Heterocycles. I. Attempted Synthesis of Mesoionic 1,3,4-Thiadiazoles

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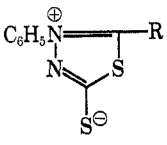
The recent report by Stewart and Kier[1] that mesoionic 1,3,4-thiadiazoles **1** had the same bactericidal activity as penicillin G prompted us to prepare some of these compounds. In the course of this work, we needed an example of **1** containing a long-chain alkyl group. Preparation of this material by reaction of potassium phenyldithiocarbazinate with palmitoyl chloride (**2**)[1,2] in benzene gave only a white, crystalline solid, A, analyzing for $C_{22}H_{38}N_2O$. When an excess of **2** was used, another compound, B, analyzing for $C_{38}H_{68}N_2O_2$, was isolated.

We first assumed A to be 1-palmitoyl-2-phenylhydrazine (**3**) from reaction of phenylhydrazine with **2**. Compound B would then be 1,2-dipalmitoyl-1-phenylhydrazine (**4**). Comparison of A with authentic[3] **3** proved this was not the case.

B was also obtained by reaction of either A or **3** with palmitoyl chloride. Further, reaction of A with benzaldehyde gave hydrazone **5**, whereas hydrazine **3**, as expected, gave no such derivative. Thus the only possible structure of A is **6**, and for B is, indeed, **4**.[4,5]



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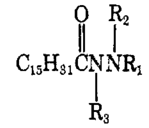
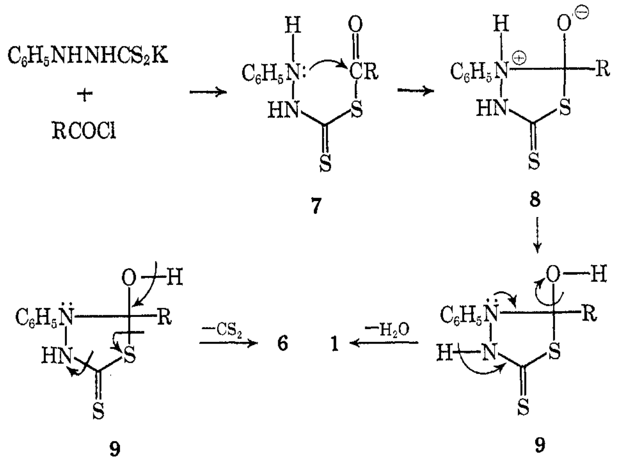


$$C_{15}H_{31}\overset{\overset{O}{\|}}{C}\underset{\underset{R_3}{|}}{N}\overset{\overset{R_2}{|}}{N}R_1$$

3, $R_1 = C_6H_5$; $R_2 = H$; $R_3 = H$
4, $R_1 = C_6H_5$; $R_2 = C_{15}H_{31}C{=}O$; $R_3 = H$
5, $R_1 = C_6H_5CH{=}$; $R_3 = C_6H_5$
6, $R_1 = H$; $R_2 = H$; $R_3 = C_6H_5$

The mechanism leading to **6** is similar to that proposed by Stewart and Kier[1] for formation of thiadiazoles **1** from potassium dithiocarbazinates and acid chlorides (**7** → **8** → **9** → **1**). We propose the same intermediates, but must allow for decomposition of **9** in a different manner as illustrated in **9** → **6** (Scheme I). We suggest that both mechanisms are simultaneously operative, and that the hydrazides had previously gone unisolated.[4] Changes in solvent or acid chloride will determine which pathway predominates.[6]

Scheme I



Experimental Section[7]

1-Palmitoyl-1-phenylhydrazine (6).—Potassium phenyldithiocarbazinate[1] (28.6 g, 12.9 mmol) was suspended in anhydrous benzene (600 ml). The suspension was warmed to 50° and palmitoyl chloride (26 g, 9.5 mmol) added at such a rate as to maintain a yellow color in the reaction mixture. After 40 min, the reaction mixture had turned green; it was stirred 15 min longer, then cooled and washed with water. The organic layer was separated, dried and concentrated. The residue was crystallized twice from ethanol to give 6 (17.8 g, 53%): mp 92–94°, white crystals; λ_{max} 3.02, 3.10, 3.15, 6.05, 6.13, 6.26 μ. *Anal.* Calcd for $C_{22}H_{38}N_2O$: C, 76.25; H, 11.05; N, 8.08. Found: C, 76.45; H, 11.00; N, 8.28.

1,2-Dipalmitoyl-1-phenylhydrazine (4). A.—Potassium phenyldithiocarbazinate was treated as above with twice the quantity of 2. After cooling, the reaction mixture was filtered and the resulting solid washed with water, dried and crystallized from ethanol to give 4 (44.7 g, 81%), mp 96–100°, as a white solid. The analytical sample, mp 95–97°, was prepared by recrystallization from ethanol: λ_{max} 3.13, 5.88, 6.08, and 6.28 μ. *Anal.* Calcd for $C_{38}H_{68}N_2O_2$: C, 78.02; H, 11.72; N, 4.79. Found: C, 78.11; H, 11.63; N, 4.81.

B.—Phenylhydrazine in hot ethanol was treated with 2 equiv of 2 and allowed to cool. The resulting solid was filtered and recrystallized from ethanol to give 6, mp 96–96.5°, whose infrared was superimposable with the previous sample's.

C.—*Hydrazine* 3, *in hot dioxane was* treated with 1 equiv of 2 and allowed to cool. The resulting solid was filtered and recrystallized from ethanol to give 6, mp 95–96°, whose infrared spectrum was identical with previous sample's.

1-Palmitoyl-2-phenylhydrazine (3), mp 102–105° (lit.[3] mp 100–101°), was prepared according to Joshi:[3] λ_{max} 3.10–3.15, 5.90 sh, 6.01, 6.07, 6.22 μ.

1-Palmitoyl-1-phenylbenzalhydrazone (5).—Hydrazine 6 (1.80 g, 5.2 mmol) in refluxing ethanol was treated with benzaldehyde (0.53 g, 5.0 mmol) and the solid obtained on cooling was collected and dried. It was recrystallized from ethanol to give 5 (1.80 g, 78%): mp 89–90.5°; λ_{max} 5.93, 6.08, 6.21 μ. *Anal.* Calcd for $C_{29}H_{42}N_2O$: C, 80.13; H, 9.74; N, 6.44. Found: C, 80.04; H, 9.82; N, 6.08, 6.45.

Hydrazine 3 was recovered unchanged from a similar reaction.

Registry No.—**4**, 18239-01-5; **5**, 18239-02-6; **6**, 18181-20-9.

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(1) T. G. Stewart and L. B. Kier, *J. Pharm. Sci.*, **54**, 731 (1965).

(2) W. Baker, W. D. Ollis, A. Phillips, and T. Strawford, *J. Chem. Soc.*, 289 (1951).

(3) K. C. Joshi, *Indian J. Appl. Chem.*, **23**, 127 (1960); *Chem. Abstr.*, **55**, 8738*i* (1961).

(4) M. Ohta, K. Kato, and T. Kaneko [*Bull. Chem. Soc. Jap.*, **40**, 579 (1967)] reported similar results. They isolated N,N′-dibenzoylphenylhydrazine under several reaction conditions. It is interesting that they reported the isolation of N′-benzoylphenylhydrazine, and not N-benzoylphenylhydrazine, from the reaction of triethylammonium dithiocarbazinate and benzoyl chloride in triethylamine.

(5) One of the referees suggested acetone as the solvent of choice for thiadiazole formation. Use of this reagent led to formation of hydrazides **4** and **6**.

(6) In the case of palmitoyl chloride, the reaction was insensitive to minor temperature changes (60–50°), method of preparation of the dithiocarbazinate, rate of addition of acid chloride, and the solvent (benzene, toluene, and acetone). Furthermore, 1 (R = C_6H_5) was recovered unchanged from treatment with palmitoyl chloride.

(7) All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5 spectrophotometer (potassium bromide pellets). Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. The standard drying agent used was magnesium sulfate, and solvents were removed on a rotary evaporator.