Reactions of 3-hydroxy-1,2-dihydroquinazolin-4-ones with aldehydes

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The reactions of 3-hydroxy-2-(2-hydroxyalkyl)- [or (2-hydroxyaryl)]-1,2-dihydroquinazolin-4-ones with formaldehyde or acetaldehyde afford 1,3-oxazino[3,4-*a*]quinazolin-4-one derivatives. The reactions with other aldehydes RCHO and 3-hydroxy-2-R'-1,2-dihydroquinazolin-4-ones can give 3-hydroxy-2-R-1,2-dihydroquinazolin-4-ones, 2-substituted quinazolin-4-ones, or dianthranilide.

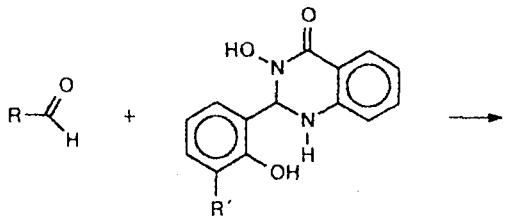
Key words: 12,13-dihydro-6*H*,11b*H*-quinazolino[1,2-*c*][1,3]benzooxazin-13-ones, 3,4,5,6-tetrahydro-1*H*-[1,3]oxazino[3,4-*a*]quinazolin-6-one, 3-hydroxy-1,2-dihydroquinazolin-4-ones, aldehydes.

The reactions of *o*-aminobenzohydroxamic acid (**1**) with aldehydes have a general character and afford 3-hydroxy-1,2-dihydroquinazolin-4-ones (HDHQs).[1] The resulting HDHQs contain at least two potential centers for the subsequent reactions with aldehydes, namely, the amine N atom and the O atom of the *N*-hydroxy group. With the aim of examining the possibilities of these reactions, we studied the reactions of HDHQs with a number of aldehydes.

The amine N atom in HDHQs is sterically hindered and the O atom of the hydroxy group is weakly nucleophilic. Therefore, the choice of particular aldehydes was governed by the necessity of using compounds with the sterically accessible and sufficiently polarized carbonyl group. We have studied formaldehyde (**2a**), acetaldehyde (**2b**), trichloroacetaldehyde (**2c**), glyoxal (**2d**), and benzaldehyde (**2e**) as aldehydes. It is known that the addition reactions of N- and O-nucleophiles with aldehydes are reversible and, consequently, primary reaction products cannot be often isolated. However, substitution of the hydroxy group in these compounds, particularly, the substitution accompanied by the formation of cyclic structures, affords, generally, quite stable compounds. This possibility exists also in the case of HDHQs due to the fact that both the amine N atom and the *N*-hydroxy group are involved in the reactions with aldehydes, which should lead to formation of an additional five-membered 1,2,4-oxadiazolidine ring in the tricyclic bridged structure. However, "fixation" of methylol (α-hydroxyalkyl) adducts in the form of products of subsequent condensations at the hydroxy group was thought to be stronger (from steric considerations) if the latter was present at the β-position of the 2-substituents in HDHQs.

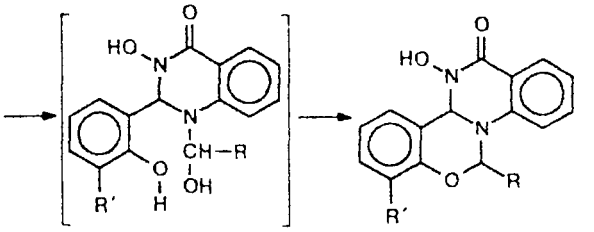
Actually, it was established that 3-hydroxy-2-(2-hydroxyphenyl)-1,2-dihydroquinazolin-4-one (**3a**) readily reacted with formaldehyde to form* quinazolinobenzooxazine **4a** in ~40% yield (Scheme 1).

Scheme 1



2a,b
a: R = H
b: R = Me

3a,b
a: R' = H
b: R' = All



4a–c
a: R = R' = H
b: R = H; R' = All
c: R = Me; R' = H

* Hereinafter, the experimental conditions were not optimized.

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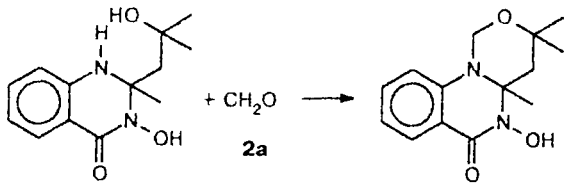
The presence of an additional substituent at position 3 of the 2-hydroxyphenyl radical does not hinder the formation of the analogous derivative **4b**. A similar reaction also occurs if the 2-hydroxyalkyl substituent rather than the 2-hydroxyaryl substituent is present at position 2 of HDHQ (Scheme 2).

Scheme 2



5a **6**

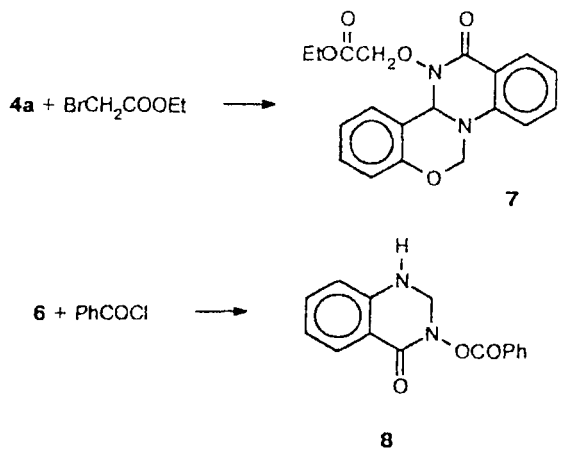
We prepared the desired dihydroquinazolinone **5a** by the reaction of compound **1** with 4-hydroxy-4-methylpentan-2-one. Its structure was established based on the spectral characteristics. The ^{13}C NMR spectrum of compound **5a** has a peak at δ 77, which is typical of position 2 of HDHQ. In the region δ > 150, only a peak of the carbonyl carbon atom (at δ 161.8) is observed. This makes it possible to rule out the structure of Schiff's base. Analogously, we confirmed the previous data,[2] according to which the reaction of compound **1** with acetone gave 3-hydroxy-2,2-dimethyl-1,2-dihydroquinazolin-4-one (**5b**). It is believed that the reactions of acid **1** with ketones, like those with aldehydes, afford HDHQs rather than Schiff's bases.

Using compound **3a** as an example, it was demonstrated that acetaldehyde can also be used in the above-mentioned reactions as the aldehyde component.

The conclusions about the structures of compounds **4a—c** and **6** were made based on the NMR spectra, the data of elemental analysis, and the positive test for the presence of the *N*-hydroxyamide group with $FeCl_3$. These compounds are rather high-melting substances, which remain unchanged upon storage. The presence of the *N*-hydroxy group opens up possibilities for the preparation of a series of *O*-derivatives based on the above compounds. Alkylation of **4a** with ethyl bromoacetate that proceeded readily in the presence of an alkali provides an example. However, *O*-benzoylation of compound **6** was accompanied by elimination of the hydroxy ketone residue and recyclization (Scheme 3).

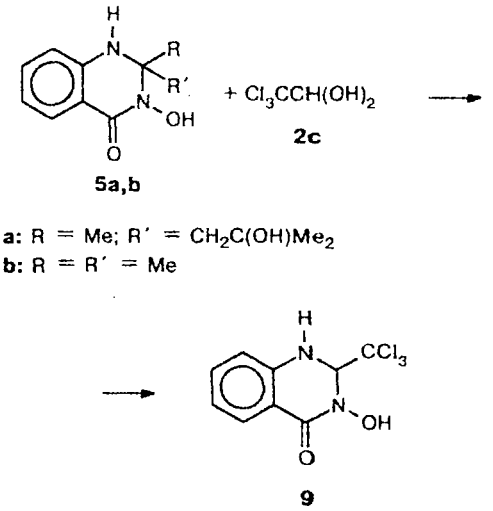
The formation of an additional six-membered heterocycle in the reactions of compounds **3** and **5** with aldehydes is typical only of the first members of the series. In going to bulkier aldehydes, alternative directions of the reactions are realized, which are governed by the structures of both HDHQ and aldehyde. However, it is believed that in these cases, the reactions also involve reversible nucleophilic addition of the NH group at the carbonyl group of the aldehyde. The exchange of

Scheme 3

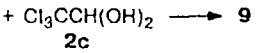


the alkylidene structural fragment that links the N atoms in HDHQ for the alkylidene residue of the aldehyde used is rather common. For example, the reaction of **5a** with chloral hydrate **2c** afforded trichloromethyl derivative **9** (Scheme 4).

Scheme 4

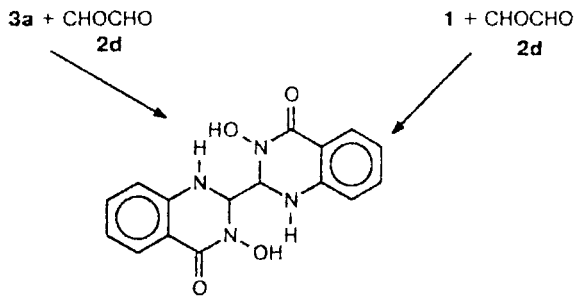


The reaction of compound **2c** with **5b** gave the same result. The structure of **9** was confirmed not only by the data of elemental analysis and the spectral characteristics, but also by the independent synthesis from **1** and **2c**.



When compound **2d** is used, both its aldehyde groups can be involved in this type of reactions (Scheme 5). Compound **10** can also be synthesized directly from **1** and **2d**.

Scheme 5



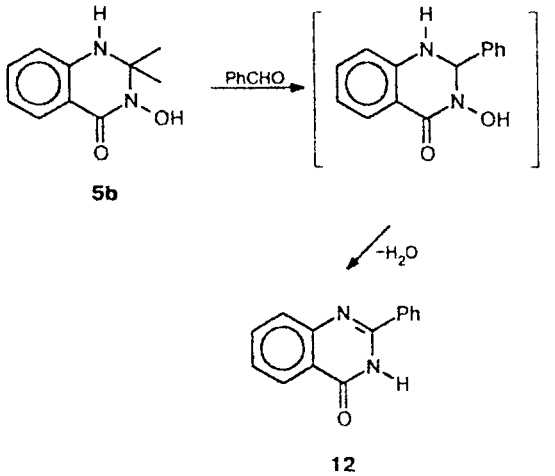
10

When the proton is present at position 2 of the initial or the resulting HDHQ, formal dehydration of HDHQ may be observed under the conditions of the reaction with aldehydes. The aforesaid is illustrated in Schemes 6 and 7.

Scheme 6

11 12

Scheme 7

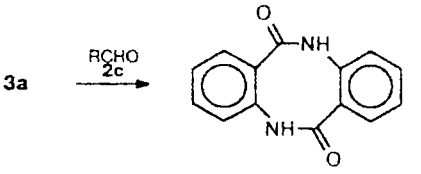


5b

12

Dehydration is not the only alternative process in the reactions of HDHQs with aldehydes. For example, it was established that heating of **3a** with **2c** or isobutyraldehyde afforded dianthranilide **13** (Scheme 8).

Scheme 8



13

No conversion of **3a** to **13** was observed in the absence of the above-mentioned aldehydes. Therefore, it is believed that aldehydes are involved in the process of conversions. Note that heating of compound **3a** with maleic anhydride or the reaction with thionyl chloride at room temperature gave analogous results. Heating of acid **1** or methyl anthranilate in alcohol did not afford **13**.

Experimental

The ^1H and ^{13}C NMR spectra were recorded on a Bruker-300AM instrument. The melting points were determined on a Kofler hot stage. Compounds **3a, 3b**, and **11** were prepared according to a known procedure.[1]

12-Hydroxy-12,13-dihydro-6*H*,11b*H*-quinazolino[1,2-*c*][1,3]benzooxazin-13-one (4a). A solution of compound **3a** (0.3 g) and compound **2a** (0.04 g) in Pr^iOH (4 mL) was refluxed for 4 h. The solvent was distilled off, and the residue was recrystallized from 40% ethanol. The yield was 0.13 g (42%), m.p. 227—228 °C. Found (%): C, 67.08; H, 4.62. $C_{15}H_{12}N_2O_3$. Calculated (%): C, 67.16; H, 4.51. ^1H NMR (DMSO-d_6), δ: 5.55 (d, 1 H, NCH_2O, J = 12 Hz); 6.12 (d, 1 H, NCH_2O, J = 12 Hz); 6.60 (s, 1 H, NCHN); 6.73 (d, 1 H, J = 10 Hz); 6.88 (t, 1 H, J = 10 Hz); 7.00 (t, 1 H, J = 10 Hz); 7.15 (t, 1 H, J = 10 Hz); 7.45—7.55 (m, 3 H); 7.75 (d, 1 H, J = 10 Hz); 10.92 (br.s, 1 H, NOH).

8-Allyl-12-hydroxy-12,13-dihydro-6*H*,11b*H*-quinazolino[1,2-*c*][1,3]benzooxazin-13-one (4b) was prepared as described above. The yield was 38%, m.p. 200—201 °C. Found (%): C, 70.03; H, 5.13. $C_{18}H_{16}N_2O_3$. Calculated (%): C, 70.12; H, 5.23. ^1H NMR (DMSO-d_6), δ: 3.32 (s, 2 H, CH_2CH); 4.95 (m, 2 H, CH_2=CH); 5.58 (d, 1 H, NCH_2O, J = 12 Hz); 5.88 (m, 1 H, CH_2=CH); 6.12 (d, 1 H, NCH_2O, J = 12 Hz); 6.58 (s, 1 H, NCHN); 6.88 (s, 1 H); 7.00 (s, 2 H); 7.42 (s, 3 H); 7.68 (d, 1 H, J = 10 Hz); 10.82 (br.s, 1 H, NOH).

12-Hydroxy-6-methyl-12,13-dihydro-6*H*,11b*H*-quinazolino[1,2-*c*][1,3]benzooxazin-13-one (4c). A solution of compound **3a** (0.2 g) and compound **2b** (0.5 mL) in ethanol (4 mL) was heated in a sealed tube at 100 °C for 16 h. The solvent was evaporated, and the residue was recrystallized from Pr^iOH. The yield was 0.1 g (43%), m.p. 196—198 °C. Found (%): C, 67.68; H, 5.00. $C_{16}H_{14}N_2O_3$. Calculated (%): C, 68.08; H, 5.00. ^1H NMR (DMSO-d_6), δ: 1.70 (d, 3 H, Me, J = 7 Hz); 6.31 (s, 1 H, NCHN); 6.42 (d, 1 H, NCHO, J = 12 Hz); 6.73 (d, 1 H, J = 10 Hz); 6.88 (t, 1 H, J = 10 Hz); 7.00 (t, 1 H, J = 10 Hz); 7.15 (t, 1 H, J = 10 Hz); 7.45 (t, 1 H, J = 10 Hz); 7.55 (m, 2 H); 7.75 (d, 1 H, J = 10 Hz); 10.82 (br.s, 1 H, NOH).

3-Hydroxy-2-methyl-2-(2-hydroxy-2-methylpropyl)-1,2-dihydroquinazolin-4-one (5a). A solution of compound **1** (0.2 g) and 4-hydroxy-4-methylpentan-2-one (0.23 mL) in ethanol

(3 mL) was refluxed for 4 h. The solvent was distilled off, and the residue was recrystallized from benzene. The yield was 0.2 g (61%), m.p. 128—130 °C. Found (%): C, 62.85; H, 7.25. $C_{13}H_{18}N_2O_3$. Calculated (%): C, 62.38; H, 7.25. ^{1}H NMR (DMSO-d_6), δ: 7.62 (d, H(5), J = 10 Hz); 6.65 (t, H(6), J = 10 Hz); 7.25 (t, H(7), J = 10 Hz); 6.65 (t, H(8), J = 10 Hz); 2.12 (d, 1 H, CH_2, J = 12 Hz); 1.90 (d, 1 H, CH_2, J = 12 Hz); 1.50 (s, 3 H, Me); 1.20 (s, 6 H, 2 Me). ^{13}C NMR (DMSO-d_6), δ: 76.97 (C-2); 161.82 (C-4); 126.91 (C-5); 113.30 (C-5a); 114.09 (C-6); 133.18 (C-7); 116.62 (C-8); 144.86 (C-8a); 69.16; 47.04; 30.70; 25.57.

3-Hydroxy-2,2-dimethyl-1,2-dihydroquinazolin-4-one (5b) was prepared according to the above-described procedure and recrystallized from 20% ethanol. The yield was 73%, m.p. 142—144 °C. Found (%): C, 62.11; H, 6.27. $C_{10}H_{12}N_2O_2$. Calculated (%): C, 62.49; H, 6.29. ^{1}H NMR (DMSO-d_6), δ: 6.18 (br.s, 1 H, NH); 7.72 (d, H(5), J = 10 Hz); 6.73 (m, H(6), J = 10 Hz); 7.25 (t, H(7), J = 10 Hz); 6.73 (m, H(8), J = 10 Hz); 1.50 (s, 6 H, 2 Me). ^{13}C NMR (DMSO-d_6), δ: 75.22 (C-2); 162.72 (C-4); 127.21 (C-5); 113.53 (C-5a); 115.00 (C-6); 133.45 (C-7); 117.13 (C-8); 145.66 (C-8a); 25.17 (Me).

5-Hydroxy-3,3,4a-trimethyl-3,4,5,6-tetrahydro-1*H*-[1,3]oxazino[3,4-*a*]quinazolin-6-one (6). A solution of compound **5a** (0.3 g) and compound **2b** (0.03 g) in ethanol (4 mL) was refluxed for 6 h. The solvent was distilled off, the residue was diluted with water, and the precipitate was filtered off and recrystallized from 20% ethanol. The yield was 0.11 g (34%), m.p. 138—139 °C. Found (%): C, 65.14; H, 6.51. $C_{14}H_{18}N_2O_3$. Calculated (%): C, 64.11; H, 6.92. ^{1}H NMR (DMSO-d_6), δ: 1.30 (s, 6 H, 2 Me); 1.42 (s, 3 H, Me); 1.95 (d, 1 H, CCH_2C, J = 12 Hz); 2.33 (d, 1 H, CCH_2C, J = 12 Hz); 4.65 (d, 1 H, OCH_2N, J = 12 Hz); 4.95 (d, 1 H, OCH_2N, J = 12 Hz); 6.95 (s, 2 H); 7.41 (s, 1 H); 7.79 (s, 1 H).

12-Ethoxycarbonylmethoxy-12,13-dihydro-6*H*,11b*H*-quinazolino[1,2-*c*][1,3]benzoxazin-13-one (7). A 45% NaOH solution (0.02 mL) and $BrCH_2COOEt$ (0.05 mL) were added to a solution of compound **4a** (0.1 g) in THF (2 mL). The reaction mixture was stirred at ~20 °C for 3 h and diluted with water. The precipitate that formed was filtered off and recrystallized from 40% ethanol. The yield was 0.05 g (40%), m.p. 144—145 °C. Found (%): C, 64.39; H, 4.97. $C_{19}H_{18}N_2O_5$. Calculated (%): C, 64.40; H, 5.12. ^{1}H NMR (DMSO-d_6), δ: 1.32 (s, 3 H, Me); 4.21 (m, 2 H, OCH_2); 4.78 (d, 1 H, $NOCH_2$, J = 16 Hz); 4.95 (d, 1 H, $NOCH_2$, J = 16 Hz); 5.55 (d, 1 H, NCH_2O, J = 12 Hz); 6.10 (d, 1 H, NCH_2O, J = 12 Hz); 6.73 (d, 1 H, J = 10 Hz); 6.8—7.0 (m, 3 H); 7.15 (s, 1 H); 7.48 (s, 3 H); 7.75 (d, 1 H, J = 10 Hz).

3-Benzoyloxy-1,2-dihydroquinazolin-4-one (8). Pyridine (0.03 mL) and then benzoyl chloride (0.05 mL) were added to a solution of compound **6** (0.2 g) in dioxane (0.3 mL). The reaction mixture was stirred at ~20°C for 3 h and diluted with water. The precipitate was filtered off and recrystallized from 40% ethanol. The yield was 0.06 g (60%), m.p. 186—187 °C. Found (%): C, 67.66; H, 4.44. $C_{15}H_{12}N_2O_3$. Calculated (%): C, 67.16; H, 4.51. ^{1}H NMR (DMSO-d_6), δ: 5.00 (s, 2 H, NCH_2N); 6.85 (m, 2 H); 7.42 (t, 2 H, J = 10 Hz); 7.62—7.78 (m, 4 H); 8.11 (d, 2 H, J = 10 Hz).

3-Hydroxy-2-trichloromethyl-1,2-dihydroquinazolin-4-one (9) was prepared from compounds **1** and **2c** according to a known procedure.[1] The yield was 41%, m.p. 167—168 °C. Found (%): C, 38.80; H, 2.49; Cl, 37.20. $C_9H_7Cl_3N_2O_2$. Calculated (%): C, 38.40; H, 2.51; Cl, 37.80. ^{1}H NMR (DMSO-d_6), δ: 5.80 (d, H(2), J = 10 Hz); 7.65 (d, H(5), J = 10 Hz); 6.91 (d, H(6), J = 10 Hz); 7.33 (s, H(7)); 6.75 (t, H(8), J = 10 Hz); 8.15 (br.s, NH); 10.60 (br.s, NOH).

When compound **5a** or **5b** reacted with an equimolar amount of **2c** in boiling 40% ethanol for 6 h, product **9** was obtained. In both cases, the yields were ~35%.

2,2'-Bi[3-hydroxy-4-oxo-1,2-dihydroquinazolinyl] (10). A 22% aqueous solution of glyoxal **2d** (0.18 mL) was added to a solution of compound **1** (0.2 g) in ethanol (4 mL). The mixture was refluxed for 1 h. The precipitate that formed was filtered off and recrystallized from ethanol. The yield of **10** was 0.23 g (54%), m.p. 225—226 °C. Found (%): C, 58.97; H, 4.29. $C_{16}H_{14}N_4O_4$. Calculated (%): C, 58.89; H, 4.32. ^{1}H NMR (DMSO-d_6), δ: 5.48 (s, 2 H, H(2), H(2')); 6.55 (d, 2 H, H(8), H(8'), J = 10 Hz); 6.72 (t, 2 H, H(6), H(6'), J = 10 Hz); 6.78 (br.s, 2 H, NH, NH'); 7.21 (d, 2 H, H(7), H(7'), J = 10 Hz); 7.55 (d, 2 H, H(5), H(5'), J = 10 Hz); 9.80 (br.s, 2 H, NOH, NOH').

Heating of compound **3a** (0.2 g) with a 22% aqueous solution of **2d** (0.06 mL) for 24 h gave a precipitate of product **10** in ~10% yield.

1*H*-2-Phenylquinazolin-4-one (12). A solution of compound **5b** (0.1 g) and compound **2e** (0.06 g) in 40% ethanol (2 mL) was refluxed for 4 h. The precipitate was filtered off and recrystallized from 40% ethanol. The yield of compound **12** was 0.05 g (47%), m.p. 238—239 °C (*cf.* Ref. 3: m.p. 240 °C). ^{1}H NMR (DMSO-d_6), δ: 7.55 (m, 4 H); 7.75 (d, 1 H, J = 12 Hz); 7.85 (t, 1 H, J = 12 Hz); 8.20 (m, 3 H).

A solution of compound **11** (0.1 g) in 40% ethanol was heated with compound **2c** (0.07 g) for 4 h. The precipitate of compound **12** that formed was filtered off and recrystallized from 40% ethanol. The yield was 31%. M.p. 238—239 °C.

Dianthranilide (13). A 45% solution of NaOH (0.05 mL) and then (after 20 min) $SOCl_2$ (0.05 mL) were added to a solution of compound **3a** (0.1 g) in THF (3 mL). The reaction mixture was stirred for 1 h and then concentrated. The residue was crystallized from 40% ethanol. The yield of **13** was 0.05 g (43%), m.p. 329—330 °C (*cf.* Ref. 4: m.p. 330 °C). ^{1}H NMR (DMSO-d_6), δ: 7.0 (m, 2 H); 7.47 (t, 1 H, J = 10 Hz); 7.55 (t, 1 H, J = 10 Hz); 7.77 (d, 1 H, J = 10 Hz); 7.87 (d, 1 H, J = 10 Hz); 8.18 (d, 1 H, J = 10 Hz); 8.25 (d, 1 H, J = 10 Hz).

A solution of compound **3a** (0.2 g) and maleic anhydride (0.07 g) in dioxane was refluxed for 10 h. The solvent was distilled off, and the residue was recrystallized from 40% ethanol. The yield of product **13** was 0.25 g (25%). M.p. 329—330 °C.

A mixture of compound **3a** and an equimolar amount of **2c** was refluxed in ethanol for 36 h. The yield of product **13** was 15%. M.p. 329—330 °C. A mixture of compound **3a** and isobutyraldehyde in ethanol was heated in a sealed tube at 100 °C for 36 h. The yield of product **13** was ~10%.

References

1. O. A. Luk'yanov and P. B. Gordeev, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 115 [*Russ. Chem. Bull.*, 1997, **46**, 110 (Engl. Transl.)].
2. H.Böhme and H. Böing, *Arch. Pharm.*, 1960, **293**, 1011.
3. E. Körner, *J. Prakt. Chem. [2]*, 1887, **36**, 156.
4. G. Schröeter, *Ber.*, 1919, **52**, 2224.

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