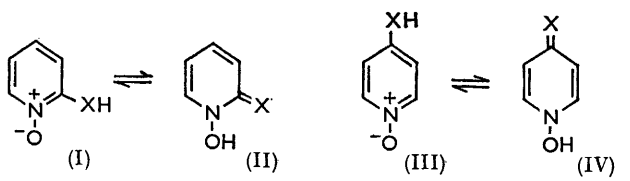
593. N-*Oxides and Related Compounds. Part XVII.*[1] *The Tautomerism of Mercapto- and Acylamino-pyridine* 1-*Oxides.*

By R. Alan Jones and A. R. Katritzky.

Basicities and spectra are recorded for 2- and 4-mercapto-, 2- and 4-acetamido-, and 2-benzamido-pyridine 1-oxide, and certain alkylated derivatives. The mercapto-compounds are shown to exist predominantly (by a relatively small factor) in the thione form, and the acylamino-compounds as such. These results are related to the general pattern of tautomerism in the pyridine series.

2- and 4-Substituted pyridine 1-oxides in which the substituent atom adjacent to the ring carries a proton are potentially tautomeric (I ⇌ II; III ⇌ IV). In previous Parts [2,3] of this series we showed that the amino-compounds exist predominantly as such but that both possible structures are important for the hydroxy-compounds. We now deal with the mercapto- and acylamino-analogues, the corresponding mercapto-[4] and acylamino-pyridines [5] having been studied recently.

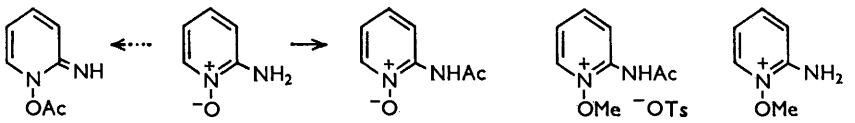


Preparation of Compounds.—1-Hydroxypyrid-2-thione was prepared from 2-chloropyridine 1-oxide by way of the isothiouronium salt (cf. preparation from 2-bromopyridine

[1] Part XVI, Katritzky, Beard, and Coats, *J.*, 1958, 3680.
[2] Gardner and Katritzky, *J.*, 1957, 4375.
[3] Katritzky, *J.*, 1957, 191.
[4] Jones and Katritzky, *J.*, 1958, 3160; Albert and Barlin, *J.*, 1959, 2384.
[5] Jones and Katritzky, *J.*, 1959, 1317.

1-oxide [6]). 2-Chloropyridine 1-oxide and sodium benzyl sulphide gave 2-benzylthiopyridine 1-oxide. The 4-analogues were prepared similarly. Attempts failed to prepare (*a*) 1-methoxypyrid-2- and -4-thione, by action of phosphorus pentasulphide on 1-methoxypyridones, and (*b*) 1-benzyloxypyrid-2- and -4-thione by attempted rearrangement of 2- and 4-benzylthiopyridine 1-oxide with boron trifluoride (contrast the successful rearrangement of 2- and 4-benzyloxyquinoline 1-oxide [7]).

2- and 4-Aminopyridine 1-oxide and 2- and 4-methylaminopyridine 1-oxide were monoacetylated and benzoylated (see p. 2941). The acylation of 2-aminopyridine 1-oxide



(V) (VI) (VII) (VIII) (IX)

was shown previously to afford as normal products the *N*-acyl (VI ⟶ VII), and not the *O*-acyl derivatives (VI ⟶ V), because the products were identical with those of *N*-oxidation of the corresponding acylamino-pyridines.[3] We now confirm this by hydrogenating (cf. ref. 8) 2-acetamidopyridine 1-oxide to 2-acetamidopyridine. The infrared spectra discussed below also show that these acylations take place on the amino-nitrogen atom.

Attempts failed to prepare 4-benzamidopyridine 1-oxide by benzoylation of 4-aminopyridine 1-oxide, and by oxidation of 4-benzamidopyridine, as did attempts to oxidise 4-acetamidopyridine. 2- and 4-Acylaminopyridine 1-oxides should be rather unstable towards hydrolysis for the amino-nitrogen atom carries two strongly electron-withdrawing

TABLE 1.

No.	Compound	pK_a [a]	σ [b]	Concn. (10^{-4}M)	Wave-length [c] (mμ)	pK_a of corresp. pyridine	ΔpK_a
1	1-Hydroxypyrid-2-thione	−1·95	0·03	0·50	299	−1·38	0·57
2		4·67	0·03	239	—	9·81	5·17
3	2-Benzylthio-pyridine 1-oxide	−0·23	0·03	0·57	237·5	3·23	3·46
4	1-Hydroxypyrid-4-thione	1·53	0·02	0·68	286	1·48	−0·05
5		3·82	0·01	212	—	8·65	4·83
6	4-Benzylthiopyridine 1-oxide	2·09	0·10	0·30	226	5·41	3·32
7	2-Acetamidopyridine 1-oxide	−0·42	0·13	1·03	285	4·09	4·51
8	2-(*N*-Methylacetamido)pyridine 1-oxide	−1·02	0·10	1·25	312	2·01	3·03
9	2-Benzamidopyridine 1-oxide	−0·44	0·16	1·20	295	3·33	3·77
10	2-(*N*-Methylbenzamido)pyridine 1-oxide	−1·39	0·03	0·63	290	1·44	2·83
11	3-Acetamidopyridine 1-oxide	0·99	0·05	0·66	246	4·46	3·47
12	4-Acetamidopyridine 1-oxide	1·59	0·09	0·84	290	5·87	4·28
13	4-(*N*-Methylacetamido)pyridine 1-oxide	1·36	0·09	0·87	270	4·62	3·26
14	4-(*N*-Methylbenzamido)pyridine 1-oxide	1·70	0·07	0·84	237	4·68	2·98

[a] Arithmetical means of 6 values. Apparent values are given; thermodynamic pK_a may be calculated by using the concentration given (cf. ref. 17). Nos. 2 and 5 refer to proton loss, others to proton addition. [b] Standard deviation. [c] An entry in this column signifies that the determination was spectrometric (otherwise potentiometric). Measurements were in phosphate buffers, or sulphuric acid of known H_0. Spectroscopic pK_a measurements were made with a Cary recording spectrophotometer (model 40M–50) and buffers of known pH which were measured on a Cambridge direct-reading pH meter with glass and calomel electrodes.

groups, and this may explain the foregoing failures. Attempts to prepare crystalline metho-salts (cf. VIII) of the acylaminopyridine 1-oxides failed: 2- and 4-acetamidopyridine 1-oxide, on being heated with methyl toluene-*p*-sulphonate, gave 2- and 4-amino-1-methoxypyridinium salts (as IX), the acetyl groups having been lost, evidently by hydrolysis.

[6] Shaw, Bernstein, Losee, and Lott, *J. Amer. Chem. Soc.*, 1950, **72**, 4362.
[7] Tanida, *J. Pharm. Soc. Japan*, 1958, **78**, 613.
[8] Katritzky and Monro, *J.*, 1958, 1263.

Basicity Measurements.—(a) *Thiones.* When the usual assumption is made that alkylation of the individual tautomeric forms has little effect on their basicity, the weaker basicity of the potentially tautomeric 1-hydroxypyridthiones than of the corresponding benzylthiopyridine 1-oxides shows that the former exist predominantly in the pyridthione form (II and IV; X = S). The thione forms are preferred by factors of $10^{1\cdot72}$ and $10^{0\cdot56}$ in the 2- and the 4-series respectively. It is of interest that changing from pyrid-2- and -4-thione to the corresponding 1-oxides little affects the strength of these compounds as bases, but makes them much more strongly acidic (Table 1, last column). This is to be expected, for the oxygen atom is introduced at the site of the acidic centre, but removed from the basic centre.

(b) *Acylamino-compounds.* The (*N*-methylacylamino)- are weaker bases than the acylamino-compounds. This is ascribed to steric inhibition of resonance; the differences (0·23—0·95 pK unit) are smaller than those for the corresponding pyridines: substituents are known to affect the basicity of pyridine 1-oxide less than that of pyridine. The pK_a

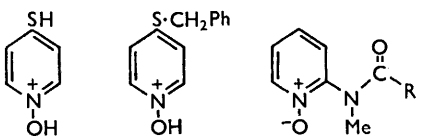
TABLE 2. *Ultraviolet spectral maxima.*

	Ions [b]						Neutral molecules					
No.[a]	mμ	$10^{-3}\varepsilon$	mμ	$10^{-3}\varepsilon$	mμ	$10^{-3}\varepsilon$	mμ	$10^{-3}\varepsilon$	mμ	$10^{-3}\varepsilon$	mμ	$10^{-3}\varepsilon$
1	209	17·2	241	9·3	299·5	9·2	235	10·1	261·5	7·0	322	3·6
2	242	25·1	290	11·4	329	4·6						
3		—	251	12·3	314	11·1	237·5	28·6	261·5	10·2	307·5	4·7
4	222	8·6	286	15·9			214	7·9	285	8·6	326	9·9
5	225	6·5	323	14·5			233 *	4·6				
6	226·5	11·9	308	29·3			205	30·5	299·5	29·5		—
7	235	7·4	290	9·0		—	233	28·7	262	10·0	295	3·6
8	234	11·2	270 *	1·2	313	6·1	230	10·8	258	11·8		—
9	247	14·0	296	17·4		—	246	24·7	278	10·0	295 *	8·7
10	228	13·1	290	5·3		—	243·5	15·7	(—)			—
11	216	31·3	245	18·3	279	6·3	240	24·2	255 *	14·4	295 *	1·7
12			206·5	13·9	271·5	19·2	206·5	18·9	280	23·5		—
13			203	9·7	286	15·0		—	276·5	15·3		—
14			237·5	11·9	280·5	17·5		—	285·5	15·9		—

For conditions see Figs. 1–6. [a] Numbers refer to compounds in Table 1. [b] All cations except Nos. 2 and 5 which refer to anions. * Inflection.

values are consistent with the potentially tautomeric 2- and 4-acylaminopyridine 1-oxides existing as such.

Ultraviolet Spectra.—1-Hydroxypyrid-2- and -4-thione form cations (as X) of similar structure to those (as XI) from 2- and 4-benzylthiopyridine 1-oxide. Figs. 1 and 2 show



(X) (XI) (XII)

that the ultraviolet spectra of the cations in each series are similar; the benzyl groups cause the expected bathochromic shift. However the spectral similarity does not extend to the corresponding neutral species and this is additional evidence that 1-hydroxypyrid-2- and -4-thione exist predominantly as such in aqueous solution.

In the 2-acetamido- and 2-benzamido-series (Figs. 3 and 5) a methyl group on the amide-nitrogen atom lowers the intensity of the longest wavelength band; for the neutral species this results in the coalescence of the two longest wavelength bands into a single band. Steric hindrance would be expected to be particularly severe for the 2-substituted compounds (as XII). The effect in the 4-acetamido-series is smaller (Fig. 4).

Infrared Spectra.—The infrared spectra of 1-hydroxypyrid-2- and -4-thione indicate

that these compounds exist predominantly in the thione form;[9] they do not show the characteristic bands of the pyridine 1-oxide ring as do 2-[10] and 4-benzylthiopyridine 1-oxide.[11] The acylaminopyridine 1-oxides all showed the bands characteristic both of the ·NR·COR′ substituent[12] (R = Me or H; R′ = Me or Ph) and of the 2-,[10] 3-,[1] or 4-substituted[11] pyridine 1-oxides, indicating that the potentially tautomeric acylaminopyridine 1-oxides exist predominantly as such.

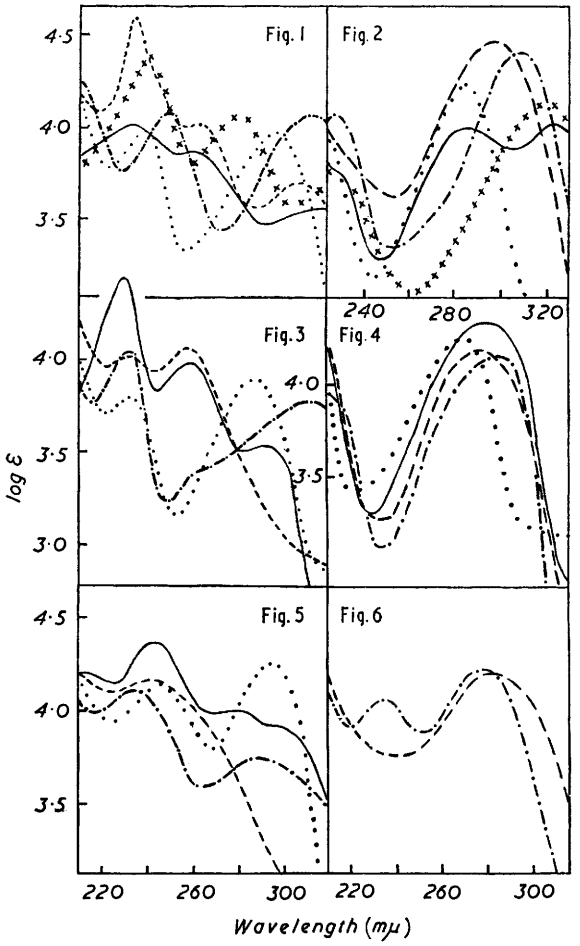


FIG. 1. 1-*Hydroxypyrid-2-thione* —— (*neutral species*, pH 1·8), × × × × (*anion*, pH 10), ... (*cations*, 20N-H_2SO_4). 2-*Benzylthiopyridine* 1-*oxide* — — — (*neutral species*, pH 10), — · — · — (*cation*, 20N-H_2SO_4).

FIG. 2. 1-*Hydroxypyrid-4-thione* —— (*neutral species*, pH 2·7), × × × × (*anion*, pH 10), ... (*cation*, 20N-H_2SO_4). 4-*Benzylthiopyridine* 1-*oxide as for* 2-*compound.*

FIG. 3. 2-*Acetamidopyridine* 1-*oxide* —— (*neutral species*, pH 10), ... (*cation*, 20N-H_2SO_4). 2-(N-*Methylacetamido*)*pyridine* 1-*oxide* — — — (*neutral species*, pH 10), — · — · — (*cation*, 20N-H_2SO_4).

FIG. 4. 4-*Acetamidopyridine* 1-*oxide and* 4-(N-*methylacetamido*)*pyridine* 1-*oxide as for* 2-*series.*

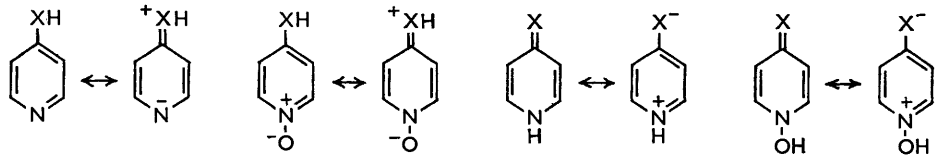
FIG. 5. 2-*Benzamidopyridine* 1-*oxide and* 2-(N-*methylbenzamido*)*pyridine* 1-*oxide as for acetamido-series.*

FIG. 6. 4-(N-*Methylbenzamido*)*pyridine* 1-*oxide as for* 2-*compound.*

Discussion.—The *N*-oxide oxygen atom of pyridine 1-oxides makes canonical forms of type (XVI) more important in stabilising structures (XV) than the stabilisation in corresponding pyridines of structures of type (XIII) by forms of type (XIV). Moreover, the *N*-oxide oxygen atom causes canonical form (XX) to stabilise (XIX) less than forms (XVIII) stabilise structures (XVII). For hydroxy- and amino-compounds the ratios of pyridine 1-oxide form to 1-hydroxypyridone form are greater by factors of *ca.* 10^3 than the corresponding ratios of pyridine to pyridone form.[2] As the pyridthione structure predominates[4] over the mercaptopyridine structure by a factor of *ca.* 10^4 the present results for 1-hydroxypyridthiones are as expected.

[9] Katritzky and Jones, *J.*, 1960, 2947.
[10] Katritzky and Hands, *J.*, 1958, 2195.
[11] Katritzky and Gardner, *J.*, 1958, 2192.
[12] Katritzky and Jones, *J.*, 1959, 2067.

Similar reasoning for the acylamino-compounds based on results for acylaminopyridines [5] leads to the expectation that the acylaminopyridine 1-oxide form should be



(XIII) (XIV) (XV) (XVI) (XVII) (XVIII) (XIX) (XX)

preferred by a factor of *ca.* 10^6. The experimental data are not at variance with this conclusion.

Experimental

1-*Hydroxypyrid-2-thione*.—2-Chloropyridine 1-oxide [3] (1·94 g.), refluxed with thiourea (1·5 g.) in ethanol (30 c.c.) for 1 hr. and then cooled, gave S-2-*pyridylisothiouronium chloride* 1-*oxide* (1·94 g., 60%) which separated from ethanol in needles, m. p. 156—157° (Found: C, 35·5; H, 4·1; N, 20·3. $C_6H_8ON_3SCl$ requires C, 35·0; H, 3·9; N, 20·4%).

The thiouronium chloride (1·25 g.) was kept for 4 hr. with aqueous sodium carbonate (1 g. in 12·5 c.c.). Acidification with 20% hydrochloric acid (2 c.c.) gave 1-hydroxypyrid-2-thione (0·3 g., 49%) which, crystallised from aqueous ethanol, had m. p. 63—64° (lit.,[6] m. p. 65—67°).

Toluene-ω-thiol (4·5 c.c.) and 2-chloropyridine 1-oxide (1·55 g.) were successively added to ethanolic sodium ethoxide (from 1 g. of sodium and 30 c.c. of ethanol). The whole was refluxed for 1 hr. and left for 2 hr. more. After basification with 10% aqueous sodium hydroxide, extraction with ethyl acetate gave (from the evaporated extracts) 2-benzylthiopyridine 1-oxide (1·92 g., 73%) which, crystallised from ethyl acetate, had m. p. 168—170° (lit.,[6] m. p. 169—170°).

1-*Hydroxypyrid-4-thione*.—4-Chloropyridine 1-oxide (2·0 g.) gave *S*-4-pyridylisothiouronium chloride 1-oxide (2·3 g., 70%), m. p. 169—170° (lit.,[13] m. p. 167°), as in the 2-series, which was converted as above into 1-hydroxypyrid-4-thione (0·8 g., 57%), needles (from aqueous ethanol, m. p. 140° (decomp.) (lit.,[14] m. p. 142°).

For 4-benzylthiopyridine 1-oxide see ref. 11.

2-*Acylaminopyridine* 1-*Oxides*.—The following were prepared by acylation of the corresponding amine: [3] 2-acetamido-, m. p. 139—140° (lit., 140·5—141°); 2-benzamido-, m. p. 121—123° (lit., 122—124°); 2-(*N*-methylacetamido)pyridine 1-oxide, m. p. 97—98° (lit., 95—97°). Infrared bands due to the ring for 2-(*N*-methylacetamido)pyridine 1-oxide [10] were 1613 (100), 1554* (25), 1500 (290), 1432 (195), 1268 (290), (—), (—), 1109* (30), 1040 (30), 838 (155).

2-Methylaminopyridine 1-oxide (0·5 g.) in benzene (12·5 c.c.) and triethylamine (1·2 c.c.) was treated with benzoyl chloride (0·56 g.) in benzene (2·5 c.c.). Precipitated triethylamine hydrochloride was filtered off and the filtrate evaporated to give 2-(N-*methylbenzamido*)*pyridine* 1-*oxide* (0·72 g., 78%), m. p. 152—153° (rhombs from ethyl acetate) (Found: C, 68·3; H, 5·6; N, 12·2. $C_{13}H_{12}O_2N_2$ requires C, 68·4; H, 5·3; N, 12·3%).

3-*Acetamidopyridine* 1-*Oxide*.—3-Acetamidopyridine (1 g.) was heated with 30% hydrogen peroxide (1·2 c.c.) and acetic acid (4 c.c.) for 24 hr. at 70°. Volatile material was removed at 100°/20 mm. and the residue in chloroform (10 c.c.) was digested with potassium carbonate (0·5 g.) for 10 min. Solid was filtered off, and evaporation of the filtrate gave 3-acetamidopyridine 1-oxide (1·0 g., 90%) which, crystallised from ethanol, had m. p. 208—211° (lit.,[15] m. p. 208—210°).

Infrared bands due to the 3-pyridine 1-oxide nucleus [1] were 1615s, 1575m, 1485m, (—), (—), 1152s, 1006m, (—), (—).

4-*Acylaminopyridine* 1-*Oxides*.—4-Aminopyridine 1-oxide (1·0 g.) was refluxed with acetic anhydride (0·9 c.c.) and ethyl methyl ketone (5 c.c.) for 45 min. Solid separated, the whole was cooled, and the solid was crystallised from ethanol–ethyl acetate (1 : 1) to yield 4-*acetamidopyridine* 1-*oxide* as needles, m. p. 260—261° (Found: C, 55·0; H, 5·4; N, 18·4. $C_7H_8O_2N_2$ requires C, 55·2; H, 5·3; N, 18·4%).

[13] Itai, *J. Pharm. Soc. Japan.*, 1954, **74**, 5648.
[14] Ochiai, *J. Org. Chem.*, 1953, **18**, 534.
[15] Leonard and Wajngust, *J. Org. Chem.*, 1956, **21**, 1077.

Infrared bands due to the 4-pyridine 1-oxide nucleus [11] were 1606s, 1480†s, 1442s, 1200s, 1174s, 1038m, 1012m, 857s, 805s.

4-Methylaminopyridine 1-oxide [2] (0·7 g.) was refluxed with acetic acid (3·0 c.c.) and acetic anhydride (1·5 c.c.) for 2 hr. Volatile material was removed at 100°/20 mm. and the residue taken up in hot chloroform (10 c.c.) and digested with potassium carbonate (0·5 g.) for 10 min. Solid was filtered off. Evaporation of the filtrate gave 4-(N-*methylacetamido*)*pyridine* 1-*oxide* (0·35 g., 38%) which separated from chloroform–light petroleum (5 : 1) in rods, m. p. 145—147° (Found: C, 57·8; H, 6·1; N, 16·6. $C_8H_{10}O_2N_2$ requires C, 57·8; H, 6·1; N, 16·9%).

4-Methylaminopyridine 1-oxide (0·85 g.), ethyl methyl ketone (50 c.c.), triethylamine (2·5 c.c.), and benzoyl chloride (1·4 g.) were kept for 15 hr. at 20°. Separated solid was then filtered off and washed with ethyl methyl ketone; the filtrate and washings were evaporated, to give 4-(N-*methylbenzamido*)*pyridine* 1-*oxide benzoate* (1·35 g., 55%) which separated from chloroform–light petroleum as needles, m. p. 116—118° (Found: C, 68·2; H, 5·3; N, 7·8. $C_{20}H_{18}O_4N_2$ requires C, 68·5; H, 5·2; N, 8·0%).

The foregoing benzoate (0·1 g.) in hot chloroform (10 c.c.) was digested with potassium carbonate (0·06 g.). Solid was removed and then evaporation of the filtrate gave 4-(N-*methylbenzamido*)*pyridine* 1-*oxide* (0·03 g., 43%) which formed cubes (from benzene), m. p. 144·5—145° (Found: C, 68·6; H, 5·8; N, 12·0. $C_{13}H_{12}O_2N_2$ requires C, 68·4; H, 5·3; N, 12·3%).

Hydrogenation of 2-*Acetamidopyridine* 1-*Oxide*.—The oxide (1·5 g.) was reduced (cf. ref. 8) to 2-acetamidopyridine (1·0 g., 80%), m. p. 69—70° (mixed m. p. 69°; lit.,[16] m. p. 71°).

Reaction of 2- *and* 4-*Acetamidopyridine* 1-*Oxide with Methyl Toluene*-p-*Sulphonate*.—2-Acetamidopyridine 1-oxide (0·7 g.) was heated with methy ltoluene-*p*-sulphonate (0·7 g.) at 105° for 12 hr. Recrystallisation of the product from ethanol–ethyl acetate (1 : 1) gave 2-amino-1-methoxypyridinium toluene-*p*-sulphonate (0·7 g., 50%), m. p. 123—124° (lit.,[3] m. p. 127—129°) (Found: C, 52·4; H, 5·3; N, 9·3. Calc. for $C_{13}H_{16}O_4N_2S$: C, 52·6; H, 5·4; N, 9·4%), $\lambda_{max.}$ 228 (ε 16,000) and 299 mμ (ε 9000) in 20N-H_2SO_4; 222 (ε 12,900), 246 (ε 11,800), and 311 mμ (ε 6200) in N-NaOH (cf. ref. 3).

Similarly 4-acetamidopyridine 1-oxide gave 4-amino-1-methoxypyridinium toluene-*p*-sulphonate (60%) m. p. 126—127° (lit.,[2] m. p. 127—129°) (Found: N, 9·4. Calc. for $C_{13}H_{16}O_4N_2S$: N, 9·4%), $\lambda_{max.}$ 209 (ε 19,100) and 272 mμ (ε 20,800) in 20N-H_2SO_4; 272 mμ (ε 27,100) in N-NaOH (cf. ref. 2).

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[16] Camps, *Arch. Pharm.*, 1902, **240**, 363.