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α-(1-PHENYLHYDRAZINO)-ALKANONE PHENYLHYDRAZONES: THE REACTION WITH CARBONYL COMPOUNDS[1]

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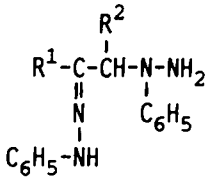
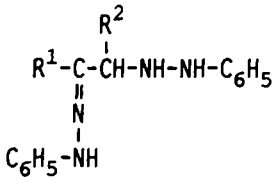
Abstract - The unsymmetrically disubstituted hydrazines **1** were condensed with carbonyl compounds. Some of the expected condensation products were isolated, but some were formed as unstable intermediates which underwent 1,4-elimination: The phenylhydrazone of the carbonyl compound used was obtained, together with the corresponding phenylazo-alkene **11** or alternatively, the 1,4-addition product of a different protic nucleophile to **11**.

INTRODUCTION

The addition of phenylhydrazine to phenylazo-alkenes **11** has been reported to yield the α-(1-phenylhydrazino)-alkanone phenylhydrazones **1** exclusively.[2] Mostly the same products **1** were obtained from the reaction of the corresponding α-chloro- or α-bromo-carbonyl compounds with phenylhydrazine; however a few exceptions were encountered, when the latter reaction gave rise to the formation of the isomeric product, the α-(2-phenylhydrazino)-alkanone phenylhydrazone **2**.



1



2

The two isomeric structures **1** and **2** are discernible by ^{1}H-NMR.[2] It was anticipated, that also chemical evidence should be obtainable to prove the unsymmetrically N,N-disubstituted hydrazine moiety (>N-NH_2) in compounds **1** as against the hydrazo group (-NH-NH-) of the isomers **2**. An appropriate reaction pertinent to the structural feature of compounds **1** is their conversion into hydrazones.

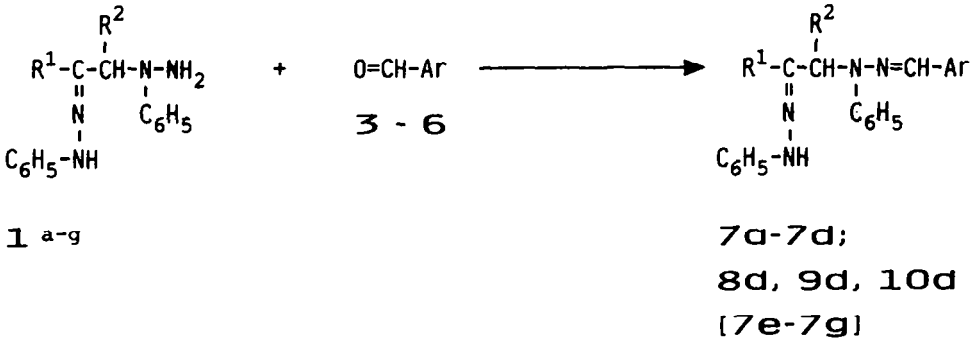
RESULTS AND DISCUSSION

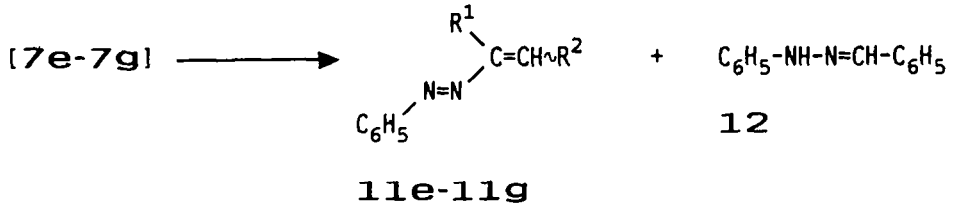
Reactions.

As expected, the α-(1-phenylhydrazino)-alkanone phenylhydrazones **1a - 1d** underwent the condensation with benzaldehyde **3**, and the corresponding hydrazones **7a - 7d** were obtained. Likewise, the aromatic aldehydes **4 - 6** converted the hydrazine derivative **1d** into the hydrazones **8d**, **9d**, and **10d**, respectively (Scheme 1).

The hydrazines **1e - 1g** reacted with benzaldehyde **3** as well, but in these cases the condensation products **7e - 7g** could not be isolated. Instead, two products, the respective phenylazo-alkenes **11e**[3], **11f**[4], and **11g**[5] along with benzaldehyde phenylhydrazone **12** were obtained. Obviously, these products arose from a 1,4-elimination reaction of the intermediately formed benzylidene derivatives **7e - 7g**.

Scheme 1.





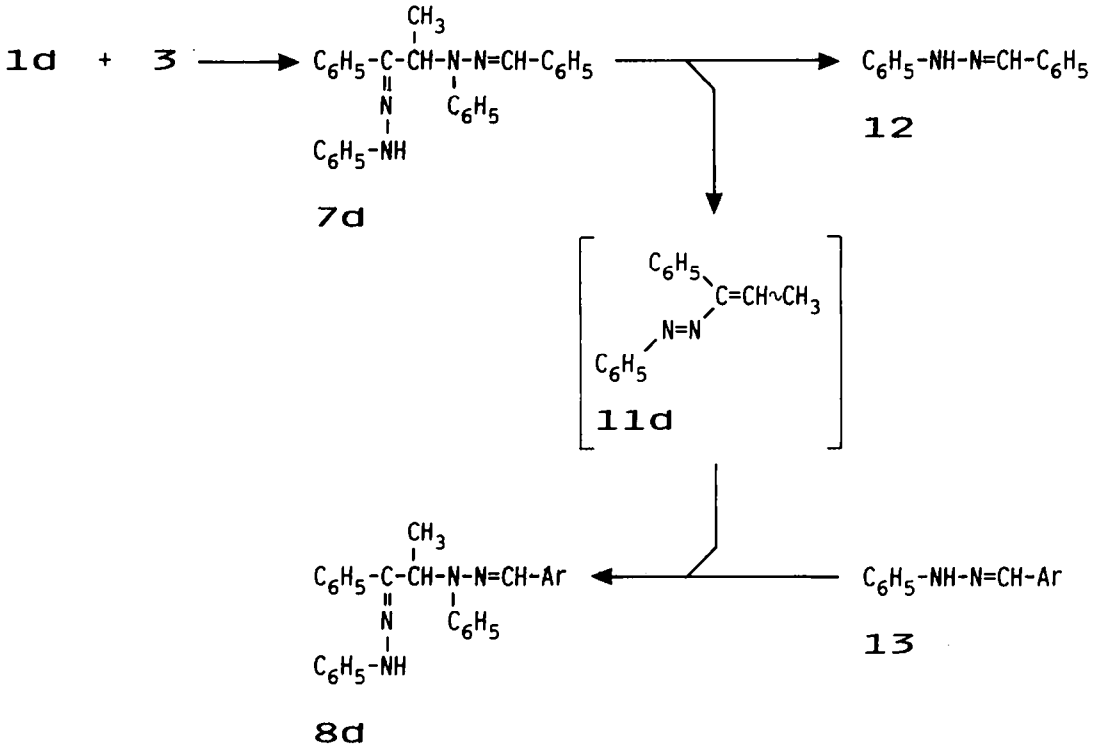
	R^1	R^2
a	H	H
b	CH_3	H
c	CH_3	CH_3
d	C_6H_5	CH_3
e	H	CH_3
f	$(CH_2)_4$	
g	CH_3	C_6H_5

	Ar
3, 7	C_6H_5
4, 8	$4\text{-}CH_3OC_6H_4$
5, 9	$4\text{-}O_2NC_6H_4$
6, 10	$C_6H_5CH{=}CH$

Also the isolated condensation products **7a - 7d** readily eliminate benzaldehyde phenylhydrazone **12**, e.g. in the course of recrystallization at elevated temperature or at the m.p. Quite reasonable, the leaving group quality of the benzylidene phenylhydrazino moiety of compounds **7** is better than that of the phenylhydrazino group in **1** (which requires protonation for its elimination[2]).

Furthermore, a cross experiment demonstrated the facile elimination of benzaldehyde phenylhydrazone **12**: The reaction of **1d** with benzaldehyde **3** in chloroform solution was carried out in the presence of anisaldehyde phenylhydrazone **13** and afforded a mixture of the condensation products **7d** and **8d** along with the phenylhydrazones **12** and **13** (Scheme 2). This result is rationalized by regarding the phenylazo-alkene **11d**[5] as an intermediate: Presumably, owing to the propensity of the benzylidene phenylhydrazino residue to behave as a leaving group, in solution an equilibrium is existing between **7d** and the 1,4-elimination products **11d** and **12**; either of the two phenylhydrazones **12** and **13** can add to the intermediate phenylazo-alkene **11d**, the latter providing the 4-methoxybenzylidene product **8d**. These additions of phenylhydrazones to azo-alkenes parallel earlier reports[6] on the addition of phenylosazones to phenylazo-alkenes.

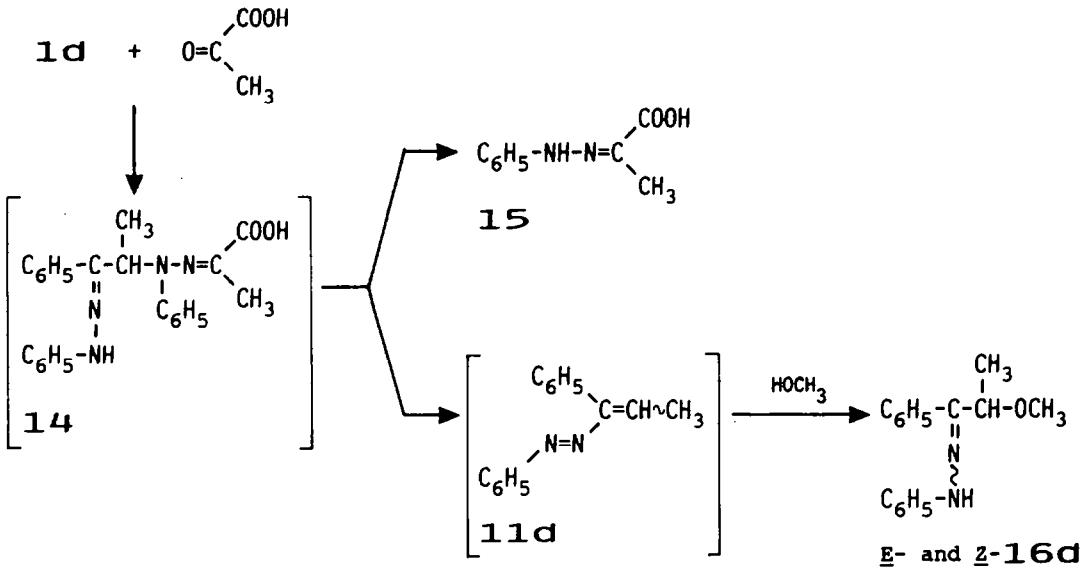
Scheme 2.



Ar : CH_3O-C_6H_4

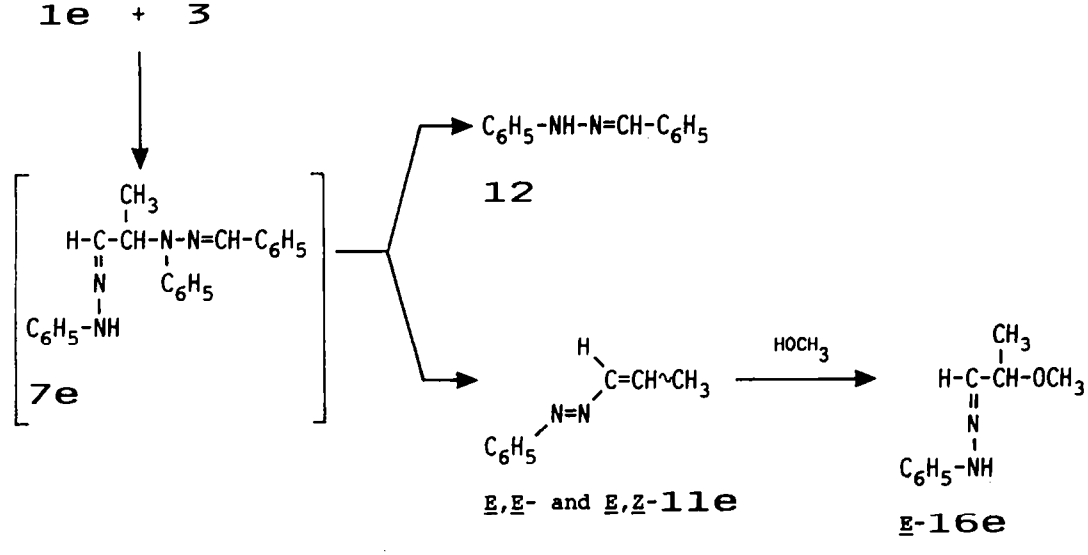
The hydrazine compound **1d** reacted with pyruvic acid in methanolic solution, but the expected hydrazone **14** was not isolated (Scheme 3). Instead, pyruvic acid phenylhydrazone **15** was obtained together with a mixture of E- and Z-2-methoxy-1-phenyl-1-propanone phenylhydrazone E- and Z-**16d**. The latter products are again indicative of the intermediate formation of the phenylazo-alkene **11d**,[5] which underwent a 1,4-addition reaction with the protic solvent.[7-10]

Scheme 3.



The products isolated from the reaction of compound **1e** with benzaldehyde **3** in methanol depend on the reaction temperature: At -20°C a mixture of the isomeric 1-phenylazo-1-propenes E,E- and E,Z-**11e**[3] and benzaldehyde phenylhydrazone **12** was obtained (Scheme 4). At room temperature, **12** and the E-2-methoxy-1-propanone phenylhydrazone E-**16e** were isolated. Evidently, the latter product results from the 1,4-addition of the solvent to the first-formed phenylazo-alkene **11e**.

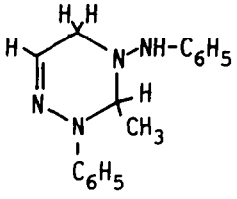
Scheme 4.



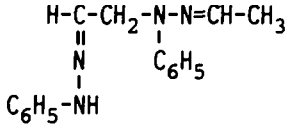
Structures.

The ^1H NMR signal of the benzylidene methine proton of the condensation products **7a - 7d**, **8d**, **9d**, and **10d** is found in the range of the aromatic proton signals: Depending on the solvent used, the methine signal is contained in the multiplet of the aromatic protons ($CDCl_3$) as revealed by signal integration, or it appears as a distinct singlet shifted slightly downfield from the aromatic multiplet (DMSO-d_6).

The range of δ 7-8 for the methine proton signal of aldehyde hydrazones (as confirmed e.g. by the corresponding signal of benzaldehyde phenylhydrazone **12** at δ 7.80, in DMSO-d_6) is significant in view of a report on the reaction of chloroacetaldehyde with phenylhydrazine.[11] The product has been supposed to be 2-(2-phenylhydrazino)-acetaldehyde phenylhydrazone **2a**, which, in turn, was allowed to react with carbonyl compounds. The resulting condensation product has been described as a tetrahydro-1,2,4-triazine derivative; thus, structure **17a** has been assigned to the product obtained from the reaction of the alleged compound **2a** with acetaldehyde. However, from the ^1H NMR data given,[11] it is evident that some of the reported chemical shifts do not meet the requirements of the proposed heterocyclic structure **17a**: In particular, one of the proton signals



17a



18a

contained in the multiplet centered at δ 7.2 was attributed to the aminal methine proton; however, the aminal methine proton is expected to resonate around δ 3.5.[6a] On the other hand, the reported ^1H NMR data are in good agreement with the structure of 2-(2-ethylidene-1-phenylhydrazino)-1-ethanone phenylhydrazone **18a**, the multiplet at δ 7.2 arising from the methine protons of both aldehyde hydrazone functions in **18a** (in addition to the signals of C_6H_5 and NH). Consequently, the structures of the alleged compound **2a** and its conversion products with carbonyl compounds[11] should be replaced by structure **1a**,[2] and by those of the respective condensation products: Thus, the reaction product with benzaldehyde **3** is **7a** (the m.p. reported[11] matches with that found for **7a**).

The 1,4-addition of nucleophiles to the azo-ene system affords α-substituted hydrazone derivatives. Mostly one single isomer is obtained, but occasionally a mixture of E- and Z-hydrazones is produced; only in some cases the configuration of the resulting hydrazones has been established.[2,6,8,12] It has been found that the α-(1-phenylhydrazino)-alkanone phenylhydrazones **1** (resulting from the 1,4-addition of phenylhydrazine to phenylazo-alkenes **7**[2]) are single isomers, and the ^1H NMR data of **1f** have been interpreted as supporting the E-configuration.[2] Accordingly, the benzylidene derivatives **7 - 10**, giving rise to one set of ^1H NMR signals, are assigned to the E-configuration of the phenylhydrazone function. The α-methylene and α-methine proton signals are shifted downfield as compared with the corresponding hydrazines **1a - 1d**, and this is reasonable with respect to the additional hydrazone function.

By contrast, the α-methoxy phenylhydrazone **16d** is formed as a mixture of E- and Z-isomers, and the structure assignment is based on the chemical shift of the α-methine protons: According to the criteria brought forward by Karabatsos and Taller[13] the high field α-methine signal is attributed to the preponderant anti-isomer E-**16d** (the chemical shift of the β-methyl protons has been found to be less reliable for this assignment[13]).

The α-methoxy phenylhydrazone **16e** was obtained as a single isomer. By comparison with **16d**, the chemical shifts of the α-methine and the β-methyl protons are in good agreement with the proposed E-configuration of **16e**.

EXPERIMENTAL

Petroleum ether refers to the fraction collected within the boiling range of 40-60°C. Column chromatography was performed on silica gel (0.05-0.2 mm, Macherey & Nagel) after deactivation by addition of 10% H_2O. Analytical t.l.c. sheets were coated with silica gel (0.25 mm; Sil G UV_{254}, Macherey & Nagel). Melting points (m.p.) were determined on a Kofler hot stage microscope (Reichert). The ^1H NMR spectra were recorded on a JEOL-PMX-60 (60 MHz) instrument. The starting compounds **1** were prepared as previously described.[2]

2-(2-Benzylidene-1-phenylhydrazino)-1-ethanone phenylhydrazone **7a**

The solution of **1a** (0.24 g, 1 mmol) and **3** (0.106 g, 1 mmol) in methanol (5 ml) was allowed to stand at r.t. for 1 h. After cooling to 0°C, the product was collected as pure crystals **7a** (0.28 g, 87%), m.p. 145°C.[14] ^1H NMR (DMSO-d_6): δ 4.78 (2H, d, J 5 Hz, CH_2); 6.5-7.8 (16H, m, 3 C_6H_5, =C<u>H</u>-CH_2); 7.86 (1H, s, =C<u>H</u>-C_6H_5); 9.87 (1H, s, NH, exchangeable with D_2O).

1-(2-Benzylidene-1-phenylhydrazino)-2-propanone phenylhydrazone **7b**

To a solution of **1b** (0.254 g, 1 mmol) in methanol (5 ml) was added **3** (0.106 g, 1 mmol) at r.t. Shortly afterwards, the product separated as pure pale yellow crystals **7b** (0.27 g, 79%), m.p. 159-163°C (methanol). Anal. Calcd. for $C_{22}H_{22}N_4$ (342.45): C, 77.16; H, 6.48; N, 16.36. Found: C, 77.19; H, 7.18; N, 16.59. ^1H NMR (DMSO-d_6): δ 1.88 (3H, s, CH_3); 4.79 (2H, s, CH_2); 6.4-7.7 (15H, m, 3 C_6H_5); 7.80 (1H, s, -CH=); 8.89 (1H, s, NH, exchangeable with D_2O).

3-(2-Benzylidene-1-phenylhydrazino)-2-butanone phenylhydrazone **7c**

To a solution of **1c** (0.268 g, 1 mmol) in methanol (5 ml) **3** was added (0.106 g, 1 mmol). After 10 min the starting materials were consumed as revealed by t.l.c., and the solvent was evaporated in vacuo. The residual red oil was subjected to column chromatography on silica gel, and the first fractions eluted with n-hexane/ether (1:1) contained the product **7c**, which after evaporation of the solvent crystallized from pentane (0.07 g, 20%), m.p. (dec.) 115-123°C. ^1H NMR (DMSO-d_6): δ 1.56 (3H, d, J 7 Hz, CH-C<u>H</u>$_3$); 1.81 (3H, s, CH_3); 4.97 (1H, q, J 7 Hz, C<u>H</u>-CH_3); 6.4-7.6 (15H, m, 3 C_6H_5); 7.64 (1H, s, -CH=); 8.88 (1H, s, NH, exchangeable with D_2O).

2-(2-Benzylidene-1-phenylhydrazino)-1-phenyl-1-propanone phenylhydrazone **7d**

A solution of **1d** (3.30 g, 10 mmol) in chloroform (10 ml) was combined with **3** (1.06 g, 10 mmol). After a few min the product **7d** began to crystallize; after cooling to 0°C and upon addition of petroleum ether (10 ml), the product was filtered off and recrystallized from chloroform/petroleum ether to give faintly yellow crystals **7d** (2.50 g, 60%), m.p. 134-135°C. Anal.: Calcd. for $C_{28}H_{26}N_4$ (418.54): C, 80.35; H, 6.26; N, 13.39. Found: C, 79.81; H, 6.48; N, 13.41. ^1H NMR ($CDCl_3$): δ 1.75 (3H, d, J 6.5 Hz, C<u>H</u>$_3$-CH); 5.05 (1H, q, J 6.5 Hz, C<u>H</u>-CH_3); 6.5-7.8 (22H, m, 4 C_6H_5, -CH=, NH; 1H exchangeable with D_2O).

2-[2-(4-Methoxybenzylidene)-1-phenylhydrazino]-1-phenyl-1-propanone phenylhydrazone **8d**

In the same way, **1d** (3.30 g, 10 mmol) and anisaldehyde **4** (1.20 g, 10 mmol) yielded yellowish crystals **8d** (2.8 g, 63%), m.p. 110-111°C (chloroform/petroleum ether). Anal. Calcd. for $C_{29}H_{28}N_4O$ (448.57): C, 77.65; H, 6.29; N, 12.49. Found: C, 76.60; H, 6.26; N, 12.30. ^1H NMR ($CDCl_3$): δ 1.75 (3H, d, J=6.5 Hz, CH_3-CH), 3.75 (3H, s, CH_3O); 5.05 (1H, q, J=6.5 Hz, CH-CH_3), 6.6-7.7 (21H, m, 3 C_6H_5, C_6H_4, -CH=, NH; 1H exchangeable with D_2O).

2-[2-(4-Nitrobenzylidene)-1-phenylhydrazino]-1-phenyl-1-propanone phenylhydrazone **9d**

Analogously, the reaction of **1d** (3.30 g, 10 mmol) and 4-nitrobenzaldehyde **5** (1.51 g, 10 mmol) yielded orange crystals **9d** (2.2 g, 48%), m.p. 159°C (chloroform/petrol ether). Anal. Calcd. for $C_{28}H_{25}N_5O_2$ (463.52): C, 72.55; H, 5.44; N, 15.11. Found: C, 72.41; H, 5.46; N, 14.98. ^1H NMR ($CDCl_3$): δ 1.80 (3H, d, J 6.5 Hz, CH_3-CH); 5.05 (1H, q, J 6.5, CH-CH_3); 6.5-7.7 (19H, m, 3 C_6H_5, AA' portion of 4-$O_2NC_6H_4$, -CH=, NH; 1H exchangeable with D_2O), 7.95-8.25 (2H, BB' portion of 4-$O_2NC_6H_4$).

1-Phenyl-2-[1-phenyl-2-(3-phenyl-2-propenylidene)-hydrazino]-1-propanone phenylhydrazone **10d**

The product obtained from **1d** (3.30 g, 10 mmol) and cinnamaldehyde **6** (1.32 g, 10 mmol) was recrystallized from chloroform/petroleum ether to give yellowish crystals **10d** (2.75 g, 61%), m.p. 119°C. Anal. Calcd. for $C_{30}H_{28}N_4$ (444.58): C, 81.05; H, 6.35; N, 12.60. Found: C, 80.47; H, 6.50; N, 12.59. ^1H NMR ($CDCl_3$): δ 1.75 (3H, d, J 6.5 Hz, CH-CH_3); 5.03 (1H, q, J 6.5 Hz, CH-CH_3); 6.43 (1H, d, J 15 Hz, -CH=); 6.8-7.8 (23H, m, 4 C_6H_5, 2 =CH-, NH; 1H exchangeable with D_2O).

Reaction of **1d** with **3** in the presence of **13**:

To a solution of **1d** (0.66 g, 2 mmol) and **13** (0.55 g, 2 mmol) in chloroform (10 ml) was added **3** (0.21 g, 2 mmol). After 1 h, t.l.c. (petroleum ether/ether, 7:3) revealed the consumption of **1d** and **3**; in addition to **13**, the formation of **7d**, **8d**, and **12** was proved by comparison with the respective authentic compounds.

E- and Z-2-Methoxy-1-phenyl-1-propanone phenylhydrazone E- and Z-**16d**

Addition of pyruvic acid (0.53 g, 6 mmol) to a stirred suspension of **1d** (1.0 g, 3 mmol) in methanol (20 ml) caused the mixture to turn yellow and to dissolve. After 2 h the solvent was removed in vacuo, and the residue was treated with ether (30 ml) to precipitate pyruvic acid phenylhydrazone **15** (0.35 g). The filtrate was extracted with saturated Na_2CO_3 solution (3 x 20 ml), the aqueous extracts were acidified with 2 N HCl to give another crop of **15** (0.10 g, total yield 0.45 g, 83%), identical with an authentic sample (mixed m.p., IR). The organic layer was washed with water until neutral, dried over $MgSO_4$, and after removal of the solvent the residual yellowish oil was subjected to column chromatography on silica gel (100 g). The first fraction eluted with ether/petroleum ether (1:1) (R_f 0.8) contained a faintly yellow oil **16d** (0.6 g, 78%), a 9:1 mixture of E- and Z-isomers as indicated by ^1H NMR; these isomers were inseparable by silica gel chromatography. ^1H NMR (DMSO-d_6): δ 1.18 (d, J 6.5 Hz, CH_3-CH, E); 1.47 (d, J 6.5 Hz, CH_3-CH, Z); 3.27 (s, OCH_3, E and Z); 4.15 (q, J 6.5 Hz, CH-CH_3, E); 4.89 (q, J 6.5 Hz CH-CH_3, Z); 6.5-7.6 (m, 2 C_6H_5, E and Z); 8.41 (s, NH, E; exchangeable with D_2O); 9.86 (s, NH, Z; exchangeable with D_2O).

The reaction of **1e** and **3**:

(a) E- and Z-1-Phenylazo-1-propene E-and Z-**11e**

To a solution of **1e** (0.254 g, 1 mmol) in methanol (1.5 ml) at -20°C a solution of **3** (0.106 g, 1 mmol) in methanol (1.5 ml) was added dropwise. The mixture was

allowed to stand for 2 h (-20°C → -5°C) and was then chromatographed on silica gel (100 g) with petroleum ether/ether (7:3). The front fractions after evaporation of the solvent yielded an orange oil (R_f 0.95) consisting of a mixture (3:2) of E,E- and E,Z-**11e**[3] (0.06 g, 41%). From the following eluate (R_f 0.4) crystalline **12** (0.13 g, 66%) was isolated.

(b) E-2-methoxy-1-propanone phenylhydrazone E-**16e**

The same reaction mixture of **1e** and **3** as before was kept at r.t. Work-up by column chromatography on silica gel (100 g) with n-hexane/ether (1:1) revealed no phenylazo-alkene **11e**. The eluates contained **12** (0.15 g, 76%) followed by the yellowish oil E-**16e** (0.04 g, 22%; R_f 0.2), an unstable compound which did not crystallize. ^{1}H NMR (DMSO-d_6): δ 1.22 (3H, d, J 6.5 Hz, CH_3-CH); 3.19 (3H, s, OCH_3); 3.82 (1H, dq, J,J 6.5 Hz, CH-CH-CH_3); 6.4-7.6 (6H, m, C_6H_5, -CH=); 9.76 (1H, s, NH, exchangeable with D_2O).

Reaction of **1f** with **3**:

The solution of **1f** (0.294 g, 1 mmol) and **3** (0.106 g, 1 mmol) in methanol (30 ml) was allowed to stand at r.t. for 16 h. The reaction mixture was concentrated in vacuo, and the separated crystals of **12** (0.061 g) were filtered off. The filtrate was chromatographed as described before to yield orange crystals **11f**[4] (0.086 g, 46%) and colorless crystals **12** (0.080 g; total 0.141 g, 72%).

Reaction of **1g** with **3**:

Addition of **3** (0.106 g, 1 mmol) to a solution of **1g** (0.330 g, 1 mmol) in methanol (5 ml) immediately caused the reaction mixture to turn red due to the formation of **11g**. Part of **12** formed (0.050 g) crystallized from the reaction mixture. Chromatography of the filtrate (as above) gave a red oil of E,E- and E,Z-**11g**[5] (0.080 g, 36%) and crystalline **12** (0.085 g, total 0.135 g, 69%).

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14. Apparently, compound **7a** has been prepared earlier (m.p. 142-143°C),[11] but the structure assignment was erroneous.