Reaction of 2-Chloromethyl-5-hydroxy-4*H*-pyran-4-one with Secondary Amines

[a]M. KONOPÍKOVÁ, [b]J. BRANSOVÁ, [a]M. UHER, [c]T. LIPTAJ, and [a]O. RAJNIAKOVÁ

[a]*Department of Organic Chemistry, Faculty of Chemical Technology, Slovak Technical University, SK-812 37 Bratislava*

[b]*Institute of Experimental Endocrinology, Slovak Academy of Sciences, SK-833 06 Bratislava*

[c]*Central Laboratories, Slovak Technical University, SK-812 37 Bratislava*

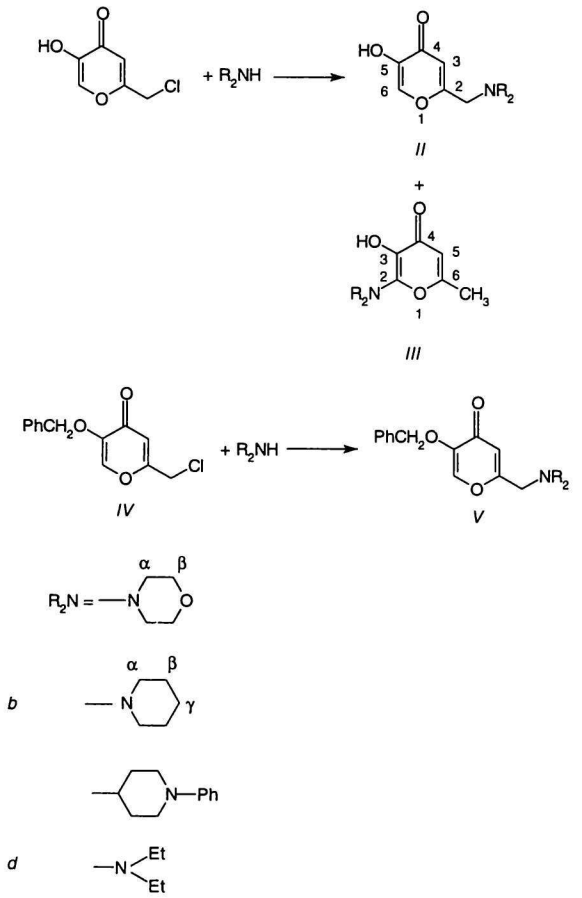
Received 16 June 1993

In this contribution there is described the reaction of 2-chloromethyl-5-hydroxy-4*H*-pyran-4-one with secondary amines. Apart from the products of nucleophilic substitution, *e.g.* 2-aminomethyl derivatives of kojic acid and also 2-amino-6-methyl derivatives of the same compound were obtained. In the case when hydroxylic group in the position 5 was substituted, the result of the reaction was only 2-aminomethyl derivative.

The great attention was paid to the study of 2-hydroxymethyl-5-hydroxy-4*H*-pyran-4-one (kojic acid) and its derivatives. The interest was focused on the synthesis of various substituted amino derivatives of kojic acid with the presumption that the introduction of amino group into the skeleton of kojic acid would increase the biological activity of these derivatives. *Atkinson et al.* [1] described the preparation of kojic acid amino derivatives as analogues of γ-aminobutanoic acid *via* reduction of 2-azidomethyl-5-hydroxy-4*H*-pyran-4-one by HBr in the mixture of phenol and acetic acid. The synthesis of a number of analogous amino derivatives (methylamino, benzylamino) was described as well. *Woods* [2] and *Ichimoto* [3] focused their attention on the preparation of kojic acid amino derivatives *via* the reaction of kojic acid with formaldehyde and various amines. Mannich reaction takes place exclusively in the position 6 of the pyranone skeleton, which is activated for the electrophilic substitution by a free hydroxylic group in the position 5. 5-Methoxy-2-hydroxymethyl-4*H*-pyran-4-one does not take part in the above-mentioned reaction, which proves that position 6 is activated for electrophilic substitution by unsubstituted hydroxylic group in the position 5 only.

Analogous results were obtained by *O'Brien et al.* [4] in the synthesis of Mannich bases of kojic acid with various amines, *e.g.* dimethylamine, diethylamine, laurylamine, stearylamine, pyrrolidine, morpholine, piperidine. In the case when position 6 was substituted the reaction did not take place. The same situation occurred if the starting product was kojic acid substituted in the position 5 while 2-chloromethyl-5-hydroxy-4*H*-pyran-4-one resulted in the presumed products of Mannich reaction. The analogous amino derivatives were prepared by the reaction of kojic acid with Schiff bases [5]. Presumption concerning the effect of the hydroxylic group on the electrophilic substitution in the position 6 was confirmed by experimental results. *Decker* [6] described the reaction of 2-chloromethyl-5-hydroxy-4*H*-pyran-4-one with dimethylamine. This reaction yielded 2-dimethylaminomethyl-5-hydroxy-4*H*-pyran-4-one as a product of nucleophilic substitution. The presence of 2-dimethylaminomethyl-3-hydroxy-6-methyl-4*H*-pyran-4-one was confirmed in low yields as well. The second product is formed by the addition of an amine to the α,β-unsaturated ketone. This reaction is followed by HCl elimination and by rearrangement of hydrogen to the exocyclic methylene group. The same course of the reaction was described in the synthesis of 5-methyl-2-furancarboxylic acid using furfuryl chloride and the CN^- as starting materials [7, 8]. The reaction of 2-chloromethyl-5-methoxy-4*H*-pyran-4-one with dimethylamine in benzene was described by *Ettel* and *Hebký* [9].

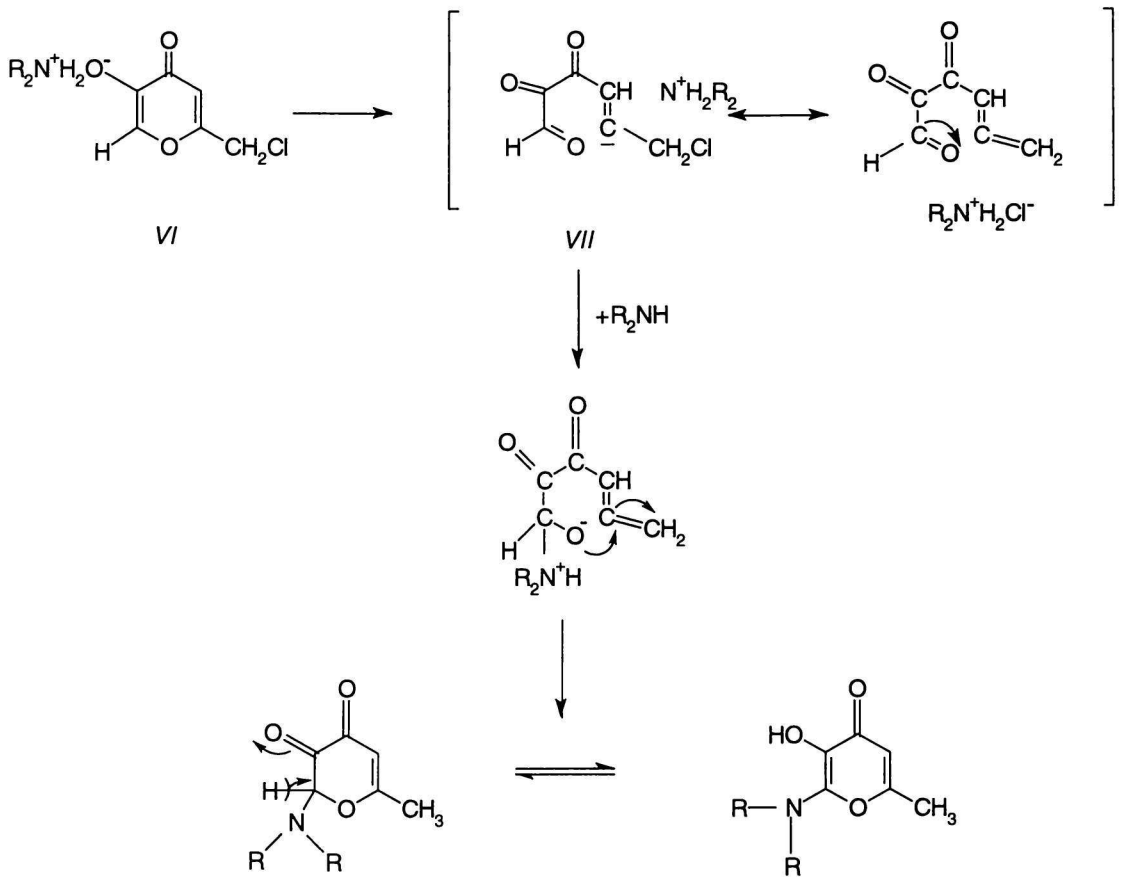
The aim of our study was the reaction of 2-chloromethyl-5-hydroxy-4*H*-pyran-4-one (Scheme 1) with some secondary amines: diethylamine, morpholine, piperidine, *N*-phenylpiperazine. The reaction of kojic acid (*I*) with the above-mentioned amines yields the presumed products of nucleophilic substitution, *e.g.* 2-aminomethyl-5-hydroxy-4*H*-pyran-4-ones (*II*) and 2-amino-3-hydroxy-6-methyl-4*H*-pyran-



Scheme 1

4-ones (*III*) as well. The structure of the prepared products was confirmed by ^{1}H NMR spectra. So ^{1}H NMR spectrum of 2-morpholinomethyl-5-hydroxy-4*H*-pyran-4-one (*IIa*) displays signals at $\delta = 2.53$ and 3.74 which correspond to the methylene protons of morpholine ring; signals at $\delta = 3.41$ are proper to the methylene group in the position 2 of the γ-pyranone ring and signals at $\delta = 6.54$ and 7.85 are assigned to the protons H-3 and H-6. ^{1}H NMR spectrum of the by-product 2-morpholino-3-hydroxy-6-methyl-4*H*-pyran-4-one (*IIIa*) displays not only signals of morpholine proton shifted to the higher values but also a singlet at $\delta = 2.2$ assigned to the methyl group. In the spectrum there is no evidence for the signal of methylene group attached to the nitrogen atom and for a singlet of the proton assigned to the —CH— group of γ-pyranone skeleton at higher values, which proves substitution in this position. There is a concordance of presumed structures with standard, APT [10] and ^{13}C NMR spectra which prove for the structure of *IIa* the presence of methylene group in the position 2 of the 4*H*-pyran-4-one skeleton ($\delta = 60.2$) and methine carbon atoms C-3 and C-6 ($\delta = 112.2$ resp. 138.4). There is no signal of methylene group in the position 2 for product *IIIa* confirmed, but there are present signals for the methyl group ($\delta = 19.4$) and methine carbon atom in the position 5 ($\delta = 109.9$). Signal of the quaternary carbon atom C-2 occurs at the higher frequency compared with the signal of the quaternary atom C-6 ($\delta = 159.1$ resp. 150.3) which is the evidence of the bond to the electronegative nitrogen atom. Reaction of dimethylamine, morpholine, and piperidine with 5-benzyloxy-2-chloromethyl-4*H*-pyran-4-one (*IV*) yields only 2-aminomethyl-5-benzyloxy-4*H*-pyran-4-ones (*V*). Presence of another product was not observed, not even confirmed by ^{1}H NMR spectroscopy, nor in the crude reaction mixture. Structure of the obtained products was confirmed equally as with the previous compounds *II*.

On the basis of our experimental results we can state that the reaction of 2-chloromethyl-5-hydroxy-4*H*-pyran-4-one with secondary amines yields two products: 2-aminomethyl-5-hydroxy-4*H*-pyran-4-ones (*II*) and 2-amino-3-hydroxy-6-methyl-4*H*-pyran-4-ones (*III*). Reaction of 5-benzyloxy-2-chloromethyl-4*H*-pyran-4-ones (*IV*) with secondary amines results into product of the nucleophilic substitution *V* In comparison with the results obtained by *Decker* [6] the fact that products *III* were obtained in greater yields than products *II* (which is in contrast with the results of the above-mentioned work) is surprising. Exclusive formation of products *V* as well as recent knowledge concerning electrophilic substitution in the position 6 of the compound *II* (which cannot be attacked by nucleophile) makes us suppose that the course of this reaction is different from that indicated by Decker. This is confirmed by the well known fact that carbonyl group of compound *I* does not participate in any reaction. Decker does not take into account the fact that the hydroxylic group situated in the position 5 of compound *I* has a phenolic character, *e.g.* an acidic hydrogen atom which in the presence of a threefold molar amount of the secondary amine produces quaternary ammonium salt. The formation of the greater amount of the product can be explained by the formation of the reaction centre in the position 6. The nucleophilic substitution takes place in this position preferably with the amine in comparison with a halo derivative. It is caused by greater nucleophilicity of an amine when compared with the halo derivative. This presumption is confirmed by the fact that in the case of substituted pyranone *IV* yields only product of normal substitution. This difference may be explicated by protection of the hydroxylic group in the position 5 by the benzyl radical and hence the resulting impossibility of the ammonium salt formation. As a consequence the potential centre for nucleophilic substitution cannot be created. Regarding our previous results, unfavourable steric effects on the course of this reaction can be eliminated as concerns the reaction of 2-hydroxymethyl-5-benzyloxy-4*H*-pyran-4-one with Schiff bases [5] (they are considerably bulkier than secondary amines). If



Scheme 2

the course of the reaction were the same as it was proposed by Decker, 2-amino-3-benzyloxy-6-methyl-4*H*-pyran-4-one would be formed as well. We did not observe formation of such a product in any case. The mechanism of the followed reaction was typical – nucleophilic substitution of the halo derivative. With regard to our presumption and facts we have discovered we propose another mechanism of this reaction which is consistent with the obtained experimental results and generally known information concerning 2-hydroxymethyl-5-hydroxy-4*H*-pyran-4-one and its reaction as well (Scheme 2). In the first stage of the reaction probably ammonium salt of *VI* is formed as a result of the reaction of compound *I* with amine. In the next stage the pyranone cycle is opened and the unstable aldehyde *VII*, or ammonium salt is formed. This is followed by a nucleophilic addition of the secondary amine. Cyclization and rearrangement of proton to the exocyclic double bond results in the oxo form of the product. The reaction is followed by the rearrangement of the proton and originating of the stable enol form of the product *II*.

Chronology or parallelism of some stages of this proposed mechanism is difficult to assign. This mechanism unambiguously explicates contradiction in the course of the reaction of 5-unsubstituted and substituted 2-chloromethyl-4*H*-pyran-4-one and is in accordance with our experimental results and is not in contradiction with known facts concerning the reactions of these derivatives.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage. ^{1}H NMR spectra of hexadeuterodimethyl sulfoxide solutions containing tetramethylsilane as an internal standard were recorded with Tesla BS 487 and Varian VXR 300 spectrometers; ^{13}C NMR spectra were taken with Varian VXR 300 spectrometer.

2-(R_2-Aminomethyl)-5-hydroxy-4*H*-pyran-4-ones (*IIa*—*IId*) and 2-(R_2-Amino)-3-hydroxy-6-methyl-4*H*-pyran-4-ones (*IIIa*—*IIId*)

To the solution of 2-chloromethyl-5-hydroxy-4*H*-pyran-4-one (1.6 g; 0.01 mol) in anhydrous dioxane (25 cm^3) the solution of corresponding amine (0.03 mol) in anhydrous dioxane (10 cm^3) was added in

such a way that temperature of the reaction did not exceed 40 °C. Stirring of the reaction mixture continued at room temperature for further 24 h. The separated aminium chloride was filtered off, the rest was solved in water (10 cm^3). This solution was acidified by 4 M hydrochloric acid (1.75 cm^3) and extracted with chloroform (5 × 10 cm^3). Organic layers were dried with sodium sulfate, chloroform was evaporated *in vacuo* and 2-(R_2-amino)-3-hydroxy-6-methyl-4*H*-pyran-4-ones (*IIIa—IIId*) were isolated.

Water layer was neutralized with 4 M solution of NaOH (1.15 cm^3) and extracted with chloroform. The chloroform extracts were dried, chloroform was evaporated *in vacuo* and the rest yielded 2-(R_2-aminomethyl)-5-hydroxy-4*H*-pyran-4-ones (*IIa—IId*).

2-Morpholinomethyl-5-hydroxy-4*H*-pyran-4-one (*IIa*)

For $C_{10}H_{13}NO_4$ (M_r = 211.2) m.p. = 129—131 °C, yield 12 %, w_i(calc.): 56.86 % C, 6.15 % H, 6.63 % N; w_i(found): 56.68 % C, 6.02 % H, 6.40 % N. ^{1}H NMR spectrum, δ: 2.5 (t, 4H, 2×CH_2-α), 3.7 (t, 4H, 2×CH_2-β), 3.4 (s, 2H, CH_2—N), 6.5 (s, 1H, H-3), 7.8 (s, 1H, H-6). ^{13}C NMR spectrum, δ: 53.7 (t, 2×C-α), 60.2 (t, C—N), 67.0 (t, 2×C-β), 112.2 (d, C-3), 138.4 (d, C-6), 146.0 (s, C-5), 166.8 (s, C-2), 174.4 (s, C-4).

2-Morpholino-3-hydroxy-6-methyl-4*H*-pyran-4-one (*IIIa*)

For $C_{10}H_{13}NO_4$ (M_r = 211.2) m.p. = 102—105 °C), yield 24 %, w_i(calc.): 56.86 % C, 6.15 % H, 6.63 % N; w_i(found): 56.70 % C, 5.98 % H, 6.45 % N. ^{1}H NMR spectrum, δ: 2.2 (s, 3H, CH_3), 3.5 (t, 4H, 2×CH_2-α), 3.8 (t, 4H, 2×CH_2-β), 6.1 (s, 1H, H-5). ^{13}C NMR spectrum, δ: 19.4 (q, CH_3), 46.6 (t, 2×C-α), 66.6 (t, 2×C-β), 109.9 (d, C-5), 128.0 (s, C-3), 150.3 (s, C-6), 159.1 (s, C-2), 173.3 (s, C-4).

2-Piperidinomethyl-5-hydroxy-4*H*-pyran-4-one (*IIb*)

For $C_{11}H_{15}NO_3$ (M_r = 209.3) m.p. = 112—115 °C, yield 17 %, w_i(calc.): 65.08 % C, 7.39 % H, 6.69 % N; w_i(found): 65.01 % C, 7.25 % H, 6.58 % N. ^{1}H NMR spectrum, δ: 1.4 (m, 2H, CH_2-γ), 1.6 (m, 4H, 2×CH_2-β), 2.4 (m, 4H, 2×CH_2-α), 3.3 (s, 2H, CH_2—N), 6.5 (s, 1H, H-3), 7.8 (s, 1H, H-6). ^{13}C NMR spectrum, δ: 23.9 (t, C-γ), 25.8 (t, 2×C-β), 54.6 (t, 2×C-α), 60.4 (t, C—N), 112.0 (d, C-3), 138.2 (d, C-6), 145.8 (s, C-5), 166.6 (s, C-2), 174.3 (s, C-4).

2-Piperidinomethyl-3-hydroxy-6-methyl-4*H*-pyran-4-one (*IIIb*)

For $C_{11}H_{15}NO_3$ (M_r = 209.3) m.p. = 98—101 °C, yield 38 %, w_i(calc.): 65.08 % C, 7.39 % H, 6.69 % N; w_i(found): 64.96 % C, 7.15 % H, 6.75 % N. ^{1}H NMR spectrum, δ: 1.66 (m, 6H, CH_2-γ and 2×CH_2-β), 2.2 (s, 3H, CH_3), 3.5 (m, 4H, 2×CH_2-α), 6.1 (s, 1H, H-5). ^{13}C NMR spectrum, δ: 19.4 (q, CH_3), 24.4 (t, C-γ), 25.83 (t, 2×C-β), 47.5 (t, 2×C-α), 109.2 (d, C-5), 127.3 (s, C-3), 151.1 (s, C-6—H), 158.8 (s, C-2), 172.7 (s, C-4).

2-(4-Phenyl-1-piperazinylmethyl)-5-hydroxy-4*H*-pyran-4-one (*IIc*)

For $C_{16}H_{18}N_2O_3$ (M_r = 286.3) m.p. = 173—176 °C, yield 21 %, w_i(calc.): 67.06 % C, 6.29 % H, 9.78 % N; w_i(found): 66.95 % C, 6.18 % H, 9.59 % N. ^{1}H NMR spectrum, δ: 2.9, 3.2 (m, 8H, 4×CH_2), 3.5 (s, 2H, CH_2—N), 6.5 (s, 1H, H-3), 6.9—7.2 (m, 5H, H_{arom}), 7.8 (s, 1H, H-6). ^{13}C NMR spectrum, δ: 49.1, 53.2 (2t, 4×CH_2), 59.6 (t, CH_2—N), 111.9 (d, C-3), 116.2, 120.0, 129.1 (C_{arom}), 138.0 (d, C-6), 145.7 (s, C-5), 151.05 (s, C_{arom}—N), 165.8 (s, C-2), 174.1 (s, C-4).

2-Diethylaminomethyl-5-hydroxy-4*H*-pyran-4-one (*IId*)

For $C_{10}H_{15}NO_3$ (M_r = 197.2) m.p. = 123—126 °C, yield 9 %, w_i(calc.): 60.90 % C, 7.61 % H, 7.10 % N; w_i(found): 60.48 % C, 7.52 % H, 7.01 % N. ^{1}H NMR spectrum, δ: 1.1 (t, 6H, 2×CH_3), 2.6 (q, 4H, 2×CH_2), 3.4 (s, 2H, CH_2—N), 6.5 (s, 1H, H-3), 7.7 (s, 1H, H-6). ^{13}C NMR spectrum, δ: 11.8 (q, 2×CH_3), 47.5 (t, 2×CH_2CH_3), 54.3 (t, CH_2N), 144.9 (s, C-5), 137.7 (d, C-6), 115.3 (d, C-3).

2-Diethylaminomethyl-3-hydroxy-6-methyl-4*H*-pyran-4-one (*IIId*)

For $C_{10}H_{15}NO_3$ (M_r = 197.2) m.p. = 113—116 °C, yield 18 %, w_i(calc.): 60.90 % C, 7.61 % H, 7.10 % N; w_i(found): 60.65 % C, 7.48 % H, 6.98 % N. ^{1}H NMR spectrum, δ: 1.2 (t, 6H, 2×CH_3), 2.2 (s, 3H, CH_3), 3.5 (q, 4H, CH_2), 6.1 (s, 1H, H-5).

2-Morpholinomethyl-5-benzyloxy-4*H*-pyran-4-one (*Va*)

For $C_{17}H_{19}NO_4$ (M_r = 301.3) m.p. = 79—82 °C, yield 16 %, w_i(calc.): 67.74 % C, 6.13 % H, 4.65 % N; w_i(found): 67.58 % C, 6.15 % H, 4.48 % N. ^{1}H NMR spectrum, δ: 2.5 (m, 4H, CH_2-α), 3.3 (s, 2H, CH_2—N), 3.7 (m, 4H, CH_2-β), 5.1 (s, 2H, OCH_2), 6.5 (s, 1H, H-3), 7.3—7.4 (m, 5H, H_{arom}), 7.5 (s, 1H, H-6). ^{13}C NMR spectrum, δ: 53.5 (t, CH_2-α), 59.6 (t, CH_2—N), 66.7 (CH_2-β), 71.9 (t, OCH_2), 114.9 (d, C-3), 127.8, 128.4, 128.7 (C_{arom}), 141.7 (d, C-6), 147.1 (s, C-5), 164.0 (s, C-2), 174.6 (s, C-4).

2-Piperidinomethyl-5-methyl-5-benzyloxy-4*H*-pyran-4-one (*Vb*)

For $C_{18}H_{21}NO_3$ (M_r = 299.3) m.p. = 92—93 °C, yield 22 %, w_i(calc.): 72.17 % C, 7.02 % H, 4.68 % N; w_i(found): 72.05 % C, 6.98 % H, 4.55 % N. ^{1}H NMR spectrum, δ: 1.4 (m, 2H, CH_2-γ), 1.6 (m, 4H, 2×CH_2-β), 2.4 (m, 4H, 2×CH_2-α), 3.3 (s, 2H, CH_2—N), 5.1 (s, 2H, OCH_2), 6.4 (s, 1H, H-3), 7.3—7.4 (m, 5H, H_{arom}), 7.5 (s, 1H, H-6). ^{13}C NMR spectrum, δ: 23.9 (t, CH_2-γ), 25.8 (t, CH_2-β), 54.6 (t, CH_2-α), 60.2 (t, CH_2—N), 71.8 (t, OCH_2), 114.8 (d, C-3), 128.3, 128.6, 127.8, 135.8 (C_{arom}), 141.6 (d, C-6), 147.0 (s, C-5), 164.9 (s, C-2), 174.7 (s, C-4).

2-Diethylaminomethyl-5-benzyloxy-4*H*-pyran-4-one (*Vd*)

For $C_{17}H_{21}NO_3$ (M_r = 287.3) m.p. = 104—106 °C, yield 15 %, w_i(calc.): 71.04 % C, 7.31 % H, 4.87 % N; w_i(found): 70.92 % C, 7.19 % H, 4.68 % N. ^{1}H NMR spectrum, δ: 1.7—1.9 (2t, 6H, 2×CH_3), 2.4—2.7 (2q, 4H, 2×CH_2), 4.9 (s, 2H, CH_2—N), 6.7 (s, 2H, OCH_2), 6.4 (s, 1H, H-3), 7.3 (m, 5H, H_{arom}), 7.4 (s, 1H, H-6).

REFERENCES

1. Atkinson, J. G., Girard, Y., Rokach, J., and Rooney, C. S., *J. Med. Chem. 22,* 99 (1979).
2. Woods, L. L., *J. Am. Chem. Soc. 68,* 2744 (1946).
3. Ichimoto, I., Ueda, H., and Tatsumi, Ch., *Arg. Biol. Chem. 29,* 94 (1965).
4. O'Brien, G., Peterson, J. M., and Meadow, J. R., *J. Org. Chem. 15,* 86 (1960).
5. Konopíková, M., Uher, M., Bransová, J., Mastihuba, V., and Hudecová, D., *Chem. Papers 48,* 182 (1994).
6. Decker, W. H., *Rec. Trav. Chim. Pays-Bas 91,* 1338 (1972).
7. Reichstein, T. and Zschoke, H., *Helv. Chim. Acta 15,* 250 (1932).
8. Novitskii, K. Yu., Gresl, Kh., and Yuriev, Yu. K., *Zh. Org. Khim. 1,* 539 (1965).
9. Ettel, V. and Hebký, J., *Collect. Czech. Chem. Commun. 15,* 356 (1950).
10. Patt, S. L. and Shoolery, J. N., *J. Magn. Reson. 46,* 435 (1982).

Translated by O. Rajniaková