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Condensation of Diethyl 2,4,6-Trioxoheptanedioate with 2-(Aryliminomethyl)phenols. A New Synthesis of Chromeno[4,3-*b*]pyridines

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Abstract—Condensation of diethyl 2,4,6-trioxoheptanedioate with 4-methoxy-2-(4-methylphenyliminomethyl)-phenol in acetone gave diethyl 5-hydroxy-9-methoxy-1-(4-methylphenyl)-4-oxo-1,4a,5,10b-tetrahydro-4*H*-chromeno[4,3-*b*]pyridine-2,5-dicarboxylate as a mixture of diastereoisomers. The major (4a*R*,5*R*,10a*R*)-isomer was isolated as individual substance, and its structure was proved by X-ray analysis.

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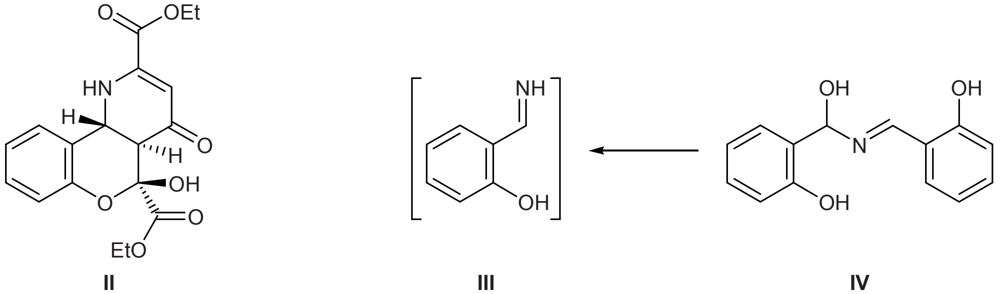
1,4a,5,10b-Tetrahydro-4*H*-chromeno[4,3-*b*]pyridines [1–18] (pyridocoumarins [19]) may be regarded as aza analogs of Δ^1-*trans*-tetrahydrocannabinol [20] and $\Delta^{1(6)}$-*trans*-tetrahydrocannabinol [21] that are well known physiologically active components isolated from *Cannabis* [22]. In the recent years, extensive studies have been performed with a view to develop methods of synthesis of this interesting tricyclic system [1–18].

We previously found that diethyl 2,4,6-trioxoheptanedioate (**I**) [23] reacts with salicylaldehyde in ethanol in the presence of ammonium acetate to give an aza analog of the heterocyclic cannabinol system [22], diethyl 5-hydroxy-4-oxo-1,4a,5,10b-tetrahydro-4*H*-chromeno[4,3-*b*]pyridine-2,5-dicarboxylate (**II**). Here, compound **I** donates the five-membered $C^2C^3C^4C^{4a}C^5$ fragment to molecule **II**; the other structural fragment of molecule **II** originates from unstable salicylaldehyde imine (**III**) which is formed as intermediate via decomposition of 2-{hydroxy[(2-hydroxyphenyl)methylideneamino]methyl}phenol (**IV**) (Scheme 1) [23].

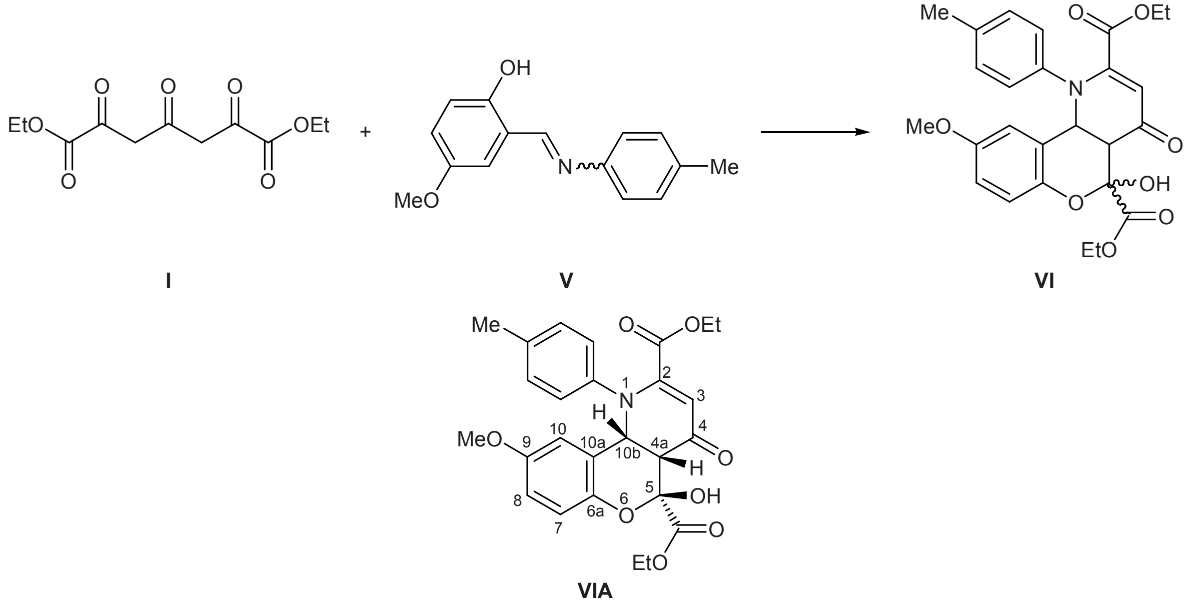
We have found that tetrahydrochromeno[4,3-*b*]pyridine system can be obtained by condensation of diethyl 2,4,6-trioxoheptanedioate (**I**) with 2-(4-methylphenyliminomethyl)phenols like **V** (the latter are readily available via reaction of *p*-toluidine with substituted salicylaldehydes [24]) instead of using the above three-component system giving rise to unstable intermediate *N*-benzylidenebenzylamine **IV** and salicylaldehyde imine (**III**). Thus the reaction of **I** with Schiff base **V** in acetone at room temperature afforded diethyl 5-hydroxy-9-methoxy-1-(4-methylphenyl)-4-oxo-1,4a,5,10b-tetrahydro-4*H*-chromeno[4,3-*b*]pyri-

Scheme 1.



II **III** **IV**

Scheme 2.



dine-2,5-dicarboxylate (**VI**) as a mixture of diastereoisomers in high yield (Scheme 2).

Molecule (**VI**) possesses three asymmetric centers, so that formation of four diastereoisomers is possible, each being a couple of enantiomers: (*SSS*/*RRR*)-**VIA**, (*RSS*/*SRR*) **VIB**, (*SRS*/*RSR*)-**VIC**, and (*RRS*/*SSR*)-**VID** (the configurations of the C^{4a}, C^5, and C^{10b} atoms, respectively, are given). Insofar as the formation of tricyclic system **VI** involves reversible closures of pyridin-4-one and pyran fragments, it is impossible to predict *a priori* the ratio of particular diastereoisomers in the final product.

The ^{1}H NMR spectrum of the crude product showed that one enantiomer couple predominated. The major diastereoisomer was isolated by recrystallization from isopropyl alcohol. Its spectrum contained five multiplet signals in the region δ 6.8–7.3 ppm. Two doublets at δ 7.23 and 7.29 ppm (*AA′BB′* system) were assigned to protons in the tolyl group, and the remaining three signals (δ, ppm: 6.84 d, 6.88 d.d, 7.19 d) constituted an *ABX* spin system (protons in the benzene ring of the chromene fragment). In the region typical of protons at an sp^2-carbon atom or sp^3-carbon atom bearing an electron-withdrawing substituent we observed a singlet (3-H) and a doublet ($J = 5.3$ Hz), the latter belonging to an *AX* spin system (10b-H). The second component of the *AX* system was a doublet at δ 3.95 ppm (4a-H, $J = 5.3$ Hz). Four signals in the regions δ 4.1–4.3 and 1.0–1.3 ppm correspond to protons in the ester ethyl groups; these signals appeared as two doublets of doublets and two complex multiplets due to the presence of three asymmetric centers in the molecule. Protons in the aromatic methyl and methoxy groups resonated as singlets at δ 2.36 and 3.73 ppm, respectively.

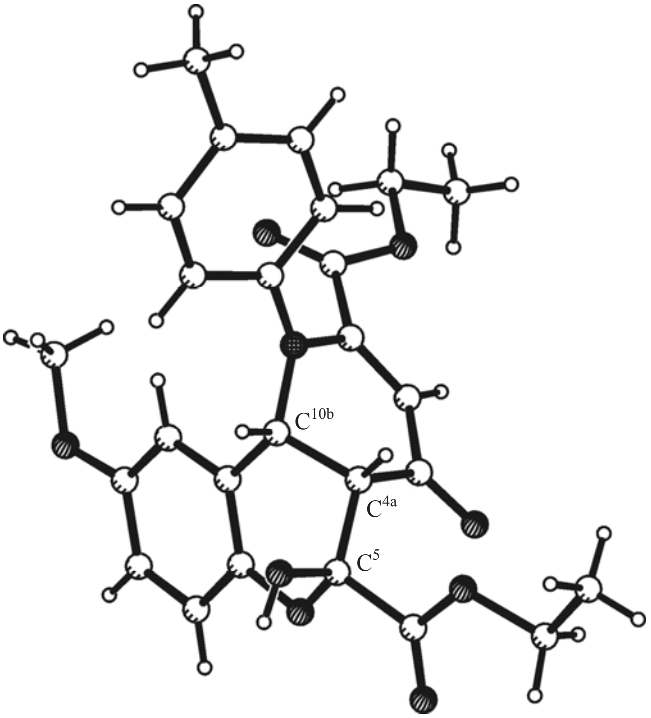
The ^{13}C NMR spectrum of **VI** contained 24 signals, the intensity of two of which corresponded to two carbon nuclei. By recording the ^{13}C NMR spectrum without decoupling from protons we succeeded in identifying signals from quaternary, tertiary, secondary, and primary carbon atoms. In the carbonyl region we observed three signals at δ_C 190.12, 172.81, and 169.09 ppm, belonging to C^4 and two ester carbonyl carbon atoms, respectively. Signals from sp^2-hybridized carbon atoms linked to electronegative atoms or electron-withdrawing groups appeared at δ_C 156.47, 149.21, 149.15, and 145.29 ppm. Analysis of long-range ^{13}C–^1H coupling constants allowed us to assign these signals to C^9, C^2, C^{6a}, and C^i in the *p*-tolyl fragment, respectively. The region δ_C 137–110 ppm contained six signals corresponding to sp^2-carbon atoms; signals at δ_C 131.80 and 122.96 ppm (2C each) belong to C^o and C^m. Two CH signals at δ_C 119.61 and 111.06 ppm are split only due to direct coupling with proton; therefore, they were assigned to C^{10} and C^3. Two quaternary sp^2-hybridized carbon atoms, C^{10a} (δ_C 136.61 ppm) and C^p (*p*-tolyl fragment (δ_C 121.61 ppm), resonated in the same region. The signal at δ_C 95.59 ppm, i.e., in the region typical of sp^3-carbon atoms, corresponds to the quaternary C^5 atom. In the upfield region of the ^{13}C NMR spectrum, signals from two sp^3-carbon atoms (C^{4a} and C^{10b}) were present

Correlation coefficients for experimental and calculated [GIAO B3LYP/6-31G(d)//HF/6-31G] chemical shifts (^{1}H: 3-H, 4a-H, 10-H, 10a-H, OCH$_3$, 2-COOCH$_2$C**H**$_3$; ^{13}C: C^2, C^3, C^4, C^{4a}, C^5, C^{6a}, C^{10b}), mean-square deviations (*rms*), slopes (*a*), standard deviations (*sd*), and mean absolute deviations (MAD = $\Sigma|\delta_{\mathrm{exp}} - \delta_{\mathrm{calcd}}|/n$) for diastereoisomers **VIA–VID**

Diastereo-isomer no.	^{1}H					^{13}C				
	R^2	*rms*	*a*	*sd*	MAD	R^2	*rms*	*a*	*sd*	MAD
VIA	0.9935	0.22	0.99	0.24	0.07	0.9995	4.86	1.05	5.25	3.85
	0.8616[a]	0.72	1.01	0.79	0.56	0.9710	9.75	0.95	10.54	8.14
VIB	0.9673	0.36	0.96	0.39	0.30	0.9986	2.67	1.02	2.88	2.34
VIV	0.9812	0.26	1.01	0.29	0.23	0.9985	2.65	1.02	2.87	2.26
VIG	0.9660	0.52	1.04	0.57	0.39	0.9985	4.48	1.05	4.84	3.83

[a] The ^{1}H and ^{13}C chemical shifts of **VI** were calculated by the additivity scheme using ChemOffice software package.

(δ_C 60.96 and 48.37 ppm, respectively); among these, the C^{10b} nucleus is deshielded to a stronger extent due to effect of the neighboring electronegative nitrogen atom. The CH$_2$ carbon atoms in the ester ethyl groups resonated at δ_C 63.52 and 62.59 ppm. The remaining four upfield signals correspond to methyl carbon atoms, the most downfield of which (δ_C 56.46 ppm) belongs to the 9-methoxy group. The signal at δ_C 21.57 ppm displayed no fine structure in the proton-coupled spectrum; therefore, it was assigned to the methyl group in the tolyl substituent. Methyl carbon atoms in the ethoxy groups gave rise to two signals at δ_C 15.02 and 14.68 ppm.



Structure of the molecule of diethyl (4a*R*,5*R*,10a*R*)-5-hydroxy-9-methoxy-1-(4-methylphenyl)-4-oxo-1,4a,5,10b-tetrahydro-4*H*-chromeno[4,3-*b*]pyridine-2,5-dicarboxylate (**VIA**) according to the X-ray diffraction data.

Thus analysis of the chemical shifts, multiplicities, and intensities of signals in the ^{1}H and ^{13}C NMR spectra confirmed the structure of the major product formed in the reaction of diethyl 2,4,6-trioxoheptanedioate (**I**) with 4-methoxy-2-(4-methylphenyliminomethyl)phenol (**V**). With a view to elucidate its steric configuration we calculated the ^{1}H and ^{13}C chemical shifts for possible diastereoisomeric structures **VIA–VID** at the GIAO B3LYP/6-31G(*d*)//RHF/6-31G level [25–29]. The most probable structure was selected on the basis of the results of regression analysis, i.e., statistical errors and correlation coefficients characterizing conformity of the calculated and experimental data. Carbon chemical shifts are sensitive to bond nature and their sequence in a molecule [30, 31], while their sensitivity to spatial orientation is lower. Therefore, as might be expected, the calculated ^{13}C chemical shifts for all four diatereoisomer showed a good correlation with the experimental values (R^2 = 0.9985 for **VIB–VId** and 0.9995 for **VIA**; see table), providing an additional support to the assumed structure. Unlike ^{13}C, proton chemical shifts in ^{1}H NMR spectra strongly depend on specificity of local magnetic environment, i.e., on the orientation of magnetically anisotropic groups relative to the corresponding protons [25]. Therefore, these data may be used to analyze fine structural parameters such as conformational and configurational features. Comparison of the calculated proton chemical shifts for four possible structures with the experimental values unambiguously indicated formation of diastereoisomer **VIA**. The correlation coefficient for structure **VIA** [R^2(^{1}H) = 0.9935] is appreciable higher than those found for structures **VIB–VID** [R^2(^{1}H) = 0.9673, 0.9812, and 0.9660, respectively].

On the other hand, it should be emphasized that empirical estimates of the ^{13}C and especially ^{1}H chemical shifts showed no good correlation with the experimental values (R^2 = 0.971 and 0.8616 for ^{13}C and ^{1}H, respectively; see table). Moreover, additivity schemes are insensitive to variations in steric structure, so that they could not be used to distinguish different diastereoisomers. Thus nonempirical estimates are valuable for analysis of both chemical structure and configurational isomerism.

The structure of compound **VI** was finally proved by X-ray analysis of its single crystal (see figure). The X-ray diffraction data unambiguously indicated relative configuration of the chiral centers as (4a*R*,5*R*,10b*R*), i.e., that corresponding to diastereoisomer **VIA**. Taking into account that crystals of **VIA** are centrosymmetric, the results coincided with the data of ^{1}H and ^{13}C NMR spectroscopy and calculation methods.

Studies on the reaction of triketo diester **I** with other derivatives of *N*-(benzylidene)anilines and its mechanism are now in progress, and their results will be reported in our subsequent publications.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded at 35°C on a Bruker Avance 600 spectrometer at 600.13 and 150.926 MHz, respectively, using DMSO-d_6 as solvent and reference (δ 2.54 ppm). The IR spectra were measured in KBr on a Bruker Vector-22 instrument in the range from 400 to 3600 cm^{-1}. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using diethyl ether–petroleum ether–methanol (2 : 1 : 0.1) as eluent. Column chromatography was performed on silica gel L (100–160 μm). The melting points were determined on a Boetius microscope.

Diethyl 5-hydroxy-9-methoxy-1-(4-methylphenyl)-4-oxo-1,4a,5,10b-tetrahydro-4*H*-chromeno-[4,3-*b*]pyridine-2,5-dicarboxylate (VI). A solution of 0.241 g (1 mmol) of 4-methoxy-2-(4-methylphenyliminomethyl)phenol (**V**) in 10 ml of acetic acid was added under stirring to a solution of 0.258 g (1 mmol) of diethyl 2,4,6-trioxoheptanedioate (**I**) in 10 ml of acetic acid, and the mixture was stirred for 35 h at 20°C. The mixture was evaporated to 1/3 of the initial volume under reduced pressure, and the yellow crystals were filtered off, washed with cold isopropyl alcohol (3×10 ml), and dried in air to obtain 0.46 g (97%) of compound **VI** as a mixture of diastereoisomer. The major diastereoisomer was isolated by column chromatography, followed by recrystallization from isopropyl alcohol. Yield 0.17 g (35%), pure (4a*R*,5*R*,10b*R*)-diastereoisomer **VIA**, mp 172–174°C. IR spectrum, ν, cm^{-1}: 3411, 3067, 1745, 1730, 1710, 1657, 1615, 1585, 1569, 1479, 1468, 1447, 1422, 1368, 1326, 1301, 1278, 1260, 1242, 1216, 1159, 1115, 1088, 1065, 1038, 930, 899, 852, 819, 786, 774, 759, 727. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 1.06 d.d (3H, $CH_2C\mathbf{H}_3$, *J* = 7.3, 7.1 Hz), 1.27 t (3H, $CH_2C\mathbf{H}_3$, *J* = 7.3, 7.1 Hz), 2.36 s (3H, CH_3), 3.73 s (3H, OCH_3), 3.95 d (1H, 4a-H, *J* = 5.5 Hz), 4.10–4.17 m (2H, OCH_2), 4.21–4.26 m (2H, OCH_2), 5.49 s (1H, 3-H), 5.49 d (1H, 10b-H, *J* = 5.5 Hz), 6.84 d (1H, 7-H, *J* = 8.88 Hz), 6.85 br.s (1H, OH), 6.88 d.d (1H, 8-H, *J* = 8.88, 2.88 Hz), 7.19 d (1H, 10-H, *J* = 2.88 Hz), 7.23 d (2H, *m*-H, *J* = 7.95 Hz), 7.29 d (2H, *o*-H, *J* = 7.95 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.68 q.t ($\mathbf{C}H_3CH_2$, *J* = 127.4, 1.8 Hz), 15.02 q.t ($\mathbf{C}H_3CH_2$, *J* = 126.8, 2.4 Hz), 21.57 q (CH_3, *J* = 126.8, 2.4 Hz), 60.96 d.d (C^{4a}, *J* = 134.0, 3.6 Hz), 48.37 d (C^{10b}, *J* = 150.8 Hz), 56.46 q (OCH_3, *J* = 126.8, 2.4 Hz), 62.59 t.q (CH_2O, *J* = 148.4, 4.8 Hz), 63.52 t.q (CH_2O, *J* = 145.4, 4.2 Hz), 95.59 d (C^5, *J* = 4.81 Hz), 111.06 d.d (C^3, *J* = 170.6, 4.2 Hz), 111.58 d.d (C^7, *J* = 158.6, 4.8 Hz), 117.93 d.d (C^8, *J* = 161.0, 5.4 Hz), 119.61 d.d (C^{10}, *J* = 157.4, 5.40 Hz), 121.61 d (C^p, *J* = 3.4 Hz), 122.96 d (C^m, *J* = 3.4 Hz), 131.80 d (C^o, *J* = 3.4 Hz), 136.61 d.d (C^{10a}, *J* = 157.4, 5.4 Hz), 145.29 d (C^i, *J* = 3.4 Hz), 149.15 d.d (C^{6a}, *J* = 4.2, 3.6 Hz), 149.21 d (C^2, *J* = 3.4 Hz), 156.47 d.d (C^9, *J* = 7.2, 7.2 Hz), 169.09 t (C=O, *J* = 3.0 Hz), 172.81 t (C=O, *J* = 3.0 Hz), 190.12 d.d (C=O, *J* = 6.6, 5.4 Hz). Found, %: C 64.73; H 5.72; N 2.80. $C_{26}H_{27}NO_8$. Calculated, %: C 64.86; H 5.65; N 2.91.

X-Ray diffraction data for a single crystal of compound VIA were acquired at room temperature (20°C) on an Enraf–Nonius CAD-4 automatic four-circle diffractometer (λCuK_α irradiation, λ = 1.54184 Å, graphite monochromator). No drop in intensity of three control reflections was observed during data acquisition. The unit cell parameters and reflection intensities were determined using MolEN program [32] on a DEC Alpha Station 200 computer. The structure was solved by the direct method using SIR program [33]. All calculations were performed using WinGX software package [34]. The structure of molecule **VIA** was plotted using PLATON software [35]. Colorless transparent prisms, monoclinic crystal system; $C_{26}H_{27}NO_8$; *M* 481.49; unit cell parameters: *a* = 11.616(1), *b* =

15.831(4), $c = 13.510(1)$ Å; $\beta = 97.833(8)°$; $V = 2461.2(7)$ Å^3; $d_{\mathrm{calc}} = 1.30$ g/cm^3; $Z = 4$; space group $P2_1/n$; $\omega/2\theta$ scanning, $4.33 \le \theta \le 64.91°$. Absorption by the crystal was taken into account empirically ($\mu\mathrm{Cu}K_\alpha = 8.1$ cm^{-1}). The structure was refined first in isotropic and then in anisotropic approximation using SHELX-97 software [36]. The coordinates of hydrogen atoms were calculated on the basis of stereochemical criteria and were refined according to the riding model. Total of 4150 independent reflections were measured, 1643 of which were with $I > 2\sigma(I)$. The final divergence factors were $R = 0.056$, $R_w = 0.140$ for 1643 reflections with $F^2 \ge 4\sigma(I^2)$. The complete set of crystallographic data was deposited to the Cambridge Crystallographic Data Center (entry no. CCDC 626992).

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