TABLE I

ALKYLATIONS OF PHENYLHYDRAZONES I[a] TO FORM II

I, R	R'X	M	II, R	II, R'	Yield, %	M.p., °C. Found	M.p., °C. Lit.
H	$C_6H_5CH_2Cl$	Na	H	$C_6H_5CH_2$	92[b,c]	109–110	111[d]
CH_3	$C_6H_5CH_2Cl$	K	CH_3	$C_6H_5CH_2$	69[e]	57–58	58[f]
C_6H_5	CH_3I	K	C_6H_5	CH_3	77[g]	76–79	81[h]
C_6H_5	n-C_4H_9Br	K	C_6H_5	n-C_4H_9Br	93[i,c]	52–54[j]	...
C_6H	$C_6H_5CH_2Cl$	Na	C_6H_5	$C_6H_5CH_2$	85[b]	108–109	105–106[k]
C_6H_5	$C_6H_5CH_2Cl$	K	C_6H_5	$C_6H_5CH_2$	90[b]	108–109[l]	105–106[k]

[a] According to eq. 1. [b] 90-min. reaction period. [c] Combined yield from two crops. [d] Ref. 2. [e] 30-min. reaction period. [f] M. Busch and K. Schmidt, *J. prakt. Chem.*, **129**, 151 (1931). [g] 1-hr. reaction period. [h] Ref. 4. [i] 3-hr. reaction period. [j] *Anal.* Calcd. for $C_{23}H_{24}N_2$: C, 84.10; H, 7.37; N, 8.53. Found: C, 84.03; H, 7.42; N, 8.66. [k] Ref. 3. [l] *Anal.* Calcd. for $C_{26}H_{22}N_2$: C, 86.15; H, 6.12; N, 7.73. Found: C, 86.45; H, 6.24; N, 8.15.

2-day reaction period.[4] The two condensations represented in eq. 2 were accomplished by us after a 20-hr. reaction period in yields of only 40 and 78%, respectively; these yields are appreciably lower than those obtained even after a much shorter reaction period according to eq. 1 (see Table I). Moreover, certain N-alkylphenylhydrazines are not readily available.

Experimental[5]

The benzaldehyde phenylhydrazone,[6] acetophenone phenylhydrazone,[7] and benzophenone phenylhydrazone[8] used in this study were prepared according to literature procedures and were recrystallized. The acetophenone phenylhydrazone should be freshly prepared.

Alkylations of Phenylhydrazones I.—To a stirred suspension of 0.025 mole of sodamide[9] in 500 ml. of commercial, anhydrous, liquid ammonia or to a stirred solution of 0.025–0.1 mole of potassium amide[10] in 250–500 ml. of commercial, anhydrous, liquid ammonia was added 1 mole equiv. of finely ground phenylhydrazone I. The solutions of the resulting alkali salts (see Table I) were colored brownish yellow, orange-tan, and blood red, respectively. After 10–15 min., 1 mole equiv. of the appropriate halide in 15–20 ml. of anhydrous ether was added; the color of the solution changed and a precipitate formed. After stirring for the appropriate length of time (see footnotes *b*, *e*, *g*, and *i* in Table I), a slight excess of 1 mol. equiv. of ammonium chloride was added. The ammonia was allowed to evaporate, and the residue was taken up in ether and water. The layers were separated. The ethereal layer was washed with saturated sodium chloride solution and combined with two ethereal extracts of the aqueous layer treated in the same manner. In the experiment with methyl iodide the ethereal solution was also washed with saturated sodium bisulfate to remove any iodine that might have been formed. The ethereal solution was dried over anhydrous magnesium sulfate and the solvent was removed. The residues were recrystallized from ethanol.

Condensations of N-Benzyl-N-phenylhydrazine Hydrochloride with Carbonyl Compounds to Form II (Eq. 2). A. With Benzaldehyde.—A solution of 1.06 g. (0.01 mole) of benzaldehyde and 2.35 g. (0.01 mole) of N-benzyl-N-phenylhydrazine hydrochloride in 5 ml. of pyridine and 45 ml. of ethanol was refluxed for 20 hr. according to a current method for the preparation of oximes.[11] There was obtained 2.32 g. (78%) of benzaldehyde benzylphenylhydrazone, m.p. 106–108° after recrystallization from ethanol. Upon admixture with the product melting at 109–110° obtained according to eq. 1, the melting point was 108–109°. The infrared spectra of the two samples were identical.

B. With Benzophenone.—The reaction involving 0.91 g. (0.005 mole) of benzophenone, 1.18 g. (0.005 mole) of N-benzyl-N-phenylhydrazine hydrochloride in 5 ml. of pyridine, and 45 ml. of ethanol, refluxed for 20 hr. as described above, yielded 0.72 g. (40%) of benzophenone benzylphenylhydrazone, m.p. and m.m.p 106–108° after recrystallization from ethanol.

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(5) Analyses are by Dr. Ing. Schoeller, Kronach, West Germany, and Galbraith Microanalytical Laboratories, Knoxville, Tenn. Melting points (Mel-Temp capillary melting point apparatus) are uncorrected.

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The Asinger Reaction with 1-Methyl-4-piperidone

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The discovery that β- and γ-mercaptoamines provided some protection against ionizing radiation[2] caused an interest in the synthesis of 3- and 4-mercaptopiperidines. The preparation of these compounds by nucleophilic displacements of halogen from 3- and 4-halopiperidines was complicated by the discovery that the former underwent rearrangement with ring contraction[3] while the latter underwent rupture of the ring[4] during solvolysis reactions. Using a *gem*-dithiol as intermediate, the synthesis of 1-methyl-4-mercaptopiperidine was accomplished,[5] but a similar route to 1-methyl-3-mercaptopiperidine was not successful. The formation of thiazolines by the Asinger reaction[6,6a] seemed to offer an alternate approach to these compounds from 1-methyl-4-piperidone, provided that the intermediate thiazoline could be hydrolyzed to give a derivative of 1-methyl-3-mercapto-4-piperidone.

1-Methyl-4-piperidone (1) gave a mildly exothermic reaction with sulfur and ammonia to form a compound having the properties expected for the thiazoline **2a**.

(1) On leave from the Pliva Pharmaceutical Co., 1962–1963.

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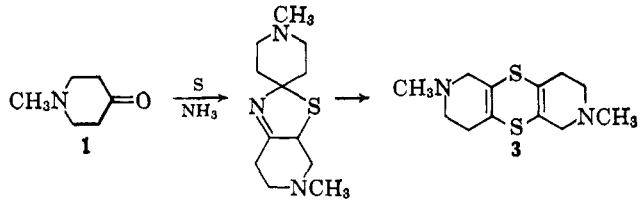
(6a) NOTE ADDED IN PROOF.—The Asinger reaction with 1-methyl-4-piperidone (**1**) has been reported by F. Asinger, W. Shäfer, and H. W. Becker, *ibid.*, **674**, 57 (1964).

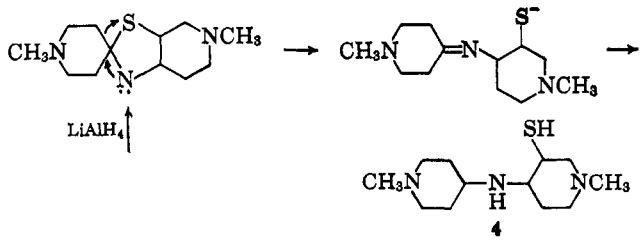
The n.m.r. and infrared spectra eliminated other double-bond isomers from consideration. A dihydrochloride (**2**) was formed by treatment of **2a** with anhydrous hydrogen chloride. The infrared spectrum of the salt **2** showed that salt formation had occurred with the two piperidine nitrogens and not with the thiazoline nitrogen. Because of the difficulty of introducing a positive charge on the thiazoline nitrogen, hydrolysis of the ring was difficult. A reaction time of 6 hr. under reflux with concentrated hydrochloric acid was required to cause rupture of the thiazoline ring. This hydrolysis gave 1 molar equiv. of 1-methyl-4-piperidone and the 1,4-dithiadiene **3**. The n.m.r. spectrum of **3** showed a multiplet at 2.1–2.6 p.p.m. with a relative intensity of 8 corresponding to the "ethano" protons, a singlet at 2.30 p.p.m. for the resonance of the NCH_3, and a triplet (J = 2.5 c.p.s.) at 2.96 p.p.m. for the methylene flanked by the nitrogen and a double bond. Splitting results from spin–spin interaction with the allylic methylene hydrogens.



1 **2a** **3**

2, dihydrochloride

It was reasoned that reduction of the thiazoline **2** to the thiazolidine would permit hydrolysis of the ring to produce 1-methyl-4-amino-3-mercaptopiperidine and 1-methyl-4-piperidone (**1**). The successful reduction of thiamine chloride[7] and numerous imines[8] with complex metal hydrides led to a study of these reductions with **2a**. Sodium borohydride gave no reaction. Lithium aluminum hydride caused reduction of the double bond, but hydrogenolysis of the thiazolidine ring may have occurred in a manner similar to that described by Eliel and co-workers[9] to give **4**. Since the product of this reaction was not purified the structure cannot be considered proven.



4

Experimental

1,6′-Dimethyl-2′,4′,5′,6′,7′,7a′-hexahydrospiro[piperidine-4,2′-thiazolo[5,4-*c*]pyridine] Dihydrochloride (2).—A suspension of 6.0 g. of sulfur in 40.0 g. of 1-methyl-4-piperidone (**1**) was stirred and cooled with ice while ammonia gas was bubbled through the mixture. The temperature of the reaction was maintained between 40–50°. The introduction of ammonia was continued until the last traces of sulfur disappeared, usually about 2 hr. The excess ammonia was removed by reducing the pressure over the reaction mixture. The warm, viscous liquid was diluted with 200 ml. of 50% potassium carbonate solution, and the mixture was extracted with five 100-ml. portions of ether. The ether solution was dried over potassium carbonate, filtered, and treated with hydrogen chloride. A yellow precipitate of 1,6′-dimethyl-2′,4′,5′,6′,7′,7a′-hexahydrospiro[piperidine-4,2′-thiazolo[5,4-*c*]-pyridine] dihydrochloride (**2**) formed immediately. The solid was removed by filtration, washed with ether, and dried under reduced pressure over calcium chloride to give 53.5 g. of **2**, m.p. 200–205° dec. An analytical sample was prepared by recrystallization from a mixture of ethanol and isopropyl alcohol. The analytical sample melted at 240–241°.

Anal. Calcd. for $C_{12}H_{23}Cl_2N_3S$: C, 46.15, H, 7.37. Found: C, 46.01; H, 7.23.

The base, 1,6′-dimethyl-2′,4′,5′,6′,7′,7a′-hexahydrospiro-[piperidine-4,2′-thiazolo[5,4-*c*]pyridine] (**2a**) was isolated by distillation of the reaction mixture from above, or was formed in quantitative yield from the dihydrochloride **2** by neutralization with potassium carbonate solution. The base thus formed was purified by distillation under reduced pressure, and the fraction, b.p. 198–202° at 16 mm., was taken as **2a**. That no structural change had occurred on conversion of the dihydrochloride to the base could be shown by treatment of the oil with hydrogen chloride and re-forming **2**, the dihydrochloride, with a melting point of 240–242°.

Anal. Calcd. for $C_{12}H_{21}N_3S$: C, 60.25; H, 8.78; S, 13.39. Found: C, 60.30; H, 9.03; S, 13.40.

Hydrolysis of 1,6′-Dimethyl-2′,4′,5′,6′,7′,7a′-hexahydrospiro-[piperidine-4,2′-thiazolo[5,4-*c*]pyridine] Dihydrochloride (2).—A mixture of 26.0 g. of **2** in 100 ml. of concentrated hydrochloric acid was heated under mild reflux for 6 hr. The excess hydrochloric acid was removed by distillation under reduced pressure and the residue was diluted with water. Potassium carbonate was added until a saturated solution was obtained, and, the mixture was extracted with ether. The ether solution was dried over potassium carbonate. Distillation of the ether solution gave approximately 1 molar equiv. of 1-methyl-4-piperidone, identified by infrared spectrum, and an intractable residue. The sulfur-containing product was isolated by saturating the dried ether extract with hydrogen chloride and separating the salt which precipitated by filtration. After drying in a vacuum desiccator, the salt was dissolved in water, and the solution was saturated with potassium carbonate. The oil which separated was taken up in ether. Evaporation of ether gave an oil which solidified on cooling overnight to give 6.3 g. (30% based on structure **3**) of solid, m.p. 88–90°. Recrystallization of the solid from petroleum ether (b.p. 30–60°) gave an analytical sample, m.p. 93–94°.

Anal. Calcd. for $C_{12}H_{18}N_2S_2$: C, 56.65; H, 7.13. Found: C, 56.66; H, 7.41.

Reduction of 2a with Lithium Aluminum Hydride.—To a stirred suspension of 5 g. of lithium aluminum hydride in tetrahydrofuran, was added 20 g. of **2a** dropwise. The mixture was heated under reflux for 3 hr. and decomposed with water. The organic layer was separated and the inorganic precipitate was washed with tetrahydrofuran and ether. The organic layers were combined, dried, and concentrated by distillation. The residue was dissolved in ether, and the solution deposited a small amount of solid, m.p. 113–115°, on standing overnight. This solid gave positive nitroprusside and lead acetate tests for mercaptans. The infrared spectrum and elemental analyses led to the tentative assignment of structure of 1-methyl-3-mercapto-4-(1-methyl-4-piperidylamino)piperidine (**4**).

Anal. Calcd. for $C_{12}H_{25}N_3S$: C, 59.27; H, 10.29. Found: C, 58.49; H, 10.23.

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