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Synthesis of 5-Alkylindole-3-acetic Acids for Use as Plant Hormone Analogues

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5-*n*-Alkyl derivatives (**9–12**) of the plant hormone indole-3-acetic acid were prepared by treating 2-(4-alkylphenyl)-hydrazono-4-cyanobutyric acid ethyl esters (**1–4**) with a mixture of 35% HCl, 85% H_3PO_4, and pyridine (3:4:1, *v/v/v*) at 115°C. The corresponding acetonitriles (**5–8**) were isolated as intermediates and characterized. Spectroscopic evidence indicates that compounds **9–12** are suitable for investigating steric substituent effects on hormonal activity without major interference of electronic effects.

INTRODUCTION

Indole-3-acetic acid and its 4-chloro derivative are naturally occurring plant hormones (auxins)[1,2]. Numerous auxin analogues, mostly carboxylic acids containing variously substituted aromatic or heterocyclic nuclei, have been synthesized and their widely different growth-promoting activities in biological tests have been rationalized in terms of the following physico-chemical properties: 1. lipophilicity, 2. electron distribution in the ring system, and 3. stereochemistry[1,3–6]. While lipophilicity has been estimated with fair accuracy[7], it proved difficult to distinguish between the effects of factors 2 and 3. It will, however, be necessary to understand, and to manipulate, the specific molecular recognition mechanisms of auxin-binding proteins which are currently being isolated from plants and characterized, and some of which may, in fact, be hormone receptors[8,9]. A set of suitable model compounds would be a series of in-

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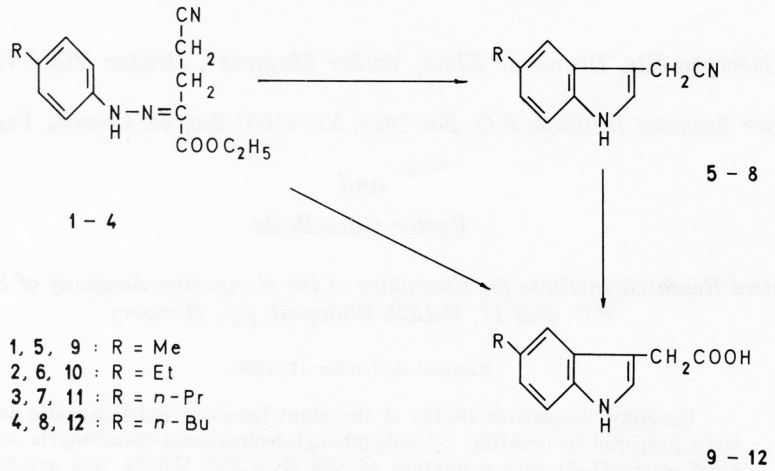
dole-3-acetic acids bearing *n*-alkyl substituents at a benzene carbon. The induced change in the electron distribution in the indole nucleus should be small and almost independent of the length of the attached hydrocarbon chain[10,11]. Physiological activity can thus be directly correlated to lipophilicity and to the bulk and spatial arrangement of the *n*-alkyl substituent. Detailed studies of this kind were not possible so far as the number of available alkylindole-3-acetic acids was too limited. To our knowledge, only the preparation of the 5-methyl[12,13], 7-methyl[13] and 7-ethyl[14] derivatives has been fully described, while 4- and 6-methyl- and 5- and 6-ethylindole-3-acetic acids have been mentioned in a patent[15], without experimental data. We, therefore, undertook the synthesis of 5-*n*-alkylindole-3-acetic acids **9-12** for use in an ongoing project concerned with the structure-activity relationship for auxins and their derivatives[16].



EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Electron impact mass spectra (70 eV, solid probe) were obtained on a Varian CH-7 (routine spectra) and a Kratos MS25RFA (exact mass measurements) instrument. IR spectra were recorded, in KBr pellets, on a Perkin-Elmer 297 spectrometer. UV absorbance was measured in 95% EtOH solution on a Pye Unicam SP-8 UV VIS-spectrometer. Routine ^{1}H and ^{13}C NMR spectra were obtained on a JEOL FX 90Q (90/22.5 MHz) and on a Bruker AM-400 (400/100 MHz) instrument. The data for compounds **9–12** reported in Tables III and IV were collected at 400/100 MHz on a Varian XL-400 spectrometer at ambient probe temperature and a digital resolution of 0.123 and 0.710 Hz/point for ^{1}H and ^{13}C spectra, respectively. Sample concentrations were 75–95 mmol/l for ^{1}H and 150–190 mmol/l for ^{13}C measurements. ^{1}H resonances, in these cases, were assigned and long-range couplings verified by homonuclear spin decoupling. ^{13}C assignments were supported by signal multiplicities in ^{1}H-coupled spectra, the values of $^{1}J(CH)$ coupling constants and selected heteronuclear (^{1}H) correlation experiments; they are in general agreement with published data[26,27,29]. For **9–12**, deuterium hydrogen exchange at N-1 occurred spontaneously in CD_3CN and $(CD_3)_2CO$, apparently catalyzed by the acidic carboxyl group. Signals belonging to N-H and N-D species were distinguished by measurements at various times after the samples had been dissolved. Isotope exchange in $(CD_3)_2CO$ solutions was extremely slow, while equilibrium was reached within about a day in CD_3CN. Chemical shifts (δ, ppm) were in all cases referenced to internal TMS. TLC was carried out on glass plates coated with Merck silica gel 60 GF254 (analytical) or PF254 (preparative). Indoles were detected by UV fluorescence and/or by spraying

with Ehrlich's reagent (1% *p*-dimethylaminobenzaldehyde in HCl-EtOH, 1:1). Solvents were redistilled; the use of peroxide-free Et_2O, EtOH-stabilized $CHCl_3$, and pure, dry pyridine was essential. 2-Acetyl-4-cyanobutyric acid ethyl ester was prepared from ethyl acetoacetate and 3-chloropropionitrile[17].

General Procedure for the Preparation of Hydrazones **1-4.**

Appropriately alkylated anilines were diazotized and reacted with 2-acetyl-4-cyanobutyric acid ethyl ester in alkaline EtOH-H_2O, at –20 °C, as described for the preparation of structurally related hydrazones[17-19,23]. Crude compounds **1–4** crystallized from the neutralized reaction mixtures, immediately or on standing overnight. They were recrystallized from MeOH-H_2O (3:1) [C_6H_6 – petrol (5:1) for **3**] until homogeneous by TLC [solvent: CH_2Cl_2-Me_2CO (40:1)]. For analysis, coloured impurities, which accumulated on exposure to air, were extracted with petrol. The residue was recrystallized from EtOH-H_2O (3:1) and dried *in vacuo* at maximally 65°C. Pure *E*-hydrazones were identified, according to Henecka *et al.*[19], by their UV (identical for **1–4**) and IR (minor shifts for some bands) spectra: UV, λ_{max} (log ε):330 (4.29), 294 (3.96), 284 (3.85), 230 (4.01), 200 (4.10) nm. IR: 3280–3300 (NH), 2255 (C≡N), 1695 (1725 for **4**, C=O), 810–840 (doublet, 2 adjacent Ar–H) cm^{-1}. ^1H NMR signals [$(CD_3)_2CO$] common for **1–4**, δ: 9.7 (s, 1H, NH), 7.3–7.0 (4H, m, Ar–H), 1.32 (3H, t, J=7.1 Hz, OCH_2CH_3), 4.25 (2H, q, OCH_2CH_3), 3.0 and 2.7 (2x2H, 2m, CH_2CH_2CN). ^{13}C NMR signals [$(CD_3)_2SO$] common for **1–4**, δ: 119.9 (C≡N), 13.4 ($CH_2C{\equiv}N$), 20.6 ($CH_2C{=}N$–), 141.9 (C=N–), 164.5 (C=O), 60.6 (OCH_2CH_3), 14.1 (OCH_2CH_3), 130.1 (arC–1 = arC–NH–), 114.0 (arC–2.6).

4-Cyano-2E-phenylhydrazonobutyric acid ethyl ester showed, as far as reported by Henecka *et al.*[19]: UV, λ_{max} (log ε): 325 (4.36) nm; IR, 1720 (C=O) cm^{-1}. ^1H NMR signals [$(CD_3)_2CO$] were as above for **1–4** (5H-multiplet for ArH). ^{13}C NMR [$(CD_3)_2SO$] was as for **1–4**, except for δ: 144.14 (C=N–), 130.93 (arC–1), 129.18 (arC–3,5), 121.50 (arC–4).

*4-Cyano-2E-(4-methylphenyl)hydrazonobutyric Acid Ethyl Ester (***1***)*

Orange platelets, mp 135–136 °C. Yield: 90% (crude), 50% (after purification). ^1H NMR [$(CD)_3)_2CO$] δ: 2.26 (3H, s, $ArCH_3$). ^{13}C NMR [$(CD_3)_2SO$] δ: 129.63 (arC–3,5), 130.31 (arC–4), 20.43 (Ar–CH_3).

Anal. $C_{14}H_{17}N_3O_2$(259.31) calc'd.: C 64.85; H 6.61; N 16.20%
found: C 65.11; H 6.35; N 16.13%.

*4-Cyano-2E-(4-ethylphenyl)hydrazonobutyric Acid Ethyl Ester (***2***)*

Yellow needles, mp 106 °C. Yield: 70% (crude), 50% (after purification). ^1H NMR [$(CD_3)_2CO$] δ: 1.18 (3H, t, J=7.5 Hz, $ArCH_2CH_3$), 2.57 (2H, q, $ArCH_2CH_3$). ^{13}C NMR [$(CD_3)_2SO$] δ: 128.33 (arC–3,5), 136.85 (arC–4), 27.54 ($ArCH_2CH_3$), 15.80 ($ArCH_2CH_3$).

Anal. $C_{15}H_{19}N_3O_2$ (273.34) calc'd: C 65.91; H 7.01; N 15.37%
found: C 66.03; H 7.10; N 15.51%.

*4-Cyano-2E-(4-n-propylphenyl)hydrazonobutyric Acid Ethyl Ester) (***3***).*

Yellow needles, mp 110–112 °C. Yield: 50% (crude), 20% (after purification). ^1H NMR [$(CD_3)_2CO$] δ: 0.90 (3H, t, J=7.2 Hz, $ArCH_2CH_2CH_3$), 1.59 (2H, sextet, $ArCH_2CH_2CH_3$), 2.53 (2H, t, J=7.3 Hz, $ArCH_2CH_2CH_3$). ^{13}C NMR [$(CD_3)_2SO$] δ: 128.95 (arC–3,5), 135.16 (arC–4), 36.68 ($ArCH_2CH_2CH_3$), 24.27 ($ArCH_2CH_2CH_3$), 14.28 ($ArCH_2CH_2CH_3$).

Anal. $C_{16}H_{21}N_3O_2$ (287.36) calc'd: C 66.88; H 7.37; N 14.62%
found: C 66.75; H 7.09; N 14.40%.

*4-Cyano-2E-(4-n-butylphenyl)hydrazonobutyric Acid Ethyl Ester (***4***).*

Off-white platelets, mp 100–101 °C. Yield: 50% (crude), 20% (after purification). ^1H NMR [$(CD_3)_2CO$] δ: 0.91 (3H, t, J=6.7 Hz, $ArCH_2(CH_2)_2CH_3$), 1.74–1.14 (4H, m, $ArCH_2(CH_2)_2CH_3$), 2.55 (2H, t, J=7.3 Hz, $ArCH_2(CH_2)_2CH_3$). ^{13}C NMR [$(CD_3)_2SO$] δ: 128.95 (arC–3,5), 135.44 (arC–

4), 34.26 (Ar*CH*$_2$CH$_2$CH$_2$CH$_3$), 33.41 (ArCH$_2$*CH*$_2$CH$_2$CH$_3$), 21.78 (ArCH$_2$CH$_2$*CH*$_2$CH$_3$), 14.93 (ArCH$_2$CH$_2$CH$_2$*CH*$_3$).

Anal. $C_{17}H_{23}N_3O_2$ (301.39) calc'd: C 67.75; H 7.69; N 13.94%
found: C 67.87; H 7.76; N 13.82%.

*General Procedure for the Preparation of 5-Alkylindole-3-acetonitriles (**5–8**) and -acetic Acids (**9–12**).*

Hydrazones **1–4** (2 mmol) were dissolved in dry pyridine (15 ml). HCl (35%, 20 ml) and H_3PO_4 (85%, 5 ml) were carefully added, and the mixture was refluxed (115°C) with stirring. CO_2 formation was monitored using a $Ba(OH)_2$ solution. Optimal reaction times were 10 h (**1**), 5.5 h (**2**), 3.5 h (**3**) and 2.5 h (**4**). The reaction mixtures obtained from **2–4** were added dropwise to a stirred solution of K_2CO_3 (27.5 g) in ice-water (150 ml), which was then extracted with Et_2O (4×150 ml). The aqueous phase (pH 6–7) was discarded (acidification and Et_2O extraction afforded no additional indoles) and the organic phase was partitioned against a $NaHSO_4$ solution (6×100 ml; pH 1.5; prepared from 55 ml concd H_2SO_4 and 55 g NaOH per litre) to remove pyridine. Further partitioning against a 10% K_2CO_3 solution (4×100 ml) left nitriles **6–8** in the Et_2O phase. Acids **10–12** were recovered from the aqueous phase by acidification (pH 2.5) and Et_2O extraction (4×150 ml). The reaction mixture obtained from **1** was added to a stirred solution of $Na_2HPO_4 \cdot 2H_2O$ (12.5 g) and K_2CO_3 (2.5 g) in ice-water (150 ml). The pH was adjusted to 2.5 and the indolic products were extracted into Et_2O (4x150 ml). Further work-up of the extract was as above. Nitriles **5–8** were purified by preparative TLC (solvent: CH_2Cl_2) and passed through a column of silica gel (25 g, particle size: 0.065–0.2 mm) eluted with C_6H_6. They were then dissolved in a minimal amount of warm C_6H_6 and precipitated with petrol. Compounds **5–8** had the following common spectroscopic properties: IR: 3320–3420 (NH), 2245–2260 (CN), 795–805 (Ar–H) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.14 (1H, s, NH), 7.4–7.0 (4H, m, ArH), 3.75 [2H, d, J=0.9 Hz (to ring H–2), *CH*$_2$CN].

Crude acids **9–12** were passed through a column (73x1.5 cm) of Sephadex LH-20 eluted with *iso*PrOH–H_2O (1:1). For further purification the products were dissolved in boiling $CHCl_3$, filtered from insoluble contaminants, and precipitated with petrol. This was repeated until white crystals of constant melting point were obtained. Analytical samples were recrystallized from EtOH–H_2O (4:6) (**9,12**) or CH_2Cl_2-cyclohexane (**10–11**) and dried *in vacuo* at 70 °C.

Compounds **9–12** showed the following common spectroscopic properties: UV, λ_{max} (log ε for **9**, **10**, **11,12**, in this order): 295 (3.54, 3.55, 3.60, 3.59), 284 (3.70, 3.70, 3.75, 3.74), 275 (3.71, 3.71, 3.76, 3.75), 222 (4.43, 4.45, 4.51, 4.50) nm, as compared to 288 (3.70), 279 (3.78), 273 (3.77), 219 (4.51) nm for unsubstituted indole-3-acetic acid. IR: 3365–3385 (NH), *ca.* 3000 (broad; COOH), 1680–1690 (CO), 790–800 (Ar–H) cm^{-1}. The corresponding bands for indole-3-acetic acid were at the same positions, except for Ar–H (737 cm^{-1}).

*5-Methylindole-3-acetonitrile (**5**)*

Off-white prisms, mp 90 °C. ^{1}H NMR ($CDCl_3$) δ: 2.45 (3H, s, ArCH$_3$). Ms, *m/z*: Calc'd for $C_{11}H_{10}N_2^+$: 170.0844. Found: M$^+$, 170.0838.

*5-Ethylindole-3-acetonitrile (**6**)*

Ochre prisms, mp 66 °C. ^{1}H NMR ($CDCl_3$) δ: 2.76 (2H, q, J=7.5 Hz, Ar*CH*$_2$CH$_3$), 1.28 (3H, t, ArCH$_2$*CH*$_3$). Ms, *m/z*: Calc'd for $C_{12}H_{12}N_2^+$: 184.1000. Found: M$^+$, 184.1001.

*5-n-Propylindole-3-acetonitrile (**7**)*

Brown prisms, mp 67 °C. ^{1}H NMR ($CDCl_3$) δ: 2.68 (2H, t, J=7.5 Hz, Ar*CH*$_2$CH$_2$CH$_3$), 1.67 (2H, sextet, ArCH$_2$*CH*$_2$CH$_3$), 0.94 (3H, t, J=7.2 Hz, ArCH$_2$CH$_2$*CH*$_3$). Ms, *m/z*: Calc'd for $C_{13}H_{14}N_2^+$: 198.1157. Found: M$^+$, 198.1210.

5-n-Butylindole-3-acetonitrile (**8**)

Brown oil. ^{1}H NMR ($CDCl_3$) δ: 2.71 (2H, t, J=7.3 Hz, ArCH_2(CH$_2$)$_2$CH$_3$). 1.8–1.2 (4H, m, ArCH$_2$(*CH*$_2$)$_2$CH$_3$), 0.92 (3H, t, J=6.9 Hz, ArCH$_2$(CH$_2$)$_2$*CH*$_3$). Ms, *m/z*: Calc'd for $C_{14}H_{16}N_2^+$: 212.1313. Found: 212.1335.

5-Methylindole-3-acetic Acid (**9**)

White platelets, mp 149–151 °C [Lit[12]: 151–152°C]. Ms, *m/z*: 189 (M^+).

Anal. $C_{11}H_{11}NO_2$ (189.22) calc'd: C 69.83; H 5.86; N 7.40%
found: C 69.70; H 6.14; N 7.44%

5-Ethylindole-3-acetic Acid (**10**)

White platelets, mp. 130–132 °C. Ms, *m/z*: 203 (M^+).

Anal. $C_{12}H_{13}NO_2$ (203.24) calc'd: C 70.92; H 6.45; N 6.89%
found: C 70.71; H 6.62; N 6.71%.

5-n-Propylindole-3-acetic Acid (**11**)

White platelets, mp 122–123 °C. Ms, *m/z*: 217 (M^+).

Anal. $C_{13}H_{15}NO_2$ (217.27) calc'd: C 71.89; H 6.96; N 6.45%
found: C 72.03; H 7.19; N 6.49%.

5-n-Butylindole-3-acetic Acid (**12**)

White platelets, mp 123–124 °C. Ms, *m/z*: 231 (M^+).

Anal. $C_{14}H_{17}NO_2$ (231.30) calc'd: C 72.70; H 7.41; N 6.06%
found: C 72.75; H 7.29; N 6.07%.

RESULTS AND DISCUSSION

Acids **9–12** were prepared by a simple two-step procedure based on known methods[17–20] from commercially available 4-alkylanilines and the readily accessible[17] 2-acetyl-4-cyanobutyric acid ethyl ester. A Japp-Klingemann condensation of the ester and the appropriate, diazotized anilines afforded, after recrystallization, pure *E*-hydrazones **1–4**. Fischer cyclization of **1–4** was performed in boiling (115 °C) aqueous pyridine-HCl-H_3PO_4, in an approximate molar ratio of 2:2:1, in accord with the procedures suggested by Robinson[20] and Welch[21]. Monitoring the reaction revealed that hydrolysis of the ethoxycarbonyl group of **1–4** and decarboxylation proceeded simultaneously with ring closure to yield acids **9–12** as the main products. TLC of the crude reaction mixtures indicated the presence of additional acid and neutral indoles (Ehrlich positive spots), but only the acetonitriles **5–8** were abundant enough to permit isolation and characterization. This is of interest, because previous attempts to cyclize 4-cyano-2-phenylhydrazonobutyric acid derivatives without concomitant hydrolysis of the nitrile group were reportedly unsuccessful[17-19,22]. We here present unequivocal spectroscopic evidence (Table II and Experimental) for the identity of nitriles **5–8** and show that, in the reaction process their yields peak before those of the corresponding acids **9–12** (Table I). This suggests that nitriles **5–8** are intermediates in the formation acids **9–12**, leaving open the question of possible simultaneous hydrolysis of the cyano group at the hydrazone (**1–4**) stage. Optimal reaction times in the Fischer cyclization decreased from 10 h for **1** to 2.5 h for **4** (Table I) The unsubstituted hydrazone reacted within 1 h[23]. There appear to be no systematic studies on the effect of *n*-alkyl ring-substituents on the rate of the Fischer cyclization; phenyl-

hydrazono-cyclohexanes methylated at benzene positions 3 or 4 react, depending on the conditions used, about two to twelve time faster than the unsubstituted homologues[24,25]. However, the hydrophobic parts of **1–4**, which are more flexible than the above cyclohexane derivatives, may aggregate to be minimally exposed to a polar condensation reagent such as aqueous pyridine-HCl-H_3PO_4. The conformation adopted would depend, in a not easily predictable manner, on the length of the *n*-alkyl group at the benzene ring. This may well affect the ease of formation of the planar, bicyclic transition state postulated for the Fischer cyclization viewed as a [3.3]-sigmatropic rearrangement[25].

The UV spectra of compounds **9–12** were identical, except for small differences in ε_{max}, and closely matched that of unsubstituted indole-3-acetic acid, indicating similar molecular orbital energy levels and, hence, comparable overall affinities to possible π-complexing sites[5] of auxin-binding proteins. Local electron densities, which may affect more specific recognition patterns, were estimated from NMR data. H-1 chemical shifts for **9–12** in acetone solution (hydrogen-bonding solvent) were 0.12–0.13 ppm upfield with respect to indole-3-acetic acid indicating a small decrease in acidity and hydrogen-bonding (donor) ability. Slightly increased electron densities at CH-4,6 in response to 5-alkylation, may be inferred from ^1H shifts (Table III) and $^1J(CH)$ values (Table IV). All these effects were, however, small as compared to those caused by other 5-substituents[27]. For the pyrrole moiety, the ^{13}C-shift differences between N-H and N-D isotopomers appear to be one of the most sensitive indicators for the electron densities at the respective carbons[27]. Yet, the values observed for **9–12** were about the same and barely different from those for unsubstituted indole-3-acetic acid. In summary, our spectroscopic data confirmed a small general effect of 5-alkylation on the electronic properties of the indole nucleus, but there appear to be no significant differences within the series of homologues **9–12**. Thus, while the plant-growth-promoting activity of **9** is known to be about 60% of that of indole-3-acetic acid[12,28], the change in auxin properties caused by an increase in the length of the 5-alkyl side chain should be mostly, if not exclusively, correlated to lipophilicity and

TABLE I

Yields of Nitriles **5–8** *and Acids* **9–12** *at Various reaction Times.*

Hydrazone	Reaction Time, h	Yield[a] (%) of	
		Nitrile	Acid
1	2	14	–[b]
	10[c]	3	42
2	2	11	–[b]
	5.5[c]	3	39
3	1.8	25	11
	3.5[c]	5	34
4	1	13	17
	2.5[c]	3	29

[a] with respect to the parent hydrazone. Determined after prep. TLC or **5–8** and after Sephadex chromatography for **9–12**.

[b] untractable mixtures. NMR and IR spectra gave no clear evidence for the presence of 5-alkylindole-3-acetic acids.

[c] optimal reaction times. Overall yields decreased if these were substantially exceeded.

TABLE II

^{13}C NMR Chemical Shift Values (δ, ppm; $CDCl_3$, 22.5 MHz) for 5-X-indole-3-acetonitriles[a]

	X=H[b]	X=methyl	X=ethyl	X=*n*-propyl	X=*n*-butyl
Indole ring:					
C-2	122.5	124.3	123.3	123.7	123.6
C-3	104.1	103.7	104.1	103.7	103.8
C-4	117.8	117.4	116.3	116.8	116.8
C-5	119.9	129.3	134.6	134.3	134.6
C-6	122.5	122.7	122.7	122.7	122.7
C-7	111.4	111.1	111.2	111.1	111.0
C-3a	125.6	126.0	126.0	125.8	125.9
C-7a	136.0	134.4	136.2	134.5	134.5
Alkyl substituent:					
$\dot{C}H_2$	–	–	28.8	38.1	35.7
$\dot{C}H_2$	–	–	–	–	34.3
$\dot{C}H_2$	–	–	–	25.2	22.3
$\dot{C}H_3$	–	21.3	16.3	13.8	13.9
Common signals: 118.2 (CN), 14.2 (CH_2-CN)					

[a] assignments according to tabulated values for structurally related indoles[26,27,29], chemical shift rules[30], and the data for the corresponding indole-3-acetic acids in Table IV. [b]commercial sample

TABLE III

^{1}H NMR Data (acetone-d_6, 400 MHz) for 5-X-indole-3-acetic acids

	Chemical shift (δ, ppm)				
	X=H	X=methyl	X=ethyl	X=*n*-propyl	X=*n*-butyl
Indole nucleus					
H-1	10.12	9.99	10.00	9.99	9.99
H-2	7.29	7.23	7.25	7.24	7.25
H-4	7.60	7.38	7.41	7.40	7.40
H-5	7.03	–	–	–	–
H-6	7.10	6.94	6.98	6.97	6.97
H-7	7.39	7.27	7.29	7.29	7.29
Side chain in ring position 3					
CH_2	3.75	3.71	3.73	3.72	3.72
Side chain in ring position 5					
$\dot{C}H_2$	–	–	2.71	2.66	2.68
$\dot{C}H_2$	–	–	–	1.66	1.63
$\dot{C}H_2$	–	–	–	–	1.37
$\dot{C}H_3$	–	2.40	1.24	0.94	0.93

J [Hz]; within indole nucleus: 1,2 = 2.2–2.4; 1,4 = 0.7; 2,6 = 0.4; 4,6 = 1.3 (X=H), 1.7 (X=alkyl); 4,7 = 0.7–0.8; 6,7 = 8.1 (X=H), 8.3 (X=alkyl); 4,5 = 7.9; 5,6 = 7.0; 5,7 = 1.0 (the latter three for X=H only); side chain-ring protons: 2, CH_2COOH = 0.9; 4,5-CH = 0.7–0.8; 6,5-CH = 0.5 (clearly visible only for X=methyl and ethyl); 7,5-CH = 0.5 (X=methyl only); within alkyl chain: H,H_{vic} = 7.5.

TABLE IV

^{13}C NMR data (100 MHz) for 5-X-Indole-3-acetic Acids

	Solvent	For solvent 1 [CD_3CN]: δ (ppm), upfield shift (in ppb) on 1-deuteration (if detectable) For solvent 2 [$(CD_3)_2CO$]: δ (ppm), multiplicity[b], $^1J(CH)$ (in Hz) where applicable				
		X=H	X=methyl	X=ethyl	X=*n*-propyl	X=*n*-butyl
Indole nucleus						
C-2	1	**124.9**, 156	**124.9**, 159	**124.9**, 159	**124.9**, 158	**124.9**, 163
	2	**124.5**, *dq, 182*	**124.6**, *dq, 182*	**124.6**, *dq, 182*	**124.6**, *dq, 181*	**124.6**, *dq, 182*
C-3	1	**109.1**, 55	**108.6**, 59	**108.7**, n.d.	**108.7**, 57	**108.7**, 60
	2	**109.0**, *td*	**108.5**, *td*	**108.6**, *td*	**108.6**, *td*	**108.6**, *td*
C-3a	1	**128.4**, 32	**128.7**, 29	**128.6**, 32	**128.6**, 30	**128.6** n.d.[a]
	2	**128.5**, *m*	**128.7**, *m*	**128.7**, *m*	**128.7**, *m*	**128.7**, *m*
C-4	1	**119.6**	**119.2**	**118.0**	**118.7**	**118.6**
	2	**119.5**, *dd, 158*	**119.1**, *dqi, 155*	**117.9**, *dq, 155*	**118.7**, *dq, 155*	**118.6**, *dq, 156*
C-5	1	**120.0**	**129.1**	**136.0**	**134.3**	**134.5**
	2	**119.6**, *dd, 158*	**128.3**, *qi*	**135.3**, *n.d.*[a]	**133.6**, *n.d.*[a]	**133.7**, *n.d.*[a]
C-6	1	**122.6**	**124.2**	**123.2**	**123.7**	**123.7**
	2	**122.2**, *dd, 157*	**123.8**, *ddq, 155*	**122.8**, *dq, 155*	**123.3**, *dq, 155*	**123.2**, *dq,155*
C-7	1	**112.4**, 53	**112.1**, 51	**112.2**, 52	**112.1**, 52	**112.1**, 53
	2	**112.1**, *dd, 159*	**111.8**, *d, 159*	**111.9**, *d, 159*	**111.8**, *d, 159*	**111.8**, *d, 159*
C-7a	1	**137.4**, 146	**135.7**, 151	**135.9**, 153	**135.9**, 151	**135.9**, 147
	2	**137.5**, *m*	**135.9**, *m*	**136.0**, *m*	**136.1**, *m*	**136.0**, *m*
Alkyl side chain						
CH_2	1	–	–	**29.7**	**38.9**	**36.5**
	2	–	–	**29.7**, *tm, 126*	**39.0**, *tm, 126*	**36.6**, *tm, 125*
CH_2	1	–	–	–	–	**35.5**
	2	–	–	–	–	**35.5**, *tm, 125*
CH_2	1	–	–	–	**26.3**	**23.2**
	2	–	–	–	**26.2**, *tm, 126*	**23.0**, *tm, 124*
CH_3	1	–	**21.6**	**17.1**	**14.2**	**14.4**
	2	–	**21.6**, *qt, 126*	**17.1**, *qt, 126*	**14.1**, *qm, 125*	**14.3**, *qm, 124*

Common signals: solvent 1: 31.3 (CH_2), 174.0 (COOH); solvent 2: 31.4 (t, J=128, CH_2), 173.4 (t, J=8, COOH).

[a] n.d. = not determined

[b] multiplets with $J<3$ Hz generally not resolved.

steric effect. Preliminary data indicate that the biological activities of **9–12** are of a similar order of magnitude (R. Konjević, personal communication). More detailed investigations are in progress.

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REFERENCES

1. K. V. Thimann, *Hormone Action in the Whole Life of Plants,* Amherst, University of Massachusetts Press, 1977.
2. K. C. Engvild, *Phytochemistry*, **25** (1986) 781.
3. A. Jönsson, *Chemical Structure and Growth Activity of Auxins and Antiauxins*, in W. Ruhland (Ed.): *Encyclopedia of Plant Physiology*, Vol. **14**, Berlin, Springer-Verlag, 1961, pp. 595–1006.
4. E. A. Schneider and F. Wightman, *Auxins* in D. S. Lethman, P. B. Goodwin, and T. J. V. Higgins (Eds.): *Phytohormones and Related Compounds — A Comprehensive Treatise*, Vol. **1**, Amsterdam, Elsevier, 1978, pp. 29–105.
5. G. F. Katekar, *Phytochemistry*, **18** (1979) 223.
6. C. Hansch, R. M. Muir, T. Fujita, P. P. Maloney, F. Geiger, and M. Streich, *J. Am. Chem. Soc.*, **85** (1963) 2817.
7. T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86** (1964) 5175.
8. K. R. Libbenga and A.M. Mennes, *Hormone Binding and Its Role in Hormone Action* in P.J. Davies (Ed.): *Plant Hormones and their Role in Plant Growth and Development*, Dordrecht, Martinus Nijhoff, 1987, pp. 194–221.
9. N. Inohara, S. Shimomura, T. Fukui, and M. Futai, *Proc. Natl. Acad. Sci. USA*, **86** (1989) 3568.
10. H. H. Jaffé, *Chem. Rev.*, **53** (1953) 191.
11. W. A. Remers, *Properties and Reactions of Indoles, Isoindoles and Their Hydrogenated Derivatives*, in W.J. Houlihan (Ed.): *Indoles*, Part 1, New York, Wiley, 1972, pp. 1–226.
12. F. Kögl and D. G. F. R. Kostermans, *Z. Physiol. Chem.*, **235** (1935) 201; S.W. Fox and M.W. Bullock, *J. Am. Chem. Soc.*, **73** (1951) 2756.
13. F. J. Stevens and H. Chien-Fan Su, *J. Org. Chem.*, **27** (1962) 500.
14. E. S. Ferdinandi, D. R. Hicks, W. Verbestel, and P. Raman, *J. Label. Compds. Radiopharm.*, **14** (1978) 411.
15. J. Rokach, Can., 926, 410; *Chem. Abstr.*, 1974, **80**, 146011c.
16. H. Duddeck, M. Hiegemann, M. F. Simeonov, B. Kojić-Prodić, B. Nigović, and V. Magnus, *Z. Naturforsch.*, **44c** (1989) 543.
17. S. Keimatsu and S. Sugasawa, *J. Pharm. Soc. Jap.*, **48** (1928) 101.
18. V. V. Feofilaktov and N. K. Semenova, *J. Gen. Chem. U.S.S.R.*, **23** (1953) 669.
19. H. Henecka, H. Timmler, R. Lorenz, and W. Geiger, *Chem. Ber.*, **90** (1957) 1060.
20. J. R. Robinson, *Can. J. Chem.*, **35** (1957) 1570.
21. W. M. Welch, *Synthesis*, 1977, 645.
22. H. R. Snyder and C. W. Smith, *J. Am. Chem. Soc.*, **65** (1943) 2452.
23. V. Magnus, R. S. Bandurski, and A. Schulze, *Plant Physiol.*, **66** (1980) 775.
24. Yu. B. Vysotskii, N. M. Przheval'skii, B. P. Zemskii, I. I. Grandberg, and L. Yu. Kostromina, *Khim. Geterotsikl. Soedin.*, (1986), 898; N.M. Przheval'skii, L.Yu. Kostromina, and I.I. Grandberg, *Khim. Geterotsikl. Soedin.*, (1988), 188.
25. N. M. Przheval'skii. L.Yu. Kostromina, and I.I. Grandberg, *Khim. Geterotsikl. Soedin.*, (1988), 867.
26. M. S. Morales-Ríos, J. Espiñeira and P. Joseph-Nathan, *Magn. Res. Chem.*, **25** (1987) 377.
27. M. S. Morales-Ríos, R. E. del Río, and P. Joseph-Nathan, *Magn. Res. Chem.*, **27** (1989) 1039.
28. W. L. Porter and K. V. Thimann, *Phytochemistry*, **4** (1965) 229.
29. M. S. Morales-Ríos, R. E. del Río, and P. Joseph-Nathan, *Magn. Res. Chem.*, **26** (1988) 552.
30. E. Pretsch, J. Seibl, W. Simon, and T. Clerc, *Tabellen zur Strukturaufklärung Organischer Verbindungen mit spektroskopischen Methoden*, 2. Edition, Berlin, Springer-Verlag, 1981.

SAŽETAK

Sinteza 5-alkilindol-3-octenih kiselina kao analoga jednog od biljnih hormona

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5-*n*-Alkil-derivati (alkil = metil, etil, *n*-propil, *n*-butil) biljnog hormona, indol-3-octene kiseline, priređeni su ciklizacijom etilnih estera 2-(4-alkilfenil)hidrazono-4-cijanomaslačnih kiselina, zagrijavanjem u smjesi 35% HCl, 85% H_3PO_4 i piridina (3:4:1, *v/v/v*: 115 °C). Od međuprodukata izolirani su i karakterizirani 5-alkilindol-3-acetonitrili. Prema spektroskopskim podacima sintetizirane 5-alkilindol-3-octene kiseline ne pokazuju bitne razlike s obzirom na raspodjelu elektrona u aromatskoj jezgri, tako da su prikladne za istraživanje steričkih efekata supstituenata na biološka svojstva.