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PROPERTIES OF 4-CHLOROMETHYL-2,2-DIMETHYL-1,2-DIHYDRO-BENZO[*f*]ISOQUINOLINE

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We have shown that 2,2-dimethyl-4-chloromethyl-1,2-dihydrobenzo[f]isoquinoline, which displays the properties of an enamine, reacts with oxalyl chloride with annelation of the dioxopyrroline ring. At the same time, this compound reacts with S-, O-, and CN-nucleophiles.

Keywords: substituted 4-chloromethyl-1,2-dihydrobenzo[*f*]isoquinoline, reactions with oxalyl chloride, O-, CN-, and S- nucleophiles, potassium cyanide, phase-transfer catalysis.

Derivatives of 1-chloromethyl-3,4-dihydroisoquinoline are known in the literature [1-4]. The chemical properties of these compounds are due primarily to two structural moieties: the halogen atom and the methylene imine group. The latter potentially has an enamine structure [5-8]. The indicated features of the structure suggest a diversity of chemical reactions, which makes the chemistry of these compounds promising for research. We have studied 2,2-dimethyl-4-chloromethyl-1,2-dihydrobenzo[*f*]isoquinoline (**1**). Such condensed structures are of interest as biologically active compounds [4, 9].

When base **1** reacts with oxalyl chloride, β-C-acylation occurs with formation of tetracyclic system **2**, which indicates the possibility that compound **1** of the enamine structure may be realized. At the same time, the reactions of this compound with other electrophilic reagents (dimethylsulfate, benzoyl chloride, *p*-tolylisocyanate) has shown that when reactions with them were carried out under conventional conditions [10, 11], in all cases the starting compounds were isolated.

It is known that molecules of nitrogen-containing heterocycles that contain a chloromethyl group in the α-position relative to the nitrogen atom, in the presence of bases are easily condensed by coupling of the molecule [12-14]. Such reactions are often complicated by further polymerization and oxidation. When an alcoholic solution of compound **1** is treated with base or sodium ethoxide, the reaction mass takes on a dark red color and a mixture of compounds is formed (TLC data). The objective of our studies was the investigation of conditions under which the reaction would proceed only along the route of formation of the chlorine nucleophilic substitution products. With this goal, we studied the possibility of using phase-transfer catalysis. The studies showed that S-nucleophiles are most reactive in the reaction under study. Thus the reaction with thiophenol in alcohol proceeds without a catalyst in 5 min (monitored by TLC) and leads to thioether **3**. Isopropylmercaptan proved to be less reactive: when the reaction was conducted under the same conditions, we did not observe formation of a new compound. At the same time, when using a standard Makosha catalyst, i.e., triethylbenzylammonium chloride (TEBAC)/NaOH [15], the reaction goes to completion in 15 min and thioether **4** is formed.

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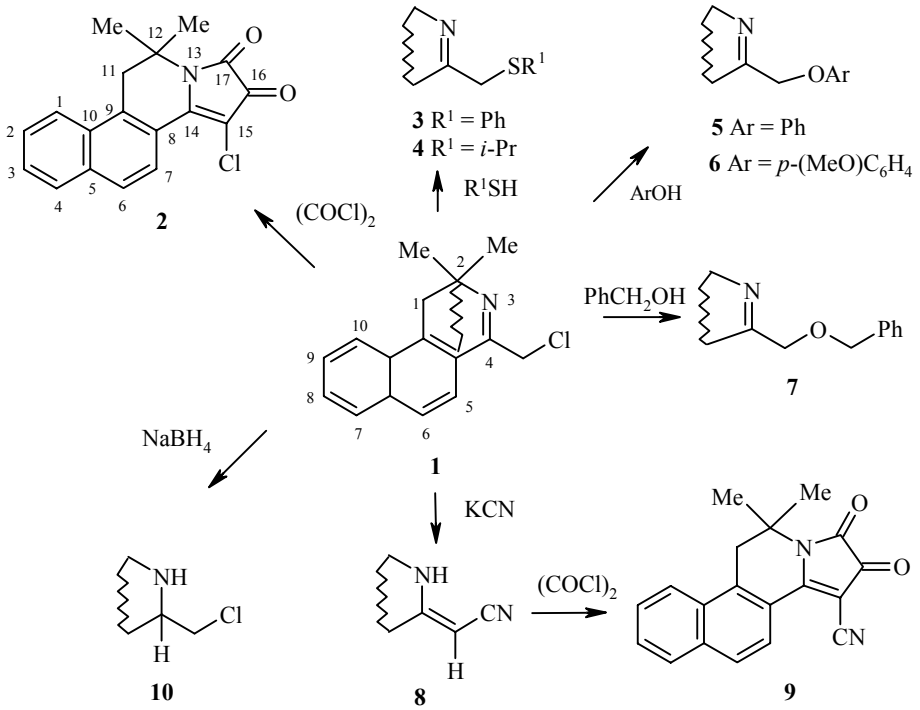

Studies of reactions of compound **1** with O-nucleophiles showed that the Makosha catalyst was not very effective in these cases. So the reaction with phenols when using TEBAC for 3 h does not go to completion, and is accompanied by appreciable tar formation. No reactions with alcohols were observed under these conditions. When a more effective catalyst, tetrabutylammonium hydrosulfate (TBAHS), was used [16], the reaction with phenols goes to completion in 1 h and the phenyl ethers **5, 6** are formed. Using harsher conditions (18-crown-6/KOH) makes it possible to obtain benzyl ether **7**.

Substitution of the halogen atom by a cyanide ion occurs when base **1** is simply boiled in alcohol. The nitrile formed in this case exists in the enamine form. The stability of the enamine structure can be explained by the strong acceptor action of the nitrile group, owing to *p*-π conjugation in the enamine moiety. Annelation at the enamine group using oxalyl chloride leads to dioxopyrroline **9**.

The azomethine group in compound **1** is easily reduced by sodium borohydride to form tetrahydroisoquinoline **10**.

Ethers **4-7** and also compound **10** (Table 1) were characterized as the hydrochlorides.

The ^{1}H NMR spectra of the compounds obtained are presented in Table 2. The tetracyclic structure of dioxopyrrolines **2** and **9** is confirmed by the absence in their spectra of signals from protons of the chloromethyl group. In the IR spectra of compounds **2** and **9**, there are characteristic absorption bands for the ketone group (1735 cm^{-1} and 1745 cm^{-1}, respectively), and also the lactam carbonyl (at 1705 cm^{-1} in both compounds) and the C≡N group at 2190 cm^{-1} (compound **9**).

The structure of the ethers **3-7** is confirmed by the presence in the NMR spectra of signals corresponding to the substituents R^1, Ar, and the benzyl residue. The IR spectra of the bases of these compounds contain a band in the 1640-1650 cm^{-1} region (C=N).

The structure of enamino nitrile **8** is confirmed by the presence in the NMR spectrum of a singlet from the vinyl proton (4.76 ppm) and the proton of the NH group (6.70 ppm). Calculations according to data in [17] give a chemical shift for the vinyl proton of 4.66 ppm for the *Z*-configuration and 5.21 ppm for the *E*-configuration. Thus for enaminonitrile **8**, the *Z*-form is most probable. The IR spectrum of this compound contains absorption bands in the 2170 cm^{-1} and 3310 cm^{-1} regions (C≡N and NH respectively).

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Cl(S)		
2	$C_{18}H_{14}ClNO_2$	69.2 / 69.4	4.3 / 4.5	4.4 / 4.5	11.3 / 11.4	229-230	37
3	$C_{22}H_{21}NS$	79.6 / 79.7	6.2 / 6.4	4.3 / 4.2	(9.6) / (9.7)	65-66	83
4*	$C_{19}H_{23}NS \cdot HCl$	68.2 / 68.3	7.1 / 7.2	4.3 / 4.2		221-223	78
5	$C_{22}H_{21}NO \cdot HCl$	74.9 / 75.1	5.8 / 6.0	3.8 / 4.0	9.8 / 10.1	148-150	52
6	$C_{23}H_{23}NO_2 \cdot HCl$	72.1 / 72.3	6.2 / 6.3	3.8 / 3.7	9.1 / 9.3	104-105	61
7	$C_{23}H_{23}NO \cdot HCl$	75.3 / 75.5	6.4 / 6.6	3.9 / 3.8	9.5 / 9.7	169-171	67
8	$C_{17}H_{16}N_2$	82.0 / 82.2	6.4 / 6.5	11.4 / 11.3	—	154-155	92
9	$C_{19}H_{14}N_2O_2$	75.3 / 75.5	4.6 / 4.7	9.4 / 9.3	—	287-288	77
10	$C_{16}H_{18}ClN \cdot HCl$	64.7 / 64.9	6.3 / 6.5	4.8 / 4.7	23.7 / 23.9	220-221	66

* Base **4**. Found, %: C 76.6; H 7.7; N 4.7; S 10.6. $C_{19}H_{23}NS$. Calculated, %: C 76.7; H 7.8; N 4.7; S 10.8.

TABLE 2. NMR Spectra of Compounds **2-10**

Compound	NMR spectrum, δ, ppm				
	2(5)-$(CH_3)_2$, s	1(6)-CH_2, s	CH_2C=N, s	aromatic protons, m	other protons*
2	1.60	3.50	—	7.60-8.65 (6H)	—
3	1.10	2.77	4.01	6.73-8.37 (11H)	—
4	1.30	3.43	4.43	7.34-8.40 (6H)	2.0 d ($2CH_3$–CH); 3.35 heptet ($2CH_3$–CH)
5	1.56	3.47	5.01	6.93-9.0 (11H)	—
6	1.47	3.40	5.65	7.60-8.47 (6H)*[2]	3.80 s (CH_3O)
7	1.55	3.50	5.30	7.70-8.30 (11H)	4.80 s ($PhCH_2O$)
8	1.30	2.50	—	7.55-8.20 (6H)	4.76 (HC=); 6.70 (NH)
9	1.65	3.50	—	7.72-8.50 (6H)	—
10	1.35; 1.80	*[3]	*[4]	7.50-8.10 (6H)	5.0 br. s (4-CH); 9.55 s, 10.80 s (NH_2^+)

* The NH^+ protons (compounds **4-8**) exchange with the water contained in DMSO-d_6.

*[2] *p*-Methoxyphenyl appears as two doublets: 6.90 ppm and 7.13 ppm.

*[3] 1-CH_2:CH_AH_B, δ_A = 3.30 pp, δ_B = 3.42 ppm, $^2J_{AB}$ = 13.2 Hz.

*[4] CH_2Cl: 4.55 dd.

The NMR spectrum of the hydrochloride of compound **10**, which is a derivative of 1,2,3,4-tetrahydroisoquinoline, is considerably different from the spectra of 3,4-dihydroisoquinolines **1-7**. In the spectrum of this compound, two singlets from the methyl groups in the 2 position (1.35 ppm and

1.80 ppm), and also the pattern for diastereotopic splitting of the 1-CH_2 protons and the protons of the chloromethyl moiety were observed (Table 2). The protons of the NH_2^+ group give different chemical shifts: 9.55 ppm and 10.80 ppm. The IR spectrum of the base of this compound contains an absorption band at 3430 cm^{-1} (NH).

EXPERIMENTAL

The NMR spectra of compounds **8, 10** were recorded on a Bruker AM-300 (300 MHz); all the rest were recorded on an RYa-2310 (60 MHz) in DMSO-d_6, except for compound **3**, the spectrum of which was recorded in $CDCl_3$, internal standard HMDS. The IR spectra were taken on a UR-20 in vaseline oil, except for base **10**, the spectrum of which was recorded in chloroform solution.

The reactions were monitored by TLC on Silufol UV-254 plates in a 1:3:6 acetone–ethanol–chloroform system, visualization by bromine vapors.

Compounds **3, 7** were recrystallized from acetonitrile; all the rest were recrystallized from isopropyl alcohol.

Compound **1** is described in [4].

1-Chloro-5,5-dimethyl-2,3,5,6-tetrahydronaphtho[1,2-*g*]indolizine-2,3-dione (2) and 1-Cyano-5,5-dimethyl-2,3,5,6-tetrahydronaphtho[1,2-*g*]indolizine-2,3-dione (9). A mixture of compound **1** (2.68 g, 10 mmol) or enamine **8** (2.48 g) and triethylamine (2.76 ml, 20 mmol) in ether (150 ml) were added over the course of 15 min to oxalyl chloride (0.86 ml, 10 mmol) in absolute ether (50 ml) at 0-5°C. The reaction mixture was brought up to 20°C and allowed to stand at this temperature for thirty more minutes. The precipitate was filtered off, dried, and recrystallized.

2,2-Dimethyl-4-phenylthio-1,2-dihydrobenzo[*f*]isoquinoline (3). Thiophenol (1.10 g, 10 mmol) was added to a solution of compound **1** (2.68 g, 10 mmol) in ethanol (50 ml) containing NaOH (0.44 g, 11 mmol). In this case, a precipitate of thioether **3** fell out immediately, which after cooling down to 20°C was filtered off, dried, and recrystallized.

4-Isopropylthio-2,2-dimethyl-1,2-dihydrobenzo[*f*]isoquinoline (4). A mixture of compound **1** (2.68 g, 10 mmol), isopropylmercaptan (1.1 ml, 12 mmol) with TEBAC (0.23 g, 1 mmol) in methylene chloride (10 ml) and 50% NaOH (5 ml) were stirred at 20°C. After 15 min (monitored by TLC), the organic layer was separated, washed with water, dried by boiling with a Dean–Stark trap, and the solvent was driven off under vacuum. The crystalline residue was filtered off, dried, and recrystallized.

4-Aryloxy-2,2-dimethyl-1,2-dihydrobenzo[*f*]isoquinolines (5, 6). A mixture of compound **1** (2.68 g, 10 mmol), the corresponding phenol (12 mmol), and TBAHS (1.36 g) in methylene chloride (20 ml) and a 50% NaOH solution (10 ml) were stirred at 60-70°C for 1 h. The mixture was cooled down to 20°C. The organic layer was removed, washed with water, and dried as for compound **4**, and the solvent was removed under vacuum. The residue was dissolved in ethylacetate (100 ml) and, by bubbling dry HCl through the solution, we obtained the corresponding hydrochlorides, which were filtered off, dried, and recrystallized.

4-Benzyloxy-2,2-dimethyl-1,2-dihydrobenzo[*f*]isoquinoline (7). A mixture of compound **1** (2.68 g, 10 mmol), benzyl alcohol (1.36 ml, 12 mmol), 18-crown-6 (0.26 g, 1 mmol), and KOH (5.8 g, 100 mmol) were boiled in benzene (50 ml) for 1 h. The mixture was cooled down to 20°C and the benzene layer was removed. The base was washed three times with portions (15 ml) of benzene and all the benzene extracts were combined. The combined benzene solution was filtered and, by bubbling dry HCl through the solution, we obtained the corresponding hydrochloride, which was filtered off, dried, and recrystallized.

(2,2-Dimethyl-1,2,3,4-tetrahydrobenzo[*f*]-isoquinolin-4-idene)acetonitrile (8). A mixture of compound **1** (2.68 g, 10 mmol) with KCN (0.70 g, 12 mmol) was boiled in ethanol (50 ml) for 2 h, cooled down to 20°C, and diluted with water (20 ml). The precipitate was filtered off, dried, and recrystallized.

4-Chloromethyl-2,2-dimethyl-1,2,3,4-tetrahydrobenzo[*f*]isoquinoline (10). A mixture of compound **1** (2.68 g, 10 mmol) and $NaBH_4$ (0.38 g, 10 mmol) was boiled for 10 min in ethanol (20 ml), cooled down to 20°C, and diluted with water (50 ml). The precipitate was filtered off, dried, and recrystallized.

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