

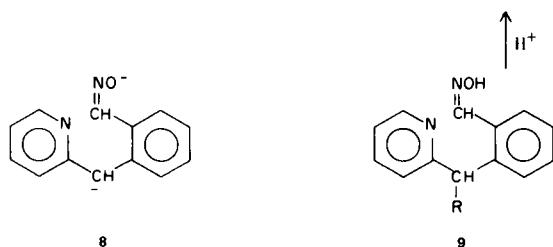
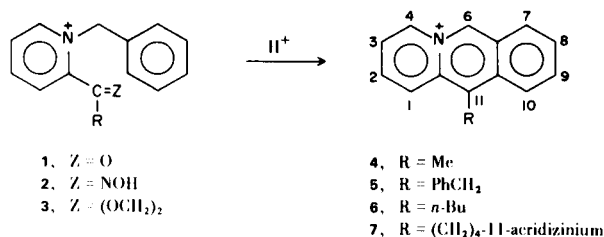
New Acridizinium Salts *via* Alkylation of a Dianion (1)

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The recent observation (2) that the rate of cycloaddition to the acridizinium ion is greatly enhanced by the presence of a methyl group at the 11 position has made it of interest to explore new methods for making 11-substituted derivatives. To date the only method reported for the synthesis of such salts has been the cyclization of the 1-benzyl salt (1) of a 2-pyridyl ketone or its derivatives. While the



quaternization of 2-benzoylpyridine and the subsequent cyclization took place in good yields, the quaternization of 2-acetopyridine occurred in very poor yield and the overall yield of 11-methylacridizinium salt was only 3% (3). It was found that the quaternization and cyclization of the oxime (2, R = CH₃) (4) and the ketal (3, R = CH₃) (5) gave higher overall yields (28 and 35%) but these modifications certainly left something to be desired in terms of yield and convenience.

It was known (6) that in the presence of hydroxylamine and bicarbonate ion the acridizinium nucleus is easily opened to afford 2-(2-oximidomethylbenzyl)pyridine (9, R = H) which is recycled readily when heated in acid. The observations of Hauser *et al.* (7) suggested that the

dianion (8) to be expected when the oxime was treated with two moles of sodium amide might be alkylated and the alkylation product (9) cyclized to afford 11-substituted acridizinium derivatives.

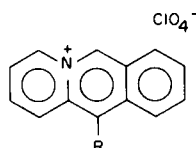
It was found that when the oxime (9, R = H) in dry tetrahydrofuran was added to a suspension of two equivalents of sodium amide in liquid ammonia a deep red color characteristic of such dianions (8) was formed. Rapid addition of benzyl chloride in dry ether caused a color change to light brown. The product of the reaction was an oil which could not be purified and instead was dissolved in hydrochloric acid and heated to effect cyclization. A 61% yield of 11-benzylacridizinium cation (5) was isolated (as the perchlorate) and was shown to be identical with a sample prepared earlier (9) in 5% overall yield *via* the ketal salt (3, R = PhCH₂). The perchlorate salt (5) seems to exist in two crystalline modifications of which only the lower melting and less stable modification was reported earlier.

Additional alkylation reactions were carried out using methyl iodide (41% yield) and butyl bromide (48% yield) (see Table I). Following the lead of Hauser (7) it was found that a two-fold alkylation could be accomplished leading to the bis compound (7).

Although several efforts were made to isolate alkylated oxime derivatives 9 no crystalline product was obtained. The possibility that oximido ethers were formed was explored by carrying out the reaction with only one equivalent of sodium amide. Under these circumstances the starting material (9, R = H) was recovered.

While the dianion (8) produced by the addition of two equivalents of sodium amide underwent alkylation by all pure halides investigated except benzhydryl chloride and 2-bromopyridine, it did not react with benzophenone, methyl benzoate or carbon dioxide. The dianion (8) could also be generated from the oxime (9, R = H) by addition of two equivalents of butyl lithium in tetrahydrofuran as evidenced by the production of the characteristic red color of the dianion and the observation that addition of deuterium oxide led to the recovery of oxime which from the nmr appeared to be 50% deuterated in the methylene position (9, R = D). The dilithio anion (8) was no more effec-

TABLE I

11-Substituted Acridizinium Perchlorates via Alkylation of **8** Followed by Cyclization

R	Yield, %	m.p. °C	Formula	C		H		N	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
Me	41	238-240 (a)	C ₁₄ H ₁₂ ClNO ₄						
PhCH ₂	61	246 (b)	C ₂₀ H ₁₆ ClNO ₄	64.95	64.88	4.37	4.18	3.79	3.60
<i>n</i> -Bu	48	206-207 (c)	C ₁₇ H ₁₈ ClNO ₄	60.80	60.63	5.41	5.44	4.17	3.97
CH ₂ CH ₂) ₂	26	> 300 (d)	C ₃₀ H ₂₆ Cl ₂ N ₂	74.22	73.97	5.41	5.51	5.77	5.58

(a) Reference **3** 243-244.5°, Reference **5** 240-241°. (b) Reference **9** 218-223°. After one recrystallization the m.p. was 223-225°, but upon a second recrystallization rose abruptly to 246°. Significantly the sample prepared earlier by Braun was now found to melt at 245° and to give an undepressed mixture m.p., nmr (trifluoroacetic acid) δ 5.15 (s, 2, CH₂). The ir spectra of the two samples were identical. (c) Nmr (DMSO-d₆) δ 3.67 (s, 2, CH₂), 1.7 (broad s, 4, CH₂), 1.00 t, 3, J = 6Hz, CH₃, uv max 233 m μ sh (log ϵ 4.44) 243 (4.62), 250 sh (4.56), 367 (3.87), 383 (3.93), 403 (3.83). (d) This was the chloride which was so insoluble it precipitated directly from the cyclization mixture; nmr (trifluoroacetic acid) 4.1 (broad s, 2 CH₂Ar) 2.4 (broad s, 2, CH₂); uv max 220 m μ (log ϵ 3.89), 237 (4.35), 247 (4.29), 367 (3.95), 383 (4.02), 403 (3.95).

tive than disodio anion in reaction with carbonyl derivatives, and in a single attempt at benzylation with benzyl chloride appeared to be much slower to react than the disodio anion.

EXPERIMENTAL

All analyses were performed by MWH Laboratories, Garden City, Michigan, 48135. The nmr spectra were obtained with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. Ultraviolet absorption spectra were determined using 1 cm quartz cells in a Beckman DB-G grating spectrometer. Melting points were taken in unsealed capillaries in the Thomas-Hoover melting point apparatus and are uncorrected. The tetrahydrofuran was distilled from lithium aluminum hydride immediately before use and the ether was dried over sodium.

Alkylation of 2-(2'-Oximidomethylbenzyl)pyridine (**9**, R = H).

A 500 ml. round-bottom, three-neck flask fitted with a glass mechanical stirrer, dry ice-acetone condenser (with sodium hydroxide drying tube) and gas inlet was half filled with distilled liquid ammonia. The inlet tube was replaced by a stopper and a small sliver of sodium metal, enough to give a persistent blue color was added. Two crystals of hydrated ferric nitrate, each about 1 mm. in diameter were added. The blue color of the solution was converted to yellow. Then 0.76 g. of sodium was added and the blue color initially formed turned to gray after stirring for 10-20 minutes.

A solution of the oxime (**9**, R = H) in 100 ml. of dry tetrahydrofuran was added from a stoppered dropping funnel with pressure-balancing side arm. Formation of the dianion (**8**) was indicated by the deep red color. Thirty minutes was allowed for the formation of the dianion after which 0.033 mole of the halide in 25-50 ml. of dry ether was added. During the 30 minutes allowed for the reaction the red color of the reaction mixture turned to an opaque brown.

The dry ice condenser was replaced by an air condenser and ether added to the reaction mixture as the ammonia was evaporated by careful warming. Water (50 ml.) was added and the mixture transferred to a separatory funnel. The ethereal extract was dried (magnesium sulfate) and concentrated, but the residual oil could not be crystallized.

The oil presumably **9**, R = alkyl was dissolved in 10% hydrochloric acid and the mixture heated on the steam bath. Usually the product was precipitated as the perchlorate salt which crystallized as yellow crystals from acetonitrile-ether.

Formation of the Dianion (**8**) by Reaction of Butyllithium with the Oxime (**9**, R = H).

To a solution of 2.12 g. (0.01 mole) of 2-(2'-oximidomethylbenzyl)pyridine in 100 ml. of dry tetrahydrofuran maintained under a dry nitrogen atmosphere 14.6 ml. of a 1.5 M solution (0.022 mole) of butyllithium was added. While the red color of the dianion formed at once an additional 30 minutes was allowed before addition of reagents.

When the above preparation was allowed to react with 1.38 g. (0.011 mole) of benzyl chloride the red color of the dianion still persisted after 4 hours. The mixture was neutralized with 10% hydrochloric acid and cyclized as before giving a crude yield of only 12% of 11-benzylacridizinium perchlorate as compared with a crude yield of 83% obtained by the sodium amide procedure.

The dilithio salt **8** failed to react with benzophenone, methyl benzoate or solid carbon dioxide.

A similar preparation of the dilithio anion was quenched with deuterium oxide resulting in the recovery of oxime in which one of the methylene protons was deuterated (**9**, R = D); nmr (DMSO-d₆) δ 4.30 (s, 1, CDH).

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(1) This research was supported by Public Health Service research grant No. CA 05509 of the National Cancer Institute of the

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