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Formation of 1,2-Dihydroquinazolin-4(3*H*)-ones. Reinvestigation of a Recently Reported 1,3,4-Benzotriazepine Synthesis

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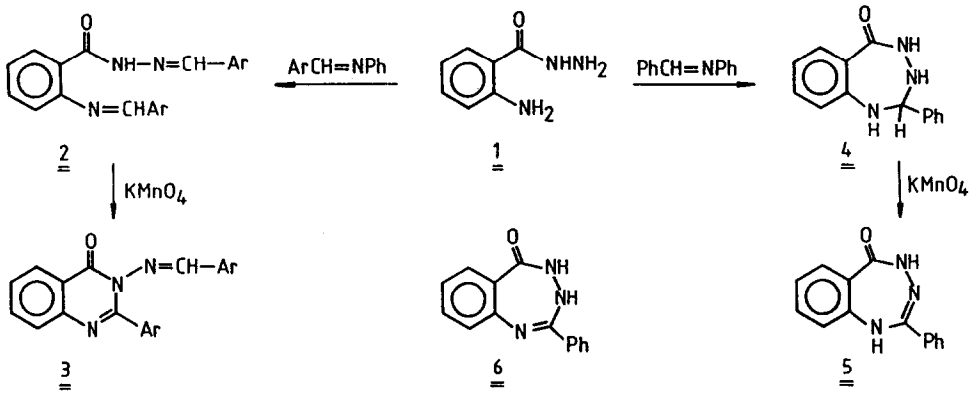
Abstract: A recent paper[15] *(Bull. Chem. Soc. Jpn. 59, 1575 /1986/) reported that the reactions of o-aminobenzoylhydrazine with benzylideneanilines lead to the formation of 1,3,4-benzotriazepin-5-one or 1-(o-benzylideneaminobenzoyl)-2-benzylidenehydrazines, depending on the substituents used. This is shown by the present paper to be incorrect. Depending on the proportions of the reagents, the above reactions lead to 1-(o-aminobenzoyl)-2-benzylidenehydrazines (7) or 2-aryl-3-benzylideneamino-1,2-dihydroquinazolin-4(3H)-ones (8).*

The cyclization of *o*-aminobenzoylhydrazines **1** is a thoroughly studied field of heterocyclic chemistry, since a great variety of potential pharmacon heterocycles[1-9] can be produced in this way, depending on the reagents and conditions.

Because of the appreciable number of possible products, certain compounds were initially reported with erroneous structures, which were later corrected.[10-14]



Scheme 1

Reddy and coworkers recently reported[15] that the reactions of **1** with one equivalent of benzylideneanilines containing *p*OMe, *p*Me, *p*NMe_2, *p*Cl, *p*NO_2 and *o*Cl substituents gave products **2**, derived from one mole of **1** and two moles of the Schiff base (Scheme 1). When the unsubstituted benzylideneaniline was reacted with **1**, the product was **4**. $KMnO_4$ oxidation of **2** resulted in quinazolinones **3**, while oxidation of **4** resulted in benzotriazepinone **5**. Product **5** is a tautomer of **6**, which was also described erroneously by Reddy and coworkers[16] and corrected by Peet.[14]

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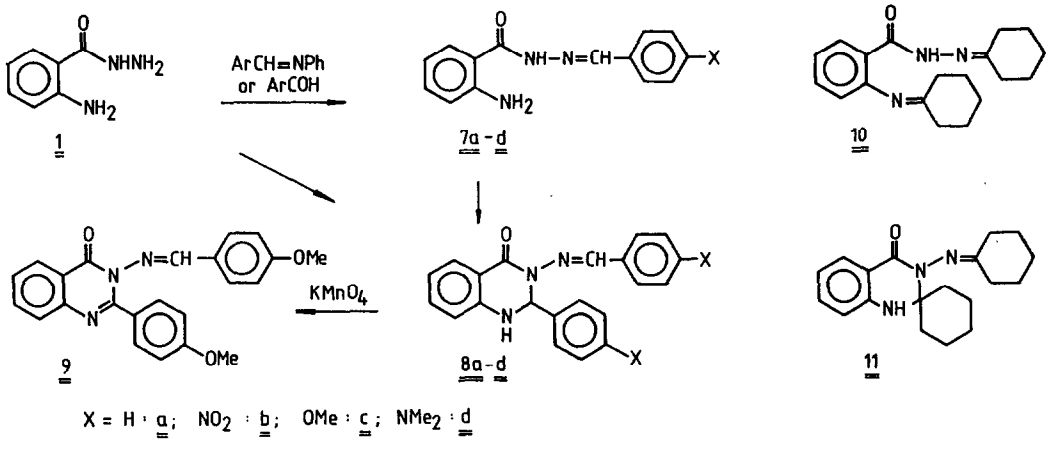
The reason why the reaction of **1** should give two different products, **2** or **4**, depending on the aryl substitution, is not clear. It was earlier found[17] that a closely analogous reaction yields a cyclized product: the reactions of 1-hydrazidomethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with aromatic aldehydes resulted in pyrimido[6,1-*a*]isoquinolines. Our present aim was to reinvestigate the reactions of **1** with Schiff bases.

RESULTS AND DISCUSSION

o-Aminobenzoylhydrazine was prepared from isatoic anhydride via hydrazine ring opening. Since the reactions shown in Scheme 1 involve the use of Schiff bases as aldehyde sources, in our experiments the corresponding aldehydes were also reacted under the same conditions. The reactions were carried out with benzylideneaniline, *p*-nitrobenzylideneaniline, *p*-methoxybenzylideneaniline and *p*-dimethylaminobenzylideneaniline, and with the corresponding aldehydes, using one or two equivalents of the reagent.

It was found that the reactions do not depend on the substituent, but do depend on the proportions of the reagents. With one equivalent of the reagent, benzylidene derivatives **7a-d** were formed as main product, but a small amount (< 10%) of the 1:2 product **8** was also detected.

When two equivalents of reagent were used, the main product was the 1:2 compound, which proved to be not of open type **2**, but quinazolinones **8a-d**. From **8c**, permanganate oxidation resulted in quinazolinone **9**. Formation of quinazolinone **8** instead of benzotriazepinone **4** corresponds to the suggestion of Peet[11,13] that cyclizing agents which insert one carbon unit into *o*-aminobenzoylhydrazine prefer to form a six-membered rather than a seven-membered heterocyclic system. The melting points described for **2**, formed from **1** with one equivalent of Schiff base[15], were nearly the same as we found for **8**, formed from **1** with two moles of Schiff base.



Scheme 2

Starting from **1** with an excess of cyclohexanone, the formation of **10** was described earlier[19], whereas the formation of **11** with the same mp was later reported in the same reaction.[18] Since the structure was clarified only by elementary analysis[19], low resolution MS and ^{1}H NMR,[18] this compound was also prepared, and proved to have the quinazolinone structure.

The stereochemical identity of **7a-d**, **8a-d**, **9** and **11** was deduced from their ^{1}H and ^{13}C NMR spectra. In order to achieve a complete assignment of these spectra, the multiplicity of the ^{13}C atoms was first determined in DEPT experiments, and the chemical shifts of directly attached protons were then assigned in 2D HETCOR experiments. Next, the 2D LR HETCOR spectra, optimized for the response to the large long-range ^{1}H-^{13}C coupling constants, were obtained. These gave the complete spectral assignment, together with additional stereochemical information. The ^{1}H and ^{13}C NMR data are given in Tables 1 and 2, respectively. The cross peaks (c.p.-s) observed in the 2D LR HETCOR spectra of **8a**, **9** and **11** are given in Table 3, and the 2D LR HETCOR spectrum of **8a** is shown in Fig. 1.

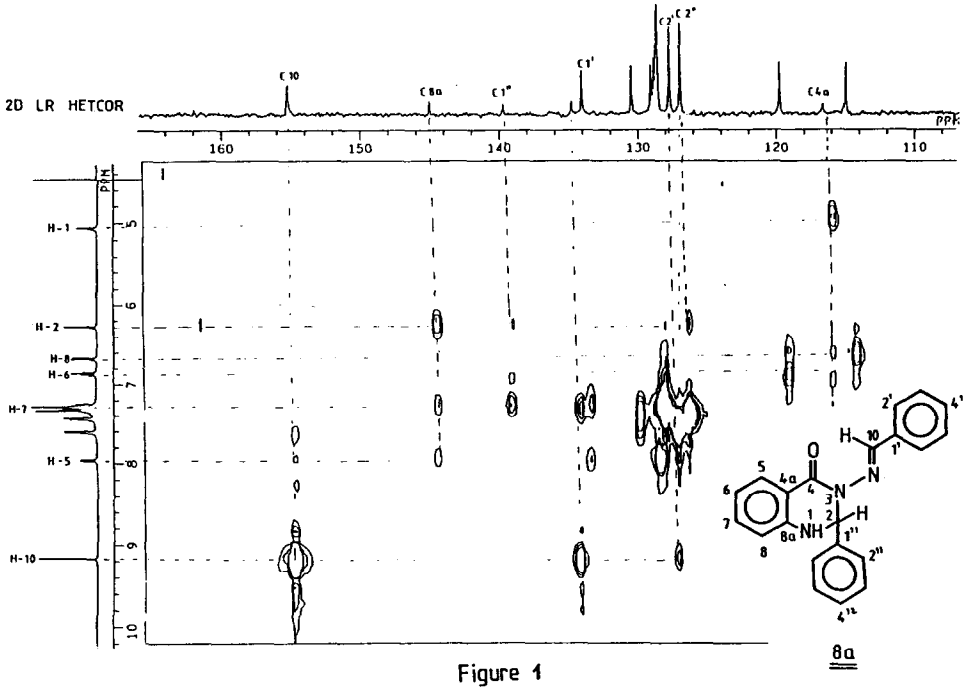
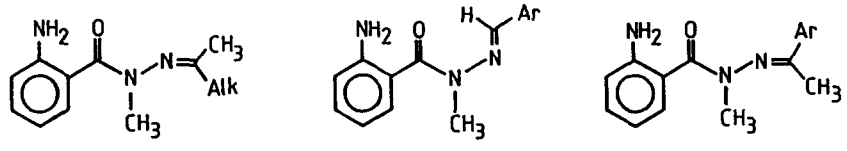


Figure 1

The ^{13}C chemical shifts for the azomethine C-10 atom in the compounds studied are comparable to those for some closely related compounds[21] (families **A** and **B**). The C-10 chemical shift is *ca* 180 ppm for an alkyl substituent at the azomethine carbon (family **A**) and *ca* 140 ppm for a phenyl(aryl) substituent (family **B**).



A B' B"

The above observation can be rationalized in terms of differences in the mesomeric (also hyperconjugative for alkyl substituents) forcing of the electron density either toward the azomethine carbon due to the attraction of the aryl group (family **B**) or toward the neighbouring hydrazine nitrogen and/or carbonyl oxygen atoms (family **A**). Moreover, the differences in the chemical shift, especially for C-10, C-4, C-2 and H-10, H-1 and H-2, in **8b**, **8c** and **9** relative to those in **8a** indicate additional electron delocalization governed by the electron donating or withdrawing properties of the

Table 1. ^{1}H Chemical Shifts for Compounds **7-9** and **11**

Position	**7a**[a]	**7b**[a]	**7c**[a]	**7d**[a]	**8a**[b]	**8b**[b]	**8c**[b]	**8d**[a]	**9**[b]	**11**[b]
H-1	7.27	7.18	7.34	7.51	4.89	4.94	4.70	7.58	-	4.71
H-2	-	-	-	-	6.29(2.6)[c]	6.39(3.0)[c]	6.20(2.6)[c]	6.23(2.4)[c]	-	
H-3	4.27	3.94	4.37	4.54	-	-	-	-	-	-
H-5	8.45	8.18	8.56	8.72	7.97	7.94	7.95	7.69	8.31	7.89
H-6	7.44	7.36	7.58	7.74	6.90	6.98	6.87	6.74	7.65	6.82
H-7	8.06	7.81	8.19	8.36	7.35	7.39	7.29	7.25	7.65	7.27
H-8	7.63	7.38	7.76	7.92	6.64	6.78	6.65	6.70	7.44	6.70
H-10	9.27	9.08	9.34	9.43	9.22	9.68	9.01	8.58	8.83	-
H-2'/6'	8.58	8.88	8.66	8.72	7.62	7.76	6.83	7.50	7.65	d
H-3'/5'	8.29	8.55	8.03	7.92	7.35	8.18	7.55	6.72	6.88	d
H-4'	8.29	-	-	-	7.35	-	-	-	-	d
H-2"/6"	-	-	-	-	7.45	7.62	6.83	7.15	7.65	d
H-3"/5"	-	-	-	-	7.35	8.21	7.36	6.63	6.88	d
H-4"	-	-	-	-	7.35	-	-	-	-	d
OCH_3'	-	-	4.82	-	-	-	3.74[e]	-	3.80[e]	-
OCH_3"	-	-	-	-	-	-	3.80[e]	-	3.82[e]	-
$N(CH_3)_2$'	-	-	-	4.14	-	-	-	2.96	-	-
$N(CH_3)_2$"	-	-	-	4.14	-	-	-	2.82	-	-

[a]In DMSO-d_6. [b]In $CDCl_3$. [c]Couplings to H-1 in parentheses. [d]Multiplets in δ 1-2.5 ppm (H-11 to H-20). [e]Alternative assignment is also possible.

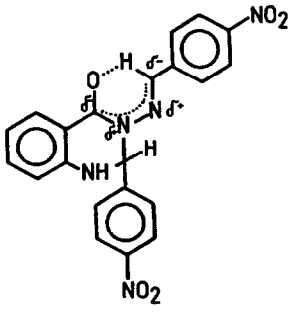
Table 2. ^{13}C Chemical Shifts for Compounds **7-9** and **11**

Position	**7a**[a]	**7b**[a]	**7c**[a]	**7d**[a]	**8a**[b]	**8b**[b]	**8c**[b]	**8d**[a]	**9**[b]	**11**[b,e]
C-2	-	-	-	-	75.3	75.4	98.2	71.9	153.6	75.4
C-4	165.4	166.0	165.1	164.9	155.3[c]	151.9[c]	156.4	153.7	166.7[c]	159.3
C-4a	113.5	112.9	113.9	114.0	116.6	117.1	117.0	114.5	121.3	116.3
C-5	128.4	128.4	128.2	128.2	128.9	129.4	128.4	127.1	127.2	128.5
C-6	116.4	116.4	116.3	116.2	119.8	121.0	119.8	117.3	127.7	118.8
C-7	132.2	132.5	132.1	131.8	134.0	135.0	133.9	133.4	134.3	133.2
C-8	114.6	114.5	114.6	114.6	115.0	115.8	114.8	114.5	126.6	114.8
C-8a	150.1	150.3	149.9	149.8	145.0	146.6	145.1	146.1	146.9	144.1
C-10	146.8	144.0	146.8	147.7	155.2[c]	151.8[c]	161.9	160.5	166.7[c]	178.7
C-1'	134.5	140.9	127.0	121.8	134.8	140.9	124.5	121.6	125.4	
C-2'/6'	128.8	127.8	128.2	128.2	127.6	128.1[d]	129.4	128.7	130.8	
C-3'/5'	126.9	124.0	114.3	111.8	128.7	124.1	114.1	111.8	113.3	
C-4'	130.0	147.7	160.6	151.3	130.5	149.0	161.7	151.8	161.0	
C-1"	-	-	-	-	139.7	146.6	132.0	132.5	159.3	
C-2"/6"	-	-	-	-	127.0	128.0[d]	127.5	128.3	131.9	
C-3"/5"	-	-	-	-	128.6	124.1	129.1	111.6	114.4	
C-4"	-	-	-	-	129.1	143.0	129.1	150.2	163.1	
OCH_3'	-	-	55.3	-	-	-	75.2[c]	-	55.4[d]	
OCH_3"	-	-	-	-	-	-	75.4[c]	-	55.5[d]	
$N(CH_3)_2$	-	-	-	39.7	-	-	-	f	-	

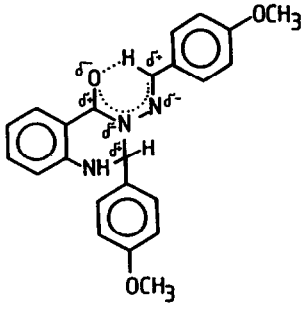
[a]In DMSO-d_6. [b]In $CDCl_3$. [c,d]Alternative assignment is also possible. [e]C-11 (35.6 ppm); C-12 (35.5 ppm); C-13 (30.8 ppm); C-14 (29.8 ppm); C-15 (27.6 ppm); C-16 (26.3 ppm); C-17 (25.7 ppm); C-18 (24.4 ppm); C-19 (22.4 ppm); C-20 (22.3 ppm). [f]Overlap with solvent signals (DMSO-d_6).

para substituents. This effect seems to be enhanced and distributed over the aromatic part of the quinazolinone ring in **9**, due to the extra N(1)=C(2) double bond in the heterocycle. Thus, downfield shifts were observed for C-10 (6.7 and 11.5 ppm) and C-4 (1.1 and 11.4 ppm) in **8c** and **9**, respectively, and upfield shifts for C-10 (0.4 ppm) and C-4 (3.4 ppm) in **8b**. Reverse effects were found for H-1, H-2 and (in two cases) H-10. The upfield shifts for the latter proton in **8c** and **9** were 0.21 and 0.39 ppm, respectively, whereas a 0.46 ppm downfield shift was observed in **8b**.

An additional comparison of the ^{13}C data on **8c** and **9** revealed a stronger charge displacement toward the carbonyl oxygen in the latter, as expected. Thus, the predominant resonance structures for **8b** and **8c, 9** can be written as I and II, respectively.



I (8b)



II (8c, 9)

The determination of the steric structure of **8a-d** and **11** (see Fig. 2) in $CDCl_3$ was based on the small values (2-3 Hz) of the vicinal coupling constants between H-1 and H-2, as well as on the c.p.-s of C-4a/H-1 and C-8a/H-2, but not of C-1"/H-1 (Table 3), which is fully consistent with the torsion angles postulated from Dreiding models. Moreover the observed c.p. of C-2"/H-2 speaks for hindered rotation around the C(2)-C(1") bond and a biased position of the phenyl(aryl) ring in the same plane as H-2, a likely explanation for the c.p. of C-2'/H-10 in the flat open-chain moiety. The c.p. of C-4a/H-1 and the chemical shift of H-1 for **11**, similar to those for **8a-c**, support the proposed stereochemistry with *equatorial* H-1 and the cyclohexane ring in a biased position.

Table 3. Cross Peaks Observed in 2D LR HETCOR Experiments for **8a**, **9** and **11**

8a	**9**	**11**
C-4a/H-1	C-2/H-2"	C-2/H-1
C-4a/H-6	C-4a/H-6	C-2/H-17
C-4a/H-8	C-4a/H-8	C-4a/H-1
C-7/H-5	C-7/H-5	C-4a/H-6
C-8/H-6	C-8a/H-5	C-5/H-7
C-8a/H-2	C-8a/H-7	C-6/H-8
C-8a/H-5	C-10/H-2'	C-7/H-5
C-8a/H-7	C-1'/H-3'	C-8/H-6
C-10/H-2'	C-1'/H-10	C-10/H-12
C-1'/H-3'	C-2'/H-10	C-10/H-14
C-1'/H-10	C-4'/H-2'	
C-2'/H-10	C-4'/OCH_3	
C-4'/H-2'	C-4"/H-2"	
C-1"/H-2	C-4"/H-OCH_3"	
C-2"/H-2		
C-4"/H-2"		

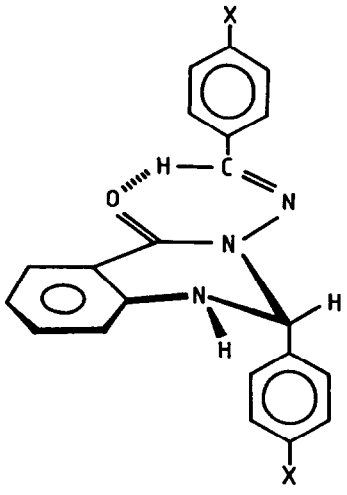


Figure 2

The above configurational assignments for the heterocycle in **8a-d** and **11** are also supported by the chemical shifts of H-5 (ca δ 7.9 ppm), which differ from that in **9** (δ 8.31 ppm), where a completely flattened heterocycle fixes the carbonyl group in the plane of H-5. All these results are indicative of the suggested strong intramolecular hydrogen-bond C=O···H-10 leading to **E** and *syn* configurations around the N(9)=C(10) and N(3)-N(9) bonds, respectively.

EXPERIMENTAL

The melting points were determined on an Electrothermal digital melting point apparatus and are uncorrected. Benzylideneanilines were prepared from aniline and the corresponding aromatic aldehydes. *o*-Aminobenzoylhydrazine **1** was prepared as reported in the literature[18], by the ring opening of isatoic anhydride with hydrazine. Analytical data on the compounds prepared are collected in Table 4.

The 1D and 2D NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on JEOL JNM GX-400 spectrometer operating at 399.78 MHz for ^1H and at 100.53 MHz for ^{13}C, using a 5 mm $^1H/^{13}C$ dual probe. The chemical shifts were referenced to the solvent (δ =7.24 ppm and δ =77.1 ppm for ^1H and ^{13}C, respectively). All 1D spectra were from 32 K data points and the point resolution was 0.2 and 0.7 Hz for ^1H and ^{13}C NMR spectra, respectively. Automatic microprograms were applied to obtain DEPT, 2D HETCOR and 2D LR HETCOR spectra. The 2D experiments consisted of a 128x2 K data matrix with NS=640 and NE=64. In 2D HETCOR and 2D LR HETCOR experiments, delays of 3.33 and 2.22 ms, and 40 and 20 ms were used to optimize the sensitivity for the response of the direct and large long-range ^1H-^{13}C coupling constants, respectively. After zero-filling in F1 and sine-bell nonshifted weighting in both dimensions, the spectra were obtained in the magnitude mode.

1-(o-Aminobenzoyl)-2-benzylidenehydrazines (**7a-d**) *(General procedure).* *o*-Aminobenzoylhydrazine (151 mg, 1 mmol) was dissolved in 5 ml methanol and the corresponding benzylideneaniline (1 mmol) or aldehyde (1 mmol) was added with thorough shaking. The mixture was left to stand for 2 h at room temperature. In cases **7a** and **7b**, the crystals that separated out were filtered off and recrystallized. In cases **7c** and **7d**, very few crystals separated out, which proved to be **8c** and **8d**. These were removed by filtration, the mother liquors were evaporated off and recrystallization of the residues resulted in pure **7c** and **7d**.

The yields were 58-75% and did not depend significantly on whether the aldehyde or the Schiff base was used.

2-Aryl-3-benzylideneamino-1,2-dihydroquinazolin-4(3H)-ones (**8**) *(General procedure).* *o*-Aminobenzoylhydrazine (151 mg, 1 mmol) was dissolved in 5 ml methanol and the corresponding benzylideneaniline (2 mmol) or aldehyde (2 mmol) was added with thorough shaking. The mixture was left to stand overnight. The crystals of **8a-d** were filtered off and recrystallized.

For the phenyl and *p*-nitrophenyl derivatives, crystallization started after a few minutes; crystals of **7a** and **7b** first separated out, but these dissolved again and after a few hours product **8** started to separate out.

The yields were 47-66%, without a significant dependence on whether the aldehyde or the Schiff base was used.

3-(4-Methoxybenzylideneamino)-2-(4-methoxyphenyl)-quinazolin-4(3H)-one (**9**). Quinazolinone **8c** (200 mg) was dissolved in 30 ml acetone, and $KMnO_4$ (1 g) was added. The mixture was refluxed for 5 h with stirring. The hot solution was filtered and the colourless filtrate was evaporated to dryness. The

residue was dissolved in 30 ml chloroform and washed with water. The chloroform layer was dried (Na_2SO_4) and evaporated, resulting in **9** as a white crystalline powder.

3-Cyclohexylideneamino-2-spirocyclohexano-1,2-dihydroquinazolin-4(3H)-one (**11**). *o*-Amino-benzoylhydrazine (604 mg, 4 mmol) was left to stand for 2 h with 1 ml cyclohexanone in 10 ml ethanol. Product **11** separated out as white crystals.

Transformation of **7a** *to* **8a**. Compound **7a** (120 mg, 0.5 mmol) was dissolved in 20 ml methanol, and one equivalent of benzaldehyde or benzylideneaniline was added. The mixture was left to stand overnight, the solvent was evaporated off and the product was recrystallized from ethanol. Mp: 164-166 °C, yield 58%. The product did not give a mp depression when mixed with **8a** prepared from **1** as described above.

Table 4. Analytical Data on Compounds Prepared

No.	Mp (°C) (Solvent)	Formula (Mw)	Analysis Calcd/Found (%)		
			C	H	N
7a[a,b]	199-200 (EtOAc)	$C_{14}H_{13}N_3O$ (239.28)	70.28/70.38	5.48/5.61	17.56/17.30
7b[c,d]	246-248 (MeOH)	$C_{14}H_{12}N_4O_3$ (284.28)	59.15/59.27	4.25/4.50	19.71/19.60
7c[e,f]	166-167 (g)	$C_{15}H_{15}N_3O_2$ (269.31)	66.90/67.02	5.61/5.74	15.60/15.44
7d[h]	178-180 (EtOAc)	$C_{16}H_{18}N_4O$ (282.35)	68.06/68.17	6.43/6.66	19.84/19.63
8a	166-167 (EtOH)	$C_{21}H_{17}N_3O$ (327.30)	77.04/76.92	5.23/5.30	12.83/12.96
8b	215-217 (i)	$C_{21}H_{15}N_5O_5$ (417.39)	60.43/60.36	3.62/3.84	16.78/16.77
8c[j]	233-234 (i)	$C_{23}H_{21}N_3O_3$ (387.44)	71.30/71.33	5.46/5.57	10.85/10.88
8d	252-254 (i)	$C_{25}H_{27}N_5O$ (413.53)	72.61/72.56	6.58/6.78	16.94/17.04
9[k]	199-200 (EtOH)	$C_{23}H_{19}N_3O_3$ (385.43)	71.68/71.70	4.97/5.13	10.90/10.68
11[l,m]	237-240 (EtOH)	$C_{19}H_{25}N_3O$ (311.43)	73.28/73.14	8.09/8.22	13.49/13.22

[a]Described[15] as **4**, mp 190 °C. [b]Described[19,20] as **7a**, mp 205 °C and 187-190 °C. [c]Described[15] as **2**, mp 234 °C. [d]Described[19] as **7b**. [e]Described[15] as **2**, mp 221 °C. [f]Described[20] as **7c**, mp 160-162 °C. [g]Diisopropyl ether:EtOH = 4:1. [h]Described[15] as **2**, mp 238 °C. [i]EtOH:DMF = 4:1. [j]Described[19] as **2**, mp 229 °C. [k]Lit[15] mp 185 °C. [l]Described as **10**, mp 235 °C. [m]Described as **11**, mp 220-222 °C.

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