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SYNTHESIS OF 2,2-DIMETHYL-1,2-DIHYDROBENZO[*f*]-ISOQUINOLINES DISPLAYING ANTIFUNGAL ACTIVITY

O. V. Surikova[1], A. V. Zachinyaeva[2], A. G. Mikhailovskii[1]*, and Ya. V. Zachinyaev[3]

The reaction of 2,2-dimethyl-1,2-dihydrobenzo[f]isoquinoline with malonic acid gave (2,2-dimethyl-1,2,3,4-tetrahydrobenzo[f]isoquinolin-4-yl)acetic acid, the acid chloride of which readily forms esters with alcohols and phenols. Reaction of the same azomethine with thioglycolic acid leads to (2,2-dimethyl-1,2,3,4-tetrahydro-benzo[f]isoquinolin-4-yl)thioacetic acid. Activation of the initial azomethine by iodomethylation enables reaction with 1,3-indanedione to be carried out. The obtained substances display antifungal action.

Keywords: 2,2-dimethyl-1,2-dihydrobenzo[*f*]isoquinoline, (2,2-dimethyl-1,2,3,4-tetrahydrobenzo[*f*]isoquinolin-4-yl)-2-thioacetic acid, (2,2-dimethyl-1,2,3,4-tetrahydrobenzo[*f*]isoquinolin-4-yl)acetic acid and its esters, malonic acid, thioglycolic acid, activation of azomethine by iodomethylation, reaction with 1,3-indanedione, antifungal action.

Condensed isoquinolines are an important group of natural and biologically active compounds [1]. Biologically active 2,2-dimethyl-1,2-dihydrobenzo[*f*]isoquinolines have been obtained previously [2, 3]. Antimicrobial and antifungal preparations are widely known among condensed six-membered heterocycles [4]. The search for new medicinal substances possessing these forms of action is urgent, since strains of pathogenic microorganisms resistant towards agents used for a long time are readily formed.

The aim of the present work was the investigation of the reactions of a cyclic azomethine derived from benzo[*f*]isoquinoline. The derivatives of condensed isoquinolines thus obtained are of interest as substances displaying activity in relation to pathogenic fungi.

The initial cyclic azomethine **1** was obtained by the cyclocondensation of the appropriate carbinol with HCN [5-7]. On reaction with 2,2-dimethyl-1,2-dihydrobenzo[*f*]isoquinoline (**1**), malonic acid [8] is added at the imino group and the process is accompanied by decarboxylation leading to acid **2**. The acid chloride **3** of this acid reacts with methanol, 2-propanol, 2-isopropyl-5-methylcyclohexanol (menthol), and 2-isopropyl-5-methylphenol (thymol) with the formation of the corresponding esters **4a-d**. Addition of thioglycolic acid to azomethine **1** is also effected fairly readily. Acid **5** is formed in this way.

* To whom correspondence should be addressed, e-mail: perm@pfa.ru.

[1]Perm State Pharmaceutical Academy, Perm 614990, Russia.
[2]S. M. Kirov Military Medical Academy, Saint Petersburg 194044, Russia; e-mail: anvz@rambler.ru.
[3]St Petersburg State Transport University, Saint Petersburg 190031, Russia; e-mail: yavz@rambler.ru.

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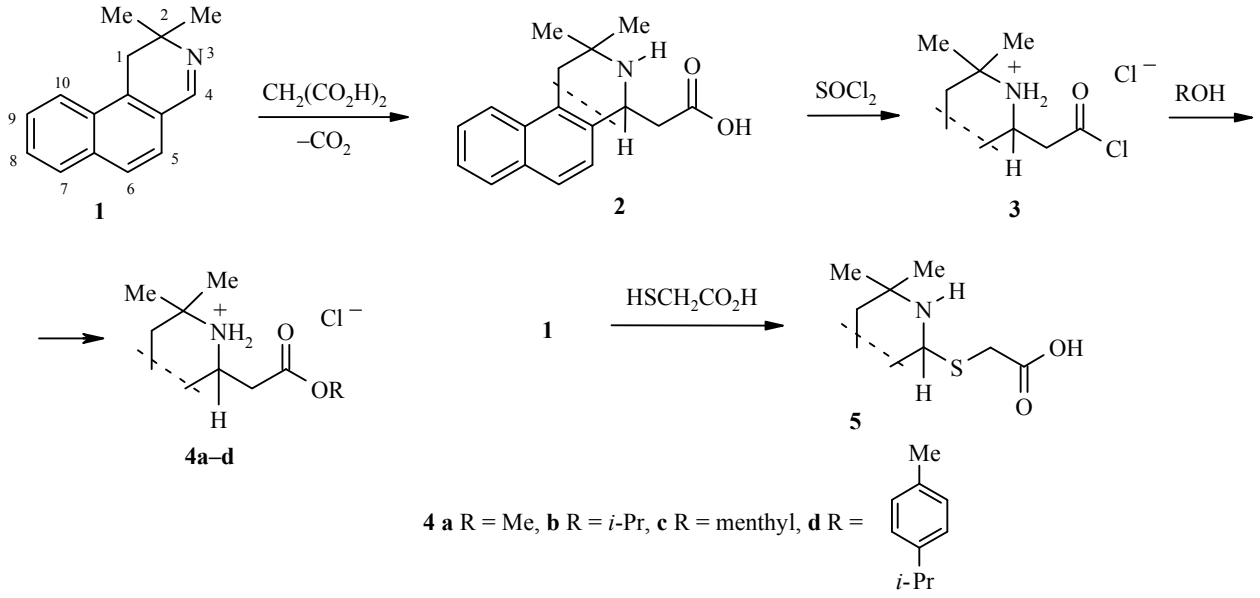
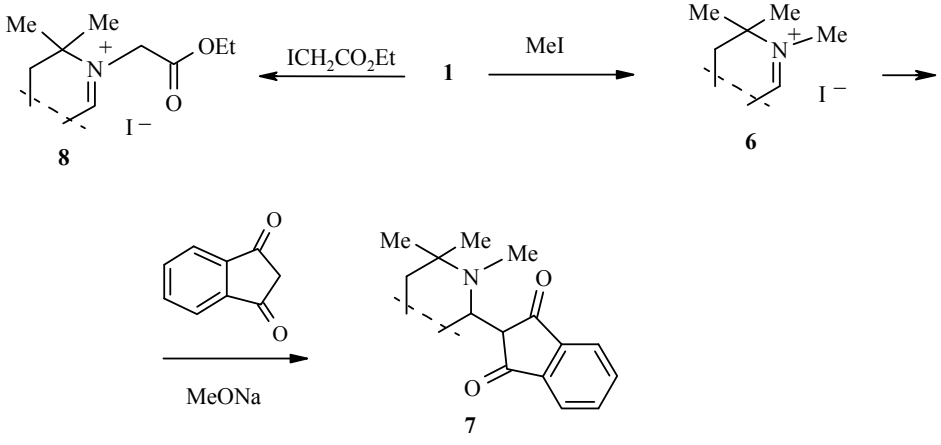


The reaction of 2,2-dimethyl-1,2-dihydrobenzo[*f*]isoquinoline (**1**) with such CH acid as 1,3-indanedione leads to diketone **7**, however the process requires activation of the substrate, which is effected by quaternization of the nitrogen atom (formation of iodomethylate **6**). Salt **8** is formed on reaction with iodoacetic acid ethyl ester, and is a potential dipole in dipolar [3+2] cycloaddition reactions.



All the compounds obtained were yellow or white crystalline substances. Iodides **6** and **8** were poorly soluble in water.

In the ^{1}H NMR spectra of compounds **2, 4a-d** (Table 2), unlike the spectrum of the initial imine **1** [**7**], the singlet of the azomethine proton was missing from the region ~8.00, a doublet was displayed for the protons of the methylene group in the 3.07-3.64 region, and also a triplet for the CH group in position 4 in the 4.41-5.12 ppm region. The signal for the protons of the 1-CH_2 group in the spectra of compounds **6**, **8** was displayed in the form of a singlet which distinguishes the structure of a 3,4-dihydroisoquinoline from the corresponding 1,2,3,4-tetrahydro derivatives. The spectrum of base **7** contains two doublets for the CH groups (4.90 and 5.00 ppm) which points in favor of the diketone form. The spectra of acids **2** and **5** have broadened singlets for the two NH_2^+ protons, which proves the structure of the bipolar ion. All the spectra also contain the proton signals of the substituents.

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Cl		
2	$C_{17}H_{19}NO_2$	75.9 / 75.8	7.2 / 7.1	5.3 / 5.2	—	248-250	80
4a	$C_{18}H_{21}NO_2 \cdot HCl$	67.7 / 67.6	6.8 / 6.9	4.4 / 4.4	11.1 / 11.0	200-202	76
4b	$C_{20}H_{25}NO_2 \cdot HCl$	69.1 / 69.0	7.6 / 7.5	4.1 / 4.0	10.1 / 10.2	224-226	65
4c	$C_{27}H_{37}NO_2 \cdot HCl$	73.1 / 73.0	8.7 / 8.6	3.2 / 3.2	7.8 / 7.9	210-212	47
4d	$C_{27}H_{31}NO_2 \cdot HCl$	74.0 / 74.0	7.5 / 7.4	3.3 / 3.2	8.1 / 8.0	186-188	52
5*	$C_{17}H_{19}NO_2S$	67.8 / 67.7	6.4 / 6.3	4.7 / 4.6	—	72-73	63
6	$C_{16}H_{18}IN$	54.8 / 54.7	5.1 / 5.2	4.0 / 3.9	—	188-190	92
7	$C_{25}H_{23}NO_2$	81.5 / 81.3	6.3 / 6.2	3.8 / 3.7	—	135-136	54
8	$C_{19}H_{22}INO_2$	53.8 / 53.9	5.1 / 5.3	3.4 / 3.3	—	180-182	90

*Found, S: 10.5%; calculated, S: 10.6%.

The IR spectra of amino acids **2** and **5** contain bands for the stretching vibrations of the COOH (1650-1660) and NH^+ groups (3050-3100 cm^{-1}). The ester group of compounds **4a-d, 8** is displayed in the region of 1730-1740 cm^{-1}. In the spectrum of diketone **7** bands were observed for the stretching vibrations of two carbonyl groups in the 1700-1720 cm^{-1} region. In the mass spectrum of acid **2** there were peaks for the molecular ion 269 $[M]^+$ (5), and also peaks for ions of *m/z* 254 $[M\text{-}CH_3]^+$ (8) and 210 $[M\text{-}CH_2COOH]^+$ (75).

A disc-diffusion method, enabling a primary selection of substances possessing fungicidal activity, was used to determine the sensitivity of fungi (*Candida glabrata, Aspergillus niger, Trichoderma viride, Saccharomyces cerevisiae, Alternaria alternata*) to the antiseptic. Muller-Hinton medium with added Methylene Blue and glucose was used for the investigation. The screening results showed that 7 out of 9 of the compounds synthesized displayed activity in relation to the test-cultures used (exceptions were compounds **2** and **4d**). The range of growth inhibition of the fungus was from 12 to 30 mm.

EXPERIMENTAL

The IR spectra were obtained on a Specord-80 spectrometer in nujol. The ^1H NMR spectra were recorded on a Bruker-300 (300 MHz) instrument in $CDCl_3$, internal standard was HMDS (0.05 ppm from TMS). The mass spectrum of compound **2** was recorded on a Finnigan MAT Incos 50 spectrometer (70 eV, EI). A check on the purity of the obtained substances was effected by TLC on Silufol UV-254 plates in the system acetone–ethanol–chloroform, 1:3:6.

Compound **2** was recrystallized from a methanol–water, 1:1, mixture, the remainder from isopropyl alcohol.

(2,2-Dimethyl-1,2,3,4-tetrahydrobenzo[*f*]isoquinolin-4-yl)acetic Acid (2). A mixture of azomethine **1** (2.09 g, 10 mmol) and malonic acid (1.04 g, 10 mmol) was heated for ~30 min at 120°C with constant stirring until the end of carbon dioxide evolution. After cooling to room temperature, methanol (50 ml) was added. The resulting solid was filtered off, dried, and recrystallized.

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

Compound	Chemical shifts, δ, ppm (*J*, Hz)						
	$(CH_3)_2$	1-CH_2	Arom protons, m	NH_2^+ ring	4-C<u>H</u>–NH_2^+	CH_2CO_2	Other protons
2	1.13 (3H, s); 1.31 (3H, s)	2.81 (1H, d, $^2J_{AB}$ = 12); 2.85 (1H, d, $^2J_{AB}$ = 12)	7.21-7.95 (6H)	8.90 (2H, br. s)	4.41 (t, ^3J = 7)	3.06 (1H, d, $^2J_{AB}$ = 12); 3.10 (1H, d, $^2J_{AB}$ = 12)	—
4a	1.52 (3H, s); 1.88 (3H, s)	3.21 (1H, d, $^2J_{AB}$ = 12); 3.25 (1H, d, $^2J_{AB}$ = 12)	7.25-7.90 (6H)	8.20 (1H, s); 11.90 (1H, s)	5.10 (t, ^3J = 6)	3.60 (1H, d, $^2J_{AB}$ = 9); 3.63 (1H, d, $^2J_{AB}$ = 9)	3.61 (3H, s, OCH_3)
4b	1.51 (3H, s); 1.88 (3H, s)	3.47 (1H, d, $^2J_{AB}$ = 12); 3.51 (1H, d, $^2J_{AB}$ = 12)	7.12-7.90 (6H)	8.10 (1H, s); 12.10 (1H, s)	5.11 (t, ^3J = 6)	3.62 (1H, d, $^2J_{AB}$ = 9); 3.65 (1H, d, $^2J_{AB}$ = 9)	1.16 (6H, d, ^3J = 8, C<u>H</u>$_3$CHC<u>H</u>$_3$); 4.80 (1H, hept., ^3J = 5, C<u>H</u>$(CH_3)_2$)
4c	1.50 (3H, s); 1.86 (3H, s)	3.14 (1H, d, $^2J_{AB}$ = 12); 3.18 (1H, d, $^2J_{AB}$ = 12)	7.05-7.95 (6H)	8.10 (1H, s); 12.1 (1H, br. s)	4.93 (t, ^3J = 6)	3.64 (1H, d, $^2J_{AB}$ = 9); 3.61 (1H, d, $^2J_{AB}$ = 9)	0.62 (6H, d ^3J = 5, CH(C<u>H</u>$_3$)$_2$); 0.73 (3H, d, ^3J = 6, CHC<u>H</u>$_3$); 0.77 (1H, m, C<u>H</u>$(CH_3)_2$); 0.88 (1H, m, C<u>H</u>CH_3); 0.91-1.69 (7H, m, $3CH_2$ + CH); 4.90 (1H, m, OCH)
4d	1.19 (3H, s); 1.21 (3H, s)	3.18 (1H, d, $^2J_{AB}$ = 12); 3.14 (1H, d, $^2J_{AB}$ = 12)	7.15-7.80 (9H)	12.16 (1H, s); 12.59 (1H, s)	5.12 (t, ^3J = 7)	3.22 (1H, d, $^2J_{AB}$ = 9); 3.25 (1H, d, $^2J_{AB}$ = 9)	1.25 and 0.97 (6H, 2d, ^3J = 8, C<u>H</u>$_3$CHC<u>H</u>$_3$); 2.15 (3H, s, C<u>H</u>$_3$Ar); 4.82 (1H, hept., ^3J = 6, C<u>H</u>$(CH_3)_2$)
5	1.35 (3H, s); 1.47 (3H, s)	3.29 (4H, br. s)	7.25-7.90 (6H)	8.80 (2H, br. s)	3.62 (1H, br. s)	—	
6	1.23 (6H, s, $2CH_3$)	3.22 (2H, s)	7.25-8.10 (6H)	—	—	2.47 (3H, s, CH_3N); 9.33 (1H, s, HC=N)	
7	1.25 (3H, s); 1.61 (3H, s)	3.33 (1H, d, $^2J_{AB}$ = 6); 3.31 (1H, d, $^2J_{AB}$ = 6)	7.15-.86 (10H)	—	—	—	2.80 (3H, s, CH_3N); 4.90 (1H, d, ^3J = 4, CH–N); 5.00 (1H, d, ^3J = 4, COCHCO)
8	1.35 (6H, s, $2CH_3$)	3.62 (4H, br. s)	7.15-8.10 (6H)	—	—	—*	1.96(3H, t, ^2J = 7, OCH_2C<u>H</u>$_3$); 4.15 (2H, q, ^2J = 7, OC<u>H</u>$_2CH_3$); 9.35 (1H, s, HC=N)

*In the composition of br. s, at 3.29 and 3.62 ppm respectively.

Hydrochlorides of the Methyl (4a), Isopropyl (4b), Menthyl (4c), and Thymyl (4d) Esters of (2,2-Dimethyl-1,2,3,4-tetrahydrobenzo[*f*]isoquinolin-4-yl)acetic Acid. Thionyl chloride (15 ml) was added to acid **2** (2.68 g, 10 mmol), and the mixture was boiled for 40 min until the solution was black. The excess of thionyl chloride was distilled off on a water bath. Methanol (1.2 ml, 30 mmol) (for compound **4a**), 2-propanol (2.3 ml, 30 mmol) (compound **4b**), menthol (2.3 g, 15 mmol) (compound **4c**), or thymol (2.2 g, 15 mmol) (compound **4d**) was added to the obtained residue of acid chloride **3**. The reaction mixture formed was heated for 30 min (compounds **4c**,**d**) or 15 min (compounds **4a**,**b**). On using thymol (ester **4d**) the reaction was carried out in benzene (30 ml). After cooling to 20°C the mixture was treated with ether (100 ml). The solid formed after 15-20 min was filtered off, dried, and recrystallized.

(2,2-Dimethyl-1,2,3,4-tetrahydrobenzo[*f*]isoquinolin-4-yl)thioglycolic Acid (5). Thioglycolic acid (1 ml, 15 mmol) was added to azomethine **1** (2.09 g, 10 mmol) in benzene (20 ml) and the mixture boiled for 15 min. After cooling to 20°C the mixture was treated with hexane (50 ml). The precipitated solid was filtered off, dried, and recrystallized.

2,2,3-Trimethyl-1,2-dihydrobenzo[*f*]isoquinolinium Iodide (6) and 2,2-Dimethyl-3-(ethoxycarbonyl-methyl)-1,2-dihydrobenzo[*f*]isoquinolinium Iodide (8). A mixture of azomethine **1** (2.09 g, 10 mmol) in 2-propanol (20 ml) and MeI (0.8 ml, 13 mmol) or ethyl iodoacetate (2.5 g, 12 mmol) was boiled for 2 h, cooled to 20°C, the precipitated solid was filtered off, dried, and recrystallized.

2-(2,2,3-Trimethyl-1,2,3,4-tetrahydrobenzo[*f*]isoquinolin-4-yl)-1,3-indanedione (7). 1,3-Indanedione (1.46 g, 10 mmol) was added to a solution of sodium (1.0 g, 25 mmol) in methanol (50 ml). The obtained mixture was added to a solution of iodomethylate **6** (3.51 g, 10 mmol) in methanol (20 ml). The mixture was boiled for 1 h 30 min on a water bath, the solvent distilled, the resulting solid was filtered off, thoroughly washed with water, dried, and recrystallized.

REFERENCES

1. A. A. Akhrem, O. V. Gulyakevich, and A. L. Mikhal'chuk, in: V. G. Kartsev (editor), *Isoquinolines: Chemistry and Biological Activity* [in Russian], Vol. 7, MNFB, Moscow (2008), p. 11.
2. A. G. Mikhailovskii, B. Ya. Syropyatov, V. S. Shklyaev, Yu. P. Timofeeva, and A. V. Dolzhenko, *Khim.-farm. Zh.*, **32**, No. 8, 21 (1998).
3. N. N. Polygalova, V. V. Udodov, B. Ya. Syropyatov, N. G. Ismailova, A. G. Mikhailovskii, and M. I. Vakhrin, Russian Pat. 2320654: *Byull. Izobret.*, No. 9 (2008).
4. A. P. Krasil'nikov, *Handbook on Antiseptics*, Vyssh. Shkol., Minsk (1995), p. 101.
5. A. G. Mikhailovskii, B. B. Aleksandrov, and M. I. Vakhrin, *Khim. Geterotsikl. Soedin.*, 1144 (1992). [*Chem. Heterocycl. Comp.*, **28**, 966 (1992)].
6. A. G. Mikhailovskii, *Khim. Geterotsikl. Soedin.*, 579 (2000). [*Chem. Heterocycl. Comp.*, **36**, 501 (2000)].
7. A. G. Mikhailovskii, V. S. Shklyaev, and E. V. Feshina, *Khim. Geterotsikl. Soedin*., 236 (1998). [*Chem. Heterocycl. Comp.*, **34**, 211 (1998)].
8. D. Beaumont, R. D. Waigh, M. Sunbhanich, and M. W. Nott, *J. Med. Chem.*, **26**, 507 (1983).