The acid was transformed into the ethyl ester by refluxing for 20 hr. with hydrochloric acid-absolute ethanol. The melting point of the green crystals, after recrystallization in ethyl acetate–petroleum ether, was 86–89°.

Anal. Calcd. for $C_{17}H_{17}NO_3$: N, 4.94. Found: N, 5.09.

3-Acetyl-10-ethylphenoxazine (IX). A 0.72-g. sample (30 mmoles) of magnesium was treated in a nitrogen atmosphere, with 0.426 g. (20 mmoles) of methyl iodide in 15 ml. of anhydrous ether. A solution of 4.8 g. (20 mmoles) of 3-cyano-10-ethylphenoxazine in 50 ml. of benzene was added and refluxed with stirring for 2 hr. After cooling to 0°, 10 ml. of 6*N* hydrochloric acid was slowly added, and the mixture was refluxed, with stirring, for 6 hr. The benzene layer was removed, the brown precipitate was filtered and dissolved in ethanol. The solution was acidified with 10 ml. of 6*N* hydrochloric acid and refluxed for 6 hr. After diluting with water, the product was extracted with benzene. The combined benzene solutions were washed, dried, and evaporated. The residue was distilled *in vacuo* (250°/0.7 mm.). The product (2.43 g., m.p. 145–150°) was recrystallized from ethanol, and gave 1.8 g. (33%) of yellow crystals, m.p. 153–154°.

Anal. Calcd. for $C_{16}H_{15}NO_2$: N, 5.53. Found: N, 5.48.

The melting point of the *oxime* is 175–178°.

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: N, 10.44. Found: 10.66.

3,7-Diacetylphenoxazine. To a solution of 18 g. (0.085 mole) of 10-ethylphenoxazine and 6.89 g. (0.085 mole) of acetyl chloride in 300 ml. of carbon disulfide were added, slowly and with stirring, 34.5 g. (0.26 mole) of powdered aluminum chloride. After refluxing, with agitation, for 8 hr., the solvent was decanted and the residue was decomposed with crushed ice and conc. hydrochloric acid. The oily layer was extracted with ether; this solution gave, after evaporation and purification over a column of silica gel, 5 g. of unchanged 10-ethylphenoxazine. The ether insoluble residue (7.70 g., m.p. 160–165°) was extracted with benzene. The green insoluble product (2.2 g., m.p. 170–174°) gave upon recrystallization in ethanol 3,7-diacetyl-10-ethylphenoxazine, m.p. 178–180°. The benzene solution was filtered through a silica gel column and another 0.5 g. of unchanged 10-ethylphenoxazine was eluted with benzene. The 3,7-diacetyl-10-ethylphenoxazine was eluted with acetone. After evaporation and crystallization in ethanol, 2 g. of yellow green crystals, m.p. 178–180°, were obtained. The solutions of this product were strongly fluorescent.

Anal. Calcd. for $C_{18}H_{17}NO_3$: N, 4.76. Found: N, 5.26.

The *oxime* was prepared by reaction with hydroxylamine hydrochloride in pyridine-ethanol, and had melted at 236–237° dec.

Anal. Calcd. for $C_{18}H_{19}N_3O_3$: N, 12.96. Found: N, 12.28.

Acknowledgments. The author thanks Mr. G. Lambert, Institut du Cancer, Louvain, for the ultraviolet spectra and Mr. L. Verlooy for his excellent help.

LOUVAIN, BELGIUM

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

Preparation of Substituted 4,9-Naphth(2,3)imidazolediones

JAMES M. WILBUR, JR., AND ALLAN R. DAY

Received October 28, 1959

A number of substituted 4,9-naphth(2,3)imidazolediones have been synthesized. Solubility in fatty oils has been increased by introducing substituents of high carbon and hydrogen content in the 2- position. Increased solubility in water was effected by introducing the hydroxyl or carboxyl group in the side chain in the 2- position and by introducing an amino group into the 5- position.

A number of 2-substituted-4,9-naphth(2,3)-imidazolediones have been prepared by Hoover and Day.[1] Certain of these compounds have a marked inhibiting effect on the growth of mutant microorganisms.[2]

In general, the 2-substituted-4,9-naphth(2,3)-imidazolediones are difficultly soluble and are not easy compounds to test. In this particular investigation it was decided to introduce substituents which would increase either solubility in fats or solubility in water. Long chain alkyl groups were introduced into the 2- position. 2-Dodecyl-, 2-hexadecyl-, and 2-chaulmoogryl-4,9-naphth(2,3)-imidazoledione were preparred by the general procedure described by Hoover and Day.[1] These compounds, compared with the 2-methyl derivative, are more soluble in fatty oils. 2-(2′-Phenylvinyl)-4,9-naphth-(2,3)imidazoledione, and 2-hydroxymethyl-4,9 naphth(2,3)imidazoledione were prepared by the same procedure. The last two were prepared as possible intermediates for making other compounds. It is interesting to note that the 2-hydroxymethyl compound is quite unreactive and it was impossible to make the corresponding chloromethyl or bromomethyl compound by the usual methods. The unreactivity of the 2-hydroxymethyl derivative in this series is similar to the unreactivity of 2-hydroxymethylnaphth(2,3)-imidazole noted by Brown.[3]

The preparation of these compounds may be outlined as follows:

2,3-dichloro-1,4-naphthoquinone $\xrightarrow[C_2H_5OH]{NH_3}$ 2-amino-3-chloro-1,4-naphthoquinone (I)

I + RCOCl ⟶ 2-acylamino-3-chloro-1,4-naphthoquinone (II)

II in $C_6H_5NO_2$ + NH_3 ⟶ 2-acylamino-3-amino-1,4-naphthoquinone (III)

III + NaOH ⟶ 2-substituted-4,9-naphth(2,3)imidazoledione

(1) J. R. E. Hoover and A. R. Day, *J. Am. Chem. Soc.* **76**, 4148 (1954).

(2) A. R. Day, *Trans. New York Acad. Sci.*, **20**, 4 (1957).

(3) D. J. Brown, *J. Chem. Soc.*, 1974 (1958).

Two approaches were used to increase solubility in water: (1) introduction of a carboxyalkyl group in the two position; and (2) introduction of an amino group in the benzene ring of the 4,9-naphth(2,3)imidazoledione. 2-(4′)-Carboxylbutyl-4,9-naphth(2,3)imidazoledione was prepared by the usual method.[1] The sodium salt of this acid is quite soluble in water.

To introduce an amino group into the benzene ring, 4,9-naphth(2,3)imidazoledione was first nitrated with fuming nitric acid in concentrated sulfuric acid. In order to determine the position of the nitro group it was necessary to synthesize 5-nitro-4,9-naphth(2,3)imidazoledione from the known compound 5-nitro-2,3-dichloro-1,4-naphthoquinone.[4] The two nitro compounds have the same decomposition range and infrared spectra. The product of direct nitration therefore must be 5-nitro-4,9-naphth(2,3)imidazoledione. The corresponding 5-amino derivative was most conveniently prepared by reducing 5-nitro-2,3-dichloro-1,4-naphthoquinone with stannous chloride and reoxidizing the resulting amino hydroquinone with ferric chloride to 5-amino-2,3-dichloro-1,4-naphthoquinone. The latter was then converted to the corresponding imidazole by the usual procedure.[1]

These compounds are being examined for physiological activity at the University of Pennsylvania.

EXPERIMENTAL

The melting points reported are uncorrected values.

Preparations of 2-acylamino-3-chloro-1,4-naphthoquinones (Table I). *2-Dodecanoylamino-3-chloro-1,4-naphthoquinone*, (I), was prepared from 2-amino-3-chloro-1,4-naphthoquinone and lauroyl chloride in the presence of hydrogen chloride.[1] The mixture was heated at 160–170° for 2 hr. The resulting solid was broken up, washed with ether, recrystallized from ethanol and finally from benzene and benzene-petroleum ether. The product was obtained as yellow needles.

2-Hexadecanoylamino-3-chloro-1,4-naphthoquinone (II). Palmitoyl chloride was used in this case and the mixture was heated at 170–180° for 90 min. The crude product was purified by the procedure used for compound I and was obtained as yellow needles.

2-Chaulmoogrylamino-3-chloro-1,4-naphthoquinone (III). Chaulmoogryl chloride was prepared by a modification of the method of Burschkies.[5] The details of this modification are to be found in the dissertation of J. M. Wilbur, Jr.[6]

A mixture of 18 g. (0.06 mole) of chaulmoogryl chloride and 14.5 g. (0.07 mole) of 2-amino-3-chloro-1,4-naphthoquinone in 200 ml. of xylene was heated at 135–145° for 2 hr. The mixture was filtered while hot and the filtrate cooled. The resulting dark solid was dissolved in chloroform and the solution was filtered. The filtrate was chromatographed on Merck acid washed alumina using chloroform as the eluant. A yellow band moved down the column first followed by an orange band and the black tars remained on the column. The material from the yellow band was collected and the chloroform removed under reduced pressure. The crude product was recrystallized from ethanol and obtained as yellow crystals.

2-Cinnamoylamino-3-chloro-1,4-naphthoquinone (IV). A mixture of 4.15 g. (0.02 mole) of 2-amino-3-chloro-1,4-naphthoquinone and 10 g. (0.06 mole) of cinnamoyl chloride in 12 ml. of xylene was treated with dry hydrogen chloride for 5 min. and then heated at 145–150° for 3 hr. The product separated on cooling. It was washed with ether and recrystallized from benzene-petroleum ether and obtained as yellow needles. This product melted at 187–188° and was analytically pure. After standing for several weeks the melting point increased and after recrystallization from benzene-petroleum ether the compound melted at 194–195°. The analytical data for the two compounds were almost identical. It is believed that the higher melting product is the *trans* form.

2-Acetylglycolylamino-3-chloro-1,4-naphthoquinone (V). Acetylglycolyl chloride was prepared by a modification of the method of Auschutz and Bertram.[7] Acetylglycolic acid was treated with thionyl chloride in place of phosphorus trichloride.[8] The amide (V) was prepared by the procedure used for making compound IV. The product was recrystallized from ethanol and obtained as yellow needles.

Evaporation of the filtrate from V under reduced pressure gave an oil. When ether was added, crystals of the diamide separated. The product was recrystallized from ethanol and obtained as yellow plates. Analyses indicated the product to be 2-*N*,*N*-diglycolylamino-3-chloro-1,4-naphthoquinone (VI).

2-(4′-Carbomethoxypentanoyl)amino-3-chloro-1,4-naphthoquinone (VII). 5-Carbomethoxypentanoyl chloride was prepared by a previously described procedure.[8] Once the acyl chloride was obtained, the procedure that was used for making compound I was followed. The mixture was heated at 135–140° for 90 min. The product was purified by recrystallization from ethanol and was obtained as yellow crystals.

Preparations of 2-acylamino-3-amino-1,4-naphthoquinones (Table I). The following compounds were prepared by the action of ammonia on the corresponding 3-chloro compounds (I, II, III, IV and V) in nitrobenzene at 140–150°[1]: *2-dodecanoylamino-3-amino-1,4-naphthoquinone* (VIII), *2-hexadecanoylamino-3-amino-1,4-naphthoquinone* (IX), *2-chaulmoogrylamino-3-amino-1,4-naphthoquinone* (X), *2-cinnamoylamino-3-amino-1,4-naphthoquinone* (XI), *2-acetylglycolylamino-3-amino-1,4-naphthoquinone* (XII), *2-(4′-carbomethoxypentanoyl)amino-3-amino-1,4-naphthoquinone* (XIII).

Preparations of 2-substituted 4,9-naphth(2,3)imidazolediones. These preparations required modification of the original method[1] and for that reason a general method is included here.

2-Undecyl-4,9-naphth(2,3)imidazoledione (XIV). Fifty milliliters of 2*N* sodium hydroxide was added to a hot solution of 6 g. (0.016 mole) of 2-dodecanoylamino-3-amino-1,4-naphthoquinone in 200 ml. of 95% ethyl alcohol. The solution was refluxed for 30 min. The hot solution was treated with decolorizing carbon and filtered. About 100 ml. of the ethyl alcohol was removed under reduced pressure and the remainder was very carefully neutralized with 6*N* hydrochloric acid. After cooling, the product was removed, washed with water, and dried. It was purified by recrystallization from xylene and obtained as yellow crystals.

The other imidazoles which were prepared (Table II) included: *2-pentadecyl-4,9-naphth(2,3)imidazoledione* (XV), *2-[12′-(3-cyclopentenyl)dodecyl]-4,9-naphth(2,3)imidazoledione* (XVI), *2-(2′-phenylvinyl)-4,9-naphth(2,3)imidazoledione* (XVII), *2-hydroxymethyl-4,9-naphth(2,3)imidazoledione* (XVIII).

The phenylurethan of XVIII was prepared by heating it with phenylisocyanate in nitrobenzene solution. The ure-

(4) K. Fries, W. Pense, and O. Peeters, *Ber.*, **61**, 1395 (1928).

(5) K. Burschkies, *Ber.*, **71**, 233 (1938).

(6) J. M. Wilbur, Jr., Dissertation, University of Pennsylvania, 1959.

(7) R. Auschutz and W. Bertram, *Ber.*, **36**, 467 (1903).

(8) A. J. Yu and A. R. Day, *J. Org. Chem.*, **23**, 1004 (1958).

TABLE I

No.	Acyl Group	Yield, %	M.P.°	Formula	Carbon, %		Hydrogen, %		Nitrogen, %		Chlorine, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
				2-Acylamino-3-chloro-1,4-naphthoquinones								
I	Dodecanoyl	57	132–132.5	$C_{22}H_{28}O_3NCl$	67.77	67.81	7.24	7.36	3.59	3.50	9.09	8.93
II	Hexadecanoyl	53	130.5–131	$C_{26}H_{36}O_3NCl$	70.01	70.00	8.14	8.36	3.14	3.35	7.95	7.82
III	Chaulmoogryl	35	121–123	$C_{28}H_{35}O_3NCl$	71.54	71.77	7.72	7.51	2.98	3.11	7.54	7.52
IV	Cinnamoyl	46	187–188	$C_{19}H_{12}O_3NCl$	67.57	67.48	3.58	3.79	4.15	4.14	10.50	10.63
V	Acetylglycolyl	48	182–183	$C_{14}H_{10}O_5NCl$	54.64	54.70	3.28	3.23	4.55	4.50	11.52	11.44
VI	Di(glycolyl)	2	115–116	$C_{18}H_{14}O_8NCl$	53.02	53.23	3.46	3.62	3.43	3.56	8.69	8.72
VII	4-Carbomethoxypentanoyl	72	153–154	$C_{17}H_{16}O_5NCl$	58.37	58.49	4.61	4.53	4.00	4.11	10.14	10.09
				2-Acylamino-3-amino-1,4-naphthoquinones								
VIII[a]	Dodecanoyl	64	132.5–133.5	$C_{22}H_{30}O_3N_2$	71.33	71.53	8.16	8.01	7.56	7.68		
IX[b]	Hexadecanoyl	80	125–127	$C_{26}H_{38}O_3N_2$	73.20	73.47	8.98	8.76	6.57	6.50		
X[a]	Chaulmoogryl	58	118–120	$C_{28}H_{38}O_3N_2$	74.63	74.68	8.49	8.51	6.22	6.46		
XI[a]	Cinnamoyl	78	233–234	$C_{19}H_{14}O_3N_2$	71.68	71.50	4.43	4.40	8.80	8.76		
XII[b]	Acetylglycolyl	83	210.5–212	$C_{14}H_{12}O_5N_2$	58.33	58.45	4.20	4.03	9.72	9.80		
XIII[a]	4-Carbomethoxypentanoyl	86	156.5–157.5	$C_{17}H_{18}O_5N_2$	61.81	62.00	5.49	5.66	8.48	8.40		

[a] Recrystallized from ethanol. [b] Recrystallized from ethyl acetate and from ethanol.

TABLE II

No.	Substituents	Yield, %	M.P.°	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
				2-Substituted-4,9-naphth(2,3)imidazolediones						
XIV	Undecyl	71	127.5–129	$C_{22}H_{28}O_2N_2$	74.98	74.71	8.00	8.26	7.95	8.06
XV[a]	Pentadecyl	64	107–108	$C_{26}H_{36}O_2N_2$	76.42	76.47	8.88	9.02	6.86	6.83
XVI[b]	12-(3-Cyclopentenyl)dodecyl	57	110–111	$C_{28}H_{36}O_2N_2$	77.74	77.57	8.39	8.53	6.48	6.26
XVII[c]	2-Phenylvinyl	20	340–342 dec.	$C_{19}H_{12}O_2N_2$	75.99	75.82	4.03	4.15	9.33	9.12
XVIII[d]	*Hydroxymethyl*	66	275–278 dec.	$C_{12}H_8O_3N_2$	63.15	63.32	3.53	3.49	12.28	12.01
XIX[e]	4-Carboxybutyl	74	267–268 dec.	$C_{16}H_{14}O_4N_2$	64.42	64.66	4.73	4.88	9.39	9.43
XX[f]	4-Carboxamidobutyl	50	235–236 dec.	$C_{16}H_{15}O_3N_3$	64.64	64.87	5.07	4.95	14.13	13.95
				5-Substituted-4,9-naphth(2,3)imidazolediones						
XXI[e]	2-Methyl-5-amino	58	>410 dec.	$C_{12}H_9O_2N_3$	63.43	63.47	3.99	4.00	18.49	18.47
XXII[e]	5-Amino	89	>420 dec.	$C_{11}H_7O_2N_3$	61.94	61.72	3.31	3.35	19.70	19.52
XXIII[b,g]	5-Nitro	56	315–330 dec.	$C_{11}H_5O_4N_3$	54.33	54.19	2.07	2.27	17.27	17.20

[a] Recrystallized from benzene-petroleum ether. [b] Recrystallized from nitromethane. [c] Recrystallized from chloroform. [d] Recrystallized from nitrobenzene and finally from water. [e] Recrystallized from nitrobenzene. [f] Recrystallized from methanol. [g] From ring closure method.

than separated on cooling and was recrystallized from nitrobenzene.

Anal. Calcd. for $C_{19}H_{13}O_4N_3$: C, 65.70; H, 3.78; N, 12.10. Found: C, 65.55; H, 3.69; N, 11.95.

2-(4'-Carboxybutyl)-4,9-naphth(2,3)imidazoledione. (XIX). 2-(4'-Carbomethoxypentanoyl)amino-3-amino-1,4-naphthoquinone (23.5 g., 0.071 mole) was dissolved in 700 ml. of 95% ethyl alcohol. To the hot solution was added 105 ml. of 2*N* sodium hydroxide solution. The solution was refluxed for 1 hr. and most of the alcohol was then removed under reduced pressure. The residue was dissolved in 1 l. of hot water, treated with decolorizing carbon, and filtered. The filtrate was adjusted to *p*H 5 and cooled. The yellow product, so obtained, may be recrystallized from large volumes of water or from nitrobenzene.

The amide (XX) of compound XIX was prepared by converting the acid to the acid chloride by heating with thionyl chloride and then treating the acid chloride with cold conc. aqueous ammonia. The solution was treated with decolorizing carbon and filtered. The filtrate was carefully neutralized with 6*N* hydrochloric acid to precipitate the amide.

Preparation of 5-amino-2-methyl-4,9-naphth(2,3)imidazoledione (XXI). This preparation involved the initial preparation of 5-nitro-2,3-dichloro-1,4-naphthoquinone. This compound was reported in 1928.[4] As we were not able to reproduce the earlier results, we are including here a modification of their procedure. 2,3-Dichloro-1,4-naphthoquinone (246 g., 1.06 mole) was mixed with 320 ml. of conc. sulfuric acid. Then 640 ml. of red fuming nitric acid was added dropwise with stirring. After 150 ml. of nitric acid was added, a vigorous exothermic reaction occurred and cooling was necessary to keep the temperature below 100°. Above 120° decomposition occurs. The remaining nitric acid was slowly added while the temperature was maintained at 80–90°. The mixture was heated at this temperature for 7 hr. It was then poured onto cracked ice. The yellow product was removed, washed thoroughly with water and then stirred with 1*N* sodium carbonate solution for 8 hr. The product was removed, washed with water, and dried. It was purified by recrystallization from chloroform with the aid of decolorizing carbon. A 20% yield of pure compound was obtained, m.p. 174–175°.

Reduction of the nitro compound to the corresponding amino compound was accomplished with stannous chloride according to the procedure of Fries, Pense, and Peeters[4] with certain modifications.[6] The product was recrystallized from large amounts of 95% ethyl alcohol, yield 77%, m.p. 224–226°. 5-Amino-2,3-dichloro-1,4-naphthoquinone has been previously reported to melt at 220°.

The 5-amino-2,3-dichloro-1,4-naphthoquinone was converted to the corresponding 5-acetamido derivative by treatment with acetic anhydride and a few drops of conc. sulfuric acid. The acetyl derivative was recrystallized from ethanol and obtained as red crystals, yield 96%, m.p. 208–209°.

Anal. Calcd. for $C_{12}H_7O_3NCl_2$: C, 50.75; H, 2.48; N, 4.93; Cl, 24.96. Found: C, 50.66; H, 2.48; N, 4.89; Cl, 24.82.

5-Acetamido(2 or 3)-amino-(2 or 3)-chloro-1,4-naphthoquinone. 5-Acetamido-2,3-dichloro-1,4-naphthoquinone (26.7 g., 0.094 mole) was dissolved in 200 ml. of nitrobenzene. The solution was heated to 145–155° and ammonia was passed in for 1 hr. The hot solution was filtered to remove ammonium chloride and the filtrate cooled to crystallize the product. The latter was washed with ether, dried, washed with water, and again dried, yield 93%, m.p. 238–260° dec. This product was probably a mixture of isomers, but recrystallization from ethanol or benzene failed to give a single form. Attempts to separate isomers by chromatography also failed.

5-Acetamido-(2 or 3)-acetamido-(2 or 3)-chloro-1,4-naphthoquinone. A suspension of 23 g. (0.087 mole) of 5-acetamido-(2 or 3)-amino-(2 or 3)-chloro-1,4-naphthoquinone in 70 ml. of acetic anhydride was treated with 12 drops of conc. sulfuric acid. The mixture was warmed, with some stirring, until it formed a solid red mass. An additional 20 ml. of acetic anhydride and 5 drops of conc. sulfuric acid were added with stirring. After standing overnight the mixture was cooled and the solid removed by filtration. It was washed with ether, dried, and then washed with water and dried. The product was recrystallized from 95% ethyl alcohol and obtained as golden orange crystals, yield 76%, m.p. 244–245° dec.

Anal. Calcd. for $C_{14}H_{11}O_4N_2Cl$: C, 54.82; H, 3.62; N, 9.14; Cl, 11.56. Found: C, 54.93; H, 3.52; N, 9.12; Cl, 11.53.

The filtrate from the above product and the ether washings were combined. By evaporation and cooling another isomer was obtained. It was recrystallized from 95% ethyl alcohol and obtained as orange needles, yield 7% m.p. 208–210° dec.

Anal. Calcd. for $C_{14}H_{11}O_4N_2Cl$: C, 54.82; H, 3.62; N, 3.62; N, 9.14; Cl, 11.56. Found: C, 54.63; H, 3.80; N, 9.05; Cl, 11.39.

5-Acetamido-(2 or 3)-acetamido-(2 or 3)-amino-1,4-naphthoquinone. 5-Acetamido-(2 or 3)-acetamido-(2 or 3)-chloro-1,4-naphthoquinone (2.3 g., 0.0075 mole) was dissolved in 30 ml. of nitrobenzene. The solution was heated to 145–150° and ammonia passed into the solution for 1 hr. After standing overnight, the product was removed, washed with ether, dried, and then washed with water and dried. It was recrystallized from ethanol and obtained as brown needles, yield 73%, m.p. 270–272° dec.

Anal. Calcd. for $C_{14}H_{13}O_4N_3$: C, 58.54; H, 4.56; N, 14.63. Found: C, 58.56; H, 4.64; N, 14.71.

5-Amino-2-methyl-4,9-naphth(2,3)imidazoledione. Fifty milliliters of 2*N* sodium hydroxide solution was added to a hot solution of 5-acetamido-(2 or 3)-acetamido-(2 or 3)-amino-1,4-naphthoquinone (5 g., 0.0174 mole) in 200 ml. of 95% ethyl alcohol. The solution was refluxed for 1 hr. and then the alcohol was removed under reduced pressure. The residue was dissolved in boiling water. The solution was treated with decolorizing carbon and filtered. The hot filtrate was carefully neutralized with 6*N* hydrochloric acid and the product crystallized on cooling. The product may be purified by dissolving it in hot 20% sulfuric acid and carefully neutralizing the solution with 2*N* sodium hydroxide solution to reprecipitate the product and finally recrystallizing from nitrobenzene. It was obtained as red crystals.

Acetylation of this compound with acetic anhydride and a few drops of conc. sulfuric acid gave a monoacetyl derivative. It was recrystallized from nitrobenzene, yield 58%, m.p. > 410° dec. This product probably is 5-acetamido-2-methyl-4,9-naphth(2,3)imidazoledione.

Anal. Calcd. for $C_{14}H_{11}O_3N_3$: C, 62.44; H, 4.12; N, 15.60. Found: C, 62.30; H, 4.29; N, 15.71.

5-Amino-4,9-naphth(2,3)imidazoledione (XXII). Five grams of 5-acetamido- (2 or 3)-amino-1,4-naphthoquinone was dissolved in 250 ml. of boiling ethyl formate. Ten milliliters of conc. sulfuric acid was added dropwise over a period of 30 min. After each drop of acid was added, a vigorous reaction occurred. After standing overnight, the mixture was cooled and the solid removed by filtration and washed with ether. The product was purified by the same procedure which was used for purifying compound XXI and was obtained as red plates.

5-Nitro-4,9-naphth(2,3)imidazoledione (XXIII). This compound was prepared by two methods: (a) direct nitration of 4,9-naphth(2,3)imidazoledione,[1] and (b) ring closure of 5-nitro-(2 or 3)-acetamido-(2 or 3)-amino-1,4-naphthoquinone. The two products have identical infrared spectra and melting point ranges, 315–330° dec.

(a) A mixture of 2.1 g. (0.01 mole) of 4,9-naphth(2,3)-imidazoledione in 10 ml. of conc. sulfuric acid and 20 ml. of red fuming nitric acid was heated at 100° for 3 hr. After cooling, the mixture was poured onto cracked ice. The product was removed by filtration and washed with water. It was dissolved in hot 2*N* sodium hydroxide solution, treated with decolorizing carbon, filtered, and the filtrate carefully neutralized with 6*N* hydrochloric acid. The product sepa-

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]

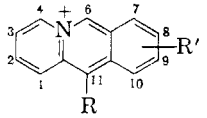
Acridizinium Compounds by the Cyclization of Oximes

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

Received August 5, 1959

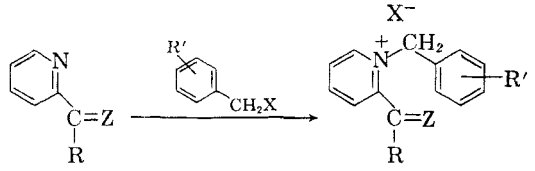
Picolinic aldoxime (III) is superior to the free aldehyde (II) with regard to the rate of reaction with benzyl halides and to the yield and purity of the resulting quaternary salts. The new 1-benzyl-2-aldoximinopyridinium salts cyclize in good yield to afford acridizinium salts (I). The overall yield 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.

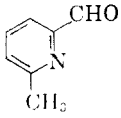


II. Z = O, R = H
III. Z = NOH, R = H
IV. Z = O, R = CH_3
V. Z = NOH, R = CH_3
VI. Z = O, R = R′ = H
VII. Z = NOH, R = R′ = H
VIII. Z = NOH, R = H, R′ = 4-CH_3
IX. Z = O, R = CH_3, R′ = H
X. Z = NOH, R = CH_3, R′ = H
XI. Z = NOH, R = CH_3, R′ = 4-CH_3
XII. Z = NOH, R = CH_3, R′ = 3-OCH_3

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.