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REACTIONS OF 7-OXO(7-IMINO)-1,2,7,10-TETRAHYDRO-1,10a-CYCLOHEXANO-2-R^1-3-R^2-4-R^3-PYRIDO[1,2-*a*]BENZIMIDAZOLES WITH C-NUCLEOPHILES AND THIOGLYCOLIC ACID

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Treatment of quinonemonoimines and an N-phenylquinonediimine of the pyrido[1,2-a]benzimidazole series with 1,3-indanedione, barbituric acid, or malononitrile and also with thioglycolic acid gives mono substitution at the 8 position. On the other hand, reaction of the N-cyclohexylquinonediimine in this series with C-nucleophiles leads to monosubstitution at position 9.

Keywords: C-nucleophiles, S-nucleophiles, pyrido[1,2-a]benzimidazole, quinonediimine, quinonemonoimine, nucleophilic reactions.

Treatment of *p*-quinoid compounds with various O-, S-, N-, and C-nucleophilic reagents has been studied quite widely [1-3]. In the case of *p*-quinones and quinoneimines the reaction occurs basically in the quinoid ring *via* a 1,4-nucleophilic type addition but in the case of methylenequinones by a 1,6-addition. At the same time, the addition of C-nucleophiles to the ring has mostly been studied for *p*-benzo(naphtho)quinones [1] while examples of the participation of quinonemonoimines [4-6], quinonediimines [7, 8], and methylenequinones [2] in similar reactions are markedly fewer in the literature. For classical *p*-methylenequinoneimines such reactions are unknown (there is an example of the addition of a C-nucleophile to a methylenequinonenitronium salt [9]). In addition, symmetrical quinoid compounds are most often used as substrates whereas the addition of C-nucleophiles to a quinoid ring in non symmetrical quinoid compounds has been investigated markedly less.

We have previously shown that the reaction of quinonemono- and diimines of the pyrido[1,2-*a*]-benzimidazole series with aniline and thiophenol occurs to give 8-monosubstituted quinoid compounds [10]. We have now studied the reaction of certain quinoid compounds of this series with thioglycolic acid and focussed mainly on a study of the previously uninvestigated reaction with C-nucleophiles.

We have studied the reaction of some quinonemonoimine **1a,b** [11] and quinonediimine **2a, 3a** [12] derivatives with 1,3-indanedione, barbituric acid, and malononitrile and, for compound **2a**, also with cyanoacetamide.

In all cases, after initial occurrence of a 1,4-addition there occurred an oxidation to give products of quinoid structure, the addition of an oxidant not being needed.

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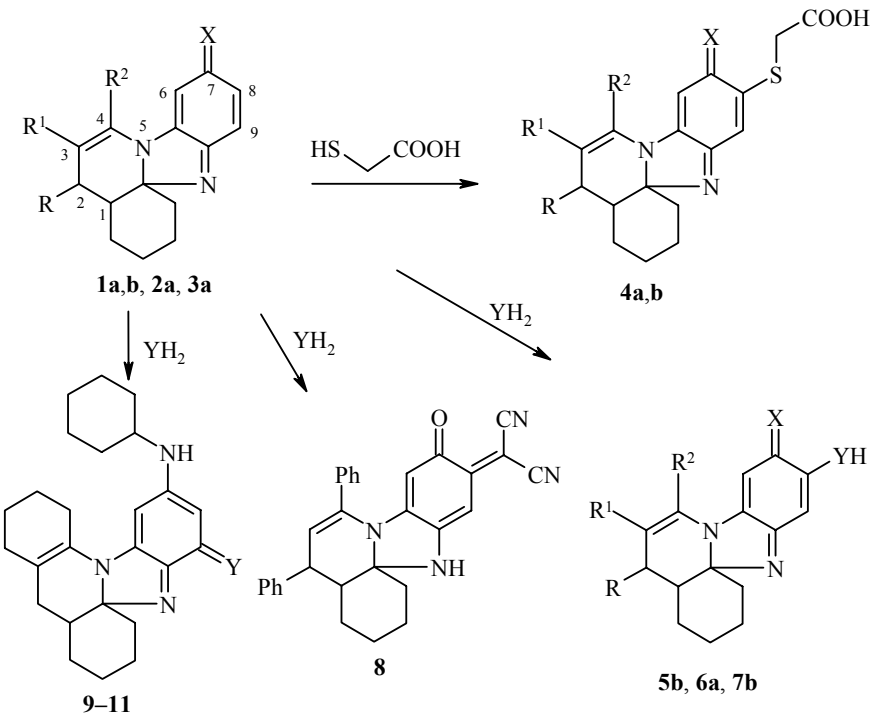
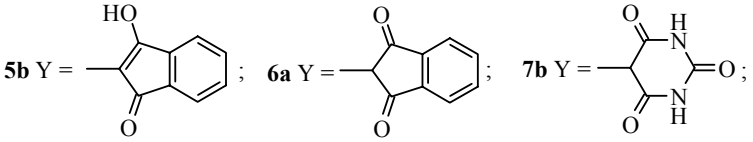
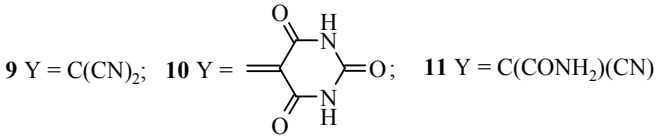


1–4, **6 a** R = H, $R^1 + R^2 = (CH_2)_4$, **1b**, **4b, 5b** R = R^2 = Ph, R^1 = H;
1a,**b**, **4a**,**b, 5b, 7b** X = O; **2**, **6** X = NPh; **3a** X = N-*cyclo*-C_6H_{11};





The reaction of the quinoneimines **1a,b** and quinonediimine **2a** with the active methylene reagents indicated above occurs regioselectively to give 8-monosubstituted *p*-quinoid products **4a,b, 5b, 6a, 7b**. Compound **8**, also 8-monosubstituted, occurs in an *o*-quinoid form. On the other hand the reaction of quinonediimine **3a** with malononitrile, barbituric acid, and cyanoacetamide proceeds by a regioselective addition to position 9 of the quinoid fragment to give *o*-quinonediimine structures (compounds **9-11**). The indanedione fragment in compound **5b** occurs in the enol form with an extremely "acidic" proton (according to the ^{1}H NMR data); as a result it is readily soluble in aqueous alcoholic Na_2CO_3 solution.

The positional selectivity of the nucleophilic addition to the quinonediimines **2a** and **3a** is governed by the presence in their molecules of exocyclic imine groups of two types, i.e. with cyclohexyl and phenyl substituents. Qualitative discussion of the effect of a substituent in terms of a traditional addition mechanism (fission with intermediate formation of an anionic σ-complex) shows that, thanks to the contribution of a resonance structure involving transfer of charge from $N_{(5)}$ to $N_{(7')}$, the addition at position 8 (σ-complex **A**) is favored by the presence of a phenyl substituent which can delocalize the negative charge (compound **2a**). The exchange of the latter for cyclohexyl results in the efficient stabilizing of the resonance structure *via* charge

transfer becoming impossible due to the +*I* effect of the cyclohexyl substituent. The σ-complex **B** is thus more stable and the addition is directed to position 9 as a result the energetically more favored *ortho*-methylenequinoneimine structures are formed.

The qualitative account given above for the positional selectivity is supported by quantum-chemical calculations for the corresponding anionic σ-complexes using the malononitrile anion as model nucleophile (*ab initio*, 3-21G basis, Dalton program [13]). The σ-complex **A** is more stable for compound **2a** by 31.6 kJ/mol whereas the σ-complex **B** is more stable for compound **3a** by 21.9 kJ/mol.

The reaction of the quinonemonoimines **1a,b** with thioglycolic acid, as in the case of thiophenol [10], needs base activation of the reagent and adds regioselectively to form the 8-monosubstituted quinonemonoimines **4a,b**.

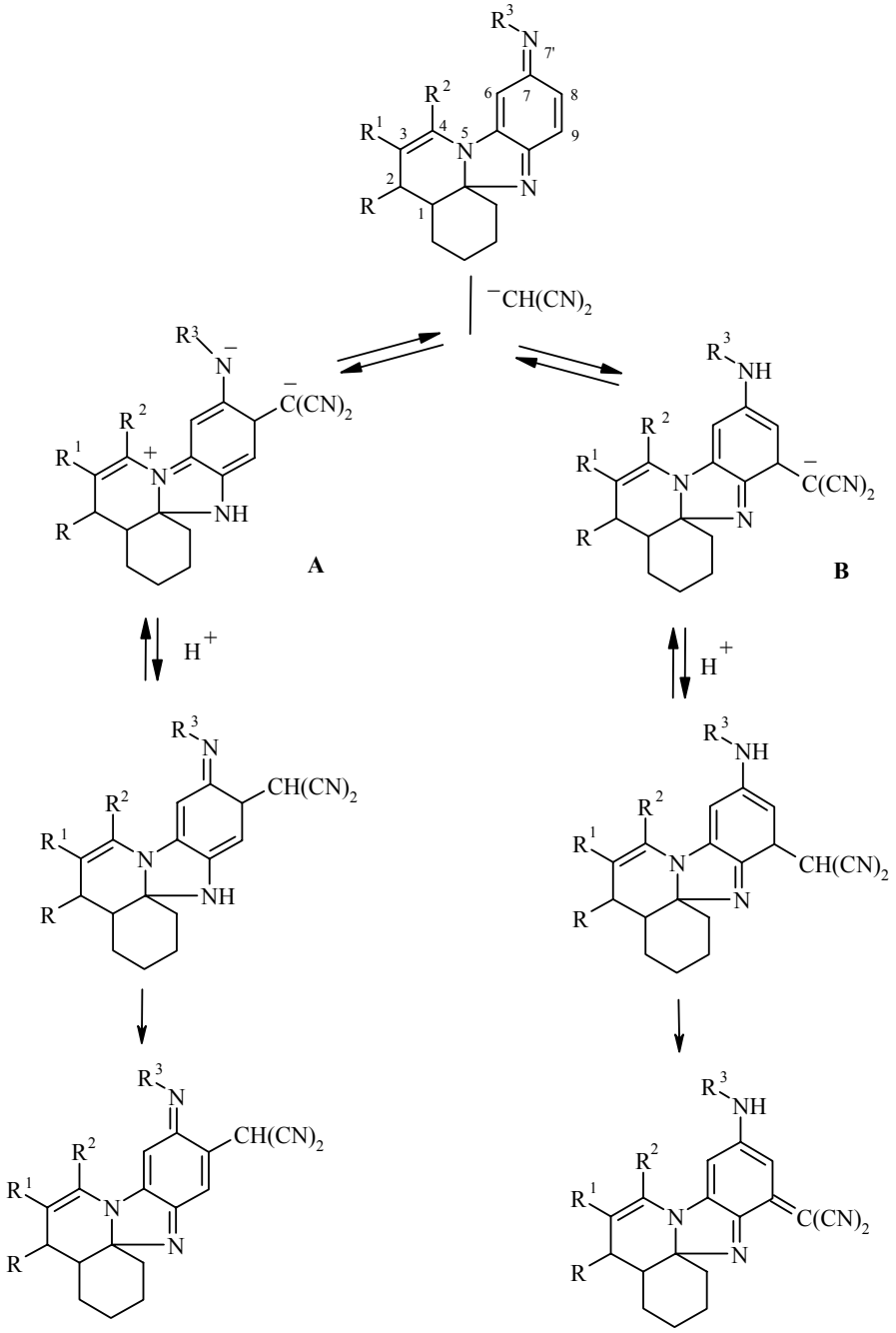
The IR spectra of all of the obtained compounds (Table 1) shows stretching bands for the C=N and C=C bonds. The spectra of compounds **4a,b** show a band at 1722 cm^{-1} for the stretching of the carbonyl group. There appears a band in the spectra of the products of reaction with 1,3-indanedione (compounds **5b, 6a**) corresponding to the stretching vibration of the carbonyl groups in the indanedione fragment at 1712-1725 cm^{-1}. In addition, the spectrum of compound **5b** shows a weak, broad and diffuse band corresponding to the stretching of the hydrogen bonded enolic hydroxyl (3200-2800 cm^{-1}). The spectra of compounds **8, 9, 11** show absorption bands for the stretching of the strongly conjugated nitrile groups (2191, 2192, 2160 cm^{-1} respectively) and the spectra of **7b, 10, 11** show amide group absorption bands in the range 3200-3400 cm^{-1}. The IR spectra of compounds **8-11** show absorption bands for the stretching of the secondary amino group pointing to an *o*-quinoid structure for the products (Scheme 1).

When compared with those of the starting compounds the ^1H NMR spectra of the 8-substituted products (Table 2) demonstrate the loss of the H-8 proton signal and the signals for the H-6 and H-9 protons become singlets. On the other hand, in the spectra of the 9-substituted compounds **9-11** the H-9 protons signal has disappeared and the H-6 and H-8 signals have become singlets. The *o*-quinoid structure in compounds **8-11** shows the presence of a one proton broad singlet (**8**) or doublet (**9-11**) for the secondary amino group signal. The spectra of compounds **6a,11** show a double set of signals for the corresponding protons and this allows us to infer the presence of a mixture of *syn*- and *anti*-isomers in different ratios. A similar pattern has been observed before in the spectra of related quinoid compounds [12]. The spectrum of compound **9** also shows a doubling of the signals for the quinoid protons and the protons of the secondary amino group. With the help of the nuclear Overhauser effect the presence of stable conformers relative to the $C_{(7)}$–$N_{(7')}$ σ-bond was demonstrated for this example. In addition the spectrum of compound **9** in deuteroacetone shows an additional splitting of the quinoid protons (J = 1.5 Hz). This was not observed when the spectra were recorded in deuterochloroform and in DMSO-d_6. The exact assignment of the signals for the quinoid protons and the NH

TABLE 1. IR Spectra of the Synthesized Compounds

Com-pound	IR spectrum, ν, cm^{-1}			
	$C_{(3)}$=$C_{(4)}$	C=O, C=N	C=C quin.	others
4a	1648	1608	1576, 1540	3500 br. (OH), 1722 (CO)
4b	1650	1605	1573, 1539	3500 br. (OH), 1725 (CO)
5b	1649	1619	1580, 1542	1715, 1687 (CO)
6a	1660	1620, 1605	1550, 1530	1725 (CO)
7b	1654	1617	1585, 1570	3214 (NH), 1718 (CO)
8	1653	1608	1595, 1540	3330 (NH), 2191 (CN)
9	1668	1640	1590, 1575	3250 (NH), 2192 (CN)
10	1648	1638	1565	3380, 3196 (NH), 1711 (CO)
11	1645	1632	1581	3402, 3325 (NH_2), 3235 (NH), 2160 (CN), 1671 (CO)

Scheme 1



group was achieved by partial suppression of the proton couplings using an internuclear double resonance method. In the spectrum of compound **7b** the presence of stable conformers relative to the σ-bond for $C_{(8)}$ and the carbon atom of barbituric acid was confirmed by the presence of signals for the protons of two NH groups. The enol form for compound **5b** was proved by the presence of a one proton singlet at 17.7 ppm which is characteristic only for a very "acidic" enolic hydroxyl proton. The chemical ionization mass spectra of all of the compounds prepared showed pseudomolecular ion peaks $[M+H]^+$ which corresponded to the calculated molecular weight.

TABLE 2. ^{1}H NMR Spectra for the Synthesized Compounds

Com-pound	Chemical shifts, δ, ppm (spin spin coupling, J, Hz)						
	H-2	H-3, d	H-6	H-8	H-9, s	H_{Ar}, m	other
4a	2.62 (m)	—	5.82 (s)	—	7.35	—	3.73 (2H, s, S$\underline{CH_2}$COOH)
4b	3.82 (dd, $J_{1,2}$= 10.0; $J_{2,3}$= 3.5)	5.60 (J = 3.5)	4.80 (s)	—	—*	7.15-7.45	3.72 (2H, m, S$\underline{CH_2}$COOH)
5b	3.90 (dd, $J_{1,2}$= 10.0; $J_{2,3}$= 3.5)	5.70 (J = 3.5)	4.93 (s)	—	8.77	7.20-7.55	17.7 (1H, s, OH–enol)
6a*[2]	–*[3]	—	5.57 (s)*[4]; 5.50 (s)*[5]	—	8.38 (s)*[4]; 8.32 (s)*[5]	7.35-7.70	5.20 (1H, s, C(O)C$\underline{H}$C(O))*[4]; 5.30 (1H, s, C(O)C$\underline{H}$C(O))*[5]
7b	4.00 (dd, $J_{1,2}$= 10.0; $J_{2,3}$ = 3.5)	5.60 (J = 3.5)	4.75 (s)	—	7.60 (s)	7.20-7.50	4.30 (1H, s); 11.33 (s, NH); 11.30 (s, NH)
8	3.89 (dd, $J_{1,2}$ = 10.0; $J_{2,3}$ = 3.0)	5.68 (J = 3.0)	4.98 (s)	—	6.76 (s)	7.15-7.55	5.72 (br. s, NH)
9	3.70 (m)	—	5.69 (br. s); 5.54 (br. s)	5.77 (br. s); 6.00 (br. s)	—	—	8.80 (d, J = 7.5, NH); 8.52 (d, J = 7.5, NH)
10	3.90 (m)	—	6.00 (s)	7.15 (s)	—	—	9.63 (2H, br. s, NH); 9.38 (d, J = 7.5, NH)
11*[6]	—*[3]	—	5.60 (s) *[4] 5.52 (s) *[5]	2.58 (s) *[4] 7.52 (s) *[5]	—	—	8.54 (d, J = 7.5, NH); 7.98 (d, J = 7.5, NH); 6.30 (2H, br. s, NH_2) *[4]; 6.05 (2H, br. s, NH_2) *[5]

* Obscured by the aromatic proton signals.

*[2] *syn-anti* ratio 4:1.

*[3] Obscured by the aliphatic protons signals.

*[4] Signals of the *syn* form.

*[5] Signals of the *anti* form.

*[6] *syn-anti* ratio 3:1.

TABLE 3. Parameters for the Synthesized Compounds

Compound	Empirical formula	Mass spectrum, *m/z* $[M+H]^+$	Found, % / Calculated, %			mp, °C	Yield, %
			C	H	N		
4a	$C_{21}H_{24}N_2O_3S$	385.3	65.82 / 65.63	6.05 / 6.25	7.38 / 7.29	191-193	65
4b	$C_{29}H_{26}N_2O_3S$	483.2	72.26 / 72.20	5.15 / 5.39	5.97 / 5.81	166-168	77
5b	$C_{36}H_{28}N_2O_3$	537.4	80.38 / 80.60	5.02 / 5.22	5.48 / 5.22	190-192	63
6a	$C_{34}H_{31}N_3O_2$	518.4	78.59 / 78.92	6.14 / 6.00	8.33 / 8.12	213-215	68
7b	$C_{31}H_{26}N_4O_4$	519.2	71.58 / 71.82	4.88 / 5.02	10.70 / 10.81	147-149	61
8	$C_{30}H_{24}N_4O$	457.5	79.05 / 78.95	5.13 / 5.26	12.25 / 12.28	217-219	64
9	$C_{28}H_{33}N_5$	440.3	76.65 / 76.54	7.40 / 7.52	16.09 / 15.95	232-234	72
10	$C_{29}H_{35}N_5O_3$	502.1	69.41 / 69.46	6.79 / 6.99	14.20 / 13.97	226-228	73
11	$C_{28}H_{35}N_5O$	458.3	73.39 / 73.52	7.52 / 7.66	15.68 / 15.32	112-114	59

EXPERIMENTAL

IR spectra were recorded on a Spectrum-1000 BX-II instrument for KBr tablets and in CH_2Cl_2 solution and ^1H NMR spectra on a Bruker WM-250 (250 MHz) instrument using $CDCl_3$, DMSO-d_6, and $(CD_3)_2CO$ solvents with TMS internal standard. Chromatograms and mass spectra were taken on a liquid chromatograph with an HP LC-MSD series 1100 mass selective detector (positive ion regime chemical ionization, fragment intensity 75 V; Shimpack FLC-NH_2 column, eluent isopropyl alcohol, methanol). Monitoring of the course of the reaction was carried out on Silufol and Sorbfil plates. The purity of the compounds obtained was assessed by HPLC-MS. Melting points were measured on a Boetius block.

The parameters for the compounds synthesized are given in Table 3.

8-Carboxymethylthio-7-oxo-1,2,7,10-tetrahydro-1,10a-cyclohexano-2-R-3-R^1-4-R^2-pyrido[1,2-*a*]-benzimidazoles (4a,b). A suspension of compound **1** (2.2 mol, 0.65 g for **1a**, 0.85 g for **1b**) in ethanol (30 ml) was heated to reflux to dissolve the starting material, cooled to 40°C, and thioglycolic acid (0.4 g, 4.5 mmol) and a suspension of NaOH (0.2 g, 4.5 mmol) in ethanol (10 ml) were added. The product was stirred for 3-4 h at about 20°C until the starting material **1** had disappeared (TLC monitoring). The reaction mixture was diluted with water to twice the volume and neutralized by a 5% solution of hydrochloric acid. In the case of compound **4a** the reaction mixture was extracted with ether, from which a pure, dark red, crystalline precipitate of compound **4a** separated. In the case of compound **4b** a precipitate formed after neutralization and this was crystallized from ethyl acetate to give pure, bright red crystals of **4b**.

8-[2-(1-Hydroxy-3-oxoinden-1-yl)]-7-oxo-2,4-diphenyl-1,2,7,10-tetrahydro-1,10a-cyclohexano-pyrido[1,2-*a*]benzimidazole (5b). A 1.5-fold molar excess of 1,3-indanedione was added with stirring to a suspension of compound **1b** (50 mmol) in ethanol (30 ml) and held for 1 day at about 20°C. Part of compound **4b** precipitated and was filtered off and the mother liquor was diluted to twice the volume with water before extraction with ether (3 × 20 ml). The extract was dried over anhydrous $MgSO_4$ and evaporated at atmospheric pressure. The combined fractions of dried material were chromatographed on Al_2O_3 (hexane–ethyl acetate, 1:1). The material separated was crystallized from a mixture of hexane and ethyl acetate (2:1).

8-[2-(1,3-Dioxoindanyl)]-7-phenylimino-1,2,7,10-tetrahydro-1,10a-cyclohexano-3,4-cyclohexeno-pyrido[1,2-a]benzimidazole (6a). A 1.5-fold excess of 1,3-indanedione was added to a solution of compound **1a** (50 mmol) in acetone (30 ml). The product was stirred for 5-6 h at 50°C until the starting material **1a** had disappeared (TLC monitoring). The dark green, powdery precipitate of compound **6a** formed on cooling to 0°C was crystallized from a mixture of chloroform and ethanol (10:1).

7-Oxo-2,4-diphenyl-8-[6-(2,4,6-trioxohexahydropyrimidinyl)]-1,2,7,10-tetrahydro-1,10a-cyclo-hexanopyrido[1,2-*a*]benzimidazole (7b). An equimolar amount of barbituric acid was added to a suspension of compound **1b** (50 mmol) in ethanol (40 ml) and stirred for 5-6 h at about 20°C to the disappearance of the starting compound **1b** from the reaction mixture (TLC monitoring). At the end of the reaction the product was diluted to twice the volume with a 5% HCl solution. The precipitated compound **7b** was filtered off, dried, and crystallized from a mixture of chloroform and ethanol (1:6).

8-Dicyanomethyleno-7-oxo-2,4-diphenyl-1,2,7,8-tetrahydro-1,10a-cycloxexanopyrido[1,2-*a*]-benzimidazole (8). A two fold molar excess of malonodinitrile was added with stirring to a suspension of compound **1b** (4 mmol) in ethanol (100 ml) and refluxed for 3-4 h to the disappearance of the starting compound **1b** from the reaction mixture (TLC monitoring). At the end of the reaction the product was cooled to 0°C and the precipitated material was crystallized from a mixture of benzene and dichloromethane (5:1).

9-[R^1,R^2-Methyleno]-7-cyclohexylamino-1,2,9,10-tetrahydro-1,10a-cyclohexanopyrido[1,2-*a*]-benzimidazoles (9-11). A 1.5-fold molar excess of malonodinitrile (synthesis of compound **9**), barbituric acid (synthesis of compound **10**) or cyanoacetamide (synthesis of compound **11**) was added with stirring to a solution of compound **1a** (4 mmol) in ethanol (100 ml) and stirred for 4-5 h at about 20°C to the disappearance of the starting compound **1a** from the reaction mixture (TLC monitoring). At the end of the reaction the product was diluted to twice the volume with water and the precipitate was filtered off and crystallized from a mixture of hexane and acetone (3:1) for compound **9**, or ethanol and DMF (5:1) for compound **10**. The precipitate of compound **11** was chromatographed on Al_2O_3 with ether as eluent.

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