*Chemistry of Heterocyclic Compounds, Vol. 34, No. 8, 1998*

# CHEMISTRY OF THE HETERO ANALOGS OF ISOFLAVONES. 22.* MANNICH REACTION IN THE BENZIMIDAZOLE AND BENZOTHIAZOLE ANALOGS OF ISOFLAVONES

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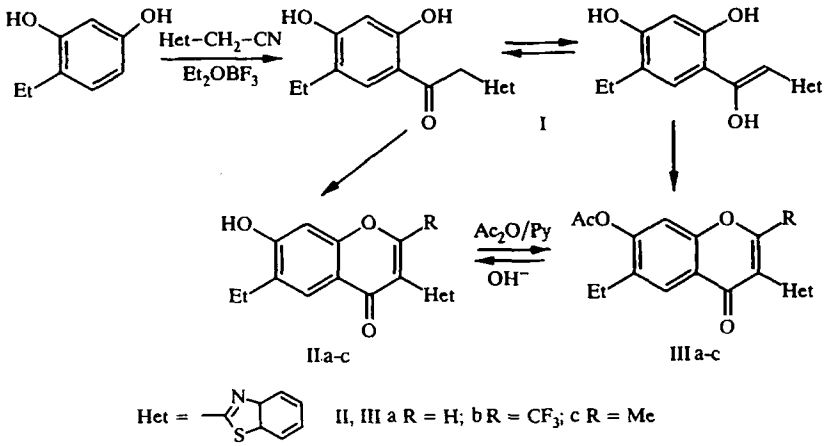
*New 3-(2-benzothiazolyl)chromones were obtained by the reaction of 2-(2,4-dihydroxy-5-ethylphenacyl)-benzothiazole with triethyl orthoformate or carboxylic acid anhydrides. Aminomethylation of the chromones and also of familiar 3-(2-benzimidazolyl)chromones by substituted 1,1-diaminomethanes gave Mannich bases.*

It is known that the N-substituted aminomethyl derivatives of both flavonoids and isoflavonoids have proved to be extremely active stimulants of the central nervous system and respiratory tracts [2, 3]. The same compounds exhibit strong anticonvulsive, antiallergic, and analgesic activity.

In the present work we synthesized the benzothiazole analogs of isoflavones containing the 4-ethylresorcinol fragment, and we also studied the possibility of aminomethylating the benzothiazole and benzimidazole analogs of isoflavones. 2-(2,4-Dihydroxy-5-ethylphenacyl)benzothiazole (I) was obtained by the condensation of 4-ethylresorcinol with 2-benzothiazolylacetonitrile under the modified conditions of the Hoesch reaction. In solution in DMSO this ketone, like its 5-propyl-substituted analog [4], exhibits keto–enol tautomerism. This is confirmed by the presence of signals for the protons of the keto and enol forms in its PMR spectrum (in DMSO-$d_6$ solution). After taking account of the integral intensity of the nonexchanging protons at positions 3 and 6 of the phenol part for both forms, we found that the ketone (I) was enolized to by 85% under the conditions of the measurement of the PMR spectrum.




The reaction of compound (I) with triethyl orthoformate and also with trifluoroacetic and acetic anhydrides in pyridine gave 3-(2-benzothiazolyl)-7-hydroxy-6-ethylchromone (IIa), its analog (IIb) with a trifluoromethyl group at position 2 of the chromone ring, and the acetylated 2-methyl-substituted analog (IIIc).

*For Communication 21, see [1].

Taras Shevchenko Kiev University, Kiev, Ukraine. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1072-1078, August, 1998. Original article submitted June 19, 1997; revision submitted November 10, 1997.

0009-3122/98/3408-0923$20.00 

TABLE 1. Characteristics of the 3-(2-Benzazolyl)chromones (IIa-c, IIIa-c, Va-j, VIa-h)

| Compound | Empirical formula | Found, % / Calculated, % | | mp, °C | Yield, % |
|---|---|---|---|---|---|
| | | N | S | | |
| IIa | $C_{18}H_{13}NO_3S$ | 4,20 / 4,33 | 9,70 / 9,91 | 319...321 | 92 |
| IIb | $C_{19}H_{12}F_3NO_3S$ | 3,78 / 3,58 | 8,40 / 8,19 | 249...251 | 93 |
| IIc | $C_{19}H_{15}NO_3S$ | 4,15 / 4,27 | 9,50 / 9,30 | 295...297 | 65 |
| IIIa | $C_{20}H_{15}NO_4S$ | 4,00 / 3,83 | 8,95 / 8,78 | 255...257 | 75 |
| IIIb | $C_{21}H_{14}F_3NO_4S$ | 3,23 / 3,45 | 7,40 / 7,68 | 137...138 | 70 |
| IIIc | $C_{21}H_{17}NO_4S$ | 3,37 / 3,69 | 8,30 / 8,45 | 128...130 | 98 |
| Va | $C_{21}H_{20}N_2O_3S$ | 7,36 / 7,52 | 8,43 / 8,50 | 210...212 | 85 |
| Vb | $C_{23}H_{24}N_2O_3S$ | 6,65 / 6,86 | 7,70 / 7,85 | 144...145 | 70 |
| Vc | $C_{23}H_{22}N_2O_4S$ | 6,55 / 6,63 | 7,48 / 7,59 | 201...203 | 73 |
| Vd | $C_{24}H_{24}N_2O_3S$ | 6,80 / 6,66 | 7,67 / 7,62 | 209...210 | 72 |
| Ve | $C_{22}H_{19}F_3N_2O_3S$ | 6,21 / 6,25 | 7,35 / 7,15 | 150...152 | 65 |
| Vf | $C_{22}H_{22}N_2O_3S$ | 6,96 / 7,10 | 8,20 / 8,13 | 234...236 | 90 |
| Vg | $C_{24}H_{26}N_2O_3S$ | 6,70 / 6,63 | 6,45 / 7,59 | 190...192 | 78 |
| Vh | $C_{24}H_{24}N_2O_4S$ | 6,55 / 6,42 | 7,20 / 7,34 | 249...250 | 87 |
| Vi | $C_{25}H_{26}N_2O_3S$ | 6,40 / 6,45 | 7,32 / 7,38 | 245...246 | 82 |
| Vj | $C_{23}H_{21}F_3N_2O_3S$ | 6,28 / 6,06 | 7,16 / 6,93 | 147...149 | 70 |
| VIa | $C_{24}H_{27}N_3O_3$ | 10,50 / 10,36 | | 142...143 | 73 |
| VIb | $C_{24}H_{25}N_3O_4$ | 9,92 / 10,02 | | 247...249 | 90 |
| VIc | $C_{25}H_{27}N_3O_3$ | 10,40 / 10,06 | | 220...222 | 88 |
| VId | $C_{25}H_{29}N_3O_3$ | 9,80 / 10,02 | | 187...188 | 68 |
| VIe | $C_{25}H_{27}N_3O_3$ | 9,60 / 9,69 | | 207...209 | 82 |
| VIf | $C_{26}H_{29}N_3O_3$ | 9,65 / 9,74 | | 196...197 | 75 |
| VIg | $C_{23}H_{25}N_3O_3$ | 10,80 / 10,73 | | 190...192 | 60 |
| VIh | $C_{23}H_{23}N_3O_4$ | 10,30 / 10,36 | | 210...211 | 66 |

The chromones (IIa, b) are easily acetylated at the 7-OH group by the action of acetic anhydride in pyridine with the formation of the 7-acetoxy derivatives (IIIa, b) respectively; the acetoxychromones (IIIa, c) are easily transformed into the free 7-hydroxychromones (IIa, c) as a result of reaction with an equivalent amount of an aqueous alcohol solution of sodium hydroxide.

For the synthesized compounds (IIa-c) and also their familiar analogs, i.e., the 5-propyl-substituted (IId) [4] and 2-benzimidazolyl derivatives (IVa-c) [5], we studied aminomethylation in order to obtain Mannich bases containing secondary amine residues. During an attempt at the synthesis of these products from the above-mentioned 3-benzazolylchromones by the classical method (boiling the amine, formalin, and chromone in alcohol or dioxane for 6-8 h) the reaction was unsuccessful. We therefore decided to use for this purpose the aminals of the most readily obtainable secondary amines — dimethylamine,

TABLE 2. PMR Spectra,* $\delta$, ppm, of 3-(2-Benzazolyl)chromones (IIa-c, IIIa-c, Va-j, VIa-h)

| Compound | Chromone residue | | | | | | He‡ | |
|---|---|---|---|---|---|---|---|---|
| | 2-R, s | 5-H, 1H, s | 6-$R^1$ 3H, t and 2H, q† | 7-OH/7-OAc, s | 8-H/8-$CH_2N$, s | $R^2R^3$ | 4- and 7-H, 2H, m | 5- and 6-H, 2H, m |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| IIa | 9,28 (1H) | 7,88 | 1,19 and 2,63 | 11,07 (1H) | 6,97 (1H) | | 8,12 | 7,46 |
| IIb | — | 7,84 | 1,19 and 2,67 | 11,34 (1H) | 7,01 (1H) | | 8,16 | 7,56 |
| IIc | 2,99 (3H) | 7,88 | 1,21 and 2,66 | 10,96 (1H) | 6,93 (1H) | | 8,08 | 7,79 |
| IIIa | 9,24 (1H) | 8,27 | 1,30 and 2,69 | 2,39 (1H) | 7,44 (1H) | | 8,02 | 7,50 |
| IIIb | — | 8,15 | 1,27 and 2,68 | 2,40 (3H) | 7,44 (1H) | | 7,97 | 7,50 |
| IIIc | 2,33 (3H) | 7,88 | 1,24 and 2,59 | 2,43 (3H) | 6,95 (1H) | | 8,02 | 7,46 |
| Va | 9,14 (1H) | 8,07 | 1,29 and 2,73 | ** | 4,03 (2H) | 2,44 (6H, s, $2NCH_3$) | 7,96 | 7,43 |
| Vb | 9,13 (1H) | 8,04 | 1,25 and 2,71 | 11,83 (1H) | 4,12 (2H) | 2,71 (4H, q, $2NCH_2$)††, 1,17 (6H, t, $2CH_3$)†† | 8,02 | 7,43 |
| Vc | 9,16 (1H) | 8,08 | 1,29 and 2,70 | ** | 4,09 (2H) | 2,70 (4H, m, $2NCH_2$)††, 3,86 (4H, m, $2OCH_2$) | 7,97 | 7,44 |
| Vd | 9,14 (1H) | 8,06 | 1,29 and 2,72 | 11,12 (1H) | 4,04 (2H) | 2,72 (4H, m, $2NCH_2$)††, 1,70 (6H, m, $3CH_2$) | 8,00 | 7,44 |
| Ve | — | 7,94 | 1,26 and 2,71 | 10,81 (1H) | 4,00 (2H) | 2,44 (6H, s, $2NCH_3$) | 8,12 | 7,47 |
| Vf | 3,00 (3H) | 7,79 | 1,19 and 2,64 | ** | 4,11 (2H) | 2,45 (6H, s, $2NCH_3$) | 8,07 | 7,47 |
| Vg | 3,02 (3H) | 7,98 | 1,25 and 2,72 | 11,57 (1H) | 4,09 (2H) | 2,67 (4H, q, $2NCH_2$)††, 1,18 (6H, t, $2CH_3$)†† | 8,00 | 7,43 |
| Vh | 3,01 (3H) | 7,82 | 1,20 and 2,61 | ** | 4,09 (2H) | 2,61 (4H, m, $2NCH_2$)††, 3,68 (4H, m, $2OCH_2$) | 8,07 | 7,47 |

TABLE 2. (continued)

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|
| Vi | 3,03 (3H) | 8,00 | 2,71 and 1,28 | ** | 4,02 (2H) | 2,70 (4H, m, $2NCH_2$)††, 1,66 (6H, m, $3CH_2$) | 7,42 | 8,02 |
| Vj | — | 7,68 | 0,91; 1,58; 2,56 | ** | 4,17 (2H) | 2,58 (6H, s, $2NCH_3$) | 8,16 | 7,54 |
| VIa | 8,60 (1H) | 7,79 | 1,19 and 2,75 | ** | 4,19 (2H) | 2,71 (4H, q, $2NCH_2$)††, 1,13 (6H, t, $2CH_3$)†† | 7,63 | 7,28 |
| VIb | 8,64 (1H) | 7,85 | 1,21 and 2,63 | ** | 4,10 (2H) | 2,63 (4H, m, $2NCH_2$)††, 3,68 (4H, m, $2OCH_2$) | 7,63 | 7,27 |
| VIc | 8,61 (1H) | 7,81 | 1,19 and 2,63 | ** | 4,10 (2H) | 2,63 (4H, m, $2NCH_2$)††, 1,56 (6H, m, $3CH_2$) | 7,62 | 7,27 |
| VId | 2,44 (3H) | 7,91 | 1,26 and 2,71 | 11,39 (1H) | 4,10 (2H) | 2,71 (4H, q, $2NCH_2$)††, 1,19 (6H, t, $2CH_3$)†† | 7,79 | 7,33 |
| VIe | 2,46 (3H) | 7,93 | 1,25 and 2,70 | ** | 4,06 (2H) | 2,70 (4H, m, $2NCH_2$)††, 3,82 (4H, m, $2OCH_2$) | 7,80 | 7,34 |
| VIf | 2,44 (3H) | 7,90 | 1,26 and 2,72 | ** | 4,01 (2H) | 2,72 (4H, m, $2NCH_2$)††, 1,66 (6H, m, $3CH_2$) | 7,76 | 7,35 |
| VIg | 9,17 (1H) | 8,02 | 1,21 and 2,75 | 12,20 (1H) | 4,13 (2H) | 2,73 (4H, q, $2NCH_2$)††, 1,19 (4H, t, $2CH_3$)†† | 7,64 | 7,28 |
| VIh | 9,19 (1H) | 8,06 | 1,31 and 2,71 | 11,95 (1H) | 4,09 (2H) | 2,71 (4H, m, $2NCH_2$)††, 3,83 (4H, m, $2OCH_2$) | 7,77 | 7,30 |

*The spectra of compounds (IIa-c, Vf, h, j, VIa-d) were measured in DMSO-$d_6$ solution, the others in deuterochloroform.

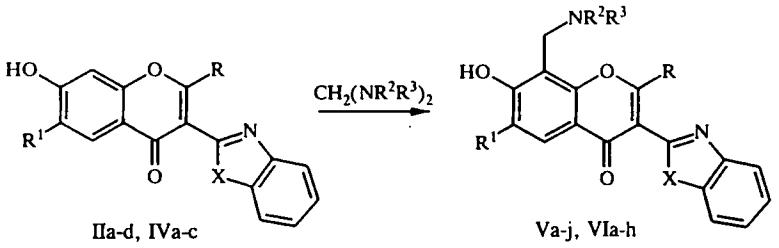
†For compound (Vj) ($R^1$ = Pr) the proton signals have the following form: 0.91 (3H, t, $CH_3$), 1.58 (2H, m, $CH_2$), 2.56 (2H, t, $CH_2$).

‡For compounds (VIa-f) (X = $NCH_3$) the signal of the protons of the N−$CH_3$ group takes the form of a three-component singlet in the region of 3.68-3.70 ppm.

**The exact position of the signals for the protons of the 7-OH group of the chromone ring and the NH group [compounds (VIg, h)] cannot be determined on account of their strong broadening.

††The integral intensity of the protons is given after deduction of the integral intensity of the protons of the 6-$CH_2CH_3$ group.

diethylamine, morpholine, and piperidine, first proposed in [6, 7]. We found that the reaction with bis(dimethylamino)methane took 0.5-1 h. Somewhat longer heating was required to complete the reaction with bis(diethylamino)methane, and in the case of the reaction with 4,4′-methylenebismorpholine or 1,1′-methylenebispiperidine boiling for about 3.5-4 h was required.




IIa-d, IVa-c — Va-j, VIa-h

IIa-d, Va-j X = S; IVa, b, VIa-f X = $NCH_3$; IVc, VIg, h X = NH; IIa, IVa, c, Va-d, VIa-c, g, h R = H; IIb, d, Ve, j R = $CF_3$; iIVb, Vf-i, VId-f R = $CH_3$; IIa-c, IVa-c, Va-i, VIa-h $R^1 = C_2H_5$; IId, Vj $R^1 = C_3H_7$; Va,e,f,j $R^2 = R^3 = CH_3$; Vb, g, VIa,d,g $R^2 = R^3 = C_2H_5$; Vc,h VIb,e,h $R^2R^3 = CH_2CH_2OCH_2CH_2$; Vd, i VIc, f $R^2R^3 = (CH_2)_5$

By boiling the 3-(2-benzothiazolyl)chromones (IIa-d) and also the 3-(2-benzimidazolyl)chromones (IVa-c) with the above-mentioned aminals in dioxane we obtained the Mannich bases (Va-j) and (VIa-h) containing secondary amine residues at position 8 of the chromone ring.

In the PMR spectra of the synthesized products (Va-j, VIa-h), in contrast to the initial compounds (IIa-d, IVa-c), there are no signals for 8-H of the chromone ring; instead there are signals for the protons of the aminoalkyl substituents. It should be noted that only the monoaminomethyl derivatives (VIg, h) were obtained in the case of 3-(2-benzimidazolyl)-7-hydroxy-6-ethylchromone (IVc), and aminomethylation of the benzimidazole NH group was not observed even with a significant excess of the alkylating agent.

Under the conditions for the measurement of the PMR spectra of the diethylaminomethylchromones (Vb, g) and (VIa, d, g) the signals for the protons of the ethyl groups of the amine residue and the substituent at position 6 of the chromone ring are observed in the form of two closely located triplets. For this reason it is only possible to calculate their overall integral intensity (6H and 9H respectively). In the case of the morpholinomethyl derivatives (Vc, h, VIb, d, h) and also the pyridinomethyl derivatives (Vd, i, VIc, f), the signals for the protons of the 6-$CH_2$ and $NCH_2$ groups are observed in the form of a common multiplet in the region of 2.61-2.72 ppm (6H).

The obtained Mannich bases are crystalline substances, readily soluble in organic solvents and in dilute mineral acids.

Thus, the aminals of secondary amines can be used as effective reagents for the selective C-aminomethylation of the hetero analogs of the isoflavones.

## EXPERIMENTAL

The reactions were monitored and the purity of the obtained compounds was assessed by TLC on Silufol UV-254 plates. The eluants were mixtures of chloroform and methanol (9:1, 19:1) and also ethyl acetate for the Mannich bases. The PMR spectra were measured on a Bruker WP-100SY instrument at 100 MHz with TMS as internal standard.

Characteristics of the synthesized compounds are given in Table 1. Data of the PMR spectra are given in Table 2.

**2-(2,4-Dihydroxy-5-ethylphenacyl)benzothiazole (I).** Compound (I) was obtained similarly to its analog (IId) by the familiar method [4] from 14.5 g (105 mmole) of 4-ethylresorcinol, 17.4 g (100 mmole) of 2-benzothiazolylacetonitrile, and 120 ml of boron trifluoride etherate. The yield was 21 g (67%). The product formed yellowish crystals; mp 216-217°C (from isopropyl alcohol). PMR spectrum, DMSO-$d_6$, ($\delta$, ppm): signals of the protons of the keto form, 11.91 (0.15H, s, 2-OH); 6.36 (0.15H, s, 3-H); 10.72 (0.15H, s, 4-OH); 7.78 (0.15H, s, 6-H); 4.93 (0.30H, s, $COCH_2-$); enolic form, 12.59 (0.85H, s, 2-OH); 6.26 (0.85H, s, 3-H); 10.04 (0.85H, s, 4-OH); 7.35 (0.85H, s, 6-H); 13.92 (0.85H, s, OH of enone); 6.69 (0.85H, s, CH of enone); signals of the protons of the benzothiazole substituent Het for both tautomers, 7.90 (2H, m, 4- and 7-H); 7.35

(2H, m, 5- and 6-H); signals of Et protons, 2.49 (2H, q, $CH_2$); 1.14 (3H, t, $CH_3$). Found %: N 4.57; S 10.13. $C_{17}H_{15}NO_3S$. Calculated %: N 4.47; S 10.23.

**3-(2-Benzothiazolyl)-7-hydroxy-5-ethylchromone (IIa).** A solution of 15.65 g (50 mmole) of the ketone (I) in 50 ml of pyridine, 50 ml of triethyl orthoformate, and 1 ml of piperidine was kept at 120-130°C for 6-8 h. The reaction mixture was cooled, and the crystals that separated were filtered off, washed with isopropyl alcohol, and crystallized from pyridine.

**3-(2-Benzothiazolyl)-7-hydroxy-2-trifluoromethyl-5-ethylchromone (IIb).** To a solution of 1.6 g (5 mmole) of the ketone (I) in the smallest amount of pyridine we added with cooling in ice 1.4 ml (10 mmole) of trifluoroacetic anhydride. The reaction mixture was kept at room temperature for 24 h and was then poured onto ice. The crystals that separated were filtered off and crystallized from acetonitrile.

**7-Acetoxy-3-(2-benzothiazolyl)-5-ethylchromone (IIIa).** To a solution of 1.62 g (5 mmole) of the chromone (IIa) in 5 ml of pyridine we added 0.7 ml (7.5 mmole) of acetic anhydride. The mixture was kept at room temperature for ~16 h. The crystals that separated were filtered off, washed with isopropyl alcohol, and crystallized from acetic anhydride.

**7-Acetoxy-3-(2-benzothiazolyl)-2-trifluoromethyl-5-ethylchromone (IIIb).** Compound (IIIb) was obtained similarly to the chromone (IIIa) from 1.57 g (4 mmole) of the chromone (I), 2 ml of pyridine, and 0.6 ml (6.4 mmole) of acetic anhydride. The product was crystallized from petroleum ether.

**7-Acetoxy-3-(2-benzothiazolyl)-2-methyl-5-ethylchromone (IIIc).** Compound (IIIc) was obtained similarly to the chromone (IIb) from 3.13 g (10 mmole) of the ketone (I) and 4.7 ml of acetic anhydride. The product was crystallized from petroleum ether.

**3-(2-Benzothiazolyl)-7-hydroxy-2-methyl-5-ethylchromone (IIc).** We dissolved 8.28 g (20 mmole) of the chromone (IIIc) by heating in 100 ml of ethanol and added 20 ml of a 1 N solution of sodium hydroxide. The mixture was boiled for 3-4 min and neutralized to pH 7-8 with hydrochloric acid solution. The crystals that separated were filtered off and crystallized from a mixture of dimethylformamide and water.

**General Procedure for the Aminomethylation of the Chromones (IIa-d, IVa-c).** A mixture of 3 mmole of the chromone, 10 ml of absolute dioxane, and 0.45 ml (3.3 mmole) of dipiperidinomethane, or 1 ml of bis(diethylamino)methane, dimorpholinomethane, or dipiperidinomethane was boiled until the chromone had dissolved, and it was then boiled for a further 20-30 min. The dioxane was evaporated under vacuum, and the residue was crystallized from a suitable solvent (diethyl ether, toluene, dioxane, or their mixtures). The products (Va-j, VIa-h) were obtained.

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