Synthesis of 5*H*-[1]Benzopyrano[4,3-*b*]pyridin-5-ones Containing an Azacannabinoidal Structure

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Starting from 7-alkoxy-4-aminocoumarins **5**, **6**, **8**, **12**, and **13** as key intermediates, this paper describes two different methods for the preparation of azacannabinoidal 5*H*[1]benzopyrano[4,3-*b*]pyridin-5-ones **24-27**, **38**, and **39** containing typical structural requirements for ZNS activity. First, Michael addition of **6** and **8** to the double bonds of alkyl vinyl ketones **14** and **15** resulted in a mixture of tetrahydropyridines **24-27** and fused pyridines **20-23** the latter of which were reduced by sodium cyanoborohydride to give the target compounds **24-27**. The second, pyridine ring closure was accomplished by a combination of Vilsmeier acetylation and formylation resulting in fused 4-chloropyridines **31-33** followed by reduction.

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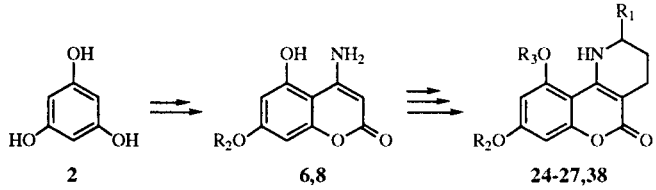
In a previous paper [1] we reported on the application of suitable annelation reactions to 4-aminocoumarins with the aim of preparing 5*H*-[1]benzopyrano[4,3-*b*]pyridin-5-ones. These target compounds are characterized by a phenanthrene-like structure as found in tetrahydrocannabinol (THC) that belongs to the few ZNS active compounds without a nitrogen atom. Since Anker and Cook [2] first synthesized so-called azacannabinoides by condensation of olivetol with 3-carbethoxy-1-methylpiperidone several authors have introduced one or more heteroatoms into this molecule in order to obtain more insight into structure-activity-relationships (SAR) [3-10]. In this context, we have explored possible routes of access to the tricyclic system of azacannabinoides. In Scheme 1 is outlined the principal pathway starting from

Scheme 1

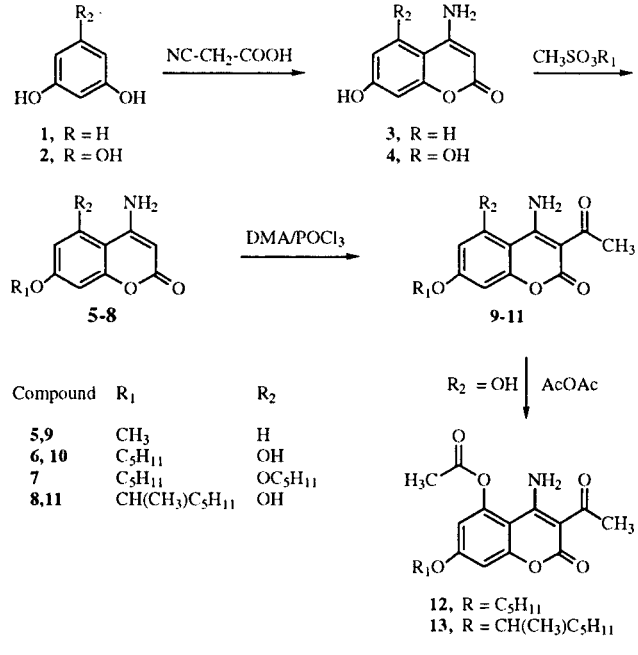


2 **6,8** **24-27,38**

R_1 = H, CH_3
R_2 = Alkyl (long chain)
R_3 = H, $COCH_3$

phloroglucinol to the compounds **24-27** and **38** with typical structure elements of THC as well as a partially hydrogenated pyridine ring system. This paper describes the endeavours that were undertaken to prepare these target compounds by two different methods. Subsequent efforts initially aimed at synthesizing the 4-aminocoumarins **9**,**12**, and **13** as key intermediates for which the preparation is depicted in Scheme 2. The acid catalyzed reaction of

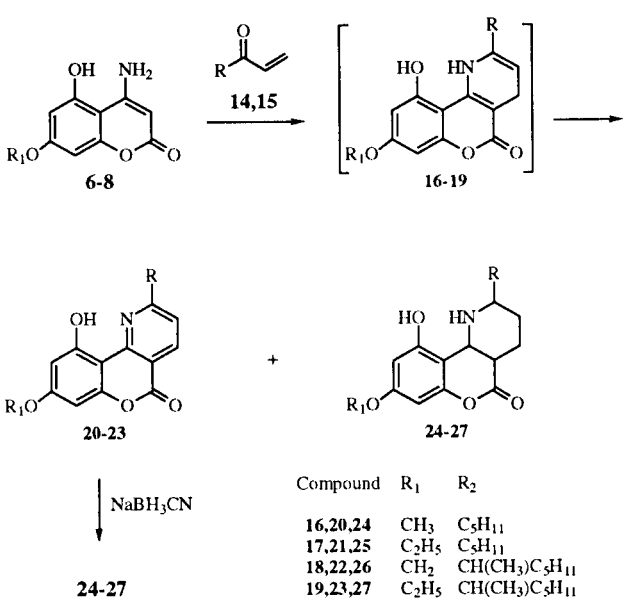
Scheme 2



phloroglucinol as well as resorcinol with cyanoacetic acid has long been known [11] to give the ketimide hydrochlorides of **3** and **4** which upon recrystallization from ethanol/water produced the corresponding 4-amino-7-hydroxycoumarins. For alkylation of the 7-position, *n*-pentyl and 1-methylhexyl, respectively, had to be chosen considering since these groups frequently occur as alkyl chains in THC analogues. Regarding metabolic processes in the organism, branching in the neighbourhood of the oxygen atom would largely diminish enzymatic dealkylation reaction. The preparation of the phenolic ethers **6-8** proved to be difficult and conventional reagents such as alkyl halides were not effective. However, upon heating 4-aminocoumarin **4** with pentyl methanesulfonate in *N*,*N*-

dimethylformamide in the presence of potassium carbonate, a mixture of the mono and dialkylated products **6** and **7** were obtained and separated by the solubility of the monoalkyl compound in alkaline solution. In the case of the 1-methylhexyl derivative no attempt was made to effect the separation of the dialkylated product. In contrast to the ring closure reaction accomplished by a combination of Vilsmeier acetylation and formylation, the 4-aminocoumarins **6** and **8** could be used for an annelation reaction with alkyl vinyl ketones without any further derivatization as outlined in Scheme 3.

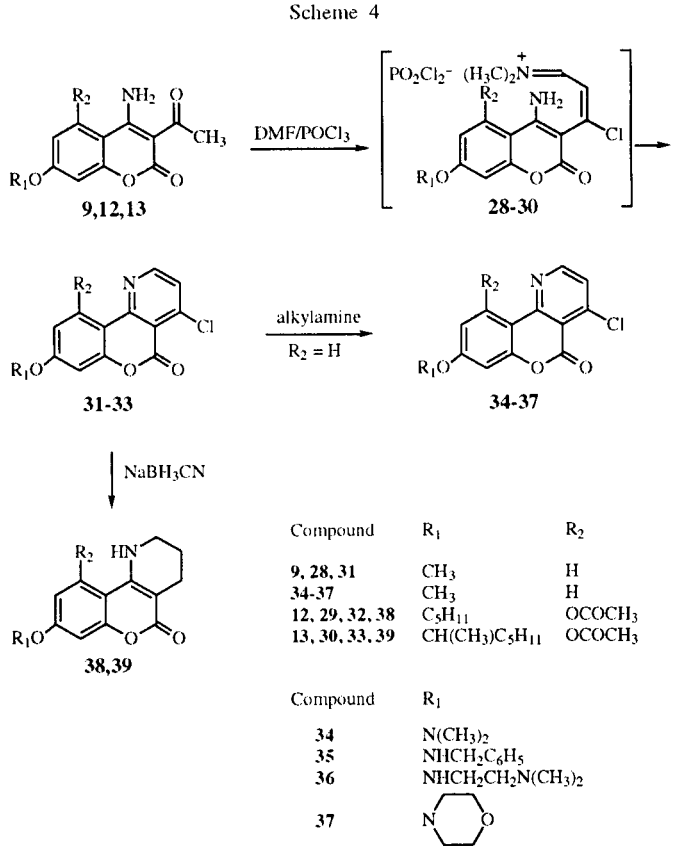
Scheme 3



Compound	R_1	R_2
16,20,24	CH_3	C_5H_{11}
17,21,25	C_2H_5	C_5H_{11}
18,22,26	CH_2	$CH(CH_3)C_5H_{11}$
19,23,27	C_2H_5	$CH(CH_3)C_5H_{11}$

The utilization of enamines in the Robinson annelation sequences has long been known [12] and should be a synthetic approach to compounds with cannabinoidal structure. On the other hand, the Michael addition of enaminones to methyl vinyl ketone or Mannich bases gave rise to a mixture of pyridine and tetrahydropyridine derivatives [13,14]. To clarify the question whether nitrogen containing heterocycles would be formed or not, treatment of **6** with methyl vinyl ketone in glacial acetic acid was then investigated and resulted in a mixture of 5*H*-[1]benzopyrano[4,3-*b*]pyridin-5-ones **20** and **24**. The enamine function of the substrate added to the double bond in a Michael reaction and gave an intermediate dienaminone that underwent an internal condensation to form the dihydropyridine **16**. Under the reaction conditions **16** could not be isolated but its subsequent disproportionation provided the product mixture. This Hantzsch-like pyridine synthesis has also been run with ethyl vinyl ketone as well as the coumarin **8** (see Scheme 3) and it was remarkable that, on work-up, the 1-methylhexyl alkylated compounds **22** and **23** were isolated as insoluble hydrochlorides. The ^1H nmr spectra display the expected aromatic and heteroaromatic resonances between δ = 6.5 and 9.5 ppm, especially two doublets of an AB system for the pyridine protons, as well as further characteristic patterns. An important aspect of this ^1H nmr study was to assess the 2-position of the methyl group indicated by the singlet at δ = 2.67 ppm [13]. Furthermore, this assignment was supported by the measured coupling constant $J_{3,4}$ = 8 Hz in contrast to that reported [15] $J_{2,3}$ = 5 Hz. These data clearly demonstrated that the amino substituent had reacted with the carbonyl group of the alkyl vinyl ketone and consequently the 2-position of the alkyl group. In the tetrahydropyridine series any determinations concerning the stereochemistry of the 2-alkyl substituent (axial or equatorial) could not be accomplished. In the ^1H nmr spectra the signals attributable to H-2, H-3a, and H-3e were overlapped by signals of the long chain alkyl in the 8-position or of methylene protons in the 2-position. The above mentioned Michael addition of alkyl vinyl ketones **14** and **15** led to relatively small amounts of the desired azacannabinoides **24-27** due to disproportionation of the intermediate dihydropyridines. Therefore, reduction of the pyridines **20-23** had to be performed by treatment with excess sodium cyanoborohydride in glacial acetic acid at room temperature. The resulting products proved to be identical with the

Scheme 4



Compound	R_1	R_2
9, 28, 31	CH_3	H
34-37	CH_3	H
12, 29, 32, 38	C_5H_{11}	$OCOCH_3$
13, 30, 33, 39	$CH(CH_3)C_5H_{11}$	$OCOCH_3$

Compound	R_1
34	$N(CH_3)_2$
35	$NHCH_2C_6H_5$
36	$NHCH_2CH_2N(CH_3)_2$
37	

tetrahydropyridines **24-27** by comparing their analytical data with those of authentic samples. The weak basicity of the vinylogous acid amide structure prevented further reduction to the corresponding piperidines. By analogy, pyridine-3,5-dicarboxylic acid derivatives are reduced to 1,4-dihydropyridines by the same procedure [16].

To effect the synthesis of azacannabinoides unsubstituted in the 2-position an alternate synthetic approach had to be developed. It is known that according to the reaction conditions acetanilides were converted into 2-chloroquinolines or 2-chloroquinoline-3-carbaldehydes by action of the Vilsmeier's reagent in phosphorus oxychloride solution [17,18]. Considering this procedure on the one hand and the vinylogous acid amide moiety of 4-aminocoumarins **10** and **11** on the other hand, we attempted the application of this cyclization reaction in order to synthesize our target compounds. In fact, this concept proved to be correct. As shown in Scheme 4, in a mixture of *N,N*-dimethylformamide/phosphorus oxychloride the 4-aminocoumarin **9** furnished the desired 4-chloropyridine **31**. The structural assignment was unequivocally established by spectral data and was consistent with its elemental analysis. Thus, the ir spectrum did not show the presence of a ketone carbonyl group as well as NH function but an intensive carbonyl absorption band at 1765 cm^{-1} attributable to lactone carbonyl group. Furthermore, the ^{1}H-nmr spectrum was characteristic for pyrido-annelated coumarins and showed two doublets of an AB system for the pyridine protons at 8.84 and 8.01 ppm with typical vicinal coupling constants of J = 6 Hz. These facts indicated that **31** has ring closed structure. Unfortunately, the corresponding coumarins **10** and **11** did not give any uniform reaction under comparable conditions obviously due to the phenolic 5-hydroxyl group. Additional attack of the electrophilic reagent at the benzene moiety of the molecule might be a consequence. But protection of this hydroxyl group furnished the acetic acid esters **12** and **13**, respectively, and subsequent Vilsmeier formylation afforded the annelated 4-chloropyridine derivatives **32** and **33**. In none of the experiments, however, were any diformylated or ring opened products obtained to solve the problem whether the reaction was initiated by *C*-formylation or by forming an amidine intermediate. The keto function *via* the corresponding enol form was always substituted by a chlorine atom. According to the resulting 4-chloronicotinic acid structure, the C-Cl-bond should be easily cleaved by amino compounds. In order to demonstrate its ability to undergo nucleophilic substitution reactions, **31** was allowed to react with some amines in refiuxing ethanolic solution to provide 4-aminopyridines **34-37**. The constitutions were confirmed by their spectral data. In the ir spectra the lactone carbonyl absorption bands were shifted to lower wavenumbers in the range of 1700 cm^{-1} compared with the corresponding value of the chloro derivative **31** mentioned above. The ^{1}H-nmr spectra were characterized by the typical AB system of the pyridine protons. As anticipated from its high stability, the coumarin lactone function remained unattacked by the *N*-nucleophile. This particular example may illustrate numerous conversions possible for the preparation of 4-substituted azacannabinoides if the pyridine ring is subsequently reduced.

In order to accomplish the synthesis of azacannabinoides unsubstituted in the 2- and 4-positions, **32** was treated with excess sodium cyanoborohydride to form the stable acetic acid ester **38** in 65% yield. Structure proof was straightforward. The ^{1}H-nmr spectrum had separated multiplets for the axial and equatorial tetrahydropyridine protons. Additionally, the infrared spectrum showed strong absorptions at 3410 cm^{-1} (NH), 1765 cm^{-1} (phenyl ester), and 1645 cm^{-1} characteristic of a vinylogous acid amide. The reduction of **33**, however, led to a mixture from which **39** could not be separated by preparative column chromatography.

EXPERIMENTAL

Melting points were determined with a Dr. Tottoli melting point apparatus (Fa. Büchi) and are uncorrected. Microanalyses were performed at the microanalytical laboratory of Ilse Beetz, D-96317 Kronach. The ir spectra were recorded as potassium bromide pellets on a Beckman Acculab 10 spectrometer and the ^{1}H-nmr spectra were obtained on a Varian EM-360 A and a Bruker AM-400 spectrometer. Chemical shifts are expressed in δ (ppm) downfield from tetramethylsilane as an internal reference.

The 4-aminocoumarins **3-5** were prepared according to the literature method [48].

Alkylation of 4-Amino-5,7-dihydroxycoumarin **4**. General Procedure.

A mixture of (0.01 mole) of 4-amino-5,7-dihydroxycoumarin **4**, (0.02 mole) potassium carbonate, and (0.015 mole) methanesulphonic acid ester in *N,N*-dimethylformamide (50 ml) was heated for 45 minutes at 110-120° in an oil bath. After cooling, the suspension was poured onto crushed ice (150 g) and allowed to stir at room temperature for 1 hour. The dialkyl derivative **7** as insoluble material was removed by filtration, and the filtrate made acid with 3*N* hydrochloric acid. The precipitate obtained was filtered and could be directly used in the subsequent reaction with dimethylacetamide/phosphorus oxychloride.

In case of **8** the dialkylated product was not isolated. After alkylation was finished the reaction mixture was made alkaline by addition of 3*N* sodium hydroxide, followed by stirring for 3 hours, and filtration. The filtrate was extracted with petroleum ether (3 x 50 ml) and **8** was isolated from the aqueous solution acidified with 3*N* hydrochloric acid. It could be used without further purification.

The yields, analytical, and spectral data for compounds **6-8** are given in Tables 1 and 2.

General Procedure for the Preparation of 3-Acetyl-4-aminocoumarins **9-11**.

Table 1

Physical Data and IR of 4-Aminocoumarins **6-13**

Compound	Mp (°C) Yield (%)	Mol formula (Mol wt.)	Analysis Calcd./Found C	H	N	IR (cm^{-1}) (KBr)
6	204-205	$C_{14}H_{17}NO_4$	63.89	6.51	5.32	3440, 3300, 3200,
	51	263.2	63.81	6.54	5.41	2940, 1640
7	99	$C_{19}H_{27}NO_4$	68.49	8.16	4.20	3450, 3270, 2940,
	38	333.2	68.33	8.08	4.41	1675
8	232-234	$C_{16}H_{21}NO_4$	65.96	7.26	4.81	3460, 3320, 3220,
	46	291.4	66.22	7.31	4.78	2940, 1640
9	290-292	$C_{12}H_{11}NO_4$	61.80	4.75	6.01	3360, 3190 2935
	61	233.2	61.64	4.72	5.96	1680
10	203	$C_{16}H_{19}NO_5$	62.94	6.27	4.59	3415, 3360-3040,
	90	305.3	62.62	6.24	4.63	2960, 1675, 1665
11	159-160	$C_{18}H_{23}NO_5$	64.85	6.95	4.20	3445, 3170,
	94	333.4	64.94	6.90	4.23	1680
12	113-114	$C_{18}H_{21}NO_6$	62.24	6.09	4.03	3440, 3180, 2960,
	91	347.4	61.98	6.06	4.06	1775, 1715
13	81	$C_{20}H_{25}NO_6$	63.99	6.71	3.73	3445, 3160, 2940,
	88	375.4	63.84	6.74	3.76	1765, 1715

Table 2

^{1}H-NMR Spectroscopic Data for 4-Aminocoumarins **6-13**

Compound	
6	0.70-2.05 (m, 9H alkyl), 4.09 (t, J = 6 Hz, 2H, OCH_2), 4.91 (s, 1H, H-3), 6.18-6.39 (m, 2H arom), 7.02-7.20 (m, 2H, NH_2), 10.51 (s, 1H, OH) [a]
7	0.60-2.10 (m, 18H alkyl), 3.92 (t, J = 6 Hz, 2H, OCH_2), 4.04 (t, J = 6 Hz, 2H, OCH_2), 5.15 (s, 1H, H-3), 6.12-6.46 (m, 2H, NH_2), 6.18 (d, J = 2 Hz, 1H arom), 6.34 (d, J = 2 Hz, 1H arom) [b]
8	0.65-1.95 (m, 14H alkyl), 4.33-4.82 (m, 1H, OCH), 4.91 (s, 1H, H-3), 6.15-6.47 (m, 2H arom), 6.93-7.40 (m, 2H, NH_2), 10.21-10.72 (m, 1H, OH) [a]
9	2.82 (s, 3H, CH_3), 3.97 (s, 3H, OCH_3), 6.79 (d, J = 2 Hz, 1H, H-8), 6.87-7.17 (m, 1H, H-6), 7.80 (d, J = 9 Hz, 1H, H-5) [c]
10	0.71-2.03 (m, 9H alkyl), 2.43 (s, 3H, CH_3), 4.08 (t, J = 6 Hz, 2H, OCH_2), 6.17 (d, J = 2 Hz, 1H arom), 6.32 (d, J = 2 Hz, 1H arom), 8.34-8.77 (m, 1H, NH), 11.38-11.68 (m, 1H, NH) [a]
11	0.64-2.03 (m, 14H alkyl), 2.70 (s, 3H, CH_3), 4.30-4.83 (m, 1H, OCH), 6.36 (d, J = 2 Hz, 1H arom), 6.78 (s, J = 2 Hz, 1H arom), 8.66-8.98 (m, 1H, NH), 11.40-11.73 (m, 1H, NH) [b]
12	0.67-2.37 (m, 9H alkyl), 2.28 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 4.11 (t, J = 6 Hz, 2H, OCH_2), 6.33-6.66 (m, 2H arom), 8.22-8.79 (m, 1H, NH), 11.41-11.96 (m, 1H, NH) [b]
13	0.65-2.17 (m, 9H alkyl), 2.30 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 4.40-4.80 (m, 1H, OCH), 6.50 (d, J = 2 Hz, 1H arom), 6.62 (d, J = 2 Hz, 1H arom), 8.50-9.00 (m, 1H, NH), 11.50-12.00 (m, 1H, NH) [b]

[a] Recorded in dimethyl sulphoxide-d_6. [b] Recorded in deuteriochloroform. [c] Recorded in deuteriotrifluoroacetic acid.

To a solution of the coumarins **5**, **6**, and **8** (5 mmoles) respectively, in dimethylacetamide (10 ml) at 0 to 10° was added phosphorus oxychloride (10 mmoles) dropwise with stirring. After 5 hours at room temperature the reaction mixture was poured into ice-water (150 ml) and made alkaline with 3*N* sodium hydroxide. After stirring for 15 minutes the solution was acidified with 3*N* hydrochloric acid. The resulting solid was removed by filtration, washed with water, and recrystallized from 50% ethanol.

The yields, analytical, and spectral data for compounds **9-11** are given in Tables 1 and 2.

Acetylation of Coumarins **10** and **11**. General Procedure.

A solution of coumarins **10** or **11** (2 mmoles) respectively, in 10 ml of acetic anhydride was refluxed for 30 minutes. After cooling to room temperature the reaction mixture was poured onto crushed ice (50 g) in several portions and stirred overnight. The precipitate was collected by filtration and recrystallized from ethanol/water.

The yields, analytical, and spectral data for compounds **12** and **13** are given in Tables 1 and 2.

General Procedure for the Michael Addition of **6** and **8** to Alkyl Vinyl Ketones **14** and **15**.

A solution of **6** or **8** (5 mmoles) respectively, and 10 mmoles of the appropriate alkyl vinyl ketone in glacial acetic acid (10 ml) was refluxed for 1 hour. After cooling, the solution was added dropwise with stirring to a mixture of ice-water (150 ml) and 3*N* hydrochloric acid (5 ml) and stirring was continued for 1 hour. Work up was as described below. The yields, melting points, recrystallization solvents, analytical, and spectral data for compounds **20-27** are given in Tables 3 and 4.

10-Hydroxy-2-methyl-8-pentoxy-5*H*-[1]benzopyrano[4,3-*b*]-

Table 3

Physical Data of 5*H*-[1]Benzopyrano[4,3-*b*]pyridin-5-ones **20-27**

Compound	Yield (%)	Mp (°C) (recrystallization solvent)	Mol formula (Mol wt)	Analysis Calcd./Found C	H	N	Cl
20	35	198	$C_{18}H_{19}NO_4$	69.00	6.11	4.47	
		2-propanol	313.4	69.05	6.09	4.51	
21	34	180	$C_{19}H_{21}NO_4$	69.71	6.47	4.28	
		methanol	327.4	69.50	6.38	4.30	
22	26	176-178	$C_{20}H_{24}ClNO_4$	63.57	6.40	3.71	9.38
		ethanol	377.9	63.32	6.50	3.74	9.48
23	36	191	$C_{21}H_{26}ClNO_4$	64.36	6.69	3.57	9.05
		ethanol	391.9	64.44	6.78	3.60	9.12
24	27	206-207	$C_{18}H_{23}NO_4$	68 12	7.30	4.45	
		2-propanol	317.4	68.00	7.40	4.50	
25	45	164-165	$C_{19}H_{25}NO_4$	68.86	7.60	4.23	
		methanol	331.4	68.72	7.68	4.19	
26	23	155-158	$C_{20}H_{27}NO_4$	69 54	7.88	4.05	
		ethanol	345.4	69.65	7.88	4.10	
27	34	71-76	$C_{21}H_{29}NO_4$	70.17	8.13	3.90	
		ethanol	359.5	69.91	8.21	3.92	

Table 4

IR and NMR Spectral Data of 5*H*-[1]Benzopyrano[4,3-*b*]pyridin-5-ones **20-27**

Compound	IR (cm^{-1})	^{1}H-NMR (δ ppm)
20	3240, 2940, 1765	0.82-2.52 (m, 9H alkyl), 3.04 (s, 3H, CH_3), 4.52 (t, J = 6 Hz, 2H, OCH_2), 6.72-6.90 (m, 2H arom), 7.82 (d, J = 8 Hz, 1H, H-3), 9.17 (d, J = 8 Hz, 1H, H-4) [b]
21	3390, 2910 1735	0.67-2.08 (m, 12H, CH_3, alkyl), 2.87 (q, 2H, CH_2), 3.80 (m, 2H, OCH_2), 6.24-6.47 (m, 2H arom), 7.30 (d, J = 8 Hz, 1H, H-3), 8.29 (d, J = 8 Hz, 1H, H-4), 8.38-8.56 (m, 1H, OH) [a]
22	3450, 2935 2500,1765	0.77-2.37 (m, 14H alkyl), 3.07 (s, 3H, CH_3), 4.70-5.30 (m, 1H, OCH), 6.73-6.93 (m, 2H arom), 7.84 (d, J = 8 Hz, 1H, H-3), 9.17 (d, J = 8 Hz,1H, H-4) [b]
23	3450, 2940 2460, 1765	0.73-2.40 (m, 17H alkyl, CH_3), 3.40 (q, J = 8 Hz, 2H, CH_2), 4.70-5.27 (m, 1H, OCH), 6.70 (d, J = 2 Hz, 1H arom), 6.87 (d, J = 2 Hz, 1H arom), 7.83 (d, J = 8 Hz, 1H, H-3), 9.17 (d, J = 8 Hz, 1H, H-4)[b]
24	3400, 3070, 2960, 1635, 1600	0.91 (t, J = 6.90 Hz, 3H, CH_3), 1.23 (d, J = 6.33 Hz, 3H, CH_3), 1.33-1.45 (m, 5H, 2 x CH_2, H-3a), 1.78-1.81 (m, 2H, CH_2), 1.88-1.90 (m, 1H, H-3e), 2.28-2.33 (m, 1H, H-4a), 2.43-2.47 (m, 1H, H-4e), 3.40-3.50 (m, 1H, H-2), 4.05 (m, 2H, OCH_2), 6.23 (d, J = 2.12 Hz, 1H arom), 6.32 (d, J = 2.12 Hz, 1H arom), 7.45 (s, 1H, NH), 10.33 (s, 1H, OH) [a]
25	3400, 3080, 2940,1655 1605	0.90 (t, J = 6.95 Hz, 3H, CH_3), 0.97 (t, J = 7.41 Hz, 3H, CH_3), 1.30-1.48 (m, 5H, 2 x CH_2, H-3a), 1.50-1.60 (m, 2H, CH_2), 1.75-1.85 (m, 2H, CH_2), 1.86-1.95 (m, 1H, H-3e), 2.25-2.35 (m, 1H, H-4a), 2.40-2.50 (m, 1H, H-4e), 3.21-3.32 (m, 1H, H-2), 4.08 (m, 2H, OCH_2),6.23 (d, J = 1.98 Hz, 1H arom), 6.33 (d, J = 1.98 Hz, 1H arom), 7.49 (s, 1H, NH), 10.33 (s, 1H, OH) [a]
26	3400, 3080, 2940,1655, 1600	0.83-0.91 (m, 3H, CH_3), 1.20-1.49 (m, 13H, 2 x CH_3, 3 x CH_2, H-3a), 1.60-1.81 (m, 2H, CH_2), 1.88-1.96 (m, 1H, H-3e), 2.24-2.35 (m, 1H, H-4a), 2.43-2.49 (m, 1H, H-4e), 3.41-3.51 (m, 1H, H-2), 4.57-4.60 (m, 1H, OCH_3), 6.22 (d, J = 2.38 Hz, 1H arom), 6.34 (d, J = 2.38 Hz, 1H arom), 7.55 (d, J = 9.40 Hz, 1H, NH), 10.30 (s, 1H, OH) [a]
27	3400, 3150, 2930,1650, 1600	0.81-0.89 (m, 3H, CH_3), 0.98 (t, J = 7.41 Hz, 3H, CH_3), 1.19-1.35 (m, 9H, CH_3, 3 x CH_2), 1.34-1.49 (m, 1H, H-3a), 1.34-1.49 (m, 2H, CH_2), 1.58-1.97 (m, 2H, CH_2), 1.86-1.95 (m, 1H, H-3e), 2.24-2.34 (m, 1H, H-4a), 2.40-2.49 (m, 1H, H-4e), 3.28-3.35 (m, 1H, H-2), 4.54-4.63 (m, 2H, OCH), 6.22 (d, J = 2.06 Hz, 1H arom), 6.36 (d, J = 2.06 Hz, 1H arom), 7.59 (d, J = 9.40 Hz, 1H, NH), 10.26 (s, 1H, OH) [a]

[a] Recorded in dimethyl sulphoxide-d_6. [b] Recorded in deuteriotrifluoroacetic acid

pyridin-5-one **20** and 10-Hydroxy-2-methyl-8-pentoxy-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*b*]pyridin-5-one **24**.

Compound **24** was collected by filtration and **20** was isolated from the filtrate by addition of 3*N* aqueous ammonia until precipitation was completed (*p*H 6).

2-Ethyl-10-hydroxy-8-pentoxy-5*H*-[1]benzopyrano[4,3-*b*]-pyridin-5-one **21** and 2-Ethyl-10-hydroxy-8-pentoxy-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*b*]pyridine **25**.

After stirring the acid solution in the presence of ethyl acetate (20 ml) for 1 hour **25** was collected by filtration. The organic layer was removed from the filtrate and **21** was isolated as described for compound **20**.

10-Hydroxy-2-methyl-8-(1-methyl)hexyloxy-5*H*-[1]benzo-pyrano[4,3-*b*]pyridin-5-one Hydrochloride **22** and 10-Hydroxy-2-methyl-8-(1-methyl)hexyloxy-1,2,3,4-tetrahydro-5*H*-[1]ben-zopyrano[4,3-*b*]pyridin-5-one **26**.

The mixture of the reactants was added to a solution of ice-water (100 ml) and concentrated hydrochloric acid (2 ml) to give the insoluble crude product. The hydrochloride of **22** was isolated by refluxing the crude product in ethyl acetate (30 ml) for 1 minute and then cooling to room temperature. The filtrate was concentrated under reduced pressure to a volume of about 3 ml and **26** crystallized at 0°.

2-Ethyl-10-hydroxy-8-(1-methyl)hexyloxy-5*H*-[1]benzopyrano[4,3-*b*]pyridin-5-one Hydrochloride **23** and 2-Ethyl-10-hydroxy-8-(1'-methyl)hexyloxy-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*b*]pyridine **27**.

Compounds **23** and **27** were isolated as described for **22** and **26**.

Ring Closure of **9**, **12**, and **13** by Vilsmeier Formylation. General Procedure.

To a solution of **9**, **12**,or **13** (5 mmoles) respectively, in *N,N*-dimethylformamide (10 ml) at 0° was added phosphorus oxychloride (0.01 mole). The reaction mixture was stirred for 30 minutes at room temperature and then heated for 6 hours at 40-45°. The resulting solid was collected by filtration, washed with water and recrystallized from 2-propanol.

The yields, analytical, and spectral data for compounds **31**- **33** are given in Tables 5 and 6.

Table 5

Physical Data of 5*H*-[1]Benzopyrano[4,3-*b*]pyridin-5-ones **31**-**38**

Compound	Yield (%)	Mp (°C) (recrystallization solvent)	Mol formula (Mol wt)	Analysis Calcd./Found C	H	N	Cl
31	62	198-200	$C_{13}H_8ClNO_3$	59.66	3.08	5.35	13.55
		2-propanol	261.7	59.80	3.12	5.40	13.62
32	78	156- 157	$C_{19}H_{18}ClNO_5$	60.73	4.83	3.73	9.43
		2-propanol	375.8	60.81	4.91	3.80	9.29
33	23	109	$C_{21}H_{22}ClNO_5$	62.46	5.49	3.47	8.78
		2-propanol	403.9	62.40	5.54	3.51	8.81
34	49	188- 190	$C_{15}H_{14}N_2O_3$	66.65	5.22	10.36	
		ethanol	270.3	66.60	5.17	10.42	
35	55	211-212	$C_{20}H_{16}N_2O_3$	72 27	4 85	8 43	
		ethanol	332.4	72.12	4.91	8.50	
36	35	129- 130	$C_{17}H_{19}N_3O_3$	65.16	6.11	13.41	
		methanol	313.4	64.95	6.02	13.52	
37	63	171	$C_{17}H_{16}N_2O_4$	65.38	5.16	8.97	
		2-propanol	312.3	65.30	5.14	9.03	
38	65	102	$C_{19}H_{23}NO_5$	66.07	6.71	4.06	
		ethanol	345.4	66 00	6.65	4.10	

Table 6

IR and NMR Spectral Data of 5*H*-[1]benzopyrano[4,3-*b*]pyridin-5-ones **31**-**38**

Compound	IR (cm^{-1})	^{1}H-NMR (δ ppm)
31	2935, 1765, 1605	4.07 (s, 3H, OCH_3), 7.07 (d, J = 2 Hz, 1H, H-7), 7.24 (dd, J = 9/2 Hz, 1H, H-9), 8.01 (d, J = 6 Hz, 1H, H-3), 8.32 (d, J = 9 Hz, 1H, H-10), 8.84 (d, J = 6 Hz, 1H, H-2) [a]
32	2940, 1780, 1765	0.94 (t, 3H, CH_3), 1.41 (sextet, J = 7.39 Hz, 2H, CH_2), 1.56 (m, 2H, CH_2), 1.93 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 4.13 (t, J = 6.45 Hz, 2H, OCH_2), 6.78 (d, J = 2.2 Hz, 1H arom), 6.79 (d, J = 2.3 Hz, 1H arom), 7.48 (d, J = 5.05 Hz, 1H, H-3), 8.83 (d, J = 5.05 Hz, 1H, H-2) [b]
33	2960, 1760, 1745	0.67-2.10 (m, 14H alkyl), 2.10 (s, 3H, CH_3), 4.30 (m, 1H, OCH), 6.68 (d, J = 2 Hz, 1H arom), 6.75 (d, J = 2 Hz, 1H arom), 7.40 (d, J = 5Hz, 1H, H-3), 8.77 (d, J = 5 Hz, 1H, H-2) [b]
34	2950, 2885, 1715,1610	3.07 (s, 6H, 2 x CH_3), 3.87 (s, 3H, OCH_3), 6.68 (d, J = 6 Hz, 1H, H-3), 6.75 (d, J = 2 Hz,1 H, H-7), 6.87 (dd, J = 9/2 Hz, 1H, H-9), 8.34 (d, J = 9 Hz, 1H, H-10), 8.36 (d, J = 6 Hz, 1H, H-2) [b]
35	3340, 3040, 2950,1695 1610	3.84 (s, 3H, OCH_3), 4.50 (d, J = 6 Hz, 2H, CH_2), 6.41 (d, J = 6Hz, 1H, H-3), 6.74 (d, J = 2 Hz, 1H, H-7), 6.85 (dd, J = 9/2 Hz, 1H, H-9), 7.27 (s, 5H arom), 8.24 (d, J = 6 Hz, 1H, H-2), 8.33 (d, J = 9 Hz, 1H, H10), 8.97-9.37 (m, 1H, NH) [b]
36	3325, 2950, 2820,2775, 1690,1615	2.28 (s, 6H, 2 x NCH_3), 2.40-2.81 (m, 2H, CH_2), 3.36 (q, J = 6 Hz, 2H, CH_2), 3.84 (s, 3H, OCH_3), 6.42 (d, J = 6Hz, 1H, H-3), 6.76 (d, J = 2 Hz, 1H, H-7), 6.85 (dd, J = 9/2 Hz, 1H, H-9), 8.30 (d, J = 6 Hz, 1H, H-2), 8.33 (d, J = 9 Hz, 1H, H-10), 8.62-9.07 (m, 1H, NH) [b
37	2950, 2870, 1730,1610	3.20-3.44 (m, 4H, 2 x NCH_2), 3.80-4.07 (m, 4H, 2 x OCH_2), 3.87 (s, 3H, OCH_3), 6.75 (d, J = 6Hz, 1H, H-3), 6.77 (d, J = 2 Hz, 1H, H-7), 6.88 (dd, J = 9/2 Hz, 1H, H-9), 8.36 (d, J = 9 Hz, 1H, H-10), 8.50 (d, J = 6 Hz, 1H, H-2) [b]
38	3410, 2960, 1765,1645	0.74-1.62 (m, 9H alkyl), 1.55-2.13 (m, 2H, H-3a, H-3e), 2.27 (s, 3H, CH_3), 2.44-2.73 (m, 2H, H-4a, H-4e), 3.19-3.52 (m, 2H, H-2a, H-2e), 4.07 (t, J = 6 Hz, 2H, OCH_2), 6.44 (d, J = 2 Hz, 1H arom), 6.61 (d, J = 2 Hz, 1H arom), 7.33-7.59 (m, 1H, NH) [b]

[a] Recorded in deuteriotrifluoroacetic acid. [b] Recorded in deuteriochloroform.

General Procedure for the Preparation of 4-Amino-5*H*-[1]-benzopyrano[4,3-*b*]pyridin-5-ones **34-37**.

A solution of the chloro derivative **31** (2 mmoles) and the appropriate amine (10 mmoles) in ethanol (50 ml) was refluxed for 30 minutes. After cooling at 0° the crude product was collected by filtration, washed with ice-cold ethanol and recrystallized from ethanol. For isolation of **36** the solvent was evaporated to a volume of 15 ml and after addition of petroleum ether (150 ml) the precipitate filtered and recrystallized from methanol.

The yields, analytical, and spectral data for compounds **34-37** are given in Tables 5 and 6.

General Procedure for the Preparation of the 1,2,3,4-Tetrahydro-5*H*-[1]benzopyrano[4,3-*b*]pyridin-5-ones **24-27**, **38**, and **39**.

To a solution of **20-23**, **31**, or **32** (1 mmole) respectively, in 20 ml of glacial acetic acid sodium cyanoborohydride (6 mmoles) was added in small portions. After stirring for one hour at room temperature, ice-water (150 ml) was added to the reaction mixture followed by addition of 3*N* sodium hydroxide until *p*H 5-6 was reached. The precipitate was collected by fitration, washed with water and recrystallized from the solvent as indicated in Table 3.

Compounds **24**, **25**, **26**, and **27** were obtained in yields of 77%, 85%, 70%, and 72%, respectively. The yield, melting point, recrystallization solvent, analytical, and spectral data for compounds **38** are given in Tables 5 and 6.

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