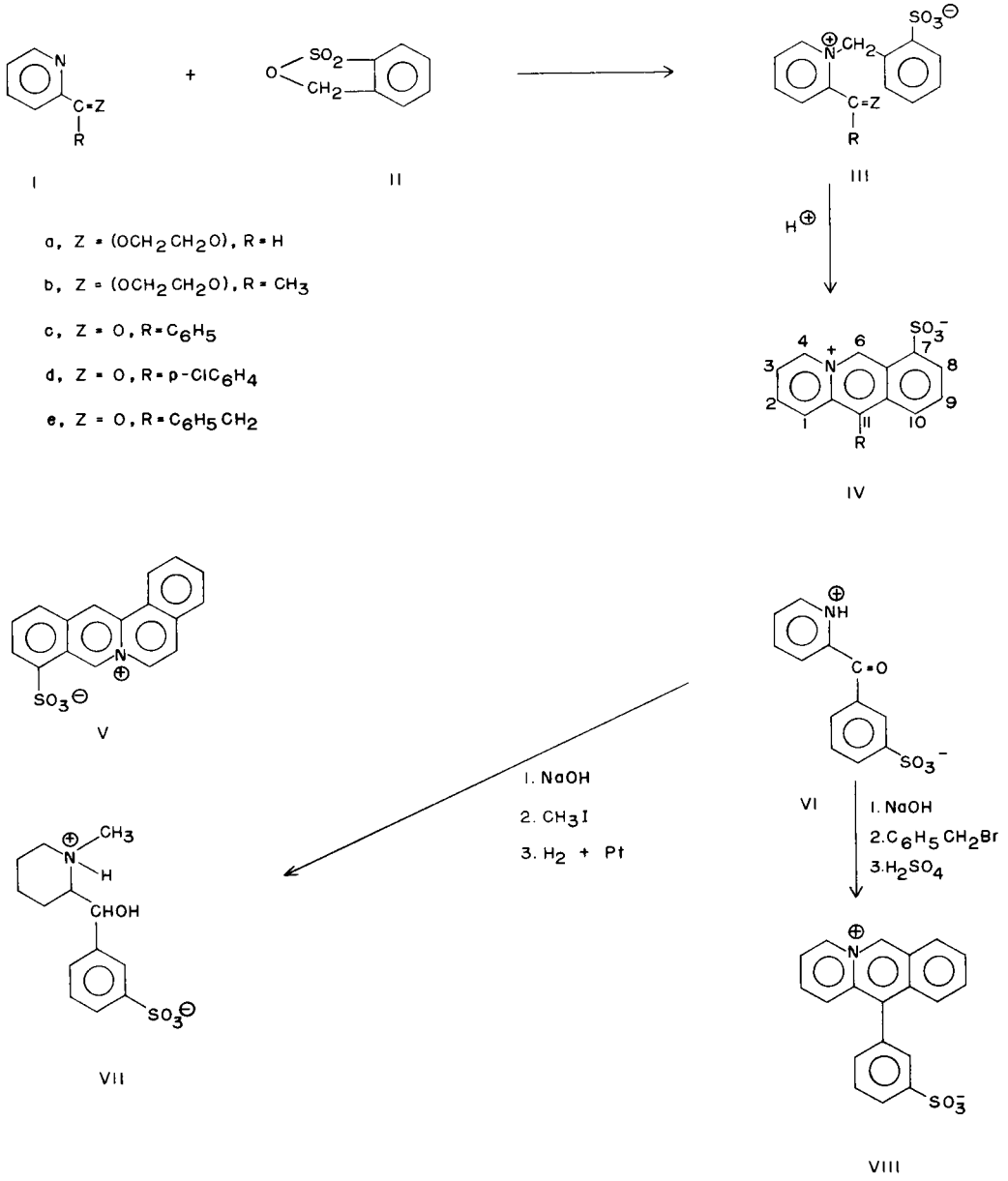
The tolyl sultone (II) was heated on the steam bath with an excess of a pyridine base I. All of the products (III) were colorless, were crystallized from methanol or methanol-ethyl acetate, and except as

TABLE I

Preparation of Sulfobetaines by Reaction of Bases with Tolyl Sultone at 100°

Base I	Excess Base, %	Time Hr.	Yield III, %	M.P.	Formula	C		H		N	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
a	60	0.7	74	261-263	$C_{15}H_{15}NO_5S$	56.06	56.17	4.71	4.61	4.36	4.59
b	0	2.0	75	236-238	$C_{16}H_{17}NO_5S$	57.30	57.39	5.11	5.28	4.18	4.46
c	20	19.0	92	235-236	$C_{19}H_{15}NO_4S$	64.57	64.21	4.28	4.32	3.96	3.90
d	10	24.0	44	258-260 (a)	$C_{19}H_{14}ClNO_4S$	58.84	58.59	3.64	3.49	3.61	3.95
e	30	17.0	51	252-253 (b)	$C_{20}H_{17}NO_4S$	65.38	65.62	4.67	5.10	3.81	4.02

(a) Plates. (b) Needles.



noted were obtained as a microcrystalline powder. The results are summarized in Table I.

Betaine of 7-Sulfoacridizinium Hydroxide (IV, R = H).

Refluxing 2.0 g. of the betaine of 1-(2'-sulfobenzyl)-2-(1,3-dioxolan-2-yl)pyridinium hydroxide (IIIa) for 21 hours in 48% hydrobromic acid, and removing the acid on the steam bath under reduced pressure, afforded a yellow solid. Crystallization of the solid from water yielded 0.92 g. (53%) of a yellow microcrystalline powder, m.p. > 400°, λ max (water), mμ (log ε) 208 (4.26), 248 sh (3.58), 270 (3.58), 358 (2.82), 375 (2.82), and 396 (2.78).

Anal. Calcd. for $C_{13}H_9NO_3S \cdot 1H_2O$: C, 56.30; H, 4.00; N, 5.05. Found: C, 56.16; H, 4.16; N, 5.38.

Betaine of 7-Sulfo-11-methylacridizinium Hydroxide (IV, R = CH_3).

Heating a solution containing 2.5 g. of the betaine of 2-(2'-sulfobenzyl)-2-[2-methyl(1,3)dioxolan-2-yl]pyridinium hydroxide (IIIb) in 20 ml. of sulfuric acid for 3 hours on the steam bath, then cooling in ice and pouring the solution into cold dry ether in an ice bath, yielded a yellow precipitate. The precipitate was collected on a filter, washed with ether and recrystallized from methanol-ethyl acetate, to afford 0.60 g. (27%) of yellow needles, m.p. 360-362°, λ max, mμ (log ε) 241 (3.78), 250 (3.75), 367 (3.28), 384 (3.34), 404 (3.30).

Anal. Calcd. for $C_{14}H_{11}NO_3S \cdot 2H_2O$: C, 54.36; H, 4.89; N, 4.53. Found: C, 54.24; H, 5.16; N, 4.73.

Attempted Cyclization of the Quaternary Salt (IIIc) from 2-Benzoylpyridine.

Concentrated sulfuric acid at 100° seemed to have little effect on the betaine of 1-(2'-sulfobenzyl)-2-benzoylpyridine (IIIc), but if 1.9 g. of the betaine was dissolved in 10 ml. of concentrated sulfuric acid and the mixture heated at 170° for 3 hours in a Wood's metal bath, the solution on cooling and pouring into ether, gave a new product. This product was collected, washed with ether and recrystallized from methanol-ethyl acetate affording 1.41 g. of a bright yellow powder, m.p. 333-337°. While the ultraviolet spectrum suggested that the compound was an acridizinium derivative, elemental analysis showed that it was not the expected betaine of 7-sulfo-11-phenylacridizinium hydroxide, but most likely a betaine having one additional sulfo group. Solutions of the substance were acidic to litmus and tests with barium chloride showed the bisulfate anion to be absent. The product was very hygroscopic and quite soluble in water. Similar results were obtained when the quaternary salts IIId and IIIe from 2-(*p*-chlorobenzoyl)pyridine or benzyl 2-pyridyl ketone were given the high temperature treatment with sulfuric acid.

Betaine of 1-(1,3-Dioxolan-2-yl)-2-(2'-sulfobenzyl)isoquinolinium Hydroxide.

The quaternization of 0.5 g. of 1-(1,3-dioxolan-2-yl)isoquinoline (5) with 0.5 g. of tolyl sultone (II) was carried out by refluxing for 48 hours in 5 ml. of reagent grade acetone. Evaporation of the solution and crystallization of the residue from methanol afforded 0.6 g. (65%) of a colorless microcrystalline powder, m.p. 246-247°.

Anal. Calcd. for $C_{19}H_{17}NO_5S$: C, 61.44; H, 4.61; N, 3.77. Found: C, 61.54; H, 4.46; N, 3.89.

Betaine of 9-Sulfobenzo[a]acridizinium Hydroxide.

One gram of tolyl sultone (II) was heated for 45 minutes on the steam bath with 1 g. of 1-(1,3-dioxolan-2-yl)isoquinoline without solvent. At the end of this period 15 ml. of 48% hydrobromic acid was added and the solution refluxed for 19 hours. The acid was removed under reduced pressure and the product crystallized from methanol-ethyl acetate to yield 0.48 g. (31%) of an orange microcrystalline powder, m.p. > 400°, λ max, mμ (log ε) 211 sh (3.73), 224 (3.87), 251 sh (3.80), 259 (3.91), 269 (3.92), 288 sh (3.96), 295 (4.02), 307 (4.10), 317 sh (3.91), 348 (3.51), 365 (3.63), 383 (3.84), 404 (3.97).

Anal. Calcd. for $C_{17}H_{11}NO_3S$: C, 66.00; H, 3.58; N, 4.53. Found: C, 65.81; H, 3.24; N, 4.36.

2-(3'-Sulfobenzoyl)pyridine (VI).

One gram of 2-benzoyl pyridine was dissolved in 10 ml. of 20% fuming sulfuric acid, cooled in an ice bath, and then permitted to stand at room temperature for one hour. The solution was poured into cold dry ether and the precipitate collected. The precipitate, washed with ether and recrystallized from ethanol-water, afforded 0.98 g. (68%) of a colorless microcrystalline substance, m.p. > 390°.

Anal. Calcd. for $C_{12}H_9NO_4S$: C, 54.74; H, 3.45; N, 5.32. Found: C, 54.46; H, 3.58; N, 5.35.

Betaine of 1-Methyl-2-(3'-sulfobenzoyl)pyridinium Hydroxide.

To 1.0 g. of 2-(3'-sulfobenzoyl)pyridine, dissolved in 50 ml. of methanol, 2.0 ml. of 10% sodium hydroxide solution was added. The solution was concentrated, and ethyl acetate added until the mixture became cloudy. The mixture was maintained at about -15° for 24 hours to permit precipitation of the sodium salt. The salt was dissolved in 8 ml. of tetramethylene sulfone at steam bath temperature, cooled to room temperature and 3 ml. of methyl iodide added. After six days at room temperature the solution was diluted with ethyl acetate and left for three hours at -15°. The precipitate was collected, washed with ethyl acetate, and recrystallized from isopropyl alcohol-water, affording 0.45 g. (43%) of colorless irregular needles, m.p. 343-344°.

Anal. Calcd. for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05. Found: C, 56.27; H, 4.11; N, 5.32.

1-Methylpiperidin-2-yl-3'-sulfophenylcarbinol (VII).

In a solution of 0.5 g. of the betaine of 1-methyl-2-(3'-sulfobenzoyl)-pyridinium hydroxide in 100 ml. of 95% ethanol, 50 mg. of platinum oxide was suspended, and the mixture hydrogenated for 24 hours at atmospheric pressure with magnetic stirring. The platinum was removed by filtration, and the resulting solution evaporated. The residue afforded 0.32 g. (62%) of colorless crystals which when heated above 150° were gradually converted into colorless foam.

Anal. Calcd. for $C_{13}H_{19}NO_4S \cdot {}^1/_4H_2O$: C, 53.86; H, 6.67; N, 4.83. Found: C, 53.97; H, 6.75; N, 4.86.

The infrared spectrum showed no significant absorption in the carbonyl region, but showed a primary absorption at 800 cm^{-1} and a secondary absorption at 720 cm^{-1} indicating 3-adjacent aromatic hydrogens (6).

Betaine of 11-(3-Sulfophenyl)acridizinium Hydroxide (VIII).

One gram of 2-(3'-sulfobenzoyl)pyridine was converted to its sodium salt as in the preparation of the 1-methylbetaine. The salt was dissolved in 5 ml. of tetramethylene sulfone, and 0.8 g. of benzyl bromide was added to the cooled solution. After 7 days, excess ethyl acetate was added, and the solution allowed to stand at -15° for 24 hours. The ethyl acetate was decanted from the colorless hygroscopic salt which was dissolved in 10 ml. of concentrated sulfuric acid. The sulfuric acid solution was heated on the steam bath for 12 hours then cooled and poured into cold dry ether, cooled in an ice bath. After the solution had stood for 12 hours at -15° the ether was decanted and the residue dissolved in water and treated with charcoal. The water was removed from the filtered solution, and the yellow residue crystallized from methanol-ethyl acetate. The product 0.95 g. (75%) was a yellow granular solid, m.p. > 400°, λ max, mμ (log ε) 244 (4.39), 366 (3.92), 384 (3.90), 405 (3.84).

Anal. Calcd. for $C_{19}H_{13}NO_5S$: C, 68.04; H, 3.91; N, 4.18. Found: C, 67.78; H, 4.05; N, 4.24.

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