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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Synthesis of Substituted Ureas from Urea and Halohydrins

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Abstract—Substituted ureas were prepared by reactions of 1,2-halohydrins with urea and were tested as antimicrobial additives to motor oils.

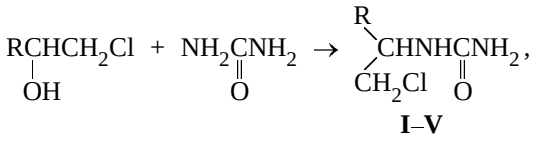
Substituted ureas attract researchers' attention thanks to a set of valuable properties allowing their use in industry, agriculture, and medicine. Substituted ureas are used as insecticides, as plant growth regulators, as effective additives of various purposes to hydrocarbon fuels, oils, and polymeric materials, as drugs, and as dyes [1].

Classical synthetic routes to substituted ureas are mostly based on reactions of amines with urea or with isocyanic acid derivatives, or on carbonylation of amino and nitro compounds [1]. These routes are diverse, but many procedures have certain drawbacks restricting their applicability. Development of new procedures is interesting from both scientific and practical viewpoints. In particular, synthesis of substituted ureas by direct reaction of aliphatic and aromatic alcohols with urea has been reported [2, 3]. However, there are no data on reactions of urea with alkoxy-substituted 1,2-halohydrins. These reactions are examined in our study.

Previously, we have studied the reactions of alkoxy- and alkylthio-substituted 1,2-chlorohydrins with thiourea in the presence of various acids [4–6]. Proceeding with analysis of the reactivity of ureas and thioureas [7], we prepared in this study *N*-substituted ureas by reactions of 1,2-halohydrins with urea in the presence of a mixture of H_2SO_4 and CH_3COOH.

The starting 1,2-halohydrins were prepared by reactions of appropriate alcohols with epichlorohydrin in the presence of $ZnCl_2$ at 65°C [8].

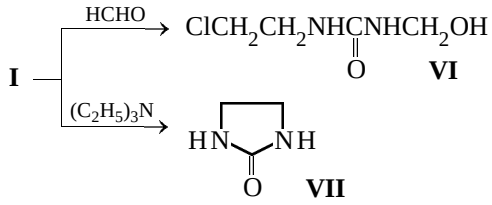
The yield of *N*-substituted ureas containing various functional groups (see table) can be optimized by varying the temperature (from 60 to 115°C), amount of H_2SO_4 (1–5 ml), and reaction time (4–8 h).



I–V

where R – H (**I**), CH_3OCH_2 (**II**), $C_2H_5OCH_2$ (**III**), $C_4H_9OCH_2$ (**IV**), $C_6H_5CH_2OCH_2$ (**V**).

By reactions of **I** with HCHO and $(C_2H_5)_3N$, we prepared *N*-hydroxymethyl-*N*'-chloroethylurea **VI** and cyclic urea **VII** (see table):



The compounds prepared were tested as antimicrobial additives to MS-11 lubricating oil [GOSTs (State Standards) 9.052–75 and 9.085–75]. The compounds showed a pronounced antimicrobial effect when present in low concentrations (0.5–1.0%); they are readily soluble in MS-11 oil and do not stimulate corrosion. Compounds **VI** and **VII** are more effective than the commercial antimicrobial additive, 8-quinolinol. With **VI**, the width of the suppression zone is 0.6–1.4 cm for bacteria and 1.0–1.9 cm for fungi. With 8-quinolinol, these parameters are 0.4–0.9 and 0.7–0.9 cm, respectively.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Bruker spectrometer (300 MHz, internal reference TMS). The

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Characteristics of **I**–**VII**

Compound no.	Yield, %	mp, °C	R_f	IR spectrum, cm^{-1}	^1H NMR spectrum, δ, ppm	Found, % / Calculated, %				Formula
						C	H	Cl	N	
I	65	200–207	0.54	3340 (NH) 3420 (NH_2) 1640 (C=O) 670 (C–Cl)	1.3–1.9 t (2H, CH_2Cl) 3.0–2.5 q (2H, CH_2) 6.5–7.5 c (3H,NH_2CONH)	29.12 29.38	5.93 5.71	29.17 28.97	22.59 22.85	$C_3H_7ClN_2O$
II	60	198–199	0.45	3325 (NH) 3490 (NH_2) 1650 (C=O) 700 (C–Cl)	1,7–1,8 c (3H, CH_3) 3.0–3.1 d (2H, CH_2O) 3.6–3.7 d (2H, CH_2Cl) 2.0–2.1 m (1H, CH) 6,5–7,5 s (3H, NH_2CONH)	36.26 36.03	6.42 6.60	21.46 21.32	16.61 16.81	$C_5H_{11}ClN_2O_2$
III	60	200–202	0.36	3330 (NH) 3460 (NH_2) 1600 (C=O) 650 (C–Cl)	1.0–1.3 t (3H, CH_3) 3.2–3.3 d (2H, CH_2Cl) 3.4–3.5 d (2H, CH_2O) 2.0–2.1 m (1H, CH) 6,0–8,0 s (3H, NH_2CONH–)	36.65 39.88	7.37 7.20	19.00 19.66	15.74 15.51	$C_6H_{13}ClN_2O_2$
IV	50	218–219	0.47	3320 (NH) 3480 (NH_2) 1640 (C=O) 600 (C–Cl)	1.0–1.2 t (3H, CH_3) 3.0–3.5 m (4H, $2CH_2$) 3.2–3.3 d (2H, CH_2Cl) 3.0–3.1 t (2H, CH_2O) 2.0–2.1 m (1H, CH) 6.5–7.7 s (3H, NH_2CONH)	46.17 46.04	8.27 8.15	17.23 17.02	13.66 13.42	$C_8H_{17}ClN_2O_2$
V	50	210–212	0.33	3340 (NH) 3500 (NH_2) 1600 (C=O) 600 (C–Cl)	7.2–7.4 d, 2t (5H, C_6H_5) 3.2–3.3 d (2H, CH_2Cl) 3.4–3.5 d (2H, CH_2O) 2.0–2.1 m (1H, CH) 5.5–7.5 s (3H, NH_2CONH)	54.28 54.43	6.31 6.18	14.44 14.63	11.72 11.54	$C_{11}H_{15}ClN_2O_2$
VI	80	240	0.52	3355(NH) 1600 (C=O) 700 (C–Cl) 3650 (OH)	1.3–1.9 t (2H, CH_2Cl) 2.5–3.0 q (2H, CH_2) 4.7–4.8 s (1H, OH) 3.5–4.0 t (2H, CH_2) 6.5–8.5 s (3H, NH_2CONH)	31.69 31.47	5.98 5.90	23.43 23.27	18.16 18.36	$C_4H_9ClN_2O_2$
VII	70	220–221	0.61	3350 (NH) 1655(C=O)	3,0–3,1 q (4H, $2CH_2$) 1.7–2.0 c (2H, 2NH)	41.99 41.86	7.17 6.97	– –	32.39 32.55	$C_3H_6N_2O$

IR spectra were measured on a Specord 75-IR spectrometer (mulls in mineral oil).

The compound purity and reaction progress were monitored by TLC (Silufol UV-254 plates, eluent isopropyl alcohol–hexane, 3 : 5).

Ureas I–III. A mixture of 0.04 mol of an appropriate halohydrin and 16.2 g of urea in 30 ml of AcOH was heated to 80°C, and 5 ml of H_2SO_4 (ρ = 1.84 g cm^{-3}) was added with vigorous stirring over a period of 10 min. Then the mixture was heated at 80°C for 4 h and cooled; the precipitate was filtered off and recrystallized from DMF or C_2H_5OH.

Ureas IV and V. A mixture of 0.01 mol of an appropriate halohydrin, 0.06 mol of urea, 15 ml of AcOH, and 1 ml of H_2SO_4 (ρ = 1.84 g cm^{-3}) was heated with stirring at 115°C for 8 h. The resulting mixture was worked up as described above.

Urea VI. A 30% aqueous solution of formaldehyde (1 ml) was added at 18–20°C with stirring to a suspension of 0.01 mol of **I** in 5 ml of water. The color-

less precipitate that formed in 1 h was filtered off, washed with water, and dried in air.

Urea VII. Triethylamine (10 mmol) was added to a suspension of 10 mmol of **I** in 25 ml of ether. The mixture was stirred at 18–20°C for 12 h, the precipitate of triethylammonium chloride was filtered off, the solvent was removed, and the product was filtered off and dried in air.

CONCLUSION

N-Substituted ureas improving the antimicrobial properties of MS-11 motor oil were prepared in good yields (50–80%) by reactions of 1,2-halohydrins with urea in the presence of a mixture of sulfuric and acetic acids.

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