STRUCTURES OF THE PRODUCTS OF AMINOALKYLATION OF 5- AND 7-HYDROXYFLAVONES

N. A. Tyukavkina, G. A. Kalabin,
V. V. Kononova, and D. F. Kushnarev

UDC 547.814.5:543.422.25

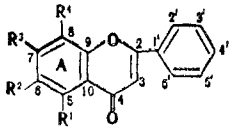
On the basis of the ^1H NMR spectra, it is shown that 7-hydroxyflavone is aminoalkylated in the 8 position, and it was established by ^{13}C NMR spectroscopy that the aminomethylation of 5-hydroxyflavone takes place in the 6 and 8 positions to give both monosubstitution and disubstitution products.

We have previously used the Mannich reaction to obtain biologically active water-soluble quercitin and dihydroquercitin derivatives [1]. Despite the large number of studies devoted to this problem [2-7], up until now there has been no rigorous proof for the structures of the products of substitution of polyhydroxyflavones. It has been shown by chemical methods [8-11] that the aminoalkylation of 7-hydroxy- and 7-methoxychromones and flavones takes place in the 8 position.

Biogenetically-induced 5,7-dihydroxy substitution of the A ring is characteristic for most natural flavonoids. These compounds can undergo the Mannich reaction through the labile hydrogen atoms in the 6 or 8 position. To determine the reactivities of these compounds we studied the structures of the aminoalkylated derivatives obtained from simple model 5- and 7-monohydroxyflavones.

A substitution product involving only the 8 position is formed in the condensation of 7-hydroxyflavone with formaldehyde and secondary amines (dimethylamine and diethylamine); this was established unambiguously from the ^1H NMR spectral data. Doublets with spin–spin coupling constants (SSCC) of 8.0 Hz [6.64 (C_6–H) and 7.81 ppm (C_5–H)] are observed in the ^1H NMR spectrum of I, and doublets with an SSCC of 8.2 Hz [6.60 (C_6–H) and 7.79 ppm (C_5–H)] are observed in the ^1H NMR spectrum of II, i.e., the SSCC attest to ortho orientation of the protons and consequently to attachment of the aminoalkyl group to the C_8 atom.

The aminomethylation of 5-hydroxyflavone (III), which we carried out for the first time in this research, gives two monosubstitution products (IV and V) and one disbustitution product (VI).



I–VI

I $R^1=R^2=H$, $R^3=OH$, $R^4=CH_2N(CH_3)_2$; II $R^1=R^2=H$, $R^3=OH$, $R^4=CH_2N(C_2H_5)_2$; III $R^1=OH$, $R^2=R^3=R^4=H$; IV $R^1=OH$, $R^2=R^3=H$, $R^4=CH_2N(CH_3)_2$; V $R^1=OH$, $R^2=CH_2N(CH_3)_2$, $R^3=R^4=H$; VI $R^1=OH$, $R^2=R^4=CH_2N(CH_3)_2$, $R^3=H$

The ^1H NMR spectra in the case of IV and V do not make it possible to unambiguously establish the position of the aminomethyl group. To solve this problem we used ^{13}C NMR spectroscopy. In our preceding communication we identified the C_6 and C_8 signals in the ^{13}C NMR spectrum of 5-hydroxyflavone (III) on the basis of a comparison of the contribution of the 5-hydroxy group to the shielding of these carbon atoms with the corresponding contributions in phenol, anisole, and similar compounds. Our assignment coincided with the results of Kingsbury and Looker [13], who studied the spectrum of 5-methoxyflavone, and turned out to be the opposite of the assignment made by Ternai and Markham [14], who studied the ^{13}C NMR spectrum of III. In this connection, it became necessary to make an additional study of the ^{13}C NMR spectrum of 5-hydroxyflavone in $CDCl_3$ instead of the previously used d_6-DMSO. Pro-

Irkutsk Institute of Organic Chemistry, Siberian Branch of the Academy of Sciences of the USSR, Irkutsk 664033. A. A. Zhdanov Irkutsk State University, Irkutsk 664033. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 609-612, May, 1978. Original article submitted May 23, 1977; revision submitted September 13, 1977.

0009-3122/78/1405-0497$07.50

TABLE 1. ^{13}C Chemical Shifts of Aminomethyl-Substituted 5-Hydroxyflavones (ppm from tetramethylsilane, 10% in d_6-DMSO, 35°C)

Compound		C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C'_1	C'_2, C'_6	C'_3, C'_5	C'_4	$C-CH_2N(CH_3)_2$
III	Exptl.	164,26	105,75	183,32	156,03	111,09	136,08	107,64	159,93	110,23	130,64	126,69	129,27	132,41	
IV	Exptl.	163,86	105,53	183,41	153,91	110,33	137,19	117,14	159,04	110,01	130,81	126,56	129,26	132,31	56,63, 44,94
	Calc.				154,5	110,8	136,6	118,1	160,4	109,9					
V	Exptl.	164,03	105,57	183,31	154,86	120,19	136,78	106,84	157,54	109,63	130,54	126,53	129,11	132,20	55,09, 44,80
	Calc.				156,5	121,6	136,6	107,3	158,4	109,9					
VI	Exptl.	163,54	105,43	183,67	152,18	119,85	138,01	116,44	156,71	109,55	130,82	126,54	129,30	132,32	56,62, 44,98, 55,18, 44,98
	Calc.				155,0	121,3	137,1	117,8	158,9	109,6					
	Calc*	163,63	105,35	183,40	152,74	119,43	137,89	116,34	156,65	109,41	130,71	126,40	129,10	132,10	
	Exptl.†	164,76	106,09	183,20	156,13	111,82	143,13	109,96	160,56	109,18	130,23	127,15	129,19	132,52	53,31, 42,67, 53,36, 42,15

*Calculated ^{13}C δ values for VI on the basis of the experimental ^{13}C δ values for III, IV, and V.
†Experimental ^{13}C δ values for the dihydrochloride of VI.

ceeding from the literature data [15], it may be assumed that this solvent will not interfere with stabilization of the planar conformation of the C_5—O—H...O=C fragment with a trans orientation of C_6 and the hydroxyl proton relative to the C_5-O bond due to a strong intramolecular hydrogen bond. In conformity with the data in [15, 16], in the ^{13}C monoresonance spectrum the C_6 signal, in addition to spin—spin coupling with H_6, also should display further coupling with both H_8 and the hydroxyl proton, i.e., a doublet of triplets appears, while the C_8 signal should appear as a doublet of doublets (SSCC with H_6 and H_8). In fact, the C_6 and C_8 signals have the hypothetical multiplicity (the SSCC of C_6 with H_8 and H-OH are approximately equal) (Fig. 1). This confirms are assignment [12], which is presented in Table 1. The C_6 and C_8 chemical shifts in the spectrum of a $CDCl_3$ solution are, respectively, 111.53 and 107.03 ppm, i.e., they differ only slightly from the values in d_6-DMSO.

Using the ^{13}C NMR spectrum of III and the known increments of the substituting $CH_2N(CH_3)_2$ group [17], which are +10.5, +0.5, —0.3, and —1.5 ppm, respectively, for C_S, C_O, C_m, and C_p of the benzene ring, one can determine the position of the substituents in IV and V. The ^{13}C δ values for C_5-C_{10} calculated with allowance for these contributions are presented in Table 1 and are in good agreement with the experimental values. Some of the deviations are appreciable for the carbon atoms with substituents or for those in the ortho positions relative to them. The signs of these deviations make it possible to assume that they are due to steric interaction of the adjacent groups. The results of a calculation based on additive allowance for the contributions of the substituents attached to C_6 and C_8, which were found from the experimental ^{13}C δ values for III, IV, and V, are additionally given for VI. The ^{13}C δ values of VI calculated in this way are in complete agreement with the experimental values. The ^{13}C NMR spectrum of the dihydrochloride of VI was studied to obtain additional information regarding the aminoalkylated structures. One's attention is drawn to the considerable difference between the ^{13}C δ values of the salt and base. It is characteristic not only for the carbon atoms directly bonded to $\overset{+}{N}R_2$ but also for the carbon atoms that are extremely far away. This long-range effect, the transmission of which along the π system is hindered by the CH_2 group, is due to the π-inductive effect of the charged substituent, which leads to appreciable π polarization of the aromatic system [18].

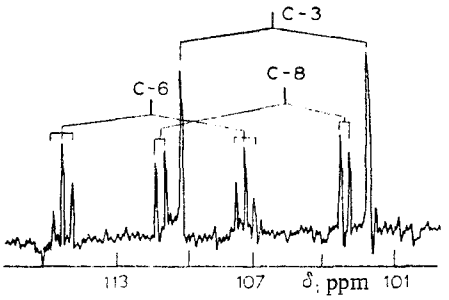


Fig. 1. Fragment of the ^{13}C NMR spectrum of 5-hydroxyflavone (III) (10 mole % in $CDCl_3$) under monoresonance conditions.

Thus IV is 8-aminomethyl-5-hydroxyflavone, and V is 6-aminomethyl-5-hydroxyflavone. The quantitative yields of the products of the Mannich reaction with 5-hydroxyflavone make it possible to deduce that the 6 position is more reactive than the 8 position by a factor of about 10. It may be assumed that the most active position in the electrophilic substitution reactions of 5-hydroxyflavone is the 6 position, whereas 7-hydroxyflavone gives only 8-substituted derivatives; this is in agreement with the increased lability of H_8, which is located between two nucleophilic substituents.

EXPERIMENTAL

The UV spectra of the compounds were recorded with an SF-4a spectrophotometer. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The ^1H NMR spectra of I and II (1-2% solutions in CCl_4) were recorded with a BS487B spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard. The ^{13}C NMR spectra of III-VI were recorded with a Varian CFT-20 Fourier spectrometer with an operating frequency for ^{13}C of 20 MHz. The spectra of both the $^{13}C-\{^1H\}$ double heteronuclear resonance, with complete suppression of the spin coupling between the nuclei, and the ^{13}C monoresonance were recorded for identification of the individual signals. The melting points were determined with a Koffler apparatus. The elementary compositions (C, H, and H) were in agreement with the calculated values.

General Method for Aminoalkylation. A mixture of 1 g (4.2 mmole) of 5- or 7-hydroxyflavone, 0.63 ml (4.2 mmole) of a 33% solution of dimethylamine or 0.307 g (4.2 mmole) of diethylamine, and 0.38 ml (5.2 mmole) of a 37% solution of formaldehyde in 12 ml of pyridine was heated with stirring at 115°C for 3-5 h in the case of 5-hydroxyflavone and at 80°C in the case of 7-hydroxyflavone. The reaction product was precipitated by the addition of water or was isolated after evaporation of the solvent. The product of the reaction of 5-hydroxyflavone was chromatographed on silica gel impregnated with 10% sodium metabisulfite in an isopropyl alcohol—ammonia system (9:1). The yields of IV-VI after chromatography were 0.03 (4.1%), 0.4 (54.8%), and 0.3 g (41.1%), respectively. The individual substances were recrystallized from petroleum ether.

8-Dimethylaminomethyl-7-hydroxyflavone (I). This compound had mp 168-170°C (mp 169-170°C) [9]. UV spectrum, λ_{max} (log ε): 260 (4.43) and 310 nm (4.24). IR spectrum: 1647 (C=O), 3070, 1590, 1455 (Ar), 1375 $(CH_3)_2$, 2965, 2865 (CH_2), 1205, 1080, 1035 (C-N, C-O-C), 3600 cm^{-1} (OH). ^1H NMR spectrum: 11.64 (1H, s, C_7-OH), 7.67 (2H, m, C'_2-H, C'_6-H), 7.38 (3H, m, C'3-H, C'_4-H, and C'_5-H), 6.41 (1H, s, C_3-H), 3.95 (2H, s, CH_2N), and 2.4 ppm (6H, s, CH_3).

8-Diethylaminomethyl-7-hydroxyflavone (II). This compound had mp 114-115°C (mp 112-113.5°C [9]). UV spectrum, λ_{max} (log ε): 260 (4.40) and 310 nm (4.13). IR spectrum: 1640 (C=O), 3060, 1590, 1440 (Ar), 1380 $(CH_3)_2$, 2970, 2865, 2855 (CH_2), 1210, 1070 (C-N, C-O-C), 3400 cm^{-1} (OH). ^1H NMR spectrum: 12.03 (1H, s, C_7-OH), 7.67 (2H, m, C'_2-H, C'_6-H), 7.39 (3H, m, C'3-H, C'_4-H, and C'_5-H), 6.41 (1H, s, C_3-H), 4.05 (2H, s, CH_2N), 2.7 (6H, q, CH_3), and 1.15 ppm (4H, t, CH_2).

8-Dimethylaminomethyl-5-hydroxyflavone (IV). This compound had mp 124-126°C. UV spectrum, λ_{max} (log ε): 270 (4.42), 285 (4.33), 340 nm (3.74). IR spectrum: 1650 (C=O), 3070, 1600, 1465 (Ar), 1385, 1140 $(CH_3)_2$, 2940, 2850 (CH_2), 1235, 1080, 1020 (C-N, C-O-C), 3200-3600 cm^{-1} (OH), $C_{18}H_{17}NO_3$.

6-Dimethylaminomethyl-5-hydroxyflavone (V). This compound had mp 130-132°C. UV spectrum, λ_{max} (log ε): 270 (4.42), 285 (4.33), 340 nm (3.74). IR spectrum: 1652 (C=O), 3020, 1600, 1465 (Ar), 1375 $(CH_3)_2$, 2945, 2765, 2815 (CH_2), 1207, 1080, 1040 (C-N, C-O-C), 3300 cm^{-1} (OH), $C_{18}H_{17}NO_3$.

Bis(dimethylaminomethyl)-5-hydroxyflavone (VI). This compound had mp 168-170°C. UV spectrum, λ_{max} (log ε): 275 (4.37), 285 (4.29), 340 nm (3.79). IR spectrum: 1652 (C=O), 3080, 1600, 1465 (Ar), 1375 $(CH_3)_2$, 2960, 2870 (CH_2), 1190, 1060, 1039 (C-N, C-O-C), 3200-3600 cm^{-1} (OH). $C_{21}H_{24}N_2O_3$.

The authors thank V. K. Voronov for recording and discussing the ^1H NMR spectra of I and II.

LITERATURE CITED

1. T. Yu. Il'yuchenok, A. I. Khomenko, L. M. Frigidova, V. P. Lepekhin, Yu. G. Verkhovskii, E. A. Zherbin, K. S. Shadurskii, N. A. Tyukavkina, K. I. Lapteva, and V. V. Kononova, Farmakol. Toksikol., No. 5, 607 (1975).
2. E. Domagalina and H. Hopkata, Ann. UMCS, D24, 4 (1969).
3. L. Jerzmanowska and E. Jurkowska-Kowalczyk, Roczn. Chem., 44, 1395 (1970).
4. L. Jerzmanowska and E. Jurkowska-Kowalczyk, Roczn. Chem., 46, 1039 (1972).
5. J. Mueller and E. Menard, Swiss Patent No. 484097 (1970); Chem. Abstr., 73, 66435j (1970).
6. J. Klosa, J. Prakt. Chem., 35, 319 (1967).
7. J. Klosa and H. Starke, East German Patent No. 27168 (1964); Ref. Zh. Khim., 10N238P (1965).
8. P. Da Re, L. Verlicchi, I. Setnikar, W. Murmann, and M. J. Magistretti, Nature, 184, 362 (1959).
9. P. Da Re, L. Verlicchi, and I. Setnikar, J. Org. Chem., 25, 1097 (1960).
10. P. Da Re, L. Verlicchi, and I. Setnikar, Arzneimittel-Forsch., No. 10, 800 (1960).
11. I. Setnikar, W. Murmann, M. J. Magistretti, and P. Da Re, J. Pharmacol., 128, 176 (1960).
12. G. A. Kalabin, N. N. Pogodaeva, N. A. Tyukavkina, and D. F. Kushnarev, Khim. Prir. Soedin., No. 4, 513 (1977).
13. C. A. Kingsbury and J. H. Looker, J. Org. Chem., 40, 1120 (1975).
14. B. Terani and K. R. Markham, Tetrahedron, 32, 565 (1976).
15. Ching-jer Chang, J. Org. Chem., 41, 1881 (1976).
16. F. W. Wehrli and T. Wirtlin, Interpretation of ^{13}C NMR Spectra, London (1976), p. 87.
17. W. Adcock, B. D. Gupta, and W. Kitching, J. Org. Chem., 41, 1498 (1976).
18. W. F. Reynolds, I. R. Peat, M. H. Freedman, and I. R. Lyerba, Can. J. Chem., 51, 1857 (1973).

SYNTHESIS OF FURAZANO[3,4-b]PYRAZINE DERIVATIVES

A. V. Eremeev, V. G. Andrianov, and I. P. Piskunova

UDC 547.793.2'866.5.07

Various furazano[3,4-b]pyrazine derivatives were synthesized by condensation of 3,4-diaminofurazan with substituted phenylglyoxals, cyclic di- and triketones, and diethyl acetylenedicarboxylate.

Aminofurazans have recently attracted attention in connection with the detection of their physiological activity. 3-Aryl-4-aminofurazans have been found to be effective anticonvulsants and depressants [1]. Substances that have anesthetizing and antibacterial action have been found among other aminofurazan derivatives [2, 3]. In this connection, it seemed of interest to us to investigate the possibilities of obtaining compounds in which the furazan ring is condensed with a pyrazine ring [4]. 3,4-Diaminofurazan (I) [5] was used as the starting reagent.

The furazan ring has pronounced electron-acceptor properties, as a consequence of which the nucleophilicity of the amino groups in furazan I is markedly lowered, and its reaction with carbonyl derivatives proceeds under more severe conditions than, let us say, with o-phenylenediamine. We obtained a number of 5-arylfurazano[3,4-b]pyrazines (II) in reactions with I with substituted phenylglyoxals.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 613-615, May, 1978. Original article submitted June 10, 1977.

 0009-3122/78/1405-0500$07.50