[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

A Synthesis of the 4-Methyldehydroquinolizinium Ion and Related Compounds[1]

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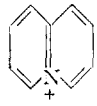
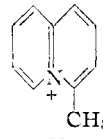
The method of synthesis for the dehydroquinolizinium ion has been extended and shown to be useful for a simple alkyl analog, the 4-methyldehydroquinolizinium ion. Methods for the dehydrogenation of quinolizinium derivatives have been improved.

In connection with another investigation we have had need of certain simple derivatives of the dehydroquinolizinium ion (I) and recently we reported on a synthesis of this interesting heterocyclic system.[2] Because of current interest in the alkyl and benzo analogs of I,[3,4] we should like to record at this time an extension of our method giving the 4-methyldehydroquinolizinium ion (II) as well as certain improvements in the final dehydrogenation step of this method.

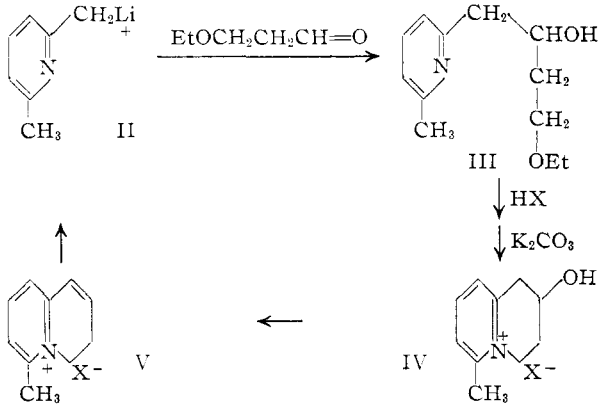


I



II

As illustrated, when 2,6-lutidyllithium was allowed to react with β-ethoxypropionaldehyde, the corresponding carbinol III was produced in 50% yield. Treatment of III with either hydriodic or hydrobromic acid followed by neutralization gave directly the corresponding cyclic quaternary halide IV which by the action of acetic anhydride containing a drop of sulfuric acid was converted in quantitative yield to V. The final step, the dehydrogenation of V, proved to be unsatisfactory following the procedure used previously but was eventually accomplished in 42% yield by means of a platinum catalyst in nitrobenzene as solvent.



The spectra and chemical properties of the final product are clearly in accord with the assigned structure II. First isolated as its picrate derivative, II was readily converted to the corresponding water-soluble bromide salt by passage over an appropriate ion-exchange column. In Table I the absorption maxima in the ultraviolet for 4-methyldehydroquinolizinium picrate are compared with those of dehydroquinolizinium picrate. With allowance for a bathochromic shift due to the methyl group, it can be seen that the spectrum of II duplicates very closely the complicated spectrum of the parent compound.

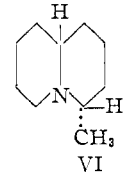
TABLE I

ABSORPTION MAXIMA OF PICRATES[a]

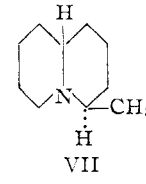
Dehydroquinolizinium (I) μ (log ε)	4-Methyldehydroquinolizinium (II) μ (log ε)
226 (4.47)	230 (4.49)
285 (3.68)	290 (3.77)
311 (4.18)	317 (4.22)
318 (4.12)	330 (4.40)
324 (4.38)	333 (4.18)

[a] In ethanol as solvent.

To establish the carbon skeleton of II it was shown that catalytic hydrogenation resulted in the uptake of five moles of hydrogen and gave 4-methylquinolizidine. Leonard and Nicolaides[5] have separated the two racemic picrates of 4-methylquinolizidine and have found their melting points to be 182–184° and 191–193°, respectively. Through comparison of infrared spectra and mixed melting point determinations, the identity of the picrate of our hydrogenation product with that of the higher melting picrate of 4-methylquinolizidine was established. If the assumption is made that the catalytic hydrogenation of 4-methyldehydroquinolizinium ion proceeds in a *cis* fashion, the racemate of 4-methylquinolizidine corresponding to the higher melting picrate can be assigned structure VI and the isomer from the lower melting picrate the alternate structure VII.



VI



VII

In the first attempts to effect dehydrogenation of V, it was found that little or none of the desired product II was being produced under the conditions used previously for obtaining the dehydroquinolizinium ion (I) from 3H,4H-quinolizinium iodide (VIII). It became necessary therefore to devote some study to the improvement of the dehydrogenation step and this was carried out with the more readily available 3H,4H-quinolizinium ion rather than with V. Details of this study are to be found

(1) Supported by the Office of Ordnance Research, Army Ordnance Contract No. DA-30-115-O.R.D.-421.

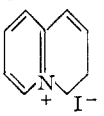
(2) V. Boekelheide and W. G. Gall, THIS JOURNAL, **76**, 1832 (1954).

(3) T. S. Stevens, *Chemistry & Industry*, 905 (1954).

(4) C. K. Bradsher and L. E. Beavers, THIS JOURNAL, **77**, 453 (1955); *Chemistry and Industry*, 1395 (1954).

(5) N. J. Leonard and E. D. Nicolaides, *ibid.*, **73**, 5210 (1951).

in the Experimental section, but the results can be summarized as follows. Of the chemical methods of dehydrogenation tried with VIII, selenium dioxide, N-bromosuccinimide and chloranil all gave an impure product in very low yield. Treatment of VIII with bromine to form the 1,2-dibromo derivative followed by dehydrohalogenation with collidine gave I in 21% yield. The catalytic dehydrogenation of VIII over palladium-on-charcoal was investigated with the bromide, iodide and picrate salts and of these the picrate salt proved to be the most convenient and satisfactory to use. Catalytic dehydrogenation of the picrate salt of VIII in boiling butanol gave I in 34% yield, an appreciable improvement over previous experiments.[2]



VIII

Oxidation of VIII, as its picrate derivative, was tried using molecular oxygen over platinum as catalyst. With either acetic acid or nitrobenzene as solvent consistent yields of about 25% of a clean product resulted. Quite possibly this method could be improved further.

Experimental[6]

4-Ethoxy-1-(6-methyl-2-pyridyl)-2-butanol (III).—This was prepared following the general procedure of Walter for 1-(α-pyridyl)-2-propanol.[7] From 50 g. of β-ethoxypropionaldehyde and 0.5 mole of 2,6-lutidyllithium, there was obtained 33.0 g. (47%) of a pale yellow oil, b.p. 135–137° at 3 mm., $n^{20}D$ 1.5009.

Anal. Calcd. for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.84; H, 9.16; N, 6.97.

2-Hydroxy-6-methyl-1,2-dihydro-3H,4H-quinolizinium Iodide (IV).—A solution of 19.0 g. of III in 100 ml. of hydriodic acid (47%) was boiled under reflux for 4 hours. Concentration of the solution under reduced pressure gave about 40 g. of a viscous yellow gum which was dissolved in water, neutralized with 10% potassium carbonate solution, and extracted with chloroform. Removal of the chloroform *in vacuo* gave a yellow oil which, when it did not crystallize, was taken up in an ethanol–ethyl acetate mixture. From this there separated 16.2 g. (61%) of cream-colored needles, m.p. 165–170°. Recrystallization from the same solvent mixture gave needles, m.p. 174–175°.

Anal. Calcd. for $C_{10}H_{14}NOI$: C, 41.24; H, 4.85; N, 4.81. Found: C, 41.47; H, 4.90; N, 4.89.

The bromide of IV was obtained from III in a similar manner using 48% hydrobromic acid and was isolated as colorless needles, m.p. 174–175°, in 53% yield.

Anal. Calcd. for $C_{10}H_{14}NOBr$: C, 49.19; H, 5.78; N, 5.74. Found: C, 49.18; H, 5.84; N, 5.69.

The picrate of IV was prepared in ethanol from the bromide salt of IV and obtained as yellow needles, m.p. 172–173°.

Anal. Calcd. for $C_{16}H_{16}N_4O_8$: C, 48.98; H, 4.11. Found: C, 48.81; H, 4.21.

6-Methyl-3H,4H-quinolizinium Iodide (V).—A solution of 3.0 g. of 2-hydroxy-6-methyl-1,2-dihydro-3H,4H-quinolizinium iodide (IV) in 17 ml. of acetic anhydride containing one drop of sulfuric acid was boiled under reflux for 5 minutes. When the solution was cooled and 30 ml. of ethyl acetate was added, there separated 2.75 g. (98%) of yellow needles, m.p. 196.5–198.5°. A sample for analysis, after recrystallization from absolute alcohol containing a drop of hydriodic acid, melted at 204–205°.

Anal. Calcd. for $C_{10}H_{12}NI$; C, 43.96; H, 4.40; N, 5.13. Found: C, 44.05; H, 4.51; N, 5.16.

The bromide of V was obtained in a similar fashion and equal yield from the bromide of IV. This, on recrystallization from an ethanol–ethyl acetate mixture gave colorless needles, m.p. 198–199°.

Anal. Calcd. for $C_{10}H_{12}NBr$: C, 53.11; H, 5.36; N, 6.20. Found: C, 53.05; H, 5.52; N, 6.52.

The picrate of V was prepared in ethanol from the corresponding bromide salt and obtained as yellow needles, m.p. 134.5–135.5°.

Anal. Calcd. for $C_{16}H_{14}N_4O_7$: C, 51.34; H, 3.74. Found: C, 51.24; H, 3.99.

4-Methyldehydroquinolizinium Picrate (II).—A solution of 250 mg. of 6-methyl-3H,4H-quinolizinium picrate in 7 ml. of nitrobenzene containing 50 mg. of prereduced platinum oxide catalyst was boiled under reflux for one hour under a nitrogen atmosphere. After removal of the catalyst, the cold reaction mixture was diluted with 100 ml. of benzene. A tarry precipitate formed which was removed and then the solution was diluted with an additional 120 ml. of ether and allowed to stand. There was collected 105 mg. (42%) of yellow crystals, m.p. 131–133°. Recrystallization from water yielded golden needles, m.p. 135–135.5°. A mixture of these crystals and the picrate of V (m.p. 134.5–135.5°) showed a large depression of melting point.

Anal. Calcd. for $C_{16}H_{12}N_4O_7$: C, 51.62; H, 3.25. Found: C, 51.67; H, 3.33.

Hydrogenation of 4-Methyldehydroquinolizinium Bromide.—A solution of 310 mg. of 4-methyldehydroquinolizinium picrate in 35 ml. of methanol was passed over an ion exchange column (Amberlite IRA-400) to convert it to the corresponding bromide salt. The eluate was concentrated and the residual solid (170 mg.) was taken up in 25 ml. of absolute ethanol and subjected to hydrogenation at room temperature and atmospheric pressure using platinum oxide (50 mg.) as catalyst. Absorption of the expected 5 moles of hydrogen was complete in 7 hours. After removal of the catalyst and solvent, the crystalline hydrobromide salt remaining was dissolved in ethanol and converted in excellent yield to the corresponding picrate, m.p. 188–190°. After recrystallization from ethanol this gave yellow crystals, m.p. 191–193°. A mixture of this with an authentic sample of the higher melting picrate of 4-methylquinolizidine (m.p. 192–194°)[8] showed no depression of melting point; also the infrared spectra of the two samples were identical.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.25; H, 5.80. Found: C, 50.32; H, 5.91.

2-Hydroxy-1,2-dihydro-3H,4H-quinolizinium Bromide.—The conversion of 4-ethoxy-1-(α-pyridyl)-2-butanol[2] to 2-hydroxy-1,2-dihydro-3H,4H-quinolizinium bromide was carried out as described above for the preparation of the bromide salt of IV. The bromide salt was obtained in 42% yield as colorless needles, m.p. 169–170°, after recrystallization from an ethanol–ethyl acetate mixture.

Anal. Calcd. for $C_9H_{12}NOBr$: C, 46.97; H, 5.26; N, 6.09. Found: C, 47.21; H, 5.43; N, 6.28.

3H,4H-Quinolizinium Bromide (VIII).—The dehydration of 2-hydroxy-1,2-dihydro-3H,4H-quinolizinium bromide was carried out as described in the preparation of V. The product was obtained in quantitative yield as colorless needles, m.p. 207–208°, after recrystallization from an ethanol–ethyl acetate mixture.

Anal. Calcd. for $C_9H_{10}NBr$: C, 50.96; H, 4.75; N, 6.61. Found: C, 51.08; H, 4.82; N, 6.91.

The picrate of VIII was obtained from ethanol as yellow flakes, m.p. 133–133.5°.

Anal. Calcd. for $C_{15}H_{12}N_4O_8$: C, 50.00; H, 3.36. Found: C, 49.89; H, 3.39.

1,2-Dibromo-1,2-dihydro-3H,4H-quinolizinium Iodide.—To a solution of 104 mg. of 3H,4H-quinolizinium iodide[2] in 2 ml. of acetic acid there was added dropwise with shaking 3.3 ml. of a 2% solution of bromine in acetic acid. There separated from solution 145 mg. (86%) of an orange solid (m.p. 139–140°) after which recrystallization from ethanol gave orange plates, m.p. 141.5–142.5°.

Anal. Calcd. for $C_9H_{10}NBr_2I$: C, 25.80; H, 2.41. Found: C, 25.74; H, 2.42.

A suspension of 600 mg. of 1,2-dibromo-1,2-dihydro-3H,4H-quinolizinium iodide in 5 ml. of γ-collidine was

(6) Microanalyses by Miss A. Smith; spectra determined by Mr. Carl Whiteman.

(7) L. A. Walter, *Org. Syntheses*, **23**, 83 (1943).

(8) V. Boekelheide and S. Rothchild, THIS JOURNAL, **71**, 879 (1949).

heated on a steam-bath for one-half hour. The solid, which separated, was removed, washed with ether and recrystallized from ethanol. Although the first crop of crystals was mainly collidine hydrobromide, concentration of the mother liquor followed by addition of ethyl acetate caused the separation of 75 mg. (21%) of yellow crystals, m.p. 206–212°, as expected for dehydroquinolizinium iodide. A sample of these crystals was converted to the corresponding picrate, m.p. 179–180°, alone or mixed with an authentic sample of dehydroquinolizinium picrate.

Dehydrogenation of the 3H,4H-Quinolizinium Ion.—The results of many experiments on the dehydrogenation of the 3H,4H-quinolizinium bromide, iodide and picrate salts can be summarized: (a) N-bromosuccinimide led to the introduction of bromine and the product on treatment with triethylamine gave the dehydroquinolizinium ion (I) in 6% yield; (b) selenium dioxide gave I in 3% yield; (c) chloranil gave I in 10% yield, (d) molecular oxygen with a reduced platinum catalyst was effective in either acetic acid or nitrobenzene as solvent giving I in yields of 23 to 26%.

The most satisfactory method thus far developed, however, was that using palladium-on-charcoal as follows. A solution of 800 mg. of 3H,4H-quinolizinium picrate in 60 ml. of *n*-butyl alcohol containing 160 mg. of a 10% palladium-on-charcoal catalyst was boiled under reflux for three hours. After the hot reaction mixture had been filtered to remove tarry impurities, the filtrate on cooling deposited 450 mg. of crude yellow crystals. These after recrystallization from ethanol gave 270 mg. (34%) of yellow needles, m.p. 180–181°.

Anal. Calcd. for $C_{15}H_{10}N_4O_7$: C, 50.28; H, 2.81. Found: C, 50.26; H, 2.94.

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[CONTRIBUTION FROM THE CHEMISTRY DIVISION, U. S. NAVAL ORDNANCE TEST STATION]

The Acidity of Nitroguanylhydrazones

BY RONALD A. HENRY, JOHN E. DE VRIES AND ROBERT H. BOSCHAN

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Acid dissociation constants for several nitroguanylhydrazones, $RCH{=}NNHC(NH_2){=}NNO_2$, have been determined spectrophotometrically; some salts have also been prepared. The products obtained in the methylation of potassium benzalnitroaminoguanidine lend support to the belief that these hydrazones exist in the nitrimino form.

The pK_a for nitroaminoguanidine, $NH_2NHC(NH_2){=}NNO_2$, was found to be 10.47 when determined by a potentiometric method,[1] and 10.60 when determined by a spectrophotometric method.[2] The acid dissociation constants for several nitroguanylhydrazones have now been measured in aqueous solution at room temperature by the spectrophotometric method. The results are summarized in Table I. These compounds are approximately 100 times more acidic than nitroaminoguanidine. The dissociation constants for the substituted benzalnitroaminoguanidines indicate a decreasing acidity with increasing electropositive character of the group; however, the pK_a's do not correlate linearly with Hammett's σ-values for groups.

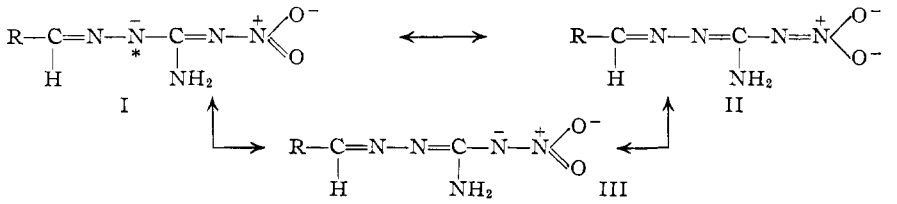
If one assumes that the nitroguanylhydrazones, like nitroaminoguanidine, exist primarily in the nitrimino form,[1,3] then the following structures contribute to the resonance hybrid for the conjugate base

TABLE I

DISSOCIATION CONSTANTS FOR NITROGUANYLHYDRAZONES

Hydrazone derived from	λ_{max}, mμ	pK_a
Acetone	285	8.60
Cyclohexanone	287	8.80
Phenylacetaldehyde	285	8.50
Cinnamaldehyde	338	8.28
Benzaldehyde	317	8.38
2-Hydroxybenzaldehyde	342	8.50
2-Methoxybenzaldehyde	338	8.70
4-Methoxybenzaldehyde	332	8.83
4-Methylbenzaldehyde	322	8.80
4-Isopropylbenzaldehyde	323	8.90
4-Dimethylaminobenzaldehyde	363	9.2 ± 0.25[a]

[a] Substantially the same value was obtained using a small secondary peak at 273 mμ. This value is considerably less precise than the others because the peak height change on going from *p*H 6.0 to 13 is not sharp, and in the 363 mμ region is complicated by the gradual shift of the peak maximum to lower wave lengths.



The stability of this anion is increased over the one derived from nitroaminoguanidine through the additional conjugation permitted by forms II and III; consequently, the hydrazones should be more acidic. In the case of the aryl derivatives the stability of the anion could be further increased by conjugation into the benzene ring. However, since the alkyl hydrazones are almost as acidic as the aryl derivatives, one has to conclude either that conjugation with the benzene ring exerts only a small influence or that hyperconjugation with the alkyl groups is causing an effect equal to that of the benzene resonance. Electropositive *ortho* and *para* substituents in the benzalnitroaminoguanidines could exert an acid weakening effect by such resonance forms as

(1) W. D. Kumler and P. P. T. Sah, *J. Org. Chem.*, **18**, 669 (1953).
(2) J. E. De Vries and E. S. C. Gantz, THIS JOURNAL, **76**, 1008 (1954).
(3) W. D. Kumler and P. P. T. Sah, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 375 (1952).