1-ALKYL-3,6-DIMETHYL-1,4-DIHYDROPYRIDAZINES FROM ACETONYLACETONE AND ALKYLHYDRAZINES

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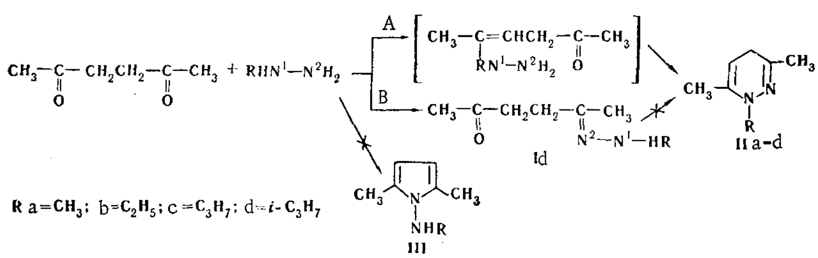
The only products in the condensation of acetonylacetone with alkylhydrazines are 1-alkyl-3,6-dimethyl-1,4-dihydropyridazines. The reaction of acetonylacetone with isopropylhydrazine leads to a mixture of acetonylacetone monoisopropylhydrazone and the corresponding dihydropyridazine.

The reaction of difunctional compounds such as monosubstituted hydrazines ($RHN-NH_2$) with acetonylacetone may lead to several products: mono- and dihydrazones, 1-aminopyrroles, and dihydropyridazines.

In addition, the condensations are frequently complicated by interconversions of the products or by other profound changes. Thus the reaction of acetonylacetone with acylhydrazines and phenylhydrazines forms 1-aminopyrroles or dihydrazones [1], 2,4-dinitrophenylhydrazine gives mono- and dihydrazones [2, 3], while the formation of 1,4-dihydropyridazine [4] and more complex products [4-6] was observed in the reaction of acetonylacetone with hydrazine itself. The results of reactions with other 1,4-dicarbonyl compounds are no less contradictory [6]. From the known data, it is difficult to predict which direction the condensation will take in each concrete case. The disconnected information on the properties of the reaction products complicates a reliable determination of their structures. In particular, the simplest aliphatic representatives (R = alkyl) of all of the enumerated classes of substances are not known at all. A study of the reaction of alkylhydrazines with acetonylacetone, the most readily accessible 1,4-diketone, is therefore of undoubted interest.

We found that the reaction with n-alkylhydrazines proceeds smoothly on refluxing in nonpolar solvents in the presence of dehydrating agents. Prolonged heating with no less than a 1.5-fold excess of hydrazine over BaO is required in order that the acetonylacetone, which has a boiling point close to the boiling points of the reaction products, react completely. After the condensation, the compounds were isolated by distillation, and their homogeneity was established by gas-liquid chromatography (GLC) (Table 1).



Both mono- and dihydrazone structures were completely excluded from the results of elementary analysis. The selection between 1-aminopyrrole (III) and 1,4-dihydropyridazine (II) structures for the compounds was realized on the basis of the IR and PMR spectra. The IR spectra of II, which are transparent from 3100-3600 cm^{-1} and thereby indicate the absence of the NH grouping characteristic for 1-aminopyrroles, have intense absorption bands at 1620-1640 cm^{-1} ($\nu_{C=N}$) and 1660-1680 cm^{-1} ($\nu_{C=C}$), and the first band corresponds to the intervals presented for unconjugated hydrazones of ketones (including that also

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TABLE 1. 1-Alkyl-3,6-dimethyl-1,4-dihydropyridazines

Compound	Reaction medium	bp, °C (mm)	d_{20}^{4}	n_D^{20}	MR_D found*	MR_D calc.	M found	M calc.	Empirical formula	Found, % C	Found, % H	Found, % N	Calc., % C	Calc., % H	Calc., % N	Yield, %
IIa	Hexane	64,4—65,0 (15,5)	0,9372	1,5000	38,96	38,36	124,8 126,4	124,18	$C_7H_{12}N_2$	67,83 67,74	9,85 9,52	22,59 22,12	67,70	9,74	22,56	50
IIb	Benzene	76,2 (19)	0,9278	1,4980	43,66	43,00	137,9 137,9	138,21	$C_8H_{14}N_2$	69,51 69,56	10,15 10,13	20,40 20,54	69,52	10,21	20,27	68
IIc	Toluene	78,8 (8)	0,9249	1,4930	47,83	47,65	151,8 151,4	152,23	$C_9H_{16}N_2$	70,95 70,89	10,49 10,52	18,38 18,57	71,01	10,59	18,40	61
IId	Toluene	74,0—74,5 (14)	0,9030	1,4900	48,74	47,65	150,9 151,1	152,23	$C_9H_{16}N_2$	71,10 71,09	10,51 10,54	18,37 18,48	71,01	10,59	18,40	15

*Some exaltations of the refraction are characteristic for hydrazine derivatives with multiple bonds as a result of the appearance of p–π conjugation (see [12], for example).

for the ketone hydrazone fragment in a six-membered ring) [7], while the second is peculiar to enamines [8] and enehydrazines [9]. The presence of C=C double bond is also confirmed by the absorption of a trisubstituted olefin at 3060 cm^{-1} ($\nu_{H-C=}$) and 790 cm^{-1} ($\nu_{H-C=}$) [10].

Absorption of the β protons of the pyrrole ring is not observed in the PMR spectra of II, but multiplet signals of a methylene group at 7.34-7.37 ppm (> C^4H_2) and of an olefin proton at 5.9 ppm (= C^5H) are present. The singlets of methyl groups in the C^3 and C^6 positions of the ring coincide and are found at 8.25-8.30 ppm. The signals of the α protons of substituents attached to the N^1 nitrogen atom correspond to the following values: 6.90 (CH_3N in IIa), 6.7 (– CH_2N in IIb-c), and 6.55 ppm (> CHN in IId), and the character of the splitting and the spin–spin coupling constants (J ~ 7 Hz) are typical for the corresponding alkyl groups. We present the spectrum of 1-ethyl-3,6-dimethyl-1,4-dihydropyridazine (Fig. 1) as an illustration.

Finally, a chemical confirmation of the dihydropyridazine structure is hydrolysis in acidic media, as a result of which, in the presence of 2,4-dinitrophenylhydrazine, acetonylacetone bis(2,4-dinitrophenyl)hydrazone was isolated. On the basis of the material set forth above, it can be concluded that the products are 1-alkyl-3,6-dimethyl-1,4-dihydropyridazines (II). They are colorless, oily liquids with a spicy odor and are readily oxidized, in connection with which, all stages of the synthesis and purification were carried out under nitrogen. (The preparations are stable in the absence of air.)

The yield of the corresponding dihydropyridazine (IId) in the reaction of acetonylacetone with isopropylhydrazine drops sharply, and the chief product of the condensation is acetonylacetone monoisopropylhydrazone (Id).

It could be assumed that hydrazone Id is an intermediate, the conversion of which to dihydropyridazine IId is inhibited by branching of the alkyl radical attached to the N^1 nitrogen atom. However, this is not so. Although hydrazone Id is unstable during vacuum distillation above 1 mm or on prolonged contract with Al_2O_3 and silica gel in chromatographic columns, itwas not altered at all after prolonged heating under the condensation conditions. The absence of cyclization cannot be explained by the syn-configuration of the substance (syn-orientation of CH_3 and N^1HR), i.e., by the orientation of the carbonyl group and N^1 nitrogen atom for which their approach is impossible. From the PMR spectrum of hydrazone Id (Fig. 2), it is easy to establish that the anti isomer [($\tau_{CH_3-C=N}$) 8.4 ppm, syn; ($\tau_{CH_3-C=N}$) 8.3 ppm, anti] predominates, which is in complete agreement with the results in [11]. It is then reasonable to assume that the more nucleophilic "alkylamine" N^1 nitrogen atom (path A) commences the reaction and that conversion to the cyclization-disinclined hydrazone (path B) competes with this process when the N^1 substituent is branched, although other possibilities cannot be excluded.

EXPERIMENTAL

The PMR spectra without a solvent were recorded with a YaMR 5535 spectrometer (40 MHz) with hydromethyldisiloxane* (HMDS) as the internal standard. The IR spectra of 20-40-μ-thick layers were recorded with a UR-10 spectrometer. The GLC analyses were per-

*As in Russian original – Publisher.

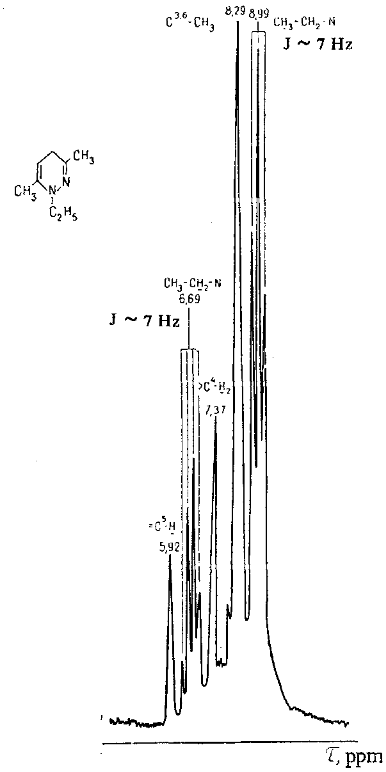

Fig. 1.

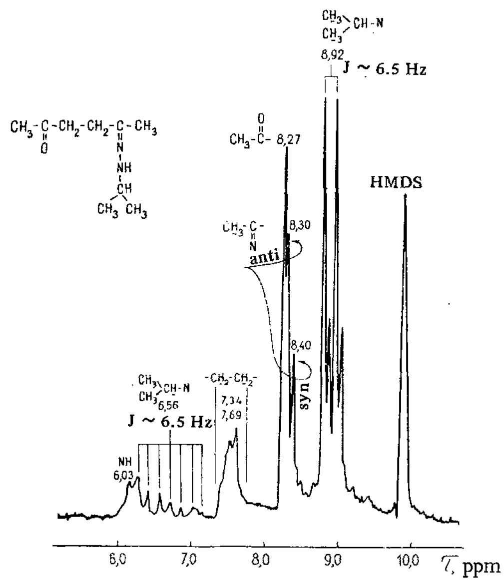

Fig. 2.

Fig. 1. PMR spectrum of 1-ethyl-3,6-dimethyl-1,4-dihydropyridazine.

Fig. 2. PMR spectrum of acetonylacetone monoisopropylhydrazone (10% solution in CCl_4).

formed with a Tswett-4 chromatograph with a 120-cm-long glass column with 20% Tween-20 on C22 Celite treated with 0.5% polyethylene polyamine with nitrogen and helium as the gas carriers at 120°C. Thin-layer chromatography was carried out on activity II Al_2O_3 with elution by hexane–acetone (5 : 1). The alkylhydrazines were synthesized by the method in [12]. Acetonylacetone was obtained by the method in [13] and was chromatographically pure.

1-Alkyl-3,6-dimethyl-1,3-dihydropyridazines (IIa-c). A mixture of 0.2 mole of acetonylacetone and 0.4 mole of hydrazine in 150 ml of solvent (Table 1) in the presence of 20 g of ground BaO was refluxed for 3 h with a Dean–Stark adapter. The drying agent was removed by filtration, the solvent was removed in vacuo, and the residue was distilled on a column with ten theoretical plates.

Acetonylacetone 2,4-Dinitrophenylhydrazone. A 0.57-g (0.005 mole) sample of IIc was refluxed for 30 min with a 1.5-fold excess of 2,4-dinitrophenylhydrazine sulfate reagent (1.49 g of 2,4-dinitrophenylhydrazine in 25 ml of 1 N H_2SO_4), and the precipitate [2.27 g (96%)] was removed by filtration and recrystallized from dimethylformamide to give a product with mp 255°C. [This product did not depress the melting point of an authentic sample, (mp 260°C) prepared from acetonylacetone [3]).

Condensation of Acetonylacetone with Isopropylhydrazine. The reaction was accomplished under standard conditions from 0.3 mole of acetonylacetone and 0.6 mole of isopropylhydrazine to give 6.9 g (15%) of IId. The residue (32 g) was a viscous, brown oil with n_D^{20} 1.4605. High-vacuum distillation with a 15-cm-long fractionating column yielded 16 g (32%) of hydrazone Id with bp 60°C (0.1 mm), d_4^{20} 0.9319, and n_D^{20} 1.4656. Found: C 63.12; 63.16; H 10.16; 10.15; N 16.76; 16.64%. MR_D 50.55. $C_9H_{18}N_2O$. Calculated: C 63.50; H 10.66; N 16.46%. MR_D 49.96. R_f 0.35. IR spectrum (ν, cm^{-1}): 1635 (C=N), 1750-1760 (C=O), 3435 (free NH group), and 3290 (NH group tied up by intermolecular hydrogen bonding with the C=O group, in agreement with the results in [10]).

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