Condensation of ethyl α-ethoxymethyleneacylacetates with *p*-bromobenzoyl- and benzylidenehydrazines

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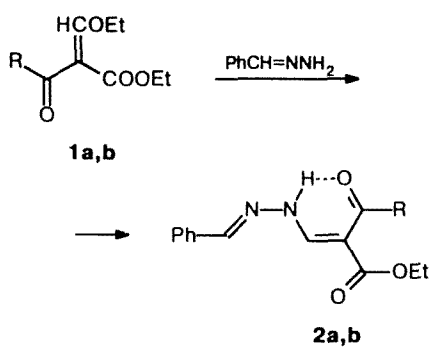
Ethyl α-ethoxymethyleneacetoacetate and α-ethoxymethylenebenzoylacetate react with benzylidenehydrazine and *p*-bromobenzoylhydrazine to give hydrazones of the corresponding ethyl α-formylacylacetates. It was established by ^{1}H NMR and IR spectroscopy that hydrazones, which were obtained from benzylidenehydrazine, and *p*-bromobenzoylhydrazone of ethyl α-formylacetoacetate exist in the ketoenamine (ketoenhydrazine) form, whereas *p*-bromobenzoylhydrazone of ethyl α-formylbenzoylacetate exists in the enolimine (enolhydrazone) form.

Key words: ethyl α-ethoxymethyleneacylacetates, *p*-bromobenzoylhydrazine, benzylidenehydrazine, condensation; hydrazones of ethyl α-formylacylacetates.

The structures of the products of the reaction of substituted hydrazines with such polyfunctional compounds as α-alkoxymethylene-β-ketoesters remain poorly studied, while quite a number of works[1–6] have been devoted to acylhydrazones of β-dicarbonyl compounds. Ethyl α-ethoxymethyleneacylacetates contain both carbonyl groups of aldehyde (in their enol ether latent form) and ketone and ester. It was shown by us that the reactions of ethyl ethoxymethyleneacetoacetate (**1a**) and ethyl ethoxymethylenebenzoylacetate (**1b**) with benzylidenehydrazine proceed at the ethoxymethylene group to give condensation products **2a,b** (Scheme 1).

Scheme 1

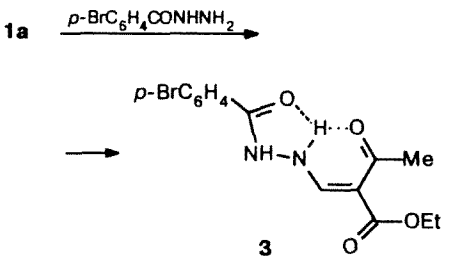


R = Me (**a**), Ph (**b**)

Ester **1a** reacts analogously with *p*-bromobenzoylhydrazine to form compound **3** (Scheme 2).

However, the reaction of *p*-bromobenzoylhydrazine with ester **1b** leads to the formation of a product with

Scheme 2



the enol structure (Scheme 3), which, according to its ^{1}H NMR spectra, is a mixture of *cis*- and *trans*-isomers **4a,b** with intramolecular hydrogen bonds (IHB) O—H...N and O—H...O. A substituted pyrazole **5** is obtained simultaneously as a result of dehydration of hydrazones **4a,b**.

Hydrazone **4** and pyrazole **5** were isolated in the individual state by threefold recrystallization of a mixture of compounds **4** and **5** from toluene or EtOH. The yields, melting points, and elemental analysis data of compounds **2a,b**, **3**, and **4** are given in Table 1.

The corresponding enhydrazone **6** was synthesized by us from benzylidenehydrazine and ethyl acetate (Scheme 4) as a model compound for interpretation of spectral data.

A broad absorption band with a maximum at 3420 cm^{-1} (ν(N—H)) and a band at 1660 cm^{-1} characteristic of the C=O group of esters, which participates in the formation of IHB, are observed in the IR spectrum of compound **6** (KBr) (Table 2). The ^{1}H NMR spectrum of this enhydrazone contains only one set of signals, which suggests the presence of one isomer (see

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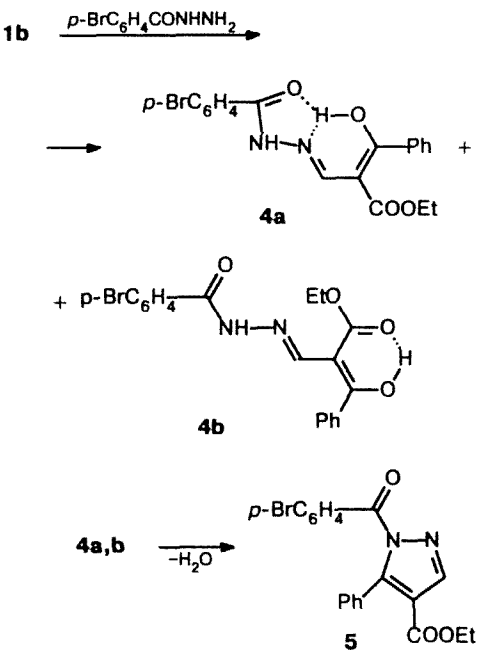
Table 1. The characteristics of compounds **2a,b**, **3**, and **4**

Compound	Yield (%)	M.p./°C (solvent)	Found / Calculated (%) C	H	N	Molecular formula
2a	77.0	84—86 (heptane)	64.67 / 64.60	6.24 / 6.20	10.67 / 10.76	$C_{14}H_{16}N_2O_3$
2b	77.0	97—98 (EtOH)	70.78 / 70.79	5.54 / 5.63	8.59 / 8.69	$C_{19}H_{18}N_2O_3$
3	52.0	173—174 (EtOAc)			7.70 / 7.89	$C_{14}H_{15}BrN_2O_4$
4	—	164—165 (toluene)			6.45 / 6.71	$C_{19}H_{17}BrN_2O_4$

Scheme 3



Scheme 4

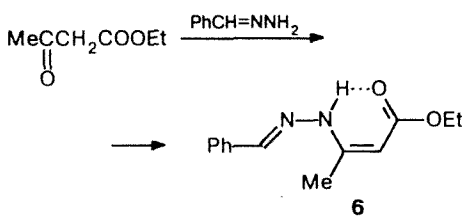


Table 2). The *anti*-configuration is most likely for the azomethine group. The chemical shift of the proton of the NH group (δ 11.65) is similar to that of the N—H bond of enhydrazines obtained from β-diketones.[5] According to our data, compound **6** has the *cis*-enamine structure, whereas aroylhydrazones of methyl acetoacetate exist as tautomeric mixtures of the ketoimine and ketoenamine forms.[6]

The parameters of the IR spectra of compounds **2a,b** and **3** are consistent with the ketoenamine structure. Thus, the spectrum of enhydrazone **2a** contains a broad band in the range of 3420 cm^{-1}, which is apparently due to the vibrations of the N—H bond that participates in the formation of an IHB with the O atom of the acetyl group. Absorption of the carbonyl group of the ethoxycarbonyl moiety is shifted to the low-frequency area (1685 cm^{-1}) but in a lesser degree than in the spectrum of enhydrazone **6**, and one can assume that this is caused by conjugation, and not by the influence of IHB. An even lesser relative shift of the absorption band of the COOEt group is observed in the spectra of compounds **2b** and **3**. The final conclusion about the structure of product **2a** was made on the basis of its ^1H NMR spectrum. The splitting of the signals of the protons of the CH—N and NH groups (J = 11.5 Hz) attests in favor of the ketoenamine structure with a strong IHB. The presence of IHB is confirmed by the low-field value of the chemical shift of the proton of the NH group. Another set of signals is also observed in the spectrum of compound **2a**. These signals correspond to an isomer in which the O atom of the ethoxycarbonyl group participates in IHB, but the content of this isomer in the mixture does not exceed 5%. Like enhydrazone **6**, the azomethine group probably has the *anti*-configuration. A similar picture is observed in the spectra of compounds **2b** and **3**.

A double set of signals close in their intensity, which correspond to isomers **4a,b**, is observed in the ^1H NMR spectrum of hydrazone **4**. The parameters of the spectra correlate well with the enolimine structure characteristic of aroylhydrazones of aroylacetaldehydes.[1,2] The absence of two pairs of doublets for the CH—N and NH groups in the spectra does not count in favor of the ketoenamine structure (the fact that Δν = 20 Hz between the two signals in the 8 ppm range is not consistent with the coupling constant for the protons of the HCNH fragment, and these signals are presumably singlets spaced closely to each other).

While the ketoenamine form, which occurs in the case of compounds **2a,b** and **3**, is common for β-dicarbonyl hydrazones, the rarer enolimine structure of product **4** can be explained by the fact that it is beneficial to involve a phenyl group in the overall system of π—p—π conjugation.

Hydrazones **2a**, **2b**, **3**, and **4** are not in equilibrium with tautomeric 5-hydroxypyrazolines, which have a characteristic signal in the 3 ppm range of their ^1H NMR spectra.[1—3]

Unfortunately, some authors,[3—6] while studying the tautomeric composition of β-dicarbonyl hydrazones, did not consider the possibility of the formation of enolimines. Taking into account the results of our investigation

Table 2. The spectral parameters of compounds **2—6**

Compound	^{1}H NMR, δ (*J*/Hz)	IR, ν/cm^{-1}
2a	1.3 [1.35][a] (t, 3 H, Me); 2.40 [2.38] (s, 3 H, MeCO); 4.2 [4.3] (q, 2 H, CH_2); 7.45—7.50 (m, 3 H, CH arom.); 7.77—7.80 (m, 2 H, CH arom.); 8.44 [8.45] (d, 1 H, CH—N, *J* = 11.5); 8.47 (s, 1 H, CH=N); 13.2 (br.d, 1 H, NH, *J* = 11.5)	3420 br (N—H); 1685 (C=O of ester); 1640—1555 (C=O, C=C, C=N)
2b	1.05 (t, 3 H, Me); 4.10 (q, 2 H, CH_2); 7.4—7.6, 7.7—7.8 (2 m, 10 H, CH arom.); 8.1 [8.0][a] (s, 1 H, CH=N); 8.6 [8.3] (d, 1 H, CH—N, *J* = 12.0); 12.95 [11.7] (br.d, 1 H, NH, *J* = 12.0)	3240 br (N—H); 1710 (C=O of ester); 1630, 1610, 1575 (C=O, C=C, C=N)
3	1.25 [1.30][b] (t, 3 H, Me); 2.40 [2.35] (s, 3 H, MeCO); 4.15 [4.25] (q, 2 H, CH_2); 7.80 (q, 4 H, CH arom., *J* = 8.5); 8.15 [8.05] (d, 1 H, CH—N, *J* = 12.5); 11.85 (br.s, 1 H, NHCO); 12.4 [10.5] (d, 1 H, NHCH, *J* = 12.5)	3210, 3120 br (N—H); 1720 (C=O of ester); 1650, 1600, 1575, 1520 (C=O, C=C, C=N)
4a,b[c]	0.90/0.95[d] (t, 3 H, Me); 4.00 (2 q, 2 H, CH_2); 7.25—7.85 (m, 9 H, CH arom.); 8.25/8.15 (s, 1 H, CH=N); 10.90/10.55 (br.s, 1 H, NH); 11.5/9.7 (br.s, 1 H, OH)	3200, 3120 br (N—H); 1720 (C=O of ester); 1670, 1650, 1645,1600, 1575, 1520 (C=C, C=N, C=O)
5	1.2 (t, 3 H, Me); 4.2 (q, 2 H, CH_2); 7.30—7.50 (m, 5 H, CH arom.); 7.65—7.85 (A_2B_2-system, 4 H, CH arom., *J* = 8.5); 8.15 (s, 1 H, CH of pyrazole)	1730 (C=O of ester); 1595, 1580
6	1.2 (t, 3 H, Me); 2.2 (s, 3 H, MeCO); 4.1 (q, 2 H, CH_2); 4.65 (s, 1 H, CH=C); 7.34—7.43 (m, 3 H, CH arom.); 7.70 (d, 2 H, CH arom., *J* = 8.2); 8.05 (s, 1 H, CH=N); 11.65 (s, 1 H, NH)	3420 br (N—H); 1660 (C=O); 1620, 1595, 1570 (C=C, C=N)

[a] The signals of the *Z,E*-isomer are given in brackets; its content <5%.
[b] The signals of the *Z*-isomer are given in brackets; its content <5%.
[c] A mixture of isomers **4a** (~55%) and **4b** (~45%).
[d] The signals of isomers **4a/4b** are given.

and of works devoted to the interaction of aroylacetaldehydes with aroylhydrazines,[1,2] one can assume that for the aroylhydrazones of aroylacetones described previously,[4] the enolimine structure is more probable (the ketoenamine structure was ascribed to these compounds, though a comparison of their spectral characteristics with the data for derivatives of the corresponding aroylacetaldehydes[1,2] gives grounds to doubt the correctness of this conclusion).

Experimental

IR spectra of compounds **2a** and **6** were recorded on a Hitachi M-20 instrument in pellets with KBr. IR spectra of compounds **2b**, **3**, **4**, and **5** were recorded on an IKS-29 instrument in Vaseline oil. ^{1}H NMR spectra of compounds **2a** and **6** were recorded in $(CD_3)_2CO$ on a Varian XL-400 spectrometer (400 MHz). ^{1}H NMR spectra of compounds **2b**, **4**, and **5** ($CDCl_3$) and **3** (DMSO-d_6) were recorded on a Bruker AC-200 spectrometer (200 MHz).

Ethyl α-ethoxymethyleneacetoacetate and **ethyl α-ethoxymethylenebenzoylacetate** were obtained by interaction of ethyl acetoacetate and ethyl benzoylacetate, respectively, with triethyl orthoformate.[7] **Benzylidenehydrazine*** was synthesized from benzaldehyde and hydrazine hydrate.[8]

* Benzylidenehydrazine was hydrolyzed rapidly by air moisture.

Condensation of benzylidenehydrazine with ethyl acetoacetate. A mixture of benzylidenehydrazine (2.7 g, 0.02 mol) and ethyl acetoacetate (2.6 g, 0.02 mol) in 20 mL of EtOH was refluxed on a water bath for 0.5 h, the solvent was removed, and the residue was distilled *in vacuo*. A fraction with b.p. 145—150 °C (3 Torr) was collected, and 2.1 g (45%) of benzylidenehydrazone of ethyl acetoacetate (**6**) was obtained.

Condensation of *p*-bromobenzoylhydrazine with ethyl α-ethoxymethylenebenzoylacetate. A solution of ethyl α-ethoxymethylenebenzoylacetate (1.0 g, 4.0 mmol) in 5 mL of EtOH was added to a solution of *p*-bromobenzoylhydrazine (0.87 g, 4.0 mmol) in 5 mL of EtOH. The mixture was refluxed on a water bath for 0.5 h and cooled, and the precipitate that formed was separated. A portion of the precipitate was recrystallized three times from toluene. *p*-Bromobenzoylhydrazone of ethyl α-formylbenzoylacetate (**4**) was obtained, m.p. 164—165 °C. After another portion of the precipitate was recrystallized three times from EtOH, ethyl 1-(*p*-bromobenzoyl)-5-phenyl-4-pyrazolecarboxylate (**5**) was isolated, m.p. 115—118 °C.

The condensation of ethyl α-ethoxymethyleneacetoacetate with benzylidenehydrazine and the condensation of ethyl α-ethoxymethyleneacetoacetate with *p*-bromobenzoylhydrazine and benzylidenehydrazine were carried out analogously. Benzylidenehydrazone of ethyl α-formylacetoacetate (**2a**), benzylidenehydrazone of ethyl α-formylbenzoylacetate (**2b**), and *p*-bromobenzoylhydrazone of ethyl α-formylacetoacetate (**3**) were obtained.

The ^{1}H NMR and IR spectral characteristics of compounds **2a,b** and **3—6** are given in Table 2.

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