Saturated Heterocycles, 162 [1]. Synthesis and Steric Structures of 3,4-Disubstituted 1,6,7,11b-Tetrahydropyrimido[6,1-*a*]isoquinolin-2-ones

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The reaction of 1-(hydrazidomethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **3** with aromatic aldehydes yield hydrazones **4a,b** or pyrimido[6,1-*a*]isoquinolines **5a-c** depending upon the proportions of the reagents. With ketones, **3** gives only hydrazones **4a-d** and **7**, which can be transformed to pyrimidoisoquinolines **10a-e** and **11** with aldehydes. The ring closures are stereospecific; the relative configurations were determined by DNOE measurements.

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Introduction.

The reactions of β-aminocarbohydrazides with oxo compounds lead to products with various structures. Depending on the substituents and the conditions employed, the products are hydrazone, pyrimidinone or triazepinone derivatives [2-5]. Mixtures of the latter compounds and their ring-chain tautomers can also be formed [5,6].

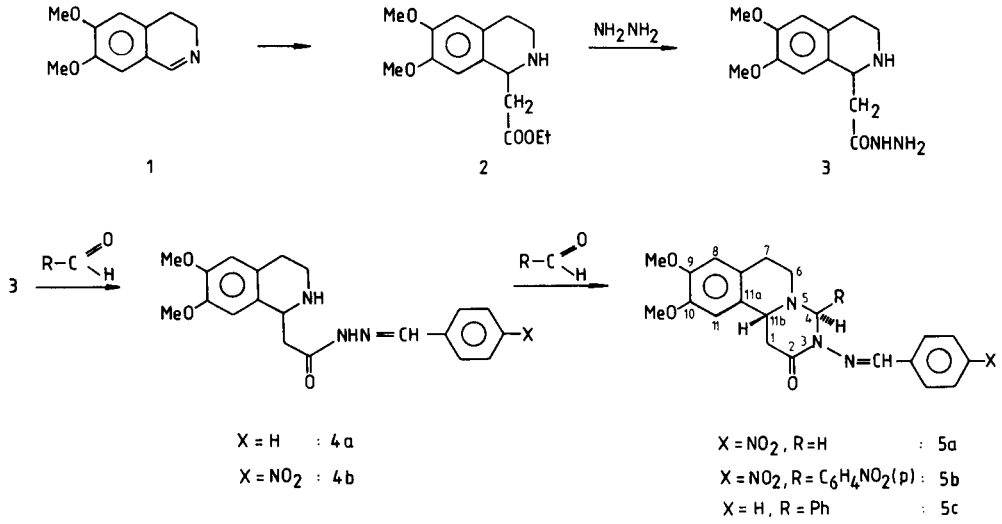
As a continuation of our synthetic and stereochemical studies [7-11] on angularly fused 1,3-heterocycles, we now report on the synthesis and stereochemical studies of 3,4-disubstituted pyrimido[6,1-*a*]isoquinolin-2-ones.

Numerous publications deal with the syntheses and investigations of compounds with a pyrimido[6,1-*a*]isoquinoline skeleton. The most frequently used synthetic route was the ring closure of suitably functionalized tetrahydroisoquinolines [12-14]. Another available method is the Bischler-Napieralsky ring closure of 1-(3,4-dimethoxyphenylethyl)barbituric acid [15,16], or a simpler version, the ring closure of (3,4-dimethoxybenzoyl-β-alanyl)veratrylethylamide [17,18]. The latter reaction furnishes the desired pyrimido[6,1-*a*]isoquinoline ring in one step.

These compounds are also important pharmacologically: the compound 2-mesitylimino-3-methyl-9,10-dimethoxy-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-one is an antihypertensive drug under the name Trequinsin [15].

Synthesis.

In the syntheses, the carbohydrazide **3** was used as the starting material. Among the known methods [19-23] for the preparation of ethyl 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-acetate (**2**) as a possible starting material for compound **3**, we have found that the most advantageous synthetic route [23] with the highest yield is that with 6,7-dimethoxy-3,4-dihydroisoquinoline (**1**) as the starting material. With malonic acid half ester **2** was first formed, and the hydrazide **3** was obtained from this with hydrazine hydrate. With an equivalent amount of benzaldehyde or *p*-nitrobenzaldehyde, compound **3** gave the hydrazones **4**. Even after the complete disappearance of



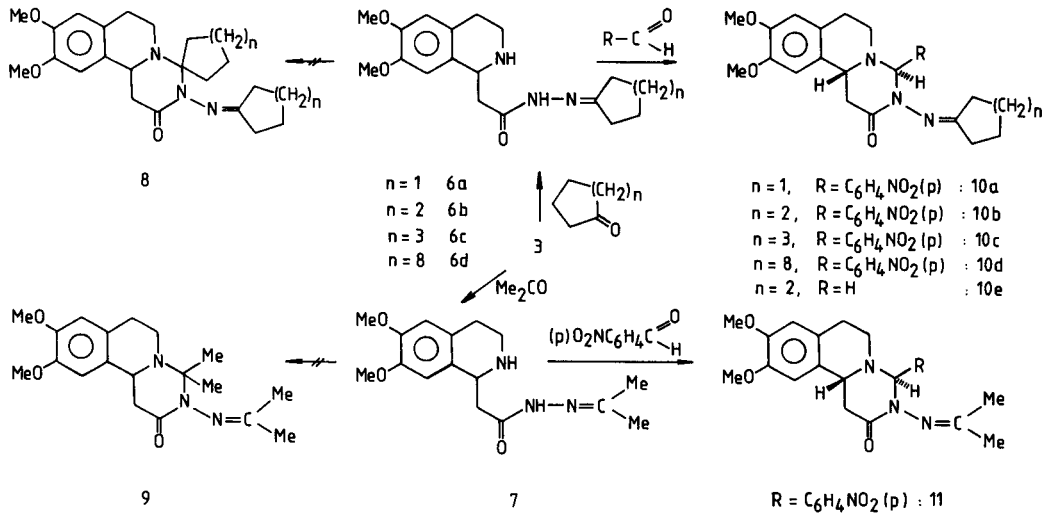


Table 1

Selected IR Frequencies (in potassium bromide, cm^{-1}) and ^1H NMR Chemical Shifts (at 250 MHz, in deuteriochloroform δ TMS = 0 ppm) of Compounds **4a,b**, **6a-d** and **7** and the Ratios of Amide Rotamers [a]

Compound	ν NH band amine	ν NH band amide	Amide-I band	H-11b	H-8,11		Ratio of rotamers
4a	3153	3200-2700	1649	~4.4 ~4.5	6.67 6.68	6.78 6.81	1:1
4b	3080	3200-2700	1668	~4.4 ~4.45	6.63	6.75 6.76	1:1
6a	3277	3200-2700	1664	4.24 4.48	6.55 6.57	6.66 6.68	11:2
6b	3269	3200-2700	1668	4.25 4.48	6.55 6.58	6.61 6.68	11:2
6c	3270	3200-2700	1680	4.24 4.48	6.56 6.57	6.60 6.68	6:1
6d	3233	3200-2700	1647	4.24 4.48	6.56 6.59	6.61 6.68	8:5
7	3312	3200-2700	1679	4.20 4.42	6.55 6.57	6.60 6.67	6:1

[a] The data in the second rows stand for the minor rotamers.

benzaldehyde, the starting material **3** is still present, because a 1:2 adduct **5** is also formed in small amount. When two equivalents of aldehyde were used, the ring-closed products **5b** and **5c** were formed in good yields. The hydrazones **4a** and **4b**, isolated as the products of the first step of the reaction, underwent reaction with benzaldehyde, *p*-nitrobenzaldehyde or formaldehyde to yield pyrimidoisoquinolines **5a-5c**.

The reactions of compound **3** with ketones resulted in the exclusive formation of hydrazones **6a-d** and **7**, independently of the amount of ketones. The tricyclic compounds **8** and **9** were not formed even during refluxing for a considerable period of time.

The analogous reaction of anthranilic acid hydrazide and cyclohexanone at room temperature gave *N*-cyclohexylideneamino-2-(spirocyclohexane)quinazolin-4-one in good yield, and no condensation product of 1:1 type was formed [2].

The alkylideneamino derivatives **6** and **7**, however, readily react with aldehydes, *e.g.* with *p*-nitrobenzaldehyde and formaldehyde, to give pyrimidoisoquinolines **10a-e** and **11**.

Structure Elucidation.

According to their ^1H nmr spectra recorded in deuteriochloroform solution, the hydrazones **4a,b**, **6a-d**, and **7** (1:1 adducts) are rotameric mixtures of carboxamides. The ^1H

Table 2

^{1}H NMR Data (chemical shifts, δ TMS = 0 ppm and coupling constants, Hz) of Compounds **5a-c**, **10a-e**, and **11** in Deuteriochloroform Solution at 250 MHz

Compound	CH_2 *m*'s [a]	OCH_3 (9, 10) 2 x *s* (2 x 3H)		H-11b (1H) [b]	H-4 *s* (1H) [c]	H-8 *s* (1H)	H-11 *s* (1H)	ArH, 2 x *m* [d] (2 x 2H)		N=CH *s* (1H)
5a	2.7-3.3	3.87	3.86	4.06	4.71	6.65	6.54	7.89	8.24	9.21
5b	2.7-3.5	3.86	3.77	3.98	5.94	6.65	6.32	7.80 7.57 [e]	8.21 8.24	9.60
5c	2.8-3.4	3.84	3.76	4.07	5.87	6.62	6.33	~7.35	7.67 [e]	8.90
10a	1.2-3.2	3.88	3.86	4.10	5.24	6.67	6.60	7.70	8.22	–
10b	1.3-3.2	3.88	3.86	4.11	5.27	6.65	6.59	7.70	8.24	–
10c	1.2-3.2	3.88	3.86	4.10	5.24	6.66	6.59	7.73	8.23	–
10d	0.7-3.2	3.88	3.86	4.09	5.30	6.66	6.60	7.71	8.21	–
10e	1.5-3.3	3.84	3.86	4.04	4.19 4.62	6.63	6.53	–	–	–
11	2.4-3.2	3.86	3.88	4.12	5.25	6.66	6.59	7.68	8.22	–

[a] Groups in positions 1, 6, 7 and in the chain. Intensity: 6H (**5a-c**, **11**), 14*H* (**10a**), 16H (**10b,e**) 18H (**10c**) and 28H (**10d**). [b] Multiplicity: *dd* for **5a-c** and **10e** (*J* = 10.0-11.5 and 4.8-7.2 Hz) or *d* for **10a-d** and **11** (*J*, 10.0-12.0 Hz). [c] Intensity: 2H for **5a** and**10e**. Instead of a singlet, in the case of **10e** the 5-methylene hydrogens have an *AB* spectrum with $J_{A,B}$ = 10.2 Hz. [d] *AA'BB'*-type *m*'s $J_{A,B}$ = 8.5-9.0 Hz. Two *m*'s (intensity, 8H + 2H) for **5c**. [e] H-2', 6' (R in **5b**, N=CHPh group in **5c**).

Table 3

^{13}C-NMR Chemical Shifts (δ TMS = 0 ppm) of Compounds **5a-c**, **6b**, **10a-e** and **11** in Deuteriochloroform Solution at 20 or 63 MHz [a]

Compound	C–1	C=O (2)	C-4	C–6	C–7	C–7a	C–8	C–9,10		C–11	C–11a	C–11b OCH_3 (9,10)			C=N
5a [b]	39.4	166.2	74.0	45.9	28.8	128.1 [c]	112.4	148.3 [d]	148.6 [d]	109.2	126.5	56.0	56.1	56.3	149.5
5b	37.7	167.0	84.7	45.5	29.1	128.2 [d]	111.8	148.1 [e]	148.4 [e]	109.1	124.7	49.2 [f]	56.1 [c]		146.1
5c	37.9	166.1	84.1	45.5	29.3	129.5 [d]	112.4	148.0	148.6	109.8	125.2	49.1 [f]	56.1 [c]		153.1
6b [g]	39.9 [d] 39.3 [d]	167.7 155.4	– –	40.7 [d] 40.4 [d]	28.6 29.3	128.8 130.3	111.9	147.7 147.2	147.9 147.5	108.9 109.4	126.2 127.6	52.4 [f]	55.8	55.9	159.9 174.0
10a [b]	40.2	161.7	83.4	46.5	28.8	127.6	111.9	148.3 [d]	148.5 [d]	108.8	126.3	57.2	56.1 [c]	56.3	187.7
10b	40.0	162.1	83.1	46.6	28.8	127.4	111.5	148.2 [d]	148.3 [d]	108.2	126.2	57.2	56.0 [c]	56.2	181.2
10c	40.1	162.1	83.5	46.6	28.8	127.4	111.5	148.2 [d]	148.3 [d]	108.1	126.2	57.3	56.0 [c]	56.2	184.2
10d	40.1	162.7	84.2	46.7	28.8	127.4	111.4	148.1 [d]	148.2 [d]	108.1	126.2	57.4	55.9 [c]	56.1	180.3
10e	38.1	162.4	72.7	46.0	28.9	128.8	112.4	148.2 [d]	148.5 [d]	109.2	125.5	56.7	56.1 [c]	56.3	179.9
11	40.1	162.2	83.4	46.4	28.8	127.6	111.9	148.3 [d]	148.5 [d]	108.8	126.3	57.3	56.1 [c]	56.3	175.7

[a] Measuring frequency: 20 MHz (**5a,c**, **10a,e** and **11**), 63 MHz (**5b**, **6b**, **10b,c,d**). Futher signals: lines for *p*-nitrophenyl groups (**5a**, **6b**, **10a-d**, **11**): C-1' : 141.3 (**5a**), 140.9 (**5b**, chain), 151.2 (**5b**, 5-aryl), 146.8-147.0 [d,h] (**10a-d**, **11**), C-2'6' : 128.1 [c] (**5a**), 128.3 [d] and 128.4 [d] (**5b**), 129.8-130.2 (**10a-d**, **11**), C-3' 5' : 123.4-124.0 [i], C-4' : 147.9-148.9 [d,i] for phenyl groups in **5c**: 135.0 and 138.7, 127.4 [d] and 127.8 [d], 128.6 [d] and 128.7 [d], 127.8 and 130.4; lines for the alicycles: C(α) 27.8 and 35.2 (**6b**), 33.0 (**10a**), 31.3 and 35.3 (**10b**), 33.6 and 36.3 (**10c**), 30.5 and 32.5 (**10d**), 30.7 and 35.6 (**10e**), C(β): 25.5 and 25.9 (**6b**), 24.1 and 24.4 (**10a**), 26.2 and 27.3 (**10b**) 28.6 and 30.3 (**10c**), 22.5-26.0 (9 lines, **10d**), 26.4 and 27.4 (**10e**), C(γ, *etc.*): 26.8 (**6b**), 25.2 (**10b**), 24.0 and 27.2 (**10c**), 25.7 (**10e**), $C(CH_3)_2$: 21.0 and 24.4. [b] Assignments were proved by DEPT measurements: the minor rotamer. For the easier comparability of the analogous data the same numbering has been used. [h] Among the C-9,10,1'4' lines two are overlapped at 148.5 ppm for 11. [i] Two lines for **5b** (overlapped in case of the C-3',5' lines).

Table 4

Physical and Analytical Data on Compounds Prepared

No.	Method	Mp (°C) Solvent	Yield (%)	Formula MW	Analysis Calcd./Found (%) C	H	N
3	A	163-166 EtOH	90	$C_{13}H_{19}N_3O_3$ 269.3	58.85 58.60	7.22 7.15	15.84 15.52
4a	B	172-175 EtOAc	44	$C_{20}H_{23}N_3O_3$ 353.4	67.97 68.02	6.56 6.58	11.89 11.58
4b	B	190-194 EtOH	80	$C_{20}H_{22}N_4O_5$ 398.41	60.29 60.32	5.57 5.67	14.06 13.99
5a	E	206-211 Toluene	67	$C_{21}H_{22}N_4O_5$ 410.42	61.45 61.32	5.40 5.19	13.65 13.62
5b	C	228-233	75	$C_{27}H_{25}N_5O_7$	61.01	4.74	13.18
	D	Toluene	56	531.51	61.12	4.86	13.40
5c	C	163-168	53	$C_{27}H_{27}N_3O_3$	73.44	6.16	9.52
	D	EtOH	49	441.51	73.46	6.32	9.64
6a	F	158-161 EtOAc	62	$C_{18}H_{25}N_3O_3$ 331.4	65.10 65.10	7.60 7.42	12.68 12.90
6b	F	140-143 [a]	77	$C_{19}H_{27}N_3O_3$ 345.43	66.06 66.18	7.88 8.10	12.16 11.82
6c	F	124-127 EtOAc	75	$C_{20}H_{29}N_3O_3$ 359.45	66.82 66.50	8.13 7.91	11.69 11.40
6d	F	154-158 EtOAc	63	$C_{25}H_{39}N_3O_3$ 429.58	69.89 69.63	9.15 9.15	9.78 10.00
7	F	140-144 EtOAc	79	$C_{16}H_{23}N_3O_3$ 305.36	62.93 62.96	7.59 7.74	13.76 13.72
10a	D	233-239 EtOH	56	$C_{25}H_{28}N_4O_5$ 464.5	64.64 64.67	6.07 6.17	12.06 12.37
10b	D	210-237 EtOH	48	$C_{26}H_{30}N_4O_5$ 478.53	65.25 65.43	6.32 6.26	11.71 12.05
10c	D	223-233 EtOH	52	$C_{27}H_{32}N_4O_5$ 492.56	65.83 65.96	6.55 6.60	11.38 11.24
10d	D	184-189 EtOH	45	$C_{32}H_{42}N_4O_5$ 563.69	68.18 68.36	7.69 7.23	9.94 10.02
10e	E	152-159 [a]	61	$C_{20}H_{27}N_3O_3$ 357.44	67.20 67.42	7.62 7.71	11.76 11.80
11	D	229-238 MeOH/ $CHCl_3$	68	$C_{23}H_{26}N_4O_5$ 438.47	62.99 63.10	5.98 6.12	12.78 12.66

[a] Ethanol/diisopropyl ether.

nmr signals are therefore doubled and the relative intensities of the corresponding signal-pairs reflect the isomeric ratio. These ratios, together with the chemical shift pairs and the characteristic ir frequencies, are collected in Table 1. The formation of rotameric mixtures in itself is evidence of the open-chain, hydrazone-like tautomeric structure. In the ^1H nmr spectra of compounds **4a,b**, the doubled azomethine singlets are found at 8.02 and 8.21, and at 8.10 and 8.22 ppm, respectively. The two C-methyl lines of the acetonide **7** are also doubled (at 1.85 and 2.01 ppm for the major, and at 1.88 and 1.98 ppm for the minor rotamer, respectively). The chemical shift of the amide NH is 11.5-11.7 ppm.

The ^1H and ^{13}C nmr data on the tricyclic 1:2 adducts **5a-c**, **10a-e** and **11** are collected in Tables 2 and 3. The amide-I band in the IR spectra appears between 1646 and 1673 cm^{-1}, while the bands of the nitro group lie in the intervals 1506-1526, 1345-1351 and 831-858 cm^{-1}. The structures of compounds **10a-d** and **11**, and hence those of the precursors **6a-d** and **7**, are unequivocally proved by the appearance of the "aldehydic" proton in the chemical shift region of the saturated CH groups, *i.e.* this proton is in the ring. This is evident from a comparison of the chemical shifts of 5.24-5.30 ppm in the ^1H nmr spectra and 83.1-83.5 ppm in the ^{13}C nmr spectra with those of the azomethine signals of compounds **5a-c** (9.21, 9.60 and 8.90, and 149.5, 146.1 and 153.1, respectively). It is also obvious that the 4-methylene group is in the ring in compounds **5a** and **10e**, as the ^1H and ^{13}C chemical shifts indicate (4.71, 4.19 and 4.62 ppm, 74.0 and 72.2 ppm, respectively).

In order to establish the relative configurations of C-11b and C-4 in compounds **5b,c**, **10a-d** and **11**, it was sufficient to establish the *cis* or *trans* configuration of H-11b and H-4 in one compound, since the analogous structure of the studied molecules is evident from the spectral data (*e.g.* the chemical shifts of H-11b and C-4 are nearly the same in all seven compounds). The corresponding intervals of chemical shifts: H-11b: 3.98-4.12, C-4: 83.1-84.7 ppm.

By means of DNOE (differential nuclear Overhauser effect) measurements on compound **5c**, it was established that H-11b and R are in the *cis* configuration, and hence the 4-aryl group (R) is *quasi-axial*. On saturation of the H-11b signal at 4.07, ppm an intensity enhancement of the *ortho* protons of the 4-phenyl ring was observed, whereas saturation of the H-4 signal caused no change in the intensity of the H-11b double doublet, while the azomethine hydrogen (and naturally also the *ortho* protons of the phenyl moiety) gave stronger signals. The first experiment proved the assignment of the H-8 and H-11 singlets: irradiation of the H-11b signal gave rise to an intensity enhancement of the line at 6.33 ppm of the adjacent H-11, indicating that the upfield singlet can be assigned to H-11, while its downfield counterpart belongs to H-8. On saturation of the H-11 signal at 6.33 ppm, the assignment of the methoxy singlets also became possible: the intensity-enhanced "upfield" line (3.76 ppm) can be assigned to the 10-methoxy group. In the same experiment, the signal of H-11 also showed an intensity enhancement, as expected.

The R moiety is obviously forced into the *axial* position by the steric hindrance due to the adjacent side-chain (the hydrazone moiety). In agreement with this steric structure, H-4 in compounds **10a-d** is much more shielded than in

5b-c, due to the anisotropic effect of the alicyclic moiety [24] in the side-chain. This assumption is supported by the chemical shifts of the 4-methylene protons (4.19 and 4.62 ppm) in compound **10e** (R = H). For **5a** (R = H) (where the aryl moiety, obviously in the preferred *E* configuration, is far from the 4-methylene group and hence can not influence the shielding of H-4), the chemical shifts of the two methylene protons are identical: they gave a singlet at 4.71 ppm. The signal at 4.62 ppm for the analog **10e** should therefore be due to protons in a similar chemical environment. Thus, its doublet pair shifted upfield by 0.43 ppm must belong to H-4 in a *quasi-equatorial* position (and *trans* to H-11b). On the other hand, this upfield shift is in the same direction and of a similar magnitude as observed for the H-4 signals of compounds **10a-d** compared to the analogs **5b,c**.

EXPERIMENTAL

The ir spectra were run in potassium bromide pellets on a Bruker IFS-113v vacuum optic FT-spectrometer. The ^1H and ^{13}C nmr spectra were recorded on Bruker WM-250 and WP-80-SY spectrometers at 250.13 MHz and 62.89 or 20.15 MHz, respectively (see Tables 1-3).

Typical parameters for ^1H measurements were as follows: internal reference: TMS; lock signal: the ^2H resonance of the solvent; pulse width: 1 μs (~20° flip angle); acquisition time 2.05 s for 16 K data points. Lorentzian exponential multiplication was used for signal-to-noise enhancement (line width 0.7 Hz).

Measuring parameters for the ^{13}C spectra at 62.89 and 20.15 MHz, respectively: pulse width: 7.5 and 3.5 μs; ~30° flip angle; pulse width: 7.5 and 3.5 μs; BB decoupling, with ca. 3.5 and 1 W power; memory size: 32 and 16 K for 16 and 5 kHz spectral width; exponential multiplications of line width 2.0 and 1.0 Hz; number of scans 2-28 K; acquisition time: 0.5 and 1.65 s.

DEPT experiments [25] were performed in a standard way [26], using only the 135° θ-pulse to separate the CH/CH_3 and CH_2 lines phased "up" and "down", respectively. Number of scans: 512-12 K, relaxation delay for protons 3s, and the 90° pulse lengths were 10.8 and 22.5 μs for the ^{13}C and ^1H nuclei, respectively. The estimated value for $J_{C,H}$ resulted in a 3.7 (Csp^3) or 3.1 (Csp^2) ms delay for polarization.

DNOE experiments were performed with the Bruker microprogram 12.5 in the Aspect 2000 pulse programmer. Gated decoupling to generate NOE was used with a delay time of 30 s and a decoupling power of 40 mW: number of scans, 32; relaxation delay, 0.1 s; dummy scans, 2.

The melting points were determined on a Boetius micro melting point apparatus and are uncorrected. The physical properties of the compounds prepared are listed in Table 3.

Method A.

To a solution of **2** (0.03 mole, 8.38 g) in 100 ml of ethanol, 15 ml of hydrazine hydrate (85% aqueous solution) was added and the mixture was refluxed for 3 hours. The solvent was evaporated off, and the crystalline product **3** was filtered off and washed several times with ether.

Method B.

To a solution of hydrazide **3** (2 mmoles, 0.53 g) in 20 ml of ethanol, 2 mmoles of aldehyde was added. After the mixture had stood for 3 days at room temperature, the solvent was evaporated off and the product was recrystallized.

Method C.

The hydrazide **3** (2 mmoles, 0.53 g) was dissolved in 20 ml of ethanol and 4 mmoles of aldehyde was added. After reflux for 2 hours, the mixture was kept for one day in a refrigerator. The product was filtered off and recrystallized.

Method D.

Hydrazone **4** and **6** (2 mmoles) was dissolved in 20 ml of ethanol and refluxed with equivalent *p*-nitrobenzaldehyde for 5-20 hours (tlc). When the reaction was complete, the mixture was kept in a refrigerator for one day. The product was filtered off and recrystallized.

Method E.

Hydrazone **4b** and **6b** (2 mmoles) was dissolved in 20 ml of ethanol and 2 equivalents of paraformaldehyde was added. After reflux for 2 hours, the solvent was evaporated off and the crystalline residue was recrystallized.

Method F.

Hydrazide **3** (2 mmoles, 0.53 g) was dissolved in 20 ml of ethanol and 2 equivalents of ketone was added. In the case of compound **9**, acetone was used as a solvent too. The mixture was refluxed for 3 hours and the solvent was evaporated off. The yellow oily residue crystallized out when a hexane-acetone mixture was added. The white crystalline product was recrystallized.

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