

SYNTHETIC ANALOGS OF NATURAL FLAVOLIGNANS
IX. SYNTHESIS OF 3-AMINO-SUBSTITUTED
ANALOGS OF HYDROCARPIN

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New 3-amino-substituted chromones with 1,3-benzodioxan and 1,4-benzodioxan nuclei in position 2 have been synthesized. The structures of the compounds obtained have been confirmed by their PMR spectra.

Many organic compounds containing an amino group possess valuable biological properties. Consequently, the synthesis of flavonoids having an amino group is of particular interest. Continuing the modification of synthetic analogs of natural flavonoids and flavolignans [1], with the aim of finding new biologically active substances we have synthesized new 3-amino-substituted analogs of hydrocarpin.

3-Aminoflavones are usually synthesized from 2'-hydroxy- α,β -dibromochalcones. The dibromochalcones required for this are obtained by various methods. One of the specific halogenating agents is pyridine perbromide.

The interaction of the chalcones (1) and (2) [2, 3] with pyridine perbromide in glacial acetic acid gave the 2'-hydroxy- α,β -dibromochalcones (3) and (4) with good yields.

The reaction of the 2'-hydroxy- α,β -dibromochalcones (3) and (4) with sodium azide in DMFA initially formed the chalcone azides, and these, without purification, were treated with a 1% solution of caustic soda in methanol. As a result, 3-aminoflavones modified with 1,3-benzodioxan and 1,4-benzodioxan nuclei, (5) and (6), were formed. The structures of the compounds obtained (3—6) were confirmed by the results of elementary analysis and by their PMR spectra. The physical constants and analytical results for the substances obtained are given in Table 1, and details of their PMR spectra in Table 2.

In the PMR spectra of the dibromochalcones (3 and 4), measured in deuterated DMSO, the signals of the protons of the 2-OH group were present in the weak field at 10.99—11.49 ppm. The α,β -methine protons gave doublets at 5.51—5.93 and 5.68—6.82 ppm (SSCC 11.0—11.2 Hz), respectively.

TABLE 1. Physicochemical Constants of the 2'-Hydroxy- α,β -dibromochalcones (3 and 4)*

Compound	Empirical formula	Yield, %	mp. °C
3a	C ₁₈ H ₁₅ BrO ₄	45.7	180-182
3b	C ₁₈ H ₁₅ Br ₃ O ₄	48.1	183-185
3c	C ₁₉ H ₁₇ Br ₃ O ₅	52.4	>270
4d	C ₁₇ H ₁₃ Br ₃ ClO ₄	58.8	164-165
4e	C ₁₇ H ₁₃ Br ₂ FO ₄	60	162-163

* Solvent for crystallization C₆H₆.

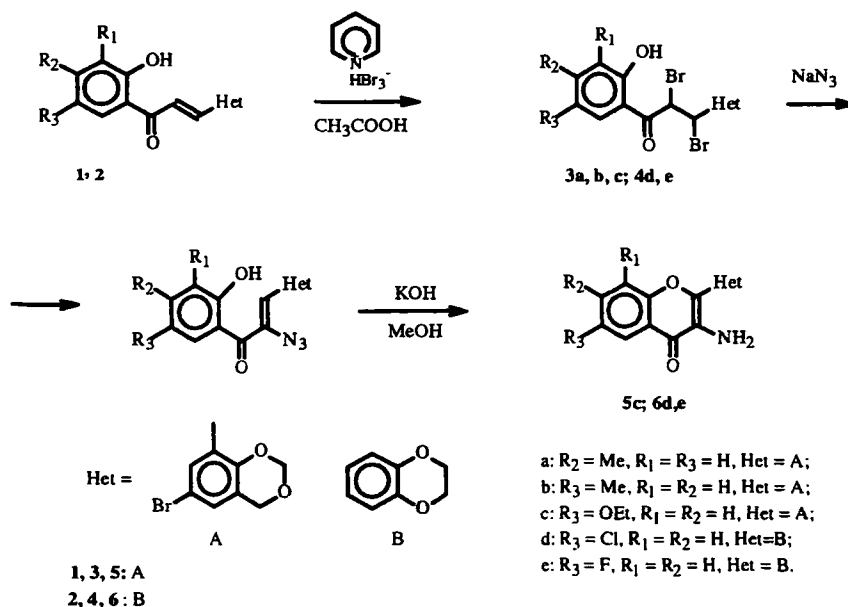
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TABLE 2. Chemical Shifts in the PMR Spectra of the 2'-Hydroxy- α,β -dibromochalcones (3 and 4) in DMSO- d_6

Compound	PMR spectrum*, δ , ppm (J, Hz)										
	Protons of the phenolic fragment					C(O)CHBrCHBr		Benzodioxan protons			
	OH-2, s	H-3	H-4	H-5	H-6	CH- α , d	CH- β , d	H-5	H-7	H-8	CH ₂ -2, CH ₂ -4 or O-(CH ₂) _n O
3a	11.49	7.20 d (1.8)	2.36 s	6.91 dd (8.0; 1.8)	8.12 d (8.0)	6.82 (11.0)	5.93 (11.0)	7.34 d (2.44)	8.00 d (2.44)	-	5.41; 4.93
3b	11.23	6.96 d (8.3)	7.43 dd (8.3; 2.0)	2.32	8.12 d (2.0)	6.79 (11.2)	5.93 (11.2)	7.36 d (2.40)	7.96 d (2.40)	-	5.40; 4.93
3c	10.99	7.00 d (8.3)	7.29 dd (8.3; 2.0)	4.06 q 1.34 t	7.94 d (2.0)	6.83 (11.2)	5.93 (11.2)	7.36 d (2.44)	7.58 d (2.44)	-	5.41; 4.93
4d*	11.71	7.33 d (9.0)	7.53 dd (9.0; 2.5)	-	7.77 d (2.0)	5.71 (11.0)	5.54 (11.0)	7.06 d (2.0)	7.2 dd (8.5; 2.0)	6.88 d (8.5)	4.31
4e*	11.54	7.22-7.4 m	7.2-7.4 m	-	7.47 dd (9.0; 3.0)	5.68 (11.)	5.51 (11.0)	7.05 d (2.0)	7.01 dd (8.5; 2.0)	6.88 d (8.0)	4.30

*These PMR spectra were taken in CDCl₃.

The aromatic protons H-5 and H-7 of the 1,3-benzodioxan ring were revealed in the form of doublets with SSCCs of 2.0 Hz in the 7.93—8.00 ppm region, and the signals of the CH₂-2 and CH₂-4 methylene groups gave two-proton singlets at 5.4 and 4.93 ppm. The methylene protons of the 1,4-benzodioxan ring gave a singlet at 4.3 ppm.



In the PMR spectrum (in CDCl₃) of the 3-aminoflavones (3 and 4) the slightly broadened two-proton singlet of the amino group appeared at 4.0 ppm and disappeared rapidly on the addition of heavy water.

Thus, it is desirable to use the azidation of α,β -dibromochalcones for the synthesis of analogs of natural flavonoids containing an amino group in position 3.

EXPERIMENTAL

For thin-layer chromatography we used Silufol UV-254 plates with the benzene—ethanol (9:1) solvent system. PMR spectra were measured on a Bruker WP-100 SV spectrophotometer with a working frequency of 100 MHz in DMSO- d_6 or $CDCl_3$ with TMS as internal standard. The elementary analyses of compounds (3—6) corresponded to the calculated figures.

The 2'-Hydroxy- α,β -dibromochalcones (3 and 4). At room temperature, with stirring, 3.19 g (10 mmole) of pyridine perbromide was added in portions to a solution of 10 mmole of the appropriate chalcone in the minimum amount of glacial acetic acid. The stirring of the reaction mixture was continued for 4—8 h. Then it was diluted with water and the resulting precipitate was filtered off and crystallized from a suitable solvent (see Table 1).

The 2-Hetaryl-3-aminochromones (5, 6). At room temperature, with stirring, 0.73 g (11.3 mmole) of sodium azide was added to a solution of the appropriate 2'-hydroxy- α,β -dibromochalcone (3 or 4) in 10 ml of DMFA. Stirring was continued for another 6—8 h. Then the reaction mixture was poured into cold water, the resulting precipitate was filtered off, and, after drying, the chalcone azide so obtained was used without purification for the following reaction.

With stirring at room temperature, 1.69 ml of a 1% solution of caustic soda was added to a suspension of 6.74 mmole of a crude 2'-hydroxy- α -azidochalcone. Stirring was continued for about 1 h, the course of the reaction being monitored by TLC. Then the reaction mixture was diluted with water and the resulting precipitate was filtered off, dried and crystallized from ethanol.

Compound (5c): yield 58.4%, mp 207—208°C. $C_{19}H_{16}BrNO_5$.

PMR spectrum ($CDCl_3$, δ , ppm): protons of the chromone ring — 4.06 (s, 2H, NH_2 -3), 7.58 (d, 1H, $J=2.93$ Hz, H-5), 4.12; 1.46 (q, t, OEt-6), 7.22 (dd, 1H, $J=9.28$; 2.93 Hz, H-7), 7.40 (d, 1H, $J=9.28$, H-8); protons of 1,3-benzodioxan — 7.26 (d, 1H, $J=2.44$ Hz, H-5), 7.62 (d, 1H, $J=2.44$ Hz, H-7), 5.31 (d, 2H, CH_2 -2), 4.96 (s, 2H, CH_2 -4).

Compound (6d): yield 75.9%, mp 189—190°C. $C_{17}H_{12}ClNO_4$.

PMR spectrum ($CDCl_3$, δ , ppm): protons of the chromone ring — 4.67 (s, 2H, NH_2 -3), 8.0 (d, 1H, H-5), 7.73 (m, 2H, H-7, H-8); protons of 1,4-benzodioxan — 7.48 (d, 1H, $J=2.60$ Hz, H-5), 7.48 (dd, 1H, $J=8.0$; 2.0 Hz, H-7), 7.04 (d, 1H, $J=8.0$ Hz, H-8), 4.32 (s, 4H, OCH_2CH_2O).

Compound (6e): yield 71.1%, mp 186—187°C. $C_{17}H_{12}ENO_4$

PMR spectrum ($CDCl_3$, δ , ppm): protons of the chromone ring — 4.00 (s, 2H, NH_2 -3), 7.57 (dd, 1H, $J=8.0$; 2.5 Hz, H-5), 7.4-7.46 (m, H-7, H-8); protons of 1,4-benzodioxan — 7.4-7.46 (m, H-5), 7.34 (dd, 1H, $J=8.5$; 2.5 Hz, H-7); 7.01 (d, 1H, $J=8.5$ Hz, H-8), 4.33 (s, 4H, OCH_2CH_2O).

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