[CONTRIBUTION FROM THE ROHM & HAAS CO.]

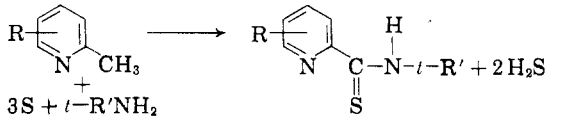
Preparation of Some *N*-*t*-Alkylthiopicolinamides

RICHARD C. MANSFIELD

Received February 26, 1959

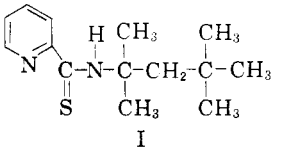
N-*t*-Alkylthiopicolinamides have been obtained from the reaction of *t*-carbinamines with sulfur and α-picoline. 2,3-Lutidine, 2,4-lutidine, 2,6-lutidine, and 2-methyl-5-ethylpyridine react with sulfur and *t*-carbinamines only at the 2-methyl group to give *N*-*t*-alkylthiopicolinamides.

A general investigation of some reactions of *t*-carbinamines and reports that methyl pyridines undergo reactions with sulfur and aromatic amines[1-6] and with sulfur and morpholine[1] prompted an investigation of the reaction of *t*-carbinamines and sulfur with α-picoline and a number of monosubstituted α-picolines.

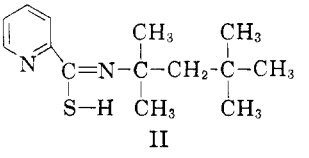


R = H, 3-CH_3, 4-CH_3, 6-CH_3, or 5-CH_2CH_3
R′ = *t*-butyl, *t*-octyl, *t*-$C_{11-14}H_{23-29}$, *t*-$C_{18-22}H_{37-45}$

The reaction of α-picoline, sulfur, and *t*-octylamine gave a good yield of *N*-*t*-octylthiopicolinamide (I). The infrared spectrum indicated that this material exists only in the thione tautomeric form. There was an intense band at 3325 cm.$^{-1}$ which can be attributed to the N—H stretching vibration. Strong absorption near 1470 cm.$^{-1}$ was attributed to the —N—C=S group. Absorption in the 2550–2600 cm.$^{-1}$ region from the S—H stretching vibration of the thioenol tautomeric form (II) was not observed.

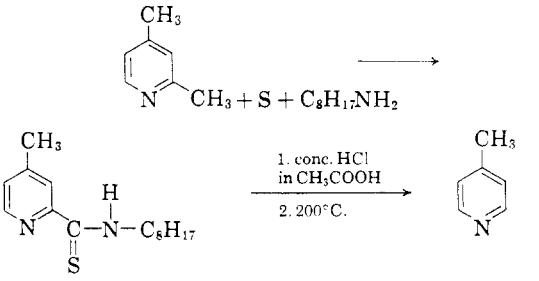


I



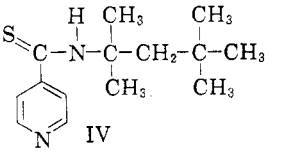
II

Reaction of *t*-octylamine and sulfur with 2,4-lutidine occurred only at the 2-methyl group to give *N*-(*t*-octyl)-4-methylthiopicolinamide (III). Hydrolysis of III, followed by decarboxylation gave only 4-methylpyridine. No 2-methylpyridine, which would have resulted if reaction had occurred at the 4-methyl group, was obtained. The thioamide (III) absorbed strongly at 832 cm.$^{-1}$, which is to be



III

expected for a 2,4-substituted pyridine. In addition, the spectra of III and I showed many points of similarity not shared by the spectrum of *N*-*t*-octylthioisonicotinamide (IV).

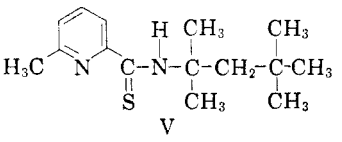


IV

Lochte and Cheavens[7] have shown preferential reaction at the 4-methyl group in the methyl iodide alkylation of 2,4-lutidine using the sodamide-liquid ammonia method. The participation of 2- and 4-methylpyridine in certain ionic reactions has been explained by resonance stabilization of the carbanions,[8] and the greater reactivity of the 4-isomer has been attributed to its enhanced ability to participate in hyperconjugation involving the more important *p*-quinoid structures.[7-9] Pryor[10] has postulated that sulfur plus any nucleophile gives polysulfides which undergo fission to yield radicals capable of abstracting benzyl hydrogens. It is possible, therefore, that the initial step in reactions of methyl pyridines with sulfur and amines is abstraction of a picolyl hydrogen by an amine polysulfide, since this would not necessarily imply preferential reaction at the 4-methyl group of 2,4-lutidine. In fact, Porter[1] has observed that 2-methylpyridine reacted more readily with sulfur and aniline than did 4-methylpyridine.

(1) H. D. Porter, *J. Am. Chem. Soc.*, **76**, 127 (1954).
(2) B. Emmert and M. Groll, *Ber.*, **86**, 208 (1953).
(3) B. Emmert and A. Holz, *Ber.*, **87**, 676 (1954).
(4) K. V. Martin, *J. Am. Chem. Soc.*, **80**, 233 (1958).
(5) F. Lions and K. V. Martin, *J. Am. Chem. Soc.*, **80**, 1591 (1958).
(6) P. E. Miller, G. L. Oliver, J. R. Dann, and J. W. Gates, Jr., *J. Org. Chem.*, **22**, 664 (1957).
(7) H. L. Lochte and T. H. Cheavens, *J. Am. Chem. Soc.*, **79**, 1667 (1957).
(8) H. C. Brown and W. A. Murphey, *J. Am. Chem. Soc.*, **73**, 3308 (1951).
(9) H. C. Brown and X. R. Mihm, *J. Am. Chem. Soc.*, **77**, 1723 (1955).
(10) W. A. Pryor, *J. Am. Chem. Soc.*, **80**, 6481 (1958).

The reaction between 2,6-lutidine, sulfur, and *t*-octylamine proceeded smoothly at only one methyl group to give *N*-(*t*-octyl)-6-methylthiopicolinamide (V). An attempt to cause V to react with



V

sulfur and *t*-octylamine was unsuccessful. Unreacted *N*-(*t*-octyl)-6-methylthiopicolinamide (V) was recovered nearly quantitatively.

The usual resonance interpretation[8,9] of the reactivity of 2- and 4-methylpyridines, which implies some exocyclic double bond character at the 2- and 4-positions, provides the basis for a possible explanation of the lack of reactivity of the second methyl group. The electron withdrawal tendency of the thione group at the 2- position in III or V might be expected to confer some exocyclic double bond character at the 2- position of the ring, thus diminishing the possibility of any exocyclic double bond character at the remaining methyl group in the 4- or 6- position. Such a resonance stabilization effect would be expected for a radical mechanism as well as for an ionic mechanism.

Products from the reactions of 2,3-lutidine and 2-methyl-5-ethylpyridine with sulfur and *t*-carbinamines were identified only by elemental analyses. While these indicate only that one methyl group reacted, it is likely that in both these materials reaction occurred at the 2 methyl group in view of the well established preferential reactivity of alkyl groups in the 2- and 4- positions of the pyridine nucleus over those in the 3- and 5- positions. This supposition is strengthened by the results of Porter,[1] who found that 3-methylpyridine, sulfur, and aniline gave no thionicotinanilide.

Good yields of *N*-*t*-alkylthiopicolinamides were obtained only when both sulfur and the methyl pyridine were used in excess. Variations in yield of *N*-*t*-octylthiopicolinamide (I) with changes in the mole ratio of reactants are shown in Table I. An attempt to carry out the reaction using a 1:1:3 mole ratio of α-picoline : *t*-octylamine : sulfur and employing 4 moles of pyridine as solvent gave only 10% of *N*-*t*-octylthiopicolinamide (I).

TABLE I

N-*t*-OCTYLTHIOPICOLINAMIDE (I)

α-Picoline, Moles	*t*-Octylamine, Moles	Sulfur, Moles	Yield, %[a]
1	1	6	10
1	1	3	13
2	1	3	44
4	1	3	76
2	1	6	94

[a] Based on *t*-octylamine. Once-distilled product containing a few percent unreacted sulfur.

Table II summarizes the preparations of *N*-*t*-alkylthiopicolinamides from the various methyl pyridines, sulfur, and *t*-carbinamines. Some of the reactions were carried out before the most desirable mole ratios had been determined and therefore may not represent the optimum yields. All the products were distillable yellow liquids. Analytical data showed that the once-distilled products contained a few percent of unreacted sulfur. Treatment with a solution of sodium sulfide in aqueous methanol successfully removed the unreacted sulfur so that subsequent distillation gave materials with elemental analyses corresponding to the theoretical values.

The attempted quaternization of *N*-*t*-octylthiopicolinamide (I) with ethyl iodide was unsuccessful.

EXPERIMENTAL

N-t-Alkylthiopicolinamides. (See Table II.) A mixture of the methyl pyridine, *t*-alkylamine, and sulfur was stirred and refluxed in a three-neck flask equipped with condenser, stirrer, and thermometer while hydrogen sulfide was evolved through the condenser. The mixture was cooled, diluted with heptane, filtered free of excess sulfur, and distilled. A mixture of the distilled product (1.0 mole), water (1.5 l.), methanol (0.5 l.), and sodium sulfide nonahydrate (0.75 mole) was stirred at 80° for 1.5 hr., cooled, and extracted with heptane. The heptane extract was dried over anhydrous potassium carbonate and distilled.

N-t-Octylthioisonicotinamide (IV). A mixture of 96 g. (3.0 moles) of sulfur, 93 g. (1.0 mole) of γ-picoline, and 65 g. (0.5 mole) of *t*-octylamine was stirred and refluxed for 12 hr., cooled, filtered, and distilled to give 75 g. of material, b.p., 140–180°/1 mm. Hg, which solidified. The distillate was stirred for 1.5 hr. at 80° with a mixture of 60 g. (0.25 mole) of sodium sulfide nonahydrate, 119 g. of methanol, and 450 g. of water. The material which solidified when the mixture was cooled was filtered off and recrystallized from heptane. There was obtained 34 g. (27%) of *N*-*t*-octylthioisonicotinamide (IV), m.p. 117.5–118.5°C.

Anal. Calcd. for $C_{14}H_{22}N_2S$: C, 67.15; H, 8.86; N, 11.19; S, 12.80. Found: C, 67.19; H, 8.90; N, 11.13; S, 13.00.

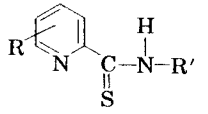
Hydrolysis and decarboxylation of N-(t-octyl)-4-methylthiopicolinamide (III). A mixture of 20 g. (0.076 mole) of *N*-(*t*-octyl)-4-methylthiopicolinamide (III), 100 g. of concentrated hydrochloric acid, and 200 g. of glacial acetic acid was stirred and refluxed for 3 hr., cooled, filtered, stripped to about 50 ml., made alkaline with excess 25% sodium hydroxide solution, and extracted with heptane. The aqueous portion was then made acidic with concentrated hydrochloric acid and stripped to near dryness. Successive extractions and evaporations were made using hot absolute ethyl alcohol to remove water and inorganic salts. The product was then taken up in isopropyl alcohol and precipitated with ether. Digestion of the precipitate with chloroform gave a solid which was dissolved in water and made to *p*H 6 with dilute aqueous sodium hydroxide. The solution was evaporated to dryness and the dried residue was extracted with warm acetone. The acetone extract was heated to distill off the acetone and then refluxed at about 200° for 5 min. in a large test tube. A picrate of the material remaining in the tube melted at 161–163° after recrystallization from ethyl alcohol. The melting point of a mixture with authentic γ-picoline picrate was 161–163°. The melting point of a mixture with authentic α-picoline was 130–140°.

Anal. Calcd. for $C_{12}H_{10}N_4O_7$: C, 44.73; H, 3.13; N, 17.39. Found: C, 44.89; H, 3.22; N, 17.24.

Attempted reaction of N-(t-octyl)-6-methylthiopicolinamide (V), *sulfur, and t-octylamine.* A mixture of 53 g. (0.20 mole) of *N*-(*t*-octyl)-6-methylthiopicolinamide (V), 19 g. (0.61

TABLE II

N-*t*-ALKYLTHIOPICOLINAMIDES



R	R′	Mole Ratio, Methyl Pyridine: Amine:S	Reflux Hr.	Final Pot Temp.	B.R./Mm. Hg	Yield,[a] %	Formula	Carbon, % Found	Carbon, % Calcd.	Hydrogen, % Found	Hydrogen, % Calcd.	Nitrogen, % Found	Nitrogen, % Calcd.	Sulfur, % Found	Sulfur, % Calcd.
H	*t*-C_8H_{17}	2:1:6	22	135	128–133/0.6	85	$C_{14}H_{22}N_2S$	66.86	67.15	8.76	8.86	11.16	11.19	12.82	12.80
H	*t*-$C_{11-14}H_{23-29}$[b]	2:1:6	20	143	160–175/0.7	87	$C_{17-20}H_{28-34}N_2S$	70.72	69.81–71.81	9.57	9.65–10.24	9.02	8.37–9.58	10.18	9.58–10.96
H	*t*-$C_{18-22}H_{37-45}$[c]	2:1:3	28	147	170–220/0.5	31	$C_{24-28}H_{42-50}N_2S$	74.05	73.78–75.27	10.80	10.84–11.28	7.05	6.27–7.17	7.82	7.18–8.21
6-CH	*t*-C_8H_{17}	2:1:6	8	164	136–151/0.6	90	$C_{15}H_{24}N_2S$	68.24	68.13	9.23	9.15	10.32	10.60	11.84	12.12
6-CH_3	*t*-$C_{11-14}H_{23-29}$	2:1:6	8	190	160–172/0.6	79	$C_{18-21}H_{30-36}N_2S$	71.06	70.53–72.35	9.81	9.87–10.41	8.57	8.04–9.14	10.13	9.20–10.46
4-CH_3	*t*-C_8H_{17}	2:1:6	4	190	150–160/1.0	82	$C_{15}H_{24}N_2S$	68.33	68.13	9.21	9.15	10.42	10.60	12.11	12.12
4-CH_3	*t*-$C_{11-14}H_{23-29}$	2:1:6	4	200	173–183/0.8	75	$C_{18-21}H_{30-36}N_2S$	71.27	70.53–72.35	9.87	9.87–10.41	8.62	8.04–9.14	9.96	9.20–10.46
5-CH_2 | CH_3	*t*-C_4H_9	4:1:3	10	162	120–123/0.4	22	$C_{12}H_{18}N_2S$	65.04	64.82	8.14	8.16	12.73	12.60	14.26	14.42
5-CH_2 | CH_3	*t*-C_8H_{17}	2:1:6	8	200	163–173/1.0	90	$C_{16}H_{26}N_2S$	69.06	69.02	9.27	9.41	10.02	10.06	11.61	11.51
5-CH_2 | CH_3	*t*-$C_{11-14}H_{23-29}$	1:1:3	6	218	175–190/0.6	50	$C_{19-22}H_{32-38}N_2S$	71.73	71.19–72.87	10.17	10.07–10.56	8.34	7.73–8.74	9.29	8.84–10.00
3-CH_3	*t*-$C_{11-14}H_{23-29}$	2:1:6	12	187	165–180/0.5	70	$C_{18-21}H_{30-36}N_2S$	71.33	70.53–72.35	9.95	9.87–10.41	8.62	8.04–9.14	9.79	9.20–10.46

[a] After purification by treatment with Na_2S. [b] Mixture of *t*-alkyl primary amines available as Primene 81-R from the Rohm and Haas Co. [c] Mixture of *t*-alkyl primary amines available as Primene JM-T from Rohm and Haas Co.

mole) of sulfur, and 13 g. (0.1 mole) of *t*-octylamine was stirred and heated at 150–175° for 2 hr. Another 13 g. (0.1 mole) of *t*-octylamine was added and the mixture was refluxed another 13 hr. The mixture was cooled, diluted with 200 ml. of heptane, and filtered. The residue was washed with heptane and dried to give 19 g. (0.61 mole) of unreacted sulfur. The combined filtrates were distilled to give 52 g. (98%) of unreacted *N*-(*t*-octyl)-6-methylthiopicolinamide (V), b.r. 135–140°/0.6 mm. Hg. There was 1 g. of residue.

Attempted quaternization of N-t-octylthiopicolinamide (I). A mixture of 25 g. (0.1 mole) of *N*-*t*-octylthiopicolinamide (I), 200 ml. of acetonitrile, and 20 g. (0.13 mole) of ethyl iodide was refluxed for 15 hr., cooled, and distilled free of ethyl iodide and acetonitrile. There remained a residue of 25 g. (0.1 mole) of unreacted *N*-*t*-octylthiopicolinamide (I).

Acknowledgment. I am indebted to Dr. C. L. Levesque and Dr. J. L. Rainey for helpful discussions, to Mrs. Alice Cannon for technical assistance, to Mr. L. A. Clement for the infrared data and interpretations, and to Mr. C. W. Nash and his associates for the elemental analyses.

BRISTOL, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF MEDICINE, WESTERN RESERVE UNIVERSITY AND THE UNIVERSITY HOSPITALS]

Preparation of Pregnane-3α,16α,20α-triol and of Two of Its Stereoisomers[1]

H. HIRSCHMANN AND MARGARET A. DAUS

Received March 2, 1959

The preparation of pregnane-3α,16α,20α-triol, of pregnane-3α,16α,20β-triol, and of pregnane-3β,16α,20β-triol is described and some of the characteristics of the infrared spectra of 16α-acetoxy steroids are pointed out.

Three 16α-hydroxysteroids with the pregnane skeleton have been isolated from urine. Two of these, allopregnane-3β,16α,20β-triol[2,3] and its 20-epimer[4,5] are found during pregnancy, while Δ⁵-pregnene-3β,16α,20α-triol[5] was encountered in a case of an adrenal tumor. The last observation suggested the possibility that the adrenal cortex might effect hydroxylations at C-16. This hypothesis was verified by Rao and Heard[6] and by Neher *et al.*[7] The Swiss group isolated 3β,-16α-dihydroxyallopregnan-20-one from an adrenal extract while the Canadian workers obtained isotopically labeled 16α-hydroxyprogesterone upon the incubation of tagged progesterone with an adrenal homogenate. If the metabolism of 16α-hydroxyprogesterone in man follows the normal pattern its chief urinary excretion product is not one of the known triols but pregnane-3α,16α,20α-triol. To facilitate the search for this compound we have carried out its synthesis from a degradation product of sapogenins, 3β-acetoxy-Δ¹⁶-pregnen-20-one.[8]

Two routes were explored. The first gave only a very low yield of the desired product, but proceeded in a stepwise manner which allowed one to deduce the structure of the final product with assurance. The 16-hydroxyl group was introduced into Ia by the benzyl alcohol method[9] which in the case of 3β-hydroxy-Δ⁵,¹⁶-pregnadien-20-one[10] and of Ib[11] has yielded hydroxy steroids with the α configuration at C-16 and the normal orientation of the side chain. The rotations of the triacetates IVb, VIIIb, and IXb corroborate these assignments also for our conversion of Ia to III. The formate group at C-3 even in the axial orientation is sufficiently reactive to allow its selective hydrolysis as was required in the conversion of III to V. The product although formulated as a 3β-hydroxysteroid failed to precipitate with digitonin. However, the structure of V follows from the disappearance of the strong formate absorption at 8.45 μ and the retention of the acetate band at 8.06 μ. The free hydroxyl group of V was oxidized with chromic acid to the acetoxydiketone VI which was reduced selectively with sodium borohydride in isopropanol[12,13] and pyr-

(1) This investigation was supported by grant C-1679 of the National Institutes of Health, U. S. Public Health Service.

(2) G. A. D. Haslewood, G. F. Marrian, and E. R. Smith, *Biochem. J.*, **28**, 1316 (1934).

(3) H. Hirschmann, F. B. Hirschmann, and M. A. Daus, *J. Biol. Chem.*, **178**, 751 (1949).

(4) S. Lieberman, B. Praetz, P. Humphries, and K. Dobriner, *J. Biol. Chem.*, **204**, 491 (1953).

(5) H. Hirschmann and F. B. Hirschmann, *J. Biol. Chem.*, **184**, 259 (1950).

(6) B. G. Rao and R. D. H. Heard, *Arch. Biochem. and Biophys.*, **66**, 504 (1957).

(7) R. Neher, P. Desaulles, E. Vischer, P. Wieland, and A. Wettstein, *Helv. Chim. Acta*, **41**, 1667 (1958).

(8) We are greatly indebted to Dr. J. J. Pfiffner of Parke, Davis and Company for a gift of this compound.

(9) H. Hirschmann, F. B. Hirschmann, and J. W. Corcoran, *J. Org. Chem.*, **20**, 572 (1955).

(10) H. Hirschmann, F. B. Hirschmann, and M. A. Daus, *J. Am. Chem. Soc.*, **74**, 539 (1952).

(11) H. Hirschmann and F. B. Hirschmann, *J. Am. Chem. Soc.*, **78**, 3755 (1956).

(12) H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955).

(13) The use of this solvent instead of methanol stabilized with alkali[14b] seems advantageous for the partial reduction of ketones (such as VI) which are sensitive to alkali.