[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, TULANE UNIVERSITY]

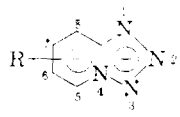
Lithium Derivatives of Pyridotetrazole and the Isomeric Methylpyridotetrazoles[1]

BY J. H. BOYER AND R. F. REINISCH[2]

RECEIVED SEPTEMBER 1, 1959

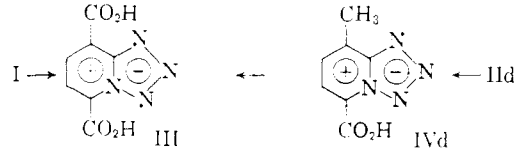
Hydrogen lability at the 5-position in 8-methylpyridotetrazole (IId), at the 5- and 8-positions in pyridotetrazole (I) and its 6-methyl derivative (IIb) and in the methyl group of 5-methylpyridotetrazole (IIa) is demonstrated in reactions with phenyllithium. Location of metalation is established by identification of carboxylic acids IV formed by carbonation of lithium salts. Dilithium derivatives of pyridotetrazole and 6-methylpyridotetrazole (IIb) give corresponding 5,8-dicarboxy derivatives III, IVb. Side-chain monometalation of 5-methylpyridotetrazole affords a good yield of 5-pyridotetrazolacetic acid (IVa). A monolithium salt of 7-methylpyridotetrazole (IIc) gives a very low yield of an unidentified acid and a monolithium salt of 8-methylpyridotetrazole (IId) gives 5-carboxy-8-methylpyridotetrazole (IVd).

An investigation of expected labile hydrogen attached to certain positions of the electron-deficient pyridine ring[3] or contained in certain side chains of the four isomeric methyl derivatives of pyridotetrazole has now been carried out by means of a metalation reaction on pyridotetrazole (I) and each of its four methyl derivatives IIa-d. Lithium salts obtained from I or IIa-d and phenyllithium, treated with carbon dioxide and acidified, give acids whose identification locates the position of litliiation.



I, R = H
IIa, R = 5-CH_3
IIb, R = 6-CH_3
IIc, R = 7-CH_3
IId, R = 8-CH_3

The formation of a product identified as 5,8-pyridotetrazoledicarboxylic acid (III) from pyridotetrazole (I) requires dilithiation. Assignment of the 8-carboxyl substituent is established by oxidation of a monocarboxylic acid (IVd) derived from 8-methylpyridotetrazole (IId) after lithiation, carbonation and acidification. This dicarboxylic acid is identical with III. Failure to form a cyclic anhydride on sublimation or in refluxing acetic anhydride permits the other carboxyl group to be at the 5- or 6-position. The former position is tentatively assigned on the basis of ultraviolet and infrared absorption and the greater reactivity expected at a position adjacent to a ring nitrogen atom in a reaction with phenyllithium.



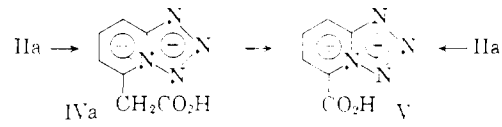
A bathochromic shift of 19 mμ is recorded (Table I) for replacing hydrogen with a carboxyl group in the 5-position of pyridotetrazole, whereas a corresponding shift of 10 mμ is found characteristic for similar substitution at the 6-position. A bathochromic shift of 18 mμ for replacing hydrogen with a carboxyl group in 8-methylpyridotetrazole supports the assignment of 5-carboxyl-8-methylpyridotetrazole. Infrared and ultraviolet spectra are respectively identical for samples of III prepared from I and from IVd.

(1) Financial support by E. Bilhuber, Inc., Orange, N. J., and by Research Grants H-2295 and CY-2895 from the National Institutes of Health is gratefully acknowledged.

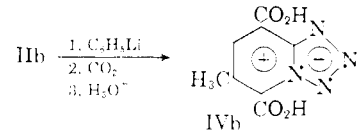
(2) Recipient of a Public Health Service Research Fellowship (predoctoral) 1956–1957.

(3) J. H. Boyer and E. J. Miller, THIS JOURNAL, **81**, 4671 (1959).

Of the isomeric methylpyridotetrazoles (IIa-d), lithiation in the side chain has been established for the 5-methyl derivative IIa.[4] Identification of 5-pyridotetrazoylacetic acid (IVa) has been accomplished by its oxidation to pyridotetrazole-5-carboxylic acid (V), also obtained from the oxidation of 5-methylpyridotetrazole (IIa). In the ultraviolet, samples of IIa and IVa in ethanol give identical absorption at 262–264 mμ, log ϵ 3.83–3.85.



Acids are obtained in low yields from each of 6- and 8-methylpyridotetrazoles. Dilithiation of the 6-methyl derivative gives a dicarboxylic acid which fails to form a cyclic anhydride on sublimation or in refluxing acetic anhydride. The tentative assignment of 6-methylpyridotetrazole-5,8-dicarboxylic acid, rather than 6-methylpyridotetrazole-5,7-dicarboxylic acid or 8-carboxypyridotetrazoyl-6-acetic acid, is supported by ultraviolet absorption and a similar transformation of pyridotetrazole. A bathochromic shift of 40 mμ in ultraviolet absorption occurs as carboxyl groups replace hydrogen in



both 5- and 8-positions of pyridotetrazole. A comparable shift of 35 mμ (Table I), observed in replacing hydrogen by carboxyl groups in 6-methylpyridotetrazole, lends support to the assignment for IVb.

An unidentified monocarboxylic acid (IVc), is obtained in very low yield from 7-methylpyridotetrazole (IIc). In view of the condensation of 1,4-dimethylpyridone-2 with ethyl oxalate,[4] the lack of reactivity of the methyl group in 7-methylpyridotetrazole toward phenyllithium is unexpected and demonstrates a marked decrease in hydrogen lability relative to 5-methylpyridotetrazole. An explanation cannot be offered for the nearly complete lack of lithiation (if it occurs at all) at either the 5- or 8-positions of IIc.

(4) In the condensation with ethyl oxalate, intermediate metalation of 1,4- and 1,6-dimethyl-2-pyridone in the C-methyl side-chain is analogous (R. Adams and A. Schrecker, THIS JOURNAL, **71**, 1186 (1949)).

TABLE I

ULTRAVIOLET ABSORPTION[a]

Compound	Max., mμ	log ε
Pyridotetrazole[b]	260	3.72
5-Methylpyridotetrazole	262	3.85
6-Methylpyridotetrazole	260	3.72
7-Methylpyridotetrazole	260	3.72
8-Methylpyridotetrazole	260	3.86
5,7-Dimethylpyridotetrazole	264	3.91
5-Carboxypyridotetrazole	279	3.54
	249	3.40
6-Carboxypyridotetrazole	270	3.61
7-Carboxypyridotetrazole	280	3.67
8-Carboxypyridotetrazole	283	3.68
5-Carboxy-8-methylpyridotetrazole	278	3.85
X-Carboxy-7-methylpyridotetrazole	288	3.25
	254	3.25
5,8-Dicarboxypyridotetrazole[c]	300	3.58
	282	3.79
5,8-Dicarboxy-6-methylpyridotetrazole	295	3.96
	250	3.40
5-Pyridotetrazoylacetic acid	264	3.83

[a] Absolute ethanol solutions were examined in a model DK Beckman quartz automatic recording spectrophotometer. [b] Neither the position nor the intensity of absorption changed in mineral acid or alkaline solution. [c] Identical absorption bands for samples from I and IVd.

Acknowledgment.—We are indebted to Mr. R. T. O'Connor, Southern Regional Research Laboratory, for infrared absorption data.

Experimental[5]

Methyl-2-bromopyridine Isomers (Table II).—According to the Craig procedure[6] 113.4 g. (1.05 moles) of a methyl-2-aminopyridine was added to 530 ml. (5 moles) of 48% hydrobromic acid in a 3-liter three-necked round-bottom flask equipped with stirrer, dropping funnel and thermometer. The temperature, maintained at 5–10° by external cooling during the addition of the amine, was dropped below 0° and 161 ml. (3.2 moles) of bromine was added slowly with vigorous stirring. To the cold mixture, 185 g. (2.7 moles) of sodium nitrite in 270 ml. of water was added at such a rate that the temperature remained under 0°. Stirring was continued 30 minutes and 402 g. (10 moles) of sodium hydroxide in 400 ml. of water was added as the temperature was held below 20°. Four ether extracts (250 ml. each) of the yellow reaction mixture were combined, dried over potassium hydroxide and distilled. Yields and physical properties are recorded in Table II.

TABLE II

METHYL DERIVATIVES OF 2-BROMOPYRIDINE

Substituent(s)	Yield, %	B.p. °C.	Mm.
3-Methyl[a]	82	116–120	21
4-Methyl[b]	84	87–92	6
5-Methyl[b]	84	[c]	
6-Methyl[d]	64	64–69	5
4,6-Dimethyl[e]	31	67–68	0.8

[a] R. P. Mariella and V. Kvinge, THIS JOURNAL, **70**, 3126 (1948). [b] F. H. Case, *ibid.*, **68**, 2574 (1946). [c] M.p. 43–44°. F. H. Case, ref. *b*, reported m.p. 49–50°. [d] H. D. T. Wilink, Jr., and J. P. Wibaut, *Rec. trav. chim.*, **53**, 417 (1934). [e] $n^{25}D$ 1.5520, d^{20} 1.4347. Calcd. for C_7H_8NBr: C, 45.18; H, 4.33; N, 7.52; Br, 42.84. Found: C, 45.07; H, 4.39; N, 7.32; Br, 42.99.

(5) Semi-micro analyses by Alfred Bernhardt, Max Planck Institut Microanalytisches Laboratorium, Mülheim (Ruhr), Germany, and Midwest Microlab, Inc., Indianapolis, Ind. Melting points are uncorrected.

(6) L. C. Craig, THIS JOURNAL, **56**, 231 (1934).

Methylpyridotetrazole Isomers (Table III).—According to a procedure previously reported[7] 318 ml. of 10% hydrochloric acid was added slowly to 100 g. (0.634 mole) of a methyl-2-bromopyridine and 65.0 g. (1.0 mole) of sodium acid in 500 ml. of 50% ethanol in a 1-liter round-bottom three-necked flask equipped with a dropping funnel with a pressure equalizing arm, reflux condenser and thermometer. The mixture was heated at reflux temperature for 48 hours and then concentrated to about half of the original volume by distillation. The residue was cooled in a refrigerator, filtered and recrystallized. The colorless solid tetrazoles are described in Table III.

TABLE III

METHYLPYRIDOTETRAZOLES

Substituent	Yield, %	M.p., °C.	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
5-Methyl	90	145–146	$C_6H_6N_4$	53.73	53.44	4.51	4.51	41.76	41.59
6-Methyl	65	144–145[a]	$C_6H_6N_4$	53.73	53.63	4.51	4.61	41.76	41.98
7-Methyl	61	95–97	$C_6H_6N_4$	53.73	51.86[b]	4.51	4.74	41.76	41.76
8-Methyl	71	142–143	$C_6H_6N_4$	53.73	53.42	4.51	4.72	41.76	42.06
5,7-Dimethyl	50	123–124[a]	$C_7H_8N_4$	...	..	..	..	...	...

[a] Kereszty and Wolf, German Patent 613,123; *C.A.*, **29**, 5604 (1935), reported 6-methylpyridotetrazole, m.p. 152–153°, and 5,7-dimethylpyridotetrazole, m.p. 128–129°. [b] Assumed to be in error.

Pyridotetrazolecarboxylic Acids (Table IV).—To 8.3 g. (0.05 mole) of lithium chromate dihydrate in 100 ml. of concentrated sulfuric acid cooled at 15°, 2.68 g. (0.20 mole) of a methylpyridotetrazole was added at such a rate (about one hour was required) that the temperature remained under 30° with external cooling. The green solution from 5-methylpyridotetrazole was stirred an additional hour at 15°, poured onto 300 g. of crushed ice and extracted with ether by means of a liquid–liquid extractor. The ether extract was dried over magnesium sulfate, decolorized with charcoal and concentrated to turbidity. The mixture was cooled to 0° and filtered. After several recrystallizations from hot water the 5-carboxypyridotetrazole was obtained as tan needles. Yields and other data are found in Table IV. The isomeric acids (Table IV) were isolated by precipitating each from its reaction mixture by the addition of lithium carbonate and were recrystallized from hot water.

A similar oxidation of 5-pyridotetrazoylacetic acid by lithium chromate gave 5-carboxypyridotetrazole, m.p. 208–209° dec., ultraviolet absorption and infrared absorption respectively identical with corresponding data for 5-carboxypyridotetrazole obtained from 5-methylpyridotetrazole.

Lithium Salts.—Phenyllithium was prepared from lithium ribbon (1.16 g., 0.166 mole) and bromobenzene (12.93 g., 0.083 mole) in 500 ml. of anhydrous ether. After lithium metal had disappeared (about 2 hours), 100 ml. of ether was removed by distillation and 3.35 g. (0.025 mole) of 5-methylpyridotetrazole as a slurry in 200 ml. of anhydrous ether was added all at once. The reaction mixture, which changed in color from brown to a deep purple, was stirred for 3 hours at 25° and poured on 500 g. of Dry Ice in ether. After excess Dry Ice had sublimed, the yellow mixture of lithium salts was added slowly to 100 ml. of 15% hydrochloric acid to which 200 g. of crushed ice had been added and stirred for one hour. Crude benzoic acid, 0.7 g., m.p. 105–110°, precipitated and an additional 1.39 g. of crude benzoic acid, m.p. 110–112°, was obtained on extracting the filtrate with ether (total yield 3.06 g., 43% based on bromobenzene) and recrystallized as colorless needles, m.p. and mixture m.p. 121–122°. The aqueous layer was concentrated to 20 ml. and stored 12 hours in a refrigerator. Crude 5-pyridotetrazoylacetic acid, 1.85 g. (42%), m.p. 175–178° dec., sepa-

(7) J. H. Boyer, D. I. McCane, W. J. McCarville and A. T. Tweedie, THIS JOURNAL, **75**, 5298 (1953).

TABLE IV

PYRIDOTETRAZOLECARBOXYLIC ACIDS FROM OXIDATION OF A CORRESPONDING METHYLPYRIDOTETRAZOLE WITH LITHIUM CHROMATE[a]

Substituent	Yield, %	Dec., °C.	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Oxygen, % Calcd.	Oxygen, % Found
5-Carboxy[b]	14	208–209	$C_6H_4N_4O_2$	43.91	43.77	2.46	2.44	34.14	34.09	19.49	19.69
6-Carboxy[b]	33	223–225	$C_6H_4N_4O_2$	43.91	42.99[c]	2.46	2.60	34.14	33.87	19.49	20.61[c]
7-Carboxy	33	228–230	$C_6H_4N_4O_2$	43.91	44.01	2.46	2.59	34.14	33.93	19.49	19.37
8-Carboxy[b]	33	245–247	$C_6H_4N_4O_2$	43.91	43.90	2.46	2.59	34.14	34.04	19.49	19.23
5(or 7)-Methyl-7(or 5)-carboxy[b,d]	16	238–240	$C_7H_6N_4O_2$	47.18	46.91	3.39	3.54	31.44	31.24	17.96	17.72

[a] Experiments with pyridotetrazole and 5-carboxypyridotetrazole established oxidative degradation of the pyridine ring at 85–90°. [b] Blue fluorescence to ultraviolet light. [c] Assumed to be in error. [d] Apparently a mixture of the two possible compounds. Attempts to obtain a dicarboxylic acid by oxidation at 60° were unsuccessful; at higher temperatures oxidation destroyed the molecule.

TABLE V

ACIDS FROM CARBONATION OF LITHIUM SALTS OF PYRIDOTETRAZOLE AND ITS METHYL DERIVATIVES

Lithium salt of	Acid	Yield, %	M.p., dec., °C.	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Oxygen, % Calcd.	Oxygen, % Found
I	III	28	243–244	$C_7H_4N_4O_4$	40.40	40.47	1.94	2.12	26.91	26.91	30.76	31.31
IIa	IVa	41	179–180	$C_7H_6N_4O_2$	47.18	47.47	3.39	3.50	31.44	31.43	17.96	17.67
IIb	IVb	11	207–208	$C_8H_6N_4O_4$	43.28	43.20	2.72	2.94	25.21	25.47	[a]	
IIc	IVc	5	214–215	$C_7H_6N_4O_2$	47.18	47.24	3.39	3.29	31.44	30.90	17.96	19.19[b]
IId	IVd	18	245–248	$C_7H_6N_4O_2$	47.18	46.85	3.39	3.13	31.44	32.03	17.96	18.04

[a] Not analyzed for oxygen. [b] Assumed to be in error.

rated as a tan powder which recrystallized from hot water as colorless needles, m.p. 179–180° dec.

Anal. Calcd. for $C_7H_6N_4O_2$: C, 47.18; H, 3.39; N, 31.44; O, 17.96. Found: C, 47.47; H, 3.50; N, 31.43; O, 17.67.

A similar procedure was followed in transforming pyridotetrazole[7] and its 6-, 7- and 8-methyl derivatives into carboxylic acid derivatives. The results are contained in Table V. In KBr disks, samples of 5,8-dicarboxypyridotetrazole (III) from both I and IVd gave absorption in the infrared at 3200–2400, 2000, 1695, 1621, 1575, 1515, 1422, 1342, 1307, 1266, 1202, 1135, 1120, 1088, 1033, 1003, 990, 901, 823, 800, 761, 730 and 681 cm.$^{-1}$.

Ethyl 5-pyridotetrazoyl acetate was obtained in 4% yield by treating the appropriate mixture of lithium salts with ethanol saturated with hydrogen chloride. It recrystallized from aqueous ethanol as colorless needles, m.p. 110–111.5°.

Anal. Calcd. for $C_9H_{10}N_4O_2$: C, 52.47; H, 4.89; N, 27.19; O, 15.53. Found: C, 52.35; H, 5.14; N, 27.12; O, 15.60.

NEW ORLEANS, LA.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, TULANE UNIVERSITY]

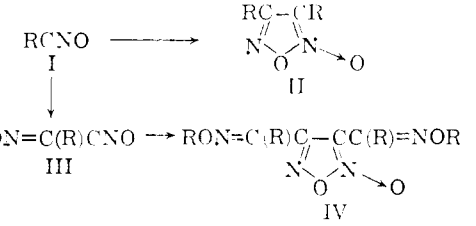
The Identification of $C_{32}H_{20}N_4O_8$, a Product from Acetophenone and Nitric Acid[1]

BY J. H. BOYER AND M. S. CHANG

RECEIVED SEPTEMBER 8, 1959

A minor product from acetophenone and nitric acid has been identified as the dibenzoate ester of bis-(benzoylformaldoximino)-furoxan (IV, R = C_6H_5CO).

The proposed formation of dibenzoylfuroxan (II, R = C_6H_5CO) by dimerization of benzoylnitrile oxide[2] (I, R = C_6H_5CO) in the reaction of acetophenone and nitric acid[3] opened a new approach to the identification of a minor product[3] which has been described as isomeric[2–5] and dimeric[6,7] with II (R = C_6H_5CO) and also is obtained from 1,6-diphenyl-1,3,4,6-hexanetetraone and nitric acid[8] and from chloroisonitrosoacetophenone in acetic acid containing sodium acetate.[4] An identification of the minor product as the dibenzoate ester of bis-(benzoylformaldoximino)-furoxan[9] (IV, R = C_6H_5CO) has developed from the observations reported here.



The molecular formula $C_{32}H_{20}N_4O_8$,[6] confirmed by new elemental analyses and molecular weight determinations, establishes the product as a tetramer of benzoylnitrile oxide. In contrast with

(1) Financial assistance under Contract No. DA-01-009-ORD-428 with the Office of Ordnance Research, U. S. Army is gratefully acknowledged.

(2) N. E. Boyer, G. M. Czerniak, H. S. Gutowsky and H. R. Snyder, THIS JOURNAL, **77**, 4238 (1955).

(3) A. F. Holleman, *Ber.*, **20**, 3359 (1887); **21**, 2835 (1888).

(4) G. Ponzio, *Gazz. chim. ital.*, **62**, 415, 633 (1932).

(5) R. Scarpati and M. Rippa *ibid.*, **88**, 804 (1958).

(6) M. J. Boeseken, *Rec. trav. chim.*, **29**, 275 (1909).

(7) G. Ruggeri, *Gazz. chim. ital.*, **54**, 72 (1924).

(8) O. Widman and E. Virgin, *Ber.*, **42**, 2798 (1909).

(9) J. H. Boyer and M. S. Chang, *Chemistry and Industry*, 730 (1959).