The Reaction of Amines with 1-Phenacyl-2-bromopyridinium Salts. A New Route to Imidazo[1,2-*a*]pyridinium, Oxazolo[3,2-*a*]pyridinium, and Dihydropyrido[2,1-*c*]-*as*-triazinium Salts[1]

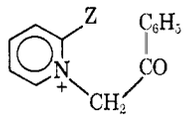
C. K. BRADSHER, R. D. BRANDAU, J. E. BOLIEK, AND T. L. HOUGH

Department of Chemistry, Duke University, Durham, North Carolina 27706

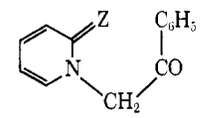
Received October 29, 1968

The reaction of 2-bromo-1-phenacylpyridinium bromide (**1**) with arylamines, acethydrazide, or butylamine leads to 1-substituted imidazo[1,2-*a*]pyridinium salts (**10**). If the reaction with butylamine was interrupted, two intermediates, 1-butyl-2-hydroxy-2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridinium (**7**, R = Bu) bromide and a 2-phenyloxazolo[3,2-*a*]pyridinium salt (**9**) were isolated. With tertiary amines the latter (**9**) became the major product. With hydrazine or methylhydrazine, 3-phenyl-1,4-dihydropyrido[2,1-*c*]*as*-triazinium ion (**13**) or its 1-methyl homolog (**15**) were obtained, while with 1,2-dimethylhydrazine the product was the 1,2-dimethyl-3-phenyl-1,2-dihydropyrido[2,1-*c*]triazinium ion (**19**). In boiling acid **19** loses a methyl group from the nitrogen at the 2 position affording **15**. In boiling acid 3-phenyl-1,4-dihydro[2,1-*c*]-*as*-triazinium ion (**13**) undergoes ring contraction to 1-amino-2-phenylimidazo[1,2-*a*]pyridinium ion (**22**).

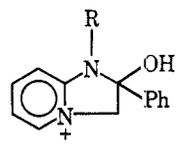
In a recent paper[2] it was shown that 2-bromo-1-phenacylpyridinium salts (**1**) and certain analogs are convenient starting materials for the synthesis of 2-substituted thiazolo[3,2-*a*]pyridinium salts (**8**) *via* cyclization of the intermediate 1-phenacyl-2-pyridinethiones (**5**). Since it is known that 1-phenacyl-2-pyridone (**6**)



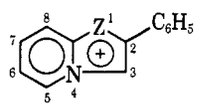
1, Z = Br
2, Z = NHR
3, Z = H
4, Z = Cl



5, Z = S
6, Z = O



7

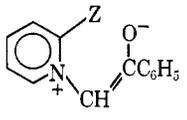


8, Z = S
9, Z = O
10, Z = NR

and its analogs may be cyclized to oxazolo[3,2-*a*]pyridinium salts (*e.g.*, **9**),[3] and since 2-alkylamino-1-phenacylpyridinium salts (**2** or **7**) must be converted readily to imidazo[1,2-*a*]pyridinium salts (**10**),[4] it seemed reasonable to expect that **1**·Br might serve also as a convenient starting material for the preparation of both the oxazolo- (**9**) and imidazopyridinium (**10**) systems. The present research, dealing with the reaction of **1** with amines, was directed toward the synthesis of imidazo-[1,2-*a*]pyridinium salts (**10**).

When 2 equiv of *n*-butylamine was added to a suspension of 2-bromo-1-phenacylpyridinium bromide (**1**) in anhydrous acetonitrile, the solution turned yellow and the reaction proceeded with sufficient vigor to cause boiling of the solvent. It was also evident from the ultraviolet absorption spectra that a change had occurred. After the mixture had been refluxed for 14 hr, 1-butyl-2-phenylimidazo[1,2-*a*]pyridinium cation (**10**, R = Bu) was obtained in 66% yield. If the reaction was interrupted after only 10 min of refluxing, two products were isolated. The first of these, obtained in smaller yield, was identified as 2-phenyloxazolo[3,2-*a*]-pyridinium ion (**9**), while the second product, isolated in 47% yield, had the properties expected for 1-butyl-2-hydroxy-2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridinium (**7**, R = Bu) bromide, the ring tautomer of 2-(butylamino)-1-phenacylpyridinium bromide (**2**, R = Bu). The butyl derivative (**7** or **2**, R = Bu) readily underwent dehydration to yield 1-butyl-2-phenylimidazo[1,2-*a*]pyridinium cation.

The isolation of 2-phenyloxazolo[3,2-*a*]pyridinium perchlorate (**9**), even though in a yield of only 11%, was very interesting in that strictly anhydrous conditions had been used, making it clear that the oxygen atom of the new heterocyclic ring originated from the carbonyl function of the phenacylpyridinium salt (**1**). Kröhnke[5] has shown that when phenacylpyridinium bromide (**3**) and suitable analogs are treated with weak bases such as sodium carbonate, orange-red betaines (*e.g.*, **12**) are



11, Z = Br
12, Z = H

formed and can actually be isolated and purified. It has been reported[6] that a cautious attempt to extend the reaction to 2-chloro-1-phenacylpyridinium ion led to the formation of 1-phenacyl-2-pyridone (**6**). Compound **9** is probably formed by the nucleophilic attack of the enolate oxygen of **11** on the carbon at position **2**. The failure to isolate any of the oxazolo[3,2-*a*]pyridinium salt when the reaction was allowed to proceed for 14 hr is understandable since 2-phenyloxazolo[3,2-*a*]-pyridinium ion (**9**) apparently undergoes ring opening when heated with butylamine. Better yields of the oxazolopyridinium salt (**9**) were obtained when tertiary amines were substituted for butylamine, triethylamine (68% yield of **9**) proving superior to the less basic dimethylaniline (51% yield of **9**).

(1) This research was supported by Public Health Service Grants No. HE-2170 of the National Heart Institute and No. CA-05509 of the National Cancer Institute.

(2) C. K. Bradsher and J. E. Boliek, *J. Org. Chem.*, **32**, 2409 (1967).

(3) (a) C. K. Bradsher and M. F. Zinn, *J. Heterocyclic Chem.*, **1**, 219 (1964); (b) *ibid.*, **4**, 66 (1967).

(4) C. K. Bradsher, E. F. Litzinger, Jr., and M. F. Zinn, *ibid.*, **2**, 331 (1965).

(5) F. Kröhnke, *Ber.*, **68**, 1177 (1935).

(6) F. Kröhnke and W. Heffe, *ibid.*, **70B**, 864 (1937).

TABLE I

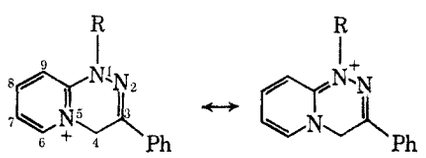
1-ARYL-2-PHENYLIMIDAZO[1,2-*a*]PYRIDINIUM (10, R = ARYL) PERCHLORATES

10, R[a]	Reflux time, hr	Yield, %	Mp, °C	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
C_6H_5	9	75	226–228[b–d]	$C_{19}H_{15}ClN_2O_4$	61.54	61.42	4.07	4.18	7.55	7.55
p-$NO_2C_6H_4$	7	58	208–210[e,f]	$C_{19}H_{14}ClN_3O_6$	54.88	54.54	3.39	3.62	10.11	10.18
p-HOC_6H_4	18	62	201–202[c,f]	$C_{19}H_{15}ClN_2O_5$	59.00	58.85	3.91	3.93	7.24	7.36
p-$EtOOCC_6H_4$	4.5	64	213–215[c,f]	$C_{22}H_{19}ClN_2O_6$	59.66	59.66	4.32	4.47	6.33	6.50
α-$C_{10}H_7$	4	66	196–227[f,g]	$C_{23}H_{17}ClN_2O_4$	65.64	65.22	4.07	4.12	6.66	6.42

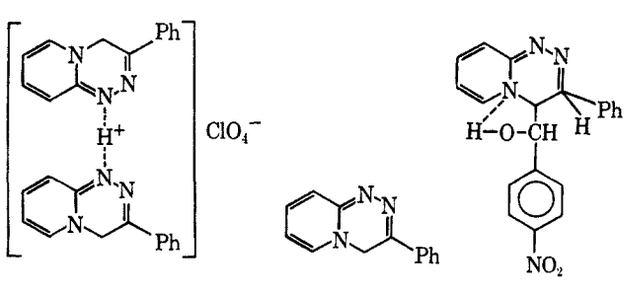
[a] See structure **10**. [b] The nmr spectrum in heavy water showed no resonance below δ 7.78 ppm. [c] Colorless prisms. [d] From methanol–ethyl acetate. [e] Pale yellow prisms. [f] From methanol. [g] Light purple prisms.

The reaction of aniline with **1** bromide is much less vigorous than that of butylamine, and the reaction mixture lacks the color to be expected of the enolate salt **11**. If the reaction mixture was refluxed for 4 hr, 1,2-diphenylimidazo[1,2-*a*]pyridinium (**10**) ion (as the perchlorate) was obtained in 75% yield. It is believed significant that no 2-phenyloxazolo[2,3-*a*]pyridinium salt (**9**) has been isolated from the reaction of aniline and its derivatives with **1**·Br, especially since it was demonstrated that the oxazolopyridinium salt **9** is recovered unchanged after heating with aniline under the usual reaction conditions. The reaction shown by aniline appears general for arylamines and, as may be seen in Table I, the yields are not greatly different whether electron-releasing or electron-attracting groups are present.

It would be anticipated that hydrazine could lead to the formation of either a new five-membered or six-membered ring. It was found that reaction of hydrazine or methylhydrazine with **1**·Br gave products which, on the basis of spectral evidence, must be six-ring compounds, 3-phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (**13**) perchlorate, or its 1-methyl homolog (**15**), respectively.



13, R = H
14, R = $COCH_3$
15, R = CH_3



16 **17** **18**

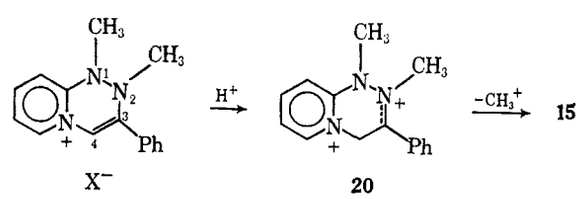
For the hydrazine derivative **13** the only nmr signal outside the aromatic region was a two-proton singlet at δ 5.52 ppm (CH_2). The positive charge of the new system is shared principally by the nitrogen atoms at positions 1 and 5, and it is not surprising that the proton on the nitrogen at position 1 is acidic. When **13** was treated with sodium bicarbonate, the yellow compound which precipitated was not the expected base **17**, but a compound having the composition of 1 mole of the base **17** plus 1 mole of the salt **13**. Acidification of the compound salt gave back the original simple salt **13**. It is proposed that in the compound salt 1 mole of the base **17** is hydrogen bonded to 1 mole of the salt **13**, the arrangement being symmetrical with respect to the 1 position, the unit positive charge being spread over both of the moities **16**. Similar structures have been discussed in a recent publication.[7]

If sodium hydroxide was added to an aqueous solution of the simple salt **13**, the product was the free base, 3-phenyl-4H-pyrido[2,1-*c*]-*as*-triazine (**17**). The nmr spectrum of the base exhibited a two-proton singlet at δ 4.81 and a total of nine protons in the aromatic region. Significantly, equimolecular quantities of the base **17** and the simple salt **13** unite to form the compound salt **16**.

The base **17** underwent acetylation or methylation with ease, presumably at position 1. The products, **14** and **15** when treated with bicarbonate did not afford a precipitate, and both exhibited nmr spectra with the characteristic downfield signals due to the presence of methylene groups. The methyl derivative was identical with the product **15** prepared by the reaction of methylhydrazine with **1**·Br.

In addition to the methylation and acetylation reactions at position 1, the base **17** reacted at position 4 with *p*-nitrobenzaldehyde. The nmr spectrum of the product **18** had a pair of one-proton doublets centered at δ 5.90 and 5.10. A broad absorption band at 2400–2750 cm^{-1} in the infrared spectrum of **18** suggested hydrogen bonding between the bridgehead nitrogen atom and the hydroxylic hydrogen.

With 1,2-dimethylhydrazine, **1**·Br gave a derivative of the 1,2-dihydro system, 1,2-dimethyl-3-phenyl-1,2-dihydropyrido[2,1-*c*]-*as*-triazinium ion (**19**). The system was easily protonated at the 4 position, for although nmr in dimethyl sulfoxide shows signals for ten hydrogen atoms in the aromatic region (with methyl signals as singlets at δ 3.51 and 2.80 ppm), the nmr in trifluoroacetic acid showed signals for only nine hydrogen atoms



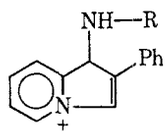
19 **20** **15**

(7) H. F. Andrew and C. K. Bradsher, *J. Heterocyclic Chem.*, **3**, 282 (1966). Crystallographic evidence for the existence of such symmetrical hydrogen bonds in potassium hydrogen malonate has been published recently: C. Ferguson, J. G. Sime, J. C. Speakman, and R. Young, *Chem. Commun.*, 162 (1968).

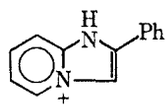
in the aromatic region plus a new two-proton singlet at δ 5.69 ppm. On heating **19** with 16% hydrobromic acid, a methyl group was lost, affording **15** isolated as the perchlorate.

The loss of a methyl group from a nitrogen atom, uncommon except with some quaternary salts, is at least partially explicable in that the protonated species **20** is essentially a bis quaternary salt.

1,1-Dimethylhydrazine reacted as a tertiary amine with **1**·Br, affording the oxazolopyridinium salt **9** as the only product isolated.



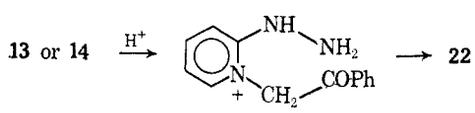
21, R = CH_3CO
22, R = H



23

Of the hydrazine derivatives studied only acetylhydrazide afforded an imidazopyridinium derivative (**21**) directly. Hydrolysis of the amide linkage afforded 1-amino-2-phenyl-imidazopyridinium bromide (**22**). The nmr of the amine **22** in trifluoroacetic acid showed signals in the aromatic region only and reaction of the amine with nitrous acid afforded the deamination product, 2-phenylimidazo[1,2-*a*]pyridinium ion (**23**), isolated as the perchlorate. The identity of the corresponding base was established by comparison with an authentic sample.[8]

It is worthy of note that **22** could also be made by ring contraction of **13**, brought about by heating it in hydrobromic acid.



24

Experimental Section

Elemental analyses were carried out by the Janssen Pharmaceutica, Beerse, Belgium, and by Galbraith Laboratories, Knoxville, Tenn. All melting points have been corrected. Ultraviolet absorption spectra were measured in 95% ethanol using 1-cm matched quartz cells in a Cary Model 14 spectrophotometer. Infrared data were determined in potassium bromide pellets using a Model 137 or Model 237 Perkin-Elmer spectrophotometer. Nmr data was determined with a Varian A-60 spectrometer using tetramethylsilane as the standard.

1-Butyl-2-hydroxy-2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridinium (7, R = Bu) Bromide.—To a suspension of 3.57 g of 2-bromo-1-phenacylpyridinium bromide[9] (**1**) in about 70 ml of anhydrous acetonitrile (distilled from P_2O_5) 2.02 g (2 equiv) of *n*-butylamine was added (exothermic reaction).

After refluxing the yellow solution for 10 min, concentration under vacuum gave a viscous red gum which was partitioned between methylene chloride and water. Addition of sodium perchlorate solution to the aqueous layer produced a colorless precipitate which, on crystallization from methanol–ethyl acetate, afforded 0.32 g (11%) of 2-phenyloxazolo[3,2-*a*]pyridinium (**9**),[3] mp 216–218°. The methylene chloride layer was dried ($MgSO_4$) and concentrated and the residue was crystallized from methanol–ethyl acetate yielding in two crops 1.65 g (47%) of colorless plates, mp 149–150°, with a strong blue fluorescence under uv light. The ir showed no strong band in the 1660–1800-cm^{-1} region (carbonyl stretching);[10] λ_{max} [mμ (log ϵ)] 333 (3.70), 241 (4.19), and 203 (4.46).

Anal. Calcd for $C_{17}H_{21}BrN_2O$: C, 58.42; H, 6.06; N, 8.02. Found: C, 58.23; H, 6.04; N, 8.13.

If the oxazolo compound **9** was heated for 2.75 hr with 5 equiv of butylamine, the product was impure **7** (ir spectra).

1-Butyl-2-phenylimidazo[1,2-*a*]pyridinium Perchlorate (10, R = Bu). A. By Dehydration of 1-Butyl-2-hydroxy-2-phenyl-2,3-dihydroimidazo[1,2-*a*]pyridinium (7, R = Bu) Bromide.—A mixture of 0.25 g of the carbinolamine bromide (**7**, R = Bu) and 10 g of polyphosphoric acid was heated with stirring on a steam bath. The mixture was cooled and diluted with ice water and excess 35% perchloric acid solution was added. The resulting precipitate was crystallized from methanol–ethyl acetate giving 0.19 g (76%) of colorless crystals, mp 93–96°. The analytical sample had mp 98.5–100°.

B. From 2-Bromo-1-phenacylpyridinium Bromide (1).—If the reaction of 7.14 g of the title compound **1** with butylamine was carried out as in the preparation of the carbinolamine **7** bromide except that refluxing was continued for 14 hr, 4.4 g (66%) of 1-butyl-2-phenylimidazo[1,2-*a*]pyridinium ion was isolated as the perchlorate, mp 99–101°. This was identical in infrared spectrum and in mixture melting point with the product obtained in A; ν_{max} 2800–3000 cm^{-1} (aliphatic C–H stretch); nmr (trifluoroacetic acid), δ 4.01 (t, 2, CH_2, J = 7 cps), 0.2–1.6 (seven remaining Bu protons), 6.9–8.3 (10 aromatic H); λ_{max} 288 mμ (log ϵ 4.15), 228 (4.32), 204 (4.51).

Anal. Calcd for $C_{17}H_{19}ClN_2O_4$: C, 58.20; H, 5.46; N, 7.98. Found: C, 58.44; H, 5.57; N, 7.83.

2-Phenyloxazolo[3,2-*a*]pyridinium (9) Perchlorate by Action of Tertiary Amines on 1.—The addition of 1.01 g of triethylamine to a suspension of 1.79 g of **1** in 50 ml of dry acetonitrile produced an orange-red solution which was refluxed for about 3 hr, the mixture being protected from contact with moisture. Addition of the cool solution to 250 ml of anhydrous ether yielded a pink precipitate which was collected and dissolved in water. Addition of 35% perchloric acid to the aqueous solution afforded **9** which was crystallized from ethanol–ethyl acetate as colorless needles, mp 216–218°, yield 1.0 g (68%).

When the above procedure was repeated using N,N-dimethylaniline in the place of triethylamine and continuing refluxing for 6 hr, 0.75 g (51%) of **9**, mp 216–218°, was obtained.

1-Aryl-2-phenylimidazo[1,2-*a*]pyridinium (10, R = Aryl) Perchlorates.—There was no color change or exothermic reaction when **1**·Br was added to an acetonitrile solution of an arylamine (2 equiv). After a 14-hr reflux, the cooled mixture was poured into ether and the resulting precipitate was dissolved in water and reprecipitated ($HClO_4$) as the perchlorate (see Table I).

3-Phenyl-1,4-dihydropyrido[2,1-*c*]*as*-triazinium (13) Bromide.—Hydrazine hydrate (2 equiv) was refluxed for 14 hr in acetonitrile with **1**·Br. When the mixture reached room temperature it was filtered to remove a small quantity of by-product and solution was concentrated *in vacuo*. The residue crystallized from ethanol–ethyl acetate as hydrated yellow needles, mp 214–215°.

Anal. Calcd for $C_{13}H_{12}BrN_3 \cdot 0.5H_2O$: C, 52.17; H, 4.40; N, 14.04. Found: C, 51.77; H, 4.45; N, 14.37.

A sample of the salt, crystallized from water as yellow needles, appeared to be the **monohydrate**, mp 125–126°.

Anal. Calcd for $C_{13}H_{12}BrN_3 \cdot H_2O$: C, 50.66; H, 4.58; N, 13.63. Found: C, 50.82; H, 4.73; N, 13.41.

Recrystallization of the hydrate from ethanol afforded the higher melting hemihydrate salt as needles, mp 214–215°.

Addition of sodium perchlorate solution to a hot solution of the bromide precipitated the **perchlorate** which crystallized from methanol–ethyl acetate as colorless needles: mp 199–200°; nmr (trifluoroacetic acid), δ 5.52 (s, 2, CH_2), 7.38–8.39 (ten protons); uv max, 360 mμ (log ϵ 3.99), 293 (4.02), 243 sh (3.96), 223 sh (4.08), 202 (4.36); ν_{max} 2600–3600 cm^{-1} (acidic H bonded to N).

Anal. Calcd for $C_{13}H_{12}ClN_3O_4$: C, 50.41; H, 3.91; N, 13.57. Found: C, 50.35; H, 3.91; N, 13.85.

3-Phenyl-4H-pyrido[2,1-*c*]-*as*-triazine (17).—To a hot solution of 2.0 g of 3-phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (**13**) perchlorate in 20 ml of water, 3 ml of 50% aqueous sodium hy-

(8) A. E. Tschitschibabin, *Ber.*, **59**, 2048 (1926).
(9) C. Djerassi and G. R. Pettit, *J. Amer. Chem. Soc.*, **76**, 4470 (1954).

(10) Although there is a possibility that the molecule exists in the open-chain form (**2**, R = Bu), and that hydrogen bonding has shifted the absorption due to the carbonyl group to a frequency low enough for it to merge with the band due to the C=N linkage, it is felt that the cyclic carbinolamine structure **7** is more probable.

droxide solution was added with stirring. The dark oil which separated solidified on cooling and was crystallized from a 10% aqueous solution of methanol as yellow needles. When dried at 80°, 1.2 g (92%) of orange-red needles was obtained; mp 222–223°; nmr ($CDCl_3$), δ 4.81 (s, 2, CH_2), 6.15–7.9 (nine protons).

Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.59; H, 5.49; N, 19.94.

Compound Salt 16. A. By Action of Bicarbonate Ion on 3-Phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (13) Perchlorate.—To a hot solution of 0.5 g of the triazinium salt **13** in water, 10 ml of saturated sodium bicarbonate solution was added. On cooling, yellow needles separated and were collected and recrystallized from methanol–ethyl acetate. The product, 0.25 g (56%), had mp 197–199° dec; ν_{max} 3400 cm^{-1} (N–H bonding); λ_{max} 360 mμ (log ε 4.25), 302 (4.16), 252 (4.28), and 206 (4.58).

B. By Addition of an Equimolecular Quantity of the Triazine Base 17 to the Triazinium Salt 13.—To a solution of 0.20 g of the triazinium salt **13** in 20 ml of methanol 0.13 g of the base **17** in 20 ml of methanol was added. Upon concentration to approximately 15 ml followed by cooling, 0.30 g (91%) of the compound salt, mp 197–199° crystallized. This material was shown by mixture melting point and ir spectra to be identical with the preparation A.

Anal. Calcd for $C_{26}H_{23}N_6ClO_4$: C, 60.17; H, 4.47; N, 16.20. Found: C, 60.42; H, 4.72; N, 16.20.

Addition of a few drops of perchloric acid to a methanol solution of the compound salt **16** followed by precipitation with ether gave back 3-phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (**13**) perchlorate in 84% yield.

1-Aceto-3-phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (14) Perchlorate. A. By Acetylation of the Bromide Salt (13).—A suspension of 4.5 g of 3-phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (**13**) bromide in 100 ml of acetic anhydride was refluxed for 5 hr then the anhydride was removed under reduced pressure. The residual gum was crystallized from methanol–ethyl acetate as colorless needles: mp 206–208°; nmr (D_2O), δ 2.48 (s, 3, CH_3), 5.37 (s, 2, CH_2), 7.17–8.60 (nine aromatic H).

Anal. Calcd for $C_{15}H_{14}N_3OBr$: C, 54.23; H, 4.25; N, 12.65. Found: C, 53.91; H, 4.28; N, 12.40.

The **perchlorate** crystallized from ethanol–ethyl acetate as colorless needles: mp 228–230°; uv max 203.5 mμ (log ε 4.23), 223 sh (4.02), 245.5 sh (3.87), 255.5 sh (3.83), 292 (4.01), 360 (3.99).

B. By Acetylation of the Triazine Base 17.—To a sample of the base in anhydrous chloroform a few drops of acetyl chloride was added. The mixture was refluxed for 15 min and then concentrated. Addition of perchloric acid to an aqueous solution of the residue afforded a product identical in ir spectrum and melting point with the perchlorate salt prepared by method A.

Anal. Calcd for $C_{15}H_{14}ClN_3O_5$: C, 51.22; H, 4.01; N, 11.95. Found: C, 51.35; H, 4.05; N, 11.47.

Deacetylation of 1-Aceto-3-phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (14) Bromide.—A solution of **14** in 50 ml of 5% hydrobromic acid was allowed to stand for 8 hr at room temperature. The yellow monohydrate of **13**·Br, mp 125–126° crystallized from the solution. Recrystallization of the hydrate from ethanol afforded the higher melting hemihydrate as needles, mp 214–215°, yield 0.5 g (72%).

3-Phenyl-4-(α-hydroxy-4′-nitrobenzyl)pyrido[2,1-*c*]-*as*-triazine (18).—A mixture containing 0.8 g of the triazine base **17** and 0.6 g of *p*-nitrobenzaldehyde in 20 ml of chloroform was refluxed for 24 hr. The filtered solution was concentrated and the residue was crystallized from methanol as golden needles: mp 184–185°; yield 1.2 g (85%); nmr (trifluoroacetic acid), δ 5.80 (d, 1, J = 2.5 Hz, CH) 6.60 (d, 1, J = 2.0 Hz, CH), plus aromatic protons; ν_{max} 2400–2750 cm^{-1} (H bonding to N).

Anal. Calcd for $C_{20}H_{16}N_4O_3$: C, 66.66; H, 4.48; N, 15.55. Found: C, 66.31; H, 4.49; N, 15.26.

1-Methyl-3-phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (15) Perchlorate. A. By Methylation of the Triazine Base 17.—Excess methyl iodide was added to a chloroform solution of the triazine base **17** and the mixture refluxed for 10 min. The precipitate was collected and crystallized from methanol–ethyl acetate. The product (0.6 g) was dissolved in water and 70% perchloric acid was added. The resulting perchlorate crystallized from ethanol as yellow needles: mp 188°; nmr (DMSO-d_6), δ 3.72 (s, 3, CH_3), 5.48 (s, 2, CH_2), 7.33–8.42 (complex, 9); nmr (trifluoroacetic acid), δ 3.37 (s, 3, CH_3), 4.86 (s, 2, CH_2), 6.75–8.15 (complex 9).

B. From Methylhydrazine.—Following the general procedure used for the preparation of 1-arylimidazopyridinium salts (**10**) but using methylhydrazine instead of arylamine, the product **15**, obtained in 90% yield, was identical in melting point and ir spectrum with that prepared by procedure A.

Anal. Calcd for $C_{14}H_{14}N_3ClO_4$: C, 51.94; H, 4.36; N, 12.98. Found: C, 51.86; H, 4.29; N, 12.99.

1,2-Dimethyl-3-phenyl-1,2-dihydropyrido[2,1-*c*]-*as*-triazinium (19) Perchlorate.—To a suspension of 1.79 g of **1** in 50 ml of dry acetonitrile 1.33 g of 1,2-dimethylhydrazine dihydrochloride and 1.01 g of triethylamine was added and the mixture refluxed for 14 hr. The solution was concentrated to 20 ml and the salts were removed by filtration. Concentration of the filtrate under vacuum and reprecipitation of the residue from water as the perchlorate produced an orange solid which, crystallized from ethanol, had mp 210–211°; yield 1.1 g (69%); nmr (DMSO-d_6), δ 2.80 (s, 3, CH_3), 3.51 (s, 3, CH_3), 7.38–8.53 (complex 10); nmr (CF_3COOH), 3.80 (s, 3, CH_3), 3.99 (s, 3, CH_3), 5.69 (s, 2, CH_2), 7.3–8.5 (complex 9).

Anal. Calcd for $C_{15}H_{16}ClN_3O_4$: C, 53.33; H, 4.77; N, 12.44. Found: C, 53.25; H, 4.76; N, 12.54.

Loss of a Methyl Group from 1,2-Dimethyl-3-phenyl-1,2-dihydropyrido[2,1-*c*]-*as*-triazinium (19) Perchlorate.—A suspension of 0.20 g of the title compound **19** in 10 ml of 16% hydrobromic acid was heated at 100° for 12 hr, then 70% perchloric acid was added to the cooled solution. The resulting precipitate crystallized from ethanol as yellow needles, mp 188°, yield 0.18 g (94%). The product was shown to be 1-methyl-3-phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium perchlorate (ir, mixture melting point).

Reaction of 1,1-Dimethylhydrazine with 2-Bromo-1-phenylpyridinium Bromide.—When the title reagents were allowed to react in refluxing acetonitrile under essentially the same conditions used with hydrazine to produce **13**, the product, isolated in 41% yield, was **9** perchlorate, mp 216–218°.

1-Acetamido-2-phenylimidazo[1,2-*a*]pyridinium (21) Bromide.—A solution containing 1.79 g of **1**·Br and 0.74 g of acetylhydrazide in 50 ml of acetonitrile was refluxed for 15 hr, and the salt precipitated with ether and was recrystallized from methanol–ethyl acetate as colorless needles; mp 303° dec; yield 1.45 g (87%); nmr (D_2O), δ 3.08 (s, 3, CH_3CO), 8.39–9.73 (ten, aromatic).

Anal. Calcd for $C_{15}H_{14}BrN_3O$: C, 54.23; H, 4.25; N, 12.65. Found: C, 53.98; H, 4.37; N, 12.61.

The **perchlorate** crystallized from ethanol–ethyl acetate as colorless needles: mp 178–180°; uv max (95% EtOH), 204 mμ (log ε 4.47), 233.5 (4.37), 294.5 (4.01).

Anal. Calcd for $C_{15}H_{14}ClN_3O_5$: C, 51.22; H, 4.01; N, 11.95. Found: C, 50.94; H, 4.16; N, 11.61.

1-Amino-2-phenylimidazo[1,2-*a*]pyridinium (22) Perchlorate. A. By Hydrolysis of 1-Acetamido-2-phenylimidazo[1,2-*a*]pyridium (21) Bromide.—The aceto derivative **21** (1.45 g) was heated for 20 hr on a steam bath with 25 ml of 16% hydrobromic acid. The product was precipitated by addition of 35% perchloric acid and recrystallized from ethanol–ethyl acetate as colorless needles, mp 193–194°, yield 0.94 g (61%).

B. By Hydrolysis and Rearrangement of 1-Aceto-3-phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (14) Bromide.—If **14** (1.45 g) was subjected to the same conditions used in the hydrolysis of the isomer **21**, 1.06 g (68%) of colorless needles was obtained mp 193–194°.

C. By Rearrangement of 3-Phenyl-1,4-dihydropyrido[2,1-*c*]-*as*-triazinium (13) Bromide.—The title compound (1.50 g) was heated in acid under conditions used in the hydrolysis of the aceto derivatives **14** and **21**; yield 0.83 g (52%) of colorless needles: mp 193–194°; uv max (95% ethanol), 205 mμ (log ε 4.49), 234.5 (4.35), 293 (4.12); nmr (CF_3COOH), δ 7.23–8.74 (ten, vinyl and aromatic). Products obtained by methods A, B, and C were shown to be identical by ir and mixture melting points.

Anal. Calcd for $C_{13}H_{12}ClN_3O_4$: C, 50.41; H, 3.91; N, 13.57. Found: C, 50.43; H, 4.05; N, 13.60.

Action of Nitrous Acid on 1-Amino-2-Phenylimidazo[1,2-*a*]-pyridinium (22) Perchlorate.—To a solution of 1 g of **22** in 12 ml of 8 *N* sulfuric acid at 0° a sodium nitrite solution was added dropwise until there was a positive test for nitrous acid, then 70% perchloric acid was added to the cold solution until precipitation was complete. The precipitate crystallized from acetone–water as colorless needles, mp 169–170°, yield 0.7 g 77%. The composition was approximately that expected for **2-phenylimidazo[1,2-*a*]pyridinium perchlorate.**

Anal. Calcd for $C_{13}H_{11}ClN_2O_4$: C, 52.99; H, 3.76; N, 9.51. Found: C, 53.45; H, 3.92; N, 9.47.

Addition of sodium hydroxide to an aqueous solution of the product afforded a fluorescent colorless crystalline compound, mp 134–135°, which by ir spectra and mixture melting point was shown to be identical with an authentic sample[8] of 2-phenylimidazopyridine.

Registry No.—**7** (R = Bu) bromide, 19770-05-9; **9** perchlorate, 13794-84-8; **10** (R = Bu) perchlorate, 19770-06-0; **10** (R = Ph) perchlorate, 19770-07-1; **10** (R = p-$NO_2C_6H_4$) perchlorate, 19789-58-3; **10** (R = p-HOC_6H_4) perchlorate, 19770-08-2; **10** (R = $EtOOCC_6H_4$) perchlorate, 19770-09-3; **10** (R = α-$C_{10}H_7$) perchlorate, 19770-10-6; **13** bromide, 19770-11-7; **13** perchlorate, 19770-12-8; **14** bromide, 19770-13-9; **14** perchlorate, 19770-14-0; **15** perchlorate, 19770-15-1; **16**, 19770-16-2; **17**, 19770-17-3; **18**, 19770-18-4; **19** perchlorate, 19770-19-5; **21** bromide, 19770-20-8; **21** perchlorate, 19770-21-9; **22** perchlorate, 19770-22-0; **23**, 19770-23-1.

The Synthesis of Oxiranes from Aqueous Solutions of Simple Alkyl, Allyl, and Benzylsulfonium Salts[1a]

MELVIN J. HATCH[1b]

Physical Research Laboratory, Dow Chemical Company, Midland, Michigan

Received December 3, 1968

The reaction of simple sulfonium salts with warm aqueous NaOH and carbonyl compounds yields various oxiranes (epoxides). Previously, oxirane syntheses from such sulfonium salts has been achieved only in nonaqueous solutions of much stronger bases. The present work shows that often sufficient sulfonium ylide is formed in aqueous bases to permit trapping reactions. Trimethyl- or triethylsulfonium chlorides gave oxiranes with benzaldehyde (*ca.* 70%). No oxiranes were formed with formaldehyde nor acetaldehyde, since Cannizzaro or aldol condensation reactions apparently intervened. Allyldimethylsulfonium chloride reacted well with benzaldehyde (*ca.* 70% oxirane), poorly with formaldehyde (8%), and not at all with acetaldehyde. A side reaction, leading to propylene oxide, also occurred. Benzyldimethylfonium chloride gave oxiranes with both benzaldehyde and formaldehyde (85 and 87%) and, under conditions of minimal exposure to NaOH, with acetaldehyde also (48%).

Previous workers have described the formation of ylides from alkyl- or benzylsulfonium ions in *nonaqueous* solutions of very strong bases, *e.g.*, methylsulfinyl carbanion in dimethyl sulfoxide,[2] and the reaction of the unstable ylides with aldehydes or ketones to yield oxiranes.[2-5] However, the prospects appeared to be questionable for using *aqueous* solutions in this synthetic reaction of simple[6] sulfonium salts. Thus, the reaction in water of unsubstituted benzyldimethylsulfonium ion and hydroxide ion was known to give only a high yield of benzyl alcohol by an apparent SN2 mechanism.[7] This result indicated that even with the extra ylide stabilization conveyed by the phenyl group, the aqueous ylide concentration was very small, too small at least to yield any carbene and resulting olefin.[8]

The present investigation originated from the following idea. Although in aqueous NaOH, simple sulfonium ylides could be present only in concentrations so small that no olefin-producing carbene intermediate would be produced, *the ylide concentration still might be sufficient for "trapping" reactions to occur with reactive carbonyl compounds.* Preliminary experimental results

$$RCH_2\overset{+}{S}(CH_3)_2\ \bar{O}H \rightleftharpoons \bar{R}C\overset{+}{H}S(CH_3)_2 + H_2O$$

$$\bar{R}C\overset{+}{H}S(CH_3)_2 + R'COR'' \longrightarrow RCH(O)CR'R'' + S(CH_3)_2$$

indeed demonstrated that such trapping reactions are possible, and that synthetically useful yields of oxiranes might be achieved. Studies therefore were made to explore the scope and limitations of the reactions.

The experimental conditions generally were similar. Excess aqueous NaOH (50% solids) was added to a warm, stirred mixture of aqueous sulfonium salt, carbonyl compound, and (usually) an immiscible solvent. After reaction times which ranged from a few minutes to several hours at 70–80°, the immiscible solvent (or distillate) was analyzed for oxirane content by use of a pyridine–pyridine–hydrochloride mixture,[9] and product epoxide was then further isolated and/or characterized.

Reaction of Trialkylsulfonium Salts.—Even trialkylsulfonium salts were sufficiently acidic to react in

(1) (a) This work was reported at the 22nd Annual Southwest Regional Meeting of the American Chemical Society, Albuquerque, N. M., Nov 1966. (b) Chemistry Department, New Mexico Institute of Mining and Technology, Socorro, N. M. 87801.

(2) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

(3) E. J. Corey and W. O. Oppolzer, *ibid.*, **86**, 1899 (1964). One may note that this oxirane synthesis bears obvious analogy to the classical Darzen glycidic ester synthesis.

(4) A. W. Johnson, V. J. Hruby, and J. L. Williams, *ibid.*, **86**, 918 (1964).

(5) (a) V. Franzen and H. E. Fruessen, *Chem. Ber*, **96**, 1881 (1963). (b) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, pp 328–337, gives a review of the reaction. This author (p 2) also suggests the term "ylid," rather than "ylide."

(6) In this article, simple sulfonium salts are considered to be those containing only alkyl, allyl, or benzyl groups which have no substituents or at least have no strongly electron-withdrawing substituents.

(7) C. G. Swain and E. R. Thornton, *J. Amer. Chem. Soc.*, **83**, 4033 (1961).

(8) Previously known to exist in water were sulfonium ylides in which the carbanionic center is stabilized considerably by conjugation to electron-withdrawing groups in *addition* to the adjacent sulfonium center. (These, then, were nonsimple sulfonium ylides.) Thus, dimethylsulfonium fluorenylide was prepared in aqueous solution by C. K. Ingold and J. A. Jessop, *J. Chem. Soc.*, 713 (1930), and this stabilized ylide could react with certain carbonyl compounds, at least in nonaqueous solution, to yield epoxides, as shown by A. W. Johnson and R. B. LaCount, *J. Amer. Chem., Soc.*, **83**, 417 (1961). Dimethylsulfonium p-nitrobenzylide in aqueous solution was suggested as a reaction intermediate which led to the carbene and corresponding stilbene in the work of Swain and Thornton.[7] This contrasted with their above-cited results from unsubstituted benzylsulfonium ion. The phenyl group would provide far less stabilization of a carbanionic center than would the p-nitrophenyl group, of course.

(9) F. E. Critchfield, "Organic Functional Group Analysis," Pergamon Press, Inc., New York, N. Y., 1963, pp 133–136. This method is only semiquantitative with some disubstituted oxiranes. It will give 10–15% low results often in such cases, as indicated by studies in this laboratory with purified *trans*-stilbene oxide (*trans*-2,3-diphenyloxirane). With styrene oxide, the method gave results that were reproducible to ±5%, and averaged about 5% lower than theory.