Russian Journal of Organic Chemistry, Vol. 40, No. 3, 2004, pp. 368–371. Translated from Zhurnal Organicheskoi Khimii, Vol. 40, No. 3, 2004, pp. 398–401.

Chemoselective Alkylation of 3- and 4-(5-Amino-4-hetaryl-2,3-dihydro-3-oxopyrrol-1-yl)benzoic Acids

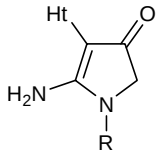
E. V. Resnyanskaya, A. V. Tverdokhlebov, Yu. M. Volovenko, and T. V. Shokol

Taras Shevchenko Kiev National University, ul. Vladimirskaya 62, Kiev, 01033 Ukraine
e-mail: atver@mail.univ.kiev.ua

Received January 17, 2003

Abstract—Alkylation of 3- and 4-(5-amino-4-hetaryl-2,3-dihydro-3-oxopyrrol-1-yl)benzoic acids with phenacyl bromides or chloroacetanilides in DMF in the presence of triethylamine occurs at the carboxy group with high selectivity and yields the corresponding phenacyl and arylcarbamoylmethyl esters. The initial pyrrolylbenzoic acids were synthesized by reaction of 3- and 4-aminobenzoic acids with 4-chloro-2-hetaryl-3-oxobutyronitriles.

We previously developed various procedures for the synthesis of 5-amino-4-hetaryl-2,3-dihydropyrrol-3-ones **I** [1–6]. Further studies of the chemical properties of compounds **I** revealed low reactivity of the 5-amino group [7], which was explained by conjugation between the amino and carbonyl groups in molecule **I**. Therefore, these compounds can be regarded as vinylogous to amides. The existence of such conjugation was proved by the X-ray diffraction data which showed considerable deviations of the corresponding bond lengths in the β-enaminoketone fragment [7] from the standard values, as well as by comparison of the spectral data of pyrrolones **I** and model compounds [8] specially synthesized for that purpose. An analogous conjugation in structurally related systems was also observed by other authors [9].



I

R = Alk, Ar.

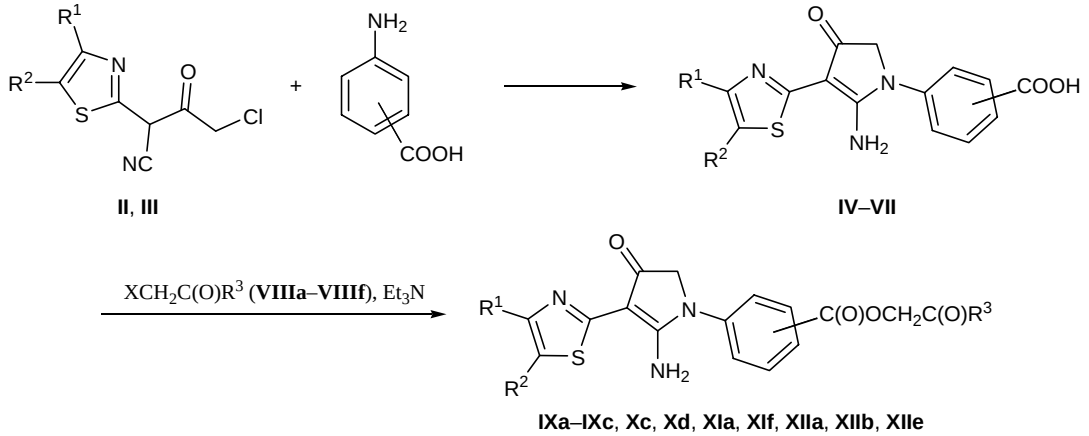
Taking into account the low reactivity of the amino group in compounds **I**, we made an attempt to introduce a functional group into the R substituent and modify it by the action of electrophilic reagents without protection of the amino group. The present communication reports on the results of this study.

In 1990s, a number of compounds exhibiting a high antitumor activity have been found among derivatives of 3- and 4-(2-aminopyrrol-1-yl)benzoic acid [10–12]. Therefore, we selected carboxy group as a functionality to be introduced into the substituent R. Following the procedure developed previously [3–6], reactions of 3- and 4-aminobenzoic acids with 2-(2-thiazolyl)- and 2-(2-benzothiazolyl)-4-chloro-3-oxobutyronitriles **II** and **III** [3, 13] afforded 70–80% of 3- and 4-(5-amino-4-hetaryl-3-oxo-2,3-dihydropyrrol-1-yl)benzoic acids **IV**–**VII** (Scheme 1). The structure of compounds **IV**–**VII** was confirmed by the data of elemental analysis and IR and ^{1}H NMR spectroscopy. The ^{1}H NMR spectra were consistent with the known data for (benzo)thiazolyl-substituted derivatives of **I** [3, 4, 6].

The carboxy group in pyrrolylbenzoic acids **IV**–**VII** was modified via the known reaction [14] of the corresponding salts with phenacyl halides. Alkylation of **IV**–**VII** with 4-chlorophenacyl bromide (**VIIIa**) in DMF in the presence of an equimolar amount of triethylamine occurred selectively at the carboxy group to give 4-chlorophenacyl 3- and 4-(5-amino-4-hetaryl-3-oxo-2,3-dihydropyrrol-1-yl)benzoates **IXa**, **XIa**, and **XIIa**. With the use of structural analogs of phenacyl halides, chloroacetanilides **VIIIb**–**VIIIf**, as alkylating agents we obtained arylcarbamoylmethyl esters **IXb**, **IXc**, **Xc**, **Xd**, **XIf**, **XIIb**, and **XIIe**. The yields of esters **IX**–**XII** ranged from 70 to 90%, and no alkylation products at the amino group were detected.

The structure of compounds **IX**–**XII** was determined on the basis of the IR and ^{1}H NMR spectra. The

Scheme 1.



II, **IV**, **V**, **IX**, **X**, R^1R^2 = benzo; **III**, **VI**, **VII**, **XI**, **XII**, R^1 = 4-ClC_6H_4, R^2 = H; **IV**, **VI**, **IX**, **XI**, 4-COOH or 4-$COOCH_2COR^3$; **V**, **VII**, **X**, **XII**, 3-COOH or 3-$COOCH_2COR^3$; **VIIIa**, X = Br; **VIIIb**–**VIIIf**, X = Cl; R^3 = 4-ClC_6H_4 (**a**), 3-$MeOC_6H_4NH$ (**b**), 3,4-$Cl_2C_6H_3NH$ (**c**), 4-$(F_2CHS)C_6H_4NH$ (**d**), 4-$EtOC_6H_4NH$ (**e**), 4-$Me_2NC_6H_4NH$ (**f**).

^{1}H NMR spectra of **IX**–**XII** in DMSO-d_6 lacked signal from the COOH proton, which was present in the spectra of initial acids **IV**–**VII** at δ 12.9–13.2 ppm. The spectra of both **IX**–**XII** and **IV**–**VII** contained a two-proton singlet at 4.3–4.5 ppm from the methylene protons in the dihydropyrrole ring and two broadened one-proton singlets at δ 8.0–9.0 ppm due to protons of the amino group; magnetic nonequivalence of the latter results from restricted rotation about the C–N bond [7, 8]. In addition, compounds **IX**–**XII** showed in the spectra a two-proton singlet from the methylene group in the ester fragment at δ 5.7–5.8 ppm for phenacyl esters **IXa**, **XIa**, and **XIIa** or at δ 4.9–5.0 ppm for arylcarbamoylmethyl esters **IXb**, **IXc**, **Xc**, **Xd**, **XIe**, **XIIb**, and **XIIe**. Resonance signals from protons in the substituents R^1, R^2, and R^3, as well as in the aminobenzoic acid moiety were located in the expected regions.

Table 1. Yields, melting points, and elemental analyses of 3- and 4-(5-amino-4-hetaryl-3-oxo-2,3-dihydropyrrol-1-yl)benzoic acids **IV**–**VII** and esters **IX**–**XII**

Comp. no.	Yield, %	mp, °C	Found, %				Formula	Calculated, %			
			C	H	N	S		C	H	N	S
IV	74	>300	61.59	3.80	12.02	9.06	$C_{18}H_{13}N_3O_3S$	61.53	3.73	11.96	9.12
V	76	>300	61.52	3.75	11.99	9.11	$C_{18}H_{13}N_3O_3S$	61.53	3.73	11.96	9.12
VI	80	>300	58.29	3.49	10.18	7.86	$C_{20}H_{14}ClN_3O_3S$	58.32	3.43	10.20	7.78
VII	76	>300	58.30	3.41	10.23	7.82	$C_{20}H_{14}ClN_3O_3S$	58.32	3.43	10.20	7.78
IXa	86	>300	61.92	3.57	8.33	6.42	$C_{26}H_{18}ClN_3O_4S$	61.97	3.60	8.34	6.36
IXb	79	>300	62.98	4.36	10.95	6.29	$C_{27}H_{22}N_4O_5S$	63.02	4.31	10.89	6.23
IXc	75	>300	56.49	3.22	10.05	5.81	$C_{26}H_{18}Cl_2N_4O_4S$	56.43	3.28	10.12	5.79
Xc	81	233	56.42	3.31	10.09	5.71	$C_{26}H_{18}Cl_2N_4O_4S$	56.43	3.28	10.12	5.79
Xd	76	>300	57.20	3.51	9.94	11.28	$C_{27}H_{20}F_2N_4O_4S_2$	57.24	3.56	9.89	11.32
XIa	84	>300	59.55	3.42	7.49	5.74	$C_{28}H_{19}Cl_2N_3O_4S$	59.58	3.39	7.44	5.68
XIf	82	>300	61.22	4.45	11.98	5.39	$C_{30}H_{26}ClN_5O_4S$	61.27	4.46	11.91	5.45
XIIa	89	>300	59.61	3.46	7.38	5.69	$C_{28}H_{19}Cl_2N_3O_4S$	59.58	3.39	7.44	5.68
XIIb	75	293	60.62	3.98	9.71	5.54	$C_{29}H_{23}ClN_4O_5S$	60.57	4.03	9.74	5.58
XIIe	76	>300	61.13	4.31	9.56	5.39	$C_{30}H_{25}ClN_4O_5S$	61.17	4.28	9.51	5.44

Table 2. ^{1}H NMR spectra of 3- and 4-(5-amino-4-hetaryl-3-oxo-2,3-dihydropyrrol-1-yl)benzoic acids **IV**–**VII** and esters **IX**–**XII**

Comp. no.	Chemical shifts δ,[a] ppm (*J*, Hz)
IV	4.42 s (2H, NCH_2CO), 7.26 t (1H, R^1R^2, *J* = 7.8), 7.41 t (1H, R^1R^2, *J* = 7.8), 7.61 d (2H, H_a, *J* = 8.4), 7.81 d (1H, RR^1, *J* = 7.8), 7.97 d (1H, R^1R^2, *J* = 7.8), 8.05 d (2H, H_a, *J* = 8.4), 8.53 s (1H, NH_2), 8.98 s (1H, NH_2), 12.94 s (1H, COOH)
V	4.38 s (2H, NCH_2CO), 7.25 t (1H, R^1R^2, *J* = 7.8), 7.40 t (1H, R^1R^2, *J* = 7.8), 7.65 t (1H, H_a, *J* = 7.5), 7.78 m (2H, H_a), 7.91 d (1H, R^1R^2, *J* = 7.8), 7.96 d (1H, R^1R^2, *J* = 7.8), 8.03 s (1H, H_a), 8.40 s (1H, NH_2), 8.83 s (1H, NH_2), 13.01 s (1H, COOH)
VI	4.41 s (2H, NCH_2CO), 7.51 d (2H, R^1, *J* = 8.4), 7.61 d (2H, H_a, *J* = 8.8), 7.82 s (1H, R^2), 7.99 d (2H, R, *J* = 8.4), 8.04 d (2H, H_a, *J* = 8.8), 8.46 s (1H, NH_2), 8.78 s (1H, NH_2), 13.10 s (1H, COOH)
VII	4.37 s (2H, NCH_2CO), 7.49 d (2H, R^1, *J* = 8.8), 7.63 t (1H, H_a, *J* = 7.6), 7.74 d (1H, H_a, *J* = 7.6), 7.79 s (1H, R^2), 7.88 d (1H, H_a, *J* = 7.6), 7.99 d (2H, R^1, *J* = 8.8), 8.02 s (1H, H_a), 8.30 s (1H, NH_2), 8.60 s (1H, NH_2), 13.19 s (1H, COOH)
IXa	4.50 s (2H, NCH_2CO), 5.60 s (2H, OCH_2CO), 7.30 t (1H, R^1R^2, *J* = 8.0), 7.46 t (1H, R^1R^2, *J* = 8.0), 7.71 m (4H, H_a, R^3), 7.86 d (1H, R^1R^2, *J* = 8.0), 8.01 d (1H, R^1R^2, *J* = 8.0), 8.07 d (2H, H_a, *J* = 8.4), 8.19 d (2H, R^3, *J* = 8.4), 8.67 s (1H, NH_2), 9.07 s (1H, NH_2)
IXb	3.72 s (3H, OCH_3), 4.45 s (2H, NCH_2CO), 4.96 s (2H, OCH_2CO), 6.66 d (1H, 4-H in R^3, *J* = 9.2), 7.12 d (1H, 6-H in R^3, *J* = 9.2), 7.23 t (1H, R^1R^2, *J* = 8.0), 7.27 m (2H, 2-H, 5-H in R^3), 7.41 t (1H, R^1R^2, *J* = 8.0), 7.67 d (2H, H_a, *J* = 8.8), 7.82 d (1H, R^1R^2, *J* = 8.0), 7.98 d (1H, R^1R^2, *J* = 8.0), 8.13 d (2H, H_a, *J* = 8.8), 8.61 s (1H, NH_2), 9.04 s (1H, NH_2), 10.20 s (1H, CONH)
IXc	4.49 s (2H, NCH_2CO), 5.00 s (2H, OCH_2CO), 7.30 t (1H, R^1R^2, *J* = 8.0), 7.45 t (1H, R^1R^2, *J* = 8.0), 7.53 d.d (1H, 6-H in R^3, *J* = 9.2, 2.4), 7.63 d (1H, 5-H in R^3, *J* = 9.2), 7.71 d (2H, H_a, *J* = 8.8), 7.86 d (1H, R^1R^2, *J* = 8.0), 8.00 m (2H, R^1R^2, 2-H in R^3), 8.17 d (2H, H_a, *J* = 8.8), 8.66 s (1H, NH_2), 9.08 s (1H, NH_2), 10.60 s (1H, CONH)
Xc	4.41 s (2H, NCH_2CO), 5.00 s (2H, OCH_2CO), 7.24 t (1H, R^1R^2, *J* = 7.2), 7.41 t (1H, R^1R^2, *J* = 7.2), 7.49 d.d (1H, 6-H in R^3, *J* = 8.8, 2.0), 7.60 d (1H, 5-H in R^3, *J* = 8.8), 7.72 t (1H, H_a, *J* = 8.0), 7.82 m (2H, H_a), 7.98 m (3H, R^1R^2, 2-H in R^3), 8.13 s (1H, H_a), 8.51 s (1H, NH_2), 8.88 s (1H, NH_2), 10.56 s (1H, CONH)
Xd	4.40 s (2H, NCH_2CO), 5.01 s (2H, OCH_2CO), 7.25 t (1H, R^1R^2, *J* = 7.6), 7.41 t (1H, R^1R^2, *J* = 7.6), 7.42 t (1H, CHF_2, *J* = 54.8), 7.55 d (2H, R^3, *J* = 8.0), 7.68 m (3H, R^3, H_a,), 7.81 d (1H, H_a, *J* = 8.0), 7.84 d (1H, H_a, *J* = 8.0), 7.97 d (1H, R^1R^2, *J* = 7.6), 8.00 d (1H, R^1R^2, *J* = 7.6), 8.13 s (1H, H_a), 8.50 s (1H, NH_2), 8.88 s (1H, NH_2), 10.49 s (1H, CONH)
XIa	4.45 s (2H, NCH_2CO), 5.55 s (2H, OCH_2CO), 7.51 d (2H, R^1, *J* = 8.4), 7.67 m (4H, H_a, R^3), 7.83 s (1H, R^2), 8.00 d (2H, R^1, *J* = 8.4), 8.05 d (2H, H_a, *J* = 8.4), 8.12 d (2H, R^3, *J* = 8.8), 8.62 s (1H, NH_2), 8.78 s (1H, NH_2)
XIf	2.87 s (6H, NMe_2), 4.44 s (2H, NCH_2CO), 4.90 s (2H, OCH_2CO), 6.74 d (2H, R^3, *J* = 8.3), 7.44 d (2H, R^3, *J* = 8.3), 7.55 d (2H, R^1, *J* = 8.4), 7.76 d (2H, H_a, *J* = 8.8), 7.87 s (1H, R^2), 8.00 d (2H, R^1, *J* = 8.4), 8.13 d (2H, H_a, *J* = 8.8), 8.55 s (1H, NH_2), 8.79 s (1H, NH_2), 9.96 s (1H, CONH)
XIIa	4.39 s (2H, NCH_2CO), 5.79 s (2H, OCH_2CO), 7.49 d (2H, R^1, *J* = 8.4), 7.68 d (2H, R^3, *J* = 8.4), 7.71 t (1H, H_a, *J* = 8.0), 7.79 s (1H, R^2), 7.83 d (1H, H_a, *J* = 8.0), 7.99 m (3H, R^1, H_a), 8.05 d (2H, R^3, *J* = 8.4), 8.11 s (1H, H_a), 8.40 s (1H, NH_2), 8.60 s (1H, NH_2)
XIIb	3.73 s (3H, OCH_3), 4.39 s (2H, NCH_2CO), 4.96 s (2H, OCH_2CO), 6.66 d.d (1H, 4-H in R^3, *J* = 8.2, 2.4), 7.11 d.d (1H, 6-H in R^3, *J* = 8.2, 2.4), 7.23 t (1H, 5-H in R^3, *J* = 8.2), 7.30 t (1H, 2-H in R^3, *J* = 2.4), 7.49 d (2H, R^1, *J* = 8.8), 7.70 t (1H, H_a, *J* = 7.8), 7.79 s (1H, R^2), 7.82 d (1H, H_a, *J* = 7.8), 7.98 m (3H, R^1, H_a), 8.12 s (1H, H_a), 8.38 s (1H, NH_2), 8.62 s (1H, NH_2), 10.24 s (1H, CONH)
XIIe	1.31 t (3H, Et, *J* = 5.8), 3.98 q (2H, Et, *J* = 5.8), 4.38 s (2H, NCH_2CO), 4.93 s (2H, OCH_2CO), 6.87 d (2H, R^3, *J* = 8.0), 7.48 m (4H, R^3, R^1), 7.69 t (1H, H_a, *J* = 6.8), 7.82 m (2H, H_a, R^2), 7.98 m (3H, R^1, H_a), 8.12 s (1H, H_a), 8.43 s (1H, NH_2), 8.55 s (1H, NH_2), 10.04 s (1H, CONH)

[a] The notation H_a refers to aromatic protons of the aminobenzoic acid moiety.

In the IR spectra of **IX**–**XII** we observed a strong band at 1700–1740 cm^{-1}, belonging to stretching vibrations of the ester carbonyl group, and two bands at 3150 and 3300 cm^{-1} due to stretching vibrations of the primary amino group. A strong carbonyl absorption band of the COR^3 fragment was located at 1680–1700 cm^{-1} for 4-chlorophenacyl esters **IXa**, **XIa**, and **XIIa** and at 1660–1670 cm^{-1} for carbamoyl derivatives **IXb**, **IXc**, **Xc**, **Xd**, **XIe**, **XIIb**, and **XIIe**. The above spectral data are in full agreement with the proposed structures of compounds **IX**–**XII**; their elemental compositions were also consistent with the calculated values.

Thus, due to reduced reactivity of the amino group in the dihydropyrrole fragment, the alkylation of 3- and 4-(5-amino-4-hetaryl-3-oxo-2,3-dihydropyrrol-1-yl)benzoic acids **IV**–**VII** involves the carboxy group with high selectivity. This reaction may be regarded as a convenient preparative route to phenacyl and arylcarbamoylmethyl aminopyrrolylbenzoates **IX**–**XII** which are structural analogs of known antitumor agents.

EXPERIMENTAL

The IR spectra were recorded on a Pye Unicam SP 3-300 spectrometer from samples pelleted with KBr. The ^1H NMR spectra were recorded on a Varian VXR-300 instrument (300 MHz) from solutions in DMSO-d_6. Chlorobutyronitriles **II** and **III** [3, 13], 4-chlorophenacyl bromide (**VIIIa**) [15], and chloroacetanilides **VIIIb**–**VIIIf** [16] were synthesized by known methods. Dimethylformamide was kept for 24 h over P_2O_5 and distilled under reduced pressure. Aminobenzoic acids and triethylamine were commercial products which were used without additional purification.

3- and 4-(5-Amino-4-hetaryl-3-oxo-2,3-dihydropyrrol-1-yl)benzoic acids IV–VII. 3- or 4-Aminobenzoic acid, 2.74 g (0.02 mol), was added to a solution of 0.01 mol of nitrile **II** or **III** in 10 ml of DMF, and the resulting solution was heated for 2 h on a boiling water bath. The mixture was cooled, and the precipitate was filtered off and recrystallized from DMF. The yields and analytical data of acids **IV**–**VII** are given in Table 1, and their spectral data are collected in Table 2.

4-Chlorophenacyl and arylcarbamoylmethyl 3- and 4-(5-amino-4-hetaryl-3-oxo-2,3-dihydropyrrol-1-yl)benzoates (IX–XII). To a solution of 2 mmol of acid **IV**–**VII** and 0.3 ml (2.2 mmol) of triethylamine in 5 ml of DMF we added 0.47 g (2 mmol) of 4-chlorophenacyl bromide (**VIIIa**) or 2 mmol of chloroacetanilide **VIIIb**–**VIIIf**, and the mixture was heated for 3 h at 110–120°C. It was then cooled and poured into 10 ml of water, and the precipitate was filtered off and recrystallized from DMF (**IXa**, **XIa**, **XIIa**) or acetic acid (**IXb**, **IXc**, **Xc**, **Xd**, **XIe**, **XIIb**, and **XIIe**). The yields and analytical and spectral data of esters **IX**–**XII** are given in Tables 1 and 2.

This study was performed under financial support by *NVP Enamin* Ltd.

REFERENCES

1. Babichev, F.S. and Volovenko, Yu.M., *Khim. Geterotsikl. Soedin*., 1977, no. 4, p. 557.
2. Volovenko, Yu.M., Gofman, L.V., and Babichev, F.S., *Ukr. Khim. Zh*., 1979, vol. 45, p. 857.
3. Volovenko, Yu.M., Shokol, T.V., Merkulov, A.S., and Babichev, F.S., *Ukr. Khim. Zh*., 1993, vol. 59, p. 55.
4. Tverdokhlebov, A.V., Volovenko, Yu.M., and Shokol, T.V., *Khim. Geterotsikl. Soedin*., 1998, no. 1, p. 50.
5. Resnyanskaya, E.V., Shokol, T.V., Volovenko, Yu.M., and Tverdokhlebov, A.V., *Khim. Geterotsikl. Soedin*., 1999, no. 10, p. 1412.
6. Volovenko, Yu.M., Volovnenko, T.A., Tverdokhlebov, A.V., and Ryabokon', I.G., *Russ. J. Org. Chem*., 2001, vol. 37, p. 1323.
7. Volovenko, Yu.M., Tverdokhlebov, A.V., Gorulya, A.P., Shishkina, S.V., Zubatyuk, R.I., and Shishkin, O.V., *Eur. J. Org. Chem*., 2002, p. 663.
8. Resnyanskaya, E.V., Tverdokhlebov, A.V., Volovenko, Yu.M., Shishkin, O.V., and Zubatyuk, R.I., *Synthesis*, 2002, p. 2717.
9. Gola, A., Samartzi, E., Bardakos, V., Petroliagi, M., Igglessi-Markopoulou, O., Markopoulos, J., and Barkley, J.V., *J. Heterocycl. Chem*., 2000, vol. 37, p. 681.
10. Missbach, M., PCT Int. Appl. WO 9 610 028, 1996; *Chem. Abstr*., 1996, vol. 125, no. 86670.
11. Aso, K., Hitaka, T., Yukishige, K., Ootsu, K., and Akimoto, H., *Chem. Pharm. Bull*., 1995, vol. 43, p. 256.
12. Akimoto, H., Hitaka, T., and Miwa, T., Eur. Pat. Appl. EP 400 562, 1990; *Chem. Abstr*., 1991, vol. 115, no. 29914.
13. Volovenko, Yu.M., Volovnenko, T.A., and Tverdokhlebov, A.V., *Khim. Geterotsikl. Soedin*., 2001, no. 8, p. 1101.
14. Shriner, R.L., Fuson, R.C., Curtin, D.Y., and Morrill, T.C., *The Systematic Identification of Organic Compounds. A Laboratory Manual*, New York: Wiley, 1978. Translated under the title *Analiz organicheskikh soedinenii*, Moscow: Mir, 1983, p. 311.
15. Ward, C.E., *J. Chem. Soc*., 1923, vol. 123, p. 2211.
16. Balls, A.K. and Kohler, F., *Chem. Ber*., 1931, vol. 64, p. 34.