rated on cooling. It was removed, dried, recrystallized from nitrobenzene, and the yellow crystals were washed with toluene and petroleum ether. The yield was 75%.

(b) Concentrated sulfuric acid (5 ml.) was added dropwise to a refluxing solution of 2 g. of 5-nitro-(2 or 3)-acetamido-(2 or 3)-amino-1,4-naphthoquinone in 100 ml. of ethyl orthoformate. The acid was added over a period of 20 min. After cooling the product was collected and washed with ether. The product was purified by the procedure used in (a). The yield was 28%.

PHILADELPHIA 4, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

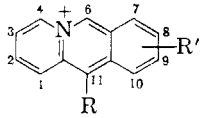
Acridizinium Compounds by the Cyclization of Oximes

C. K. BRADSHER, T. W. G. SOLOMONS, AND F. R. VAUGHAN

Received August 5, 1959

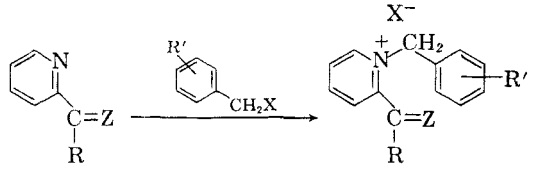
Picolinic aldoxime (III) is superior to the free aldehyde (II) with regard to the rate of reaction with benzyl halides and to the yield and purity of the resulting quaternary salts. The new 1-benzyl-2-aldoximinopyridinium salts cyclize in good yield to afford acridizinium salts (I). The overall yield is superior to that *via* the aldehyde. An improvement is observed when 2-acetylpyridine (IV) is replaced by its oxime (V) in the acridizinium synthesis.

In an earlier work it was shown[1,2] that derivatives of the acridizinium ion (I) can be synthesized



I, R = R′ = H

by cyclization of the quaternary salts (VI) formed when picolinic aldehyde (II) reacts with an appropriate benzyl halide.

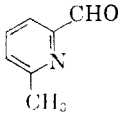


II. Z = O, R = H
III. Z = NOH, R = H
IV. Z = O, R = CH_3
V. Z = NOH, R = CH_3
VI. Z = O, R = R′ = H
VII. Z = NOH, R = R′ = H
VIII. Z = NOH, R = H, R′ = 4-CH_3
IX. Z = O, R = CH_3, R′ = H
X. Z = NOH, R = CH_3, R′ = H
XI. Z = NOH, R = CH_3, R′ = 4-CH_3
XII. Z = NOH, R = CH_3, R′ = 3-OCH_3

Despite the success met with in the use of this synthesis, there are some disadvantages which are inherent in the use of picolinic aldehyde. The aldehyde is itself unstable and deteriorates rapidly if not kept refrigerated. It is recommended that the aldehyde be stored under a nitrogen atmosphere. The quaternization of picolinic aldehyde at room temperature is quite slow, and although the rate is more rapid at higher temperatures, great care must be exercised to prevent deterioration of the aldehyde or of the quaternization product. Only a few of the quaternary salts (VI) derived from aldehydes have been obtained in a crystalline condition, and only three[3] of these in a state of analytical purity. When poor results are obtained in the over-all reaction, it is often difficult to judge at what stage the failure has occurred.

It was felt that derivative of picolinic aldehyde might offer some advantages, and the first studied has been the stable and commercially available oxime (III).

Perhaps because of the increased basicity of the ring nitrogen, picolinic aldoxime (III) quaternizes more readily than does the free aldehyde (II), and the quaternary salt (VII) is readily isolated and purified. The quaternary oximes (VII) can be cyclized by the action of hydrobromic acid under the same conditions used previously for the quater-



XIII

TABLE I

ACRIDIZINIUM SALTS BY THE OXIME METHOD

Acridizinium Salt	Yield, %			
			Overall via	
	Quatern.	Cycliz.	Oxime	Aldehyde
—	87.5	89	78	60[a]
9-CH_3	75	92.5[b]	69.5	55[a]
Benzo[h]	92	85	78	52[c]
11-CH_3	85	21	18	03[d]
9,11-$(CH_3)_2$	90	40	36	—
8-OH, 11-CH_3	90	99	90	—

[a] Reference 1a. [b] Sum of yields of bromide (28%) and picrate (64.5%). [c] Reference 1b. [d] Reference 8.

(1a) C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **77**, 4812 (1955).

(1b) C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **78**, 2459 (1956).

(2) C. K. Bradsher and J. H. Jones, *J. Am. Chem. Soc.*, **79**, 6033 (1957).

(3) C. K. Bradsher and T. W. G. Solomons, unpublished work.

TABLE II

1-ARYLMETHYL-2-(1-HYDROXIMINOALKYL)PYRIDINIUM BROMIDES

R	Ar	M.P.[a]	Formula	C		H		N	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
H	C_6H_5	202	$C_{13}H_{13}BrN_2O$	53.25	53.00	4.46	4.41	9.55	9.64
H	$4\text{-}CH_3C_6H_4$	206	$C_{14}H_{15}BrN_2O$	54.73	54.60	4.92	4.62	—	—
H	$1\text{-}C_{10}H_7$	200–201	$C_{17}H_{15}BrN_2O$	59.48	59.47[b]	4.41	4.40	8.16	8.19
CH_3	C_6H_5	153[c,d]	$C_{14}H_{15}BrN_2O.{}^1/_4H_2O$	53.93	54.03	4.97	5.12	8.98	8.84
CH_3	$4\text{-}CH_3C_6H_4$	172[c,d]	$C_{15}H_{17}BrN_2O.{}^1/_4H_2O$	55.31	55.44	5.11	5.33	8.60	8.74
CH_3	$3\text{-}CH_3OC_6H_4$	122[c,d]	$C_{15}H_{17}BrN_2O_2\cdot{}^1/_4H_2O$	52.70	52.78[e]	5.16	5.20	8.19	8.31

[a] Melting points taken in a sealed tube. [b] Reference 12. [c] With decomposition. [d] Crystallized from methanol-ethyl acetate. [e] Reference 13.

nary aldehydes (VI). From Table I, it will be noted that the overall yields obtained with the aldoxime (III) were superior to those starting with picolinic aldehyde (II).

Although 6-methyl-2-pyridinealdehyde (XIII) is available, it quaternizes too poorly[4] to provide a satisfactory synthetic route to 4-methylacridizinium salts.[5] The corresponding oxime[6] appeared to react, but as the oxime was recovered as the hydrobromide, oximino ether formation and hydrolysis may have occurred.[7]

In a recent publication[8] it was reported that 11-substituted acridizinium salts could be prepared by cyclization of the salts formed by quaternization of 2-benzoyl- or 2-acetylpyridine (IV) with benzyl halides. 2-Acetylpyridine gave very poor results (3% overall yield) with benzyl bromide, probably because of failure of the quaternization step. It has now been found that using the same halide, quaternization was much easier with the oxime (V) of 2-acetylpyridine (85% yield), and although the cyclization step went in only 21% yield, the overall yield (18%) represents a great improvement. A somewhat higher yield (36%) was obtained in the preparation of the new 9,11-dimethylacridizinium picrate.

The salt (XI) obtained from the reaction of *m*-methoxybenzyl bromide with the oxime (V) of 2-acetylpyridine cyclized (with ether cleavage) when heated in hydrobromic acid, affording 8-hydroxy-11-methylacridizinium bromide in 99% yield. Cyclization of XI in liquid hydrogen fluoride likewise yielded an 8-hydroxy-11-methylacridizinium salt (75%). The treatment of the other quaternized pyridyl oxime salts (VII, VIII, X) with hydrogen fluoride gave no isolable acridizinium salts. As hydrogen fluoride is known to produce the Beckmann rearrangement[9] of oximes, it may well be that with hydrogen fluoride, cyclization is observed only when cyclization can occur much more rapidly than rearrangement.

EXPERIMENTAL[10]

Quaternization Procedure. To a solution containing 0.01 mole of the oxime (III or V) in 5–6 ml. of dimethylformamide, 0.011 mole of the benzyl bromide was added and the mixture allowed to stand for 5 days to one week.[11] At the end

TABLE III

ACRIDIZINIUM (I) BROMIDES BY CYCLIZATION OF 1-ARYLMETHYL-2-(1-HYDROXIMINOALKYL)-PYRIDINIUM BROMIDES IN 48% HYDROBROMIC ACID

Acridizinium	Reflux Time, Hr.	Yield, %	M.P Obsd.	M.P Lit.
—	6	89	240–241	239–240[a]
$9\text{-}CH_3$	4	28[b]	192–194	191–193[a]
Benzo[h]	1.25	85	304–307	308–309[c]
$11\text{-}CH_3$	8	21	199–201	—[d]
$9,11\text{-}(CH_3)_2$	0.5	40[e]	208–209.5	—[f]
8-OH, $11\text{-}CH_3$[g]	0.75	99	302–303	—[h]

[a] Ref. 1a. [b] From the filtrate an additional 64.5% was isolated as the picrate, m.p. 248–250°, Lit.,[1] m.p. 252–253°, total yield 92.5%. [c] Reference 1b. [d] *Anal.* Calcd. for $C_{14}H_{12}BrN\cdot 1/3H_2O$: C, 60.01; H, 4.56; N, 5.00. Found[13]: C, 59.90; H, 4.89; N, 4.91. [e] The yield and melting point are for the picrate rather than the bromide. [f] *Anal.* Calcd. for $C_{21}H_{16}N_4O_7$: C, 57.79; H, 3.69; N, 12.84. Found[13]: C, 57.44; H, 3.88; N, 13.00. [g] Obtained from XII by combined cyclization and ether cleavage. [h] *Anal.* Calcd. for $C_{14}H_{12}BrNO\cdot H_2O$: C, 52.18; H, 4.38; N, 8.69. Found[12]: C, 51.97; H, 4.50; N, 8.81. The *picrate* was also prepared, as needles from acetonitrile, m.p. 201–203°. *Anal.* Calcd. for $C_{21}H_{16}N_4O_8$: C, 54.79; H, 3.22; N, 12.78. Found[13]: C, 54.74; H, 3.35; N, 12.77.

(4) The relative unreactivity of XIII as compared with picolinic aldehyde is in accord with the general observation that 2,6 disubstituted pyridines do not readily form quaternary salts, R. C. Elderfield, *Heterocyclic Compounds*, Vol. I, John Wiley & Sons, New York, N. Y. (1950), page 572.

(5) It is possible to obtain a 2.5% yield for the overall reaction by the picolinic aldehyde method.

(6) S. Ginsberg and I. B. Wilson, *J. Am. Chem. Soc.*, **79**, 481 (1957).

(7) Ginsberg and Wilson (ref. 6) have shown that the reaction of methyl iodide with 6-methylpyridine-2-aldoxime yields the oximino ether.

(8) C. K. Bradsher and T. W. G. Solomons, *J. Am. Chem. Soc.*, **81**, 2550 (1959).

(9) *Cf.*, F. Moller, O. Bayer, and H. Wilms, *Ger.* 924, 866; *Chem. Abstr.* **52**, 14672 (1958). J. H. Simons, S. Archer, and D. I. Randall, *J. Am. Chem. Soc.*, **62**, 485 (1940).

(10) Except as noted, all melting points were taken on a Fisher-Johns hot stage and are uncorrected. Unless otherwise indicated all analyses were by Drs. Weiler and Strauss, Oxford, England.

(11) With the oxime of 2-acetylpyridine 2 weeks were allowed.

(12) Analysis by Galbraith Laboratories, Knoxville, Tenn.

(13) Analysis by Dr. Ing. A. Schoeller, Kronach, West Germany.

of this period the crystalline product was triturated with ethyl acetate, and the product collected and washed with ether. Except as noted, the analytical samples formed colorless crystals from ethanol. The results of these experiments are summarized in Table II.

Cyclization of Oximes. One gram of the oxime was refluxed with 5–10 ml. of 48% hydrobromic acid, after which the hydrobromic acid was removed under reduced pressure (aspirator). About 10 ml. of ethanol was added, removed under vacuum, and the residue crystallized from ethanol. The results of these experiments are summarized in Table III.

4-Methylacridizinium Picrate. (a) *Attempted synthesis by the Oxime Method.* Quaternization of 6-methylpyridine-2-aldoxime (XIII oxime) with benzyl bromide was attempted by the usual method. The product, m.p. 208–209°, obtained by recrystallization was not the expected quaternary salt, and had the approximate composition for the hydrobromide of the original oxime.

(b) *By the Picolinic aldehyde method.*[14] Two grams of benzyl chloride and 2 g. of 6-methylpyridine-2-carboxaldehyde were refluxed for 14 hr. in 5 ml. of absolute methanol. The methanol was removed under vacuum and the residue washed with ether. The residue was dissolved in 25 ml. of conc. hydrochloric acid and refluxed for 8 hr. The residue (after removal of the hydrochloric acid *in vacuo*) was dissolved in ethanol and treated with ethanolic picric acid. The crude picrate was obtained as a dark yellow solid, m.p. 200–208° dec., yield 0.2 g. (2.5%). The analytical sample formed fine yellow needles from acetone, m.p. 230–233° dec.

Anal. Calcd. for $C_{20}H_{14}N_4O_7$: C, 56.87; H, 3.34; N, 13.27. Found[15]: C, 56.69; H, 3.89; N, 13.21.

Cyclization of 1-(3-methoxybenzyl)-2-(1-hydroximinoethyl)-pyridinium bromide (XII) *in hydrogen fluoride.* In a polyethylene bottle was placed 0.8 g. of the quaternary bromide (XII) to which 50 ml. of liquid hydrogen fluoride was added. The hydrogen fluoride was allowed to evaporate over a 2 day period. The gummy residue was dissolved in ethanol and treated with ethanolic picric acid. The picrate, crystallized from acetonitrile, was demonstrated to be *8-hydroxy-11-methylacridizinium picrate* by comparison of melting points and infrared spectra with those obtained from the sample prepared by the hydrobromic acid cyclization, yield 0.78 g. (75%).

DURHAM, N. C.

(14) This experiment was by J. H. Jones.

(15) Analysis by Micro Laboratories, Skokie, Illinois.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

1,2- and 3-Monoalkyl and 2-(β-D-Ribofuranosyl) Derivatives of 7-Dimethylamino-v-triazolo(d)pyrimidine and Related Compounds

ROBERT B. ANGIER AND JOSEPH W. MARSICO

Received October 19, 1959

Three monoethyl derivatives have been isolated from the reaction of ethyl iodide and 7-dimethylamino-v-triazolo(d)-pyrimidine (VII). Each of these monoethyl derivatives has been assigned a definite structure by comparison of their ultraviolet absorption spectra with the spectra of 7-dimethylamino-3-ethyl-3H-v-triazolo(d)pyrimidine (V) and 7-dimethylamino-2-(2,4,6-trichlorophenyl)-2H-v-triazolo(d)pyrimidine (XVIII), which have been synthesized by unequivocal methods. By the same methods the riboside obtained from the chloromercuri derivative of VII was shown to be 7-dimethylamino-2-(β-D-ribofuranosyl)-2H-v-triazolo(d)pyrimidine (IX). Similar results were obtained with 7-dimethylamino-5-methylmercapto-v-triazolo(d)pyrimidine (VI).

Analogs of 6-dimethylamino-9(3-amino-3-deoxy-β-D-ribofuranosyl)purine[1] (I) (the aminonucleoside derived from puromycin) are of interest because of the carcinostatic[2] and trypanocidal[3] properties of I. Previous reports have been concerned primarily with analogs of I containing variations either in the carbohydrate portion of the molecule[4] or in the substituents on the purine nucleus.[5] In this paper we wish to report on the results of some work carried out during an attempt to prepare the triazolo(d)pyrimidine analog 7-dimethylamino-3(3-amino-3-deoxy-β-D-ribofuranosyl)-3H-v-triazolo(d)pyrimidine (II).

When this work was begun the only reported v-triazolo(d)pyrimidines containing substituents on the triazole portion of the molecule were some 2-phenyl derivatives.[6] Therefore, in order to have available a model compound for ultraviolet absorption spectra studies, 7-dimethylamino-3-ethyl-3H-v-triazolo(d)pyrimidine (V) was synthesized by unequivocal methods. 5-Amino-6-dimethylamino-4-ethylamino-2-methylmercaptopyrimidine (III)[7] when treated with nitrous acid gave the expected 7-dimethylamino-3-ethyl-5-methylmercapto-3H-v-triazolo(d)pyrimidine (IV), which was then desulfurized with Raney nickel catalyst to give V.

(1) B. R. Baker, J. P. Joseph, and J. H. Williams, *J. Am. Chem. Soc.*, **77**, 1 (1955).

(2) P. L. Bennett, S. L. Halliday, J. J. Oleson, and J. H. Williams, *Antibiotics Annual 1954–1955*, Medical Encyclopedia, Inc., New York, N. Y., 1954, pp. 766–769.

(3) R. I. Hewitt, A. R. Gamble, W. S. Wallace, and J. H. Williams, *Antibiotics and Chemotherapy*, **4**, 1222 (1954).

(4) R. E. Schaub, M. J. Weiss, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 4692 (1958); F. J. McEvoy, M. J. Weiss and B. R. Baker, *J. Am. Chem. Soc.*, **82**, 209 (1960).

(5) L. Goldman, J. W. Marsico, and R. B. Angier, *J. Am. Chem. Soc.*, **78**, 4173 (1956).

(6) F. R. Benson, L. W. Hartzel and W. L. Savell, *J. Am. Chem. Soc.*, **72**, 1816 (1950).

(7) B. R. Baker, R. E. Schaub, and J. P. Joseph, *J. Org. Chem.*, **19**, 638 (1954).