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Note

Synthesis and C-13 NMR Spectral Assignments of 2-Methylindole-3-S-Acid Derivatives¹

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A series of 2-methylindole-3-S-alkanose acids (3a—5a) was prepared, and their C-13 NMR spectra assigned.

INTRODUCTION

We have been interested in the design of analogs of 3-substituted indole compounds as possible plant growth regulators^{6,7}. We wish to extend these investigations to other indole derivatives, and explore the reaction of 2-methyl indolylthiouronium iodide (1) with ethylchloroacetate, ethyl-3-bromopropionate and ethyl-4-chlorobutyrate in basic medium to provide the desired esters 3—5 which were hydrolyzed to their acids (Scheme I).

The structures of compounds (3a—5a) are consistent with the elemental analysis, IR spectra and their ¹³C NMR spectra (Table I). Compound (1) was synthesized according to the method of Harris^{8,9} and was also obtained by Fischer cyclization synthesis as described by Woodbridge and Dougherty¹⁰.

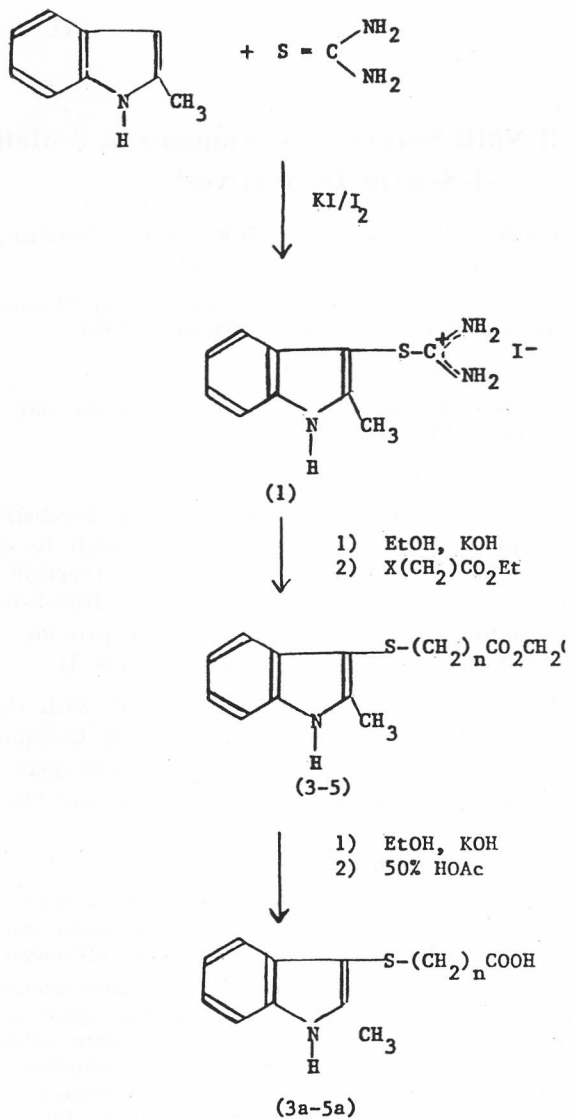
EXPERIMENTAL

Melting points were taken in open capillaries in a Buchi apparatus and are uncorrected. The microanalyses were performed by Galbraith Laboratories in Knoxville, Tennessee. IR spectra were obtained on a Perkin Elmer 727 spectrophotometer.

The ¹³C NMR spectra of 3a—5a were obtained in deuterioacetone, DMSO-d₆ or deuteriochloroform depending on solubility. Both proton noise decoupled and single-frequency off-resonance decoupled (SFORD) spectra were recorded. Assignments were made by comparison with 2-methyl-indole,¹¹ 2-methylindole-3-thioacetamide (2), by the SFORD multiplicities, and by nuclear overhauser enhancement for protonated carbons. The ¹³C spectra were obtained under the following conditions: tetramethylsilane reference, pulse width 10 μsec (90° pulse), zero delay between pulses, 1.3 Hz exponential line broadening, spectral window 4 KHz, 4 K data points, and operating frequency of 20.0 MHz on a Varian FT-80 spectrometer

Proton NMR spectra were obtained on a Varian CFT-20 spectrometer in the indicated solvent with tetramethylsilane as reference under the following conditions: Pulse width of 47 μsec, spectral width of 1000 Hz, zero delay between pulses, 8 K data points, at an operating frequency of 1000 Hz.

SCHEME I



- (3) n = 1, X = Cl; (3a) n = 1
 (4) n = 2, X = Br; (4a) n = 2
 (5) n = 3, X = Cl; (5a) n = 3

TABLE I
Carbon-13 Magnetic Resonance Parameters

Compound	1	2	3a	4a	5a
Carbon Number	1	2	3a	4a	5a
2-methyl indole					
2	135.8(s)	136.5(s)	136.0(s)	135.4(s)	135.1(s)
3	87.5(s)	100.9(s)	100.9(s)	101.0(s)	102.0(s)
4	120.7(d)	120.5(d)	120.6(d)	120.5(d)	120.3(d)
5	120.6(d)	122.1(d)	122.2(d)	122.0(d)	121.8(d)
6	119.4(d)	118.8(d)	118.9(d)	118.6(d)	118.8(d)
7	110.3(d)	111.7(d)	111.8(d)	110.6(d)	110.5(d)
8	128.8(s)	131.0(s)	131.0(s)	130.5(s)	130.5(s)
9	135.8(s)	142.2(s)	142.0(s)	140.4(s)	129.9(s)
1'	13.0(q)	12.1(q)	12.0(q)	12.1(q)	12.1(q)
2'	170.5(s)	172.4(s)	171.7(s)	177.5(s)	179.0(s)
3'		38.8(t); (38.7) ^a	38.5(t); (38.7) ^a	29.6(t); (28.7) ^a	32.7(t); (33.4) ^a
4'				34.7(t); (33.7) ^a	24.7(t); (25.9) ^a
Solvent	DMSO-d ₆	Acetone-d ₆	Deuteriochloroform	Deuteriochloroform	Acetone-d ₆

^a Calculated values (see text). ^b Assignments as in Lit (11) in dioxane.

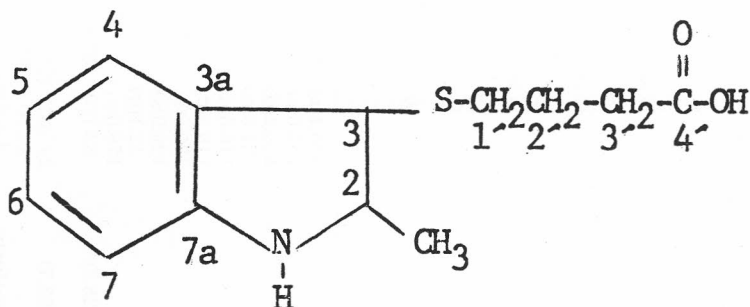


Figure 1. Numbering Scheme.

Carbon Assignments

For comparison, the chemical shifts of 2-methyl indole and the amide (2) of compound 3a are included in Table I along with their SFORD multiplicities (See also Figure 1 for numbering scheme). Note that substitution at the 2 position of indole with a methyl group shifts the C-2 resonance downfield 11.0 ppm and shifts C-3 upfield by 2.2 ppm. Changes in chemical shifts for C4, C5, C6 and C7 on the ring system are all upfield indicating some electron transfer into that system by the methyl group (11).

The resonance at 100.9, 101.0 and 102.0 for 3a—5a, respectively can be assigned to C-3 on the basis of very low intensities, nearly constant chemical shifts through the series, and by comparison with the chemical shift in 2-methyl indole of 99.9 ppm. Compound 1 shows a low intensity resonance at 87.5 which is assigned to C-3. The upfield shift of this resonance is due to the large electron releasing power of the S—C—(NH₂)₂⁺ group.

The resonance of the 2-methyl group is easily assigned because of its nearly constant chemical shift through the series of compounds at 12.0 ppm. The resonance for C-1' also are easily assigned because of chemical shift positions and the low intensities expected from tertiary carbons. The chemical shifts of the resonance due to carbons on the side chain (C-2', 3', 4'; —S—(CH₂)_nCO₂H, n = 1, 2, 3) were calculated by using the chemical shifts of the alkanes and assuming replacement of terminal hydrogen atoms by either —CO₂H or —SR (R = 2 methyl indole). The chemical shifts for the alkanes are as follows: methane (—2.3 ppm), ethane (5.7 ppm) and propane (15.4 (α) and 15.9 (β) ppm) (12). Additivity values in ppm were as follows: —COOH; α (+ 21), β (+ 3), and γ (—2) and —SR; α (+ 20), β (+ 7) and γ (—3) ppm (13). These values were added to the base alkane shifts to obtain the calculated values and used to assign the resonances. The —CONH in compound 2 was assumed, for chemical purposes, to be equivalent to —COOH. Note also there is an uncertainty in assignment of C-2' and C-4' for compound 4a as both calculated shifts are the same.

2-Methylindolyl Thiouronium Iodide (1)

A solution of potassium iodide (105 g., 0.63 moles) and of iodine (25.4 g., 0.10 moles) was prepared in 100 ml. deionized water. A solution of 2-methylindole (13.1 g., 0.10 moles), potassium hydroxide (5.6 g., 0.10 moles), and thiourea (7.6 g., 0.10 moles) was prepared in 400 ml. ethanol by constant stirring at room temperature. The potassium iodide solution was added to this solution in 10 ml portions. Concentration of the mixture in vacuo gave compound (1). The pale yellow product was filtered, washed with water and recrystallized from ethanol. An 84% yield was obtained, m. p. 192—194° [lit. (8) m. p. 214—216 dec.], IR (potassium bromide). 3450, 3050, 2950, 2925, 1700, 1620, 1540, 1480, 1450, 1400, 1320, 1300, 1240, 1200, 1160,

1140, 1100, 1080, 1010, 890, 750 cm⁻¹. ¹H NMR; [(CD₃)₂CO, δ, ppm]: 2.64 (3H, —CH₃); 6.87—7.74 (4H, indole ring); 10.15 (1H, N—H).

Anal. Calcd. for C₁₀H₁₂N₃SI: C, 36.05; H, 3.63; N, 12.61. Found: C, 36.00; H, 3.61; N, 12.58.

2-Methylindole-3-thioacetic Acid (3a)

A solution of compound (1) (7.01 g., 0.021 moles) in 50 ml. of ethanol was treated with a solution of potassium hydroxide (10.14 g., 0.18 moles) in 50 ml. deionized water under nitrogen. The resulting alkaline solution was treated with ethyl chloroacetate (3.80 g., 0.031 moles) refluxed for 2 hours, cooled and evaporated to dryness. The brick red product (3) was dissolved in 70 ml. ethanol and potassium hydroxide (10.1 g., 0.18 moles) in deionized water (20 ml.) was added. This mixture was refluxed for 1 hour, ethanol was removed under reduced pressure, and the aqueous solution was filtered and neutralized with glacial acetic acid (50%). The brown precipitate (3a) was collected after 24 hours at 0°, filtered, air dried and recrystallized from ethanol. A yield of 43% was obtained, m.p. 153—155°; IR (potassium bromide): 3450, 3100, 3050, 2970, 1710, 1420, 1280, 1260, 1240, 900, 750 cm⁻¹. ¹H NMR; [(CD₃)₂CO, δ, ppm]: 2.64 (3H, —CH₃); 2.97 (2H, —S—CH₂—), 6.86—7.72 (4H, indole ring); 10.32 (1H, N—H).

Anal. Calcd. for C₁₁H₁₁O₂NS: C, 59.71; H, 5.01; N, 6.33. Found: C, 59.71; H, 4.99; N, 6.31.

2-Methylindole-3-thiopropionic Acid (4a)

An aqueous solution of potassium hydroxide (10.03 g., 0.18 moles) was added to (1) (7.50 g., 0.023 moles) under nitrogen with stirring. This solution was treated with ethyl-3-bromopropionate (6.25 g., 0.035 moles) and the resulting mixture refluxed for 2 hours, cooled and evaporated to dryness under reduced pressure. The crude product was stirred in deionized water (50 ml.) for 24 hours, and the deep orange product (4) was filtered, washed with water and air dried (yield 4.12 g., 67.7%). Compound (4) was refluxed in an ethanol solution (70%) containing potassium hydroxide (0.10 g., 0.0018 moles) for 1 hour, cooled, and the ethanol removed under reduced pressure. The product thus obtained was dissolved in 35 ml. water, filtered and acidified with acetic acid (50%). The brown precipitate (4a) was collected at 0° after 12 hours, filtered, washed, air dried and recrystallized from ethanol. The yield was 54%, m.p. 144—146°; IR (potassium bromide): 3650, 3425, 2900, 1700, 1600, 1580, 1540, 1440, 1400, 1340, 1280, 1240, 1200, 1150, 1130, 1080, 1010, 940, 750 cm⁻¹. ¹H NMR; [CDCl₃, δ, ppm]: 2.63 (3H, —CH₃); 1.56 (2H, S—CH₂—); 1.25 (2H, C—CH₂—C); 7.11—7.25 (4H, indole ring); 10.33 (1H, N—H).

Anal. Calcd. for C₁₂H₁₃O₂NS: C, 61.25; H, 5.57; N, 5.95. Found: C, 60.25; H, 5.50; N, 5.93.

2-Methylindole-3-thiobutanoic Acid (5a)

A 60 ml. aqueous solution of potassium hydroxide (16.2 g., 0.29 moles) was added to 23.1 g. (0.069 moles) of (1) in 60 ml. ethanol under nitrogen. To the resulting pale yellow mixture, 15.6 g. (0.10 moles) of ethyl-4-chlorobutyrate was added under nitrogen. The mixture was refluxed for 2 hours and concentrated under vacuum. The dark brown product (5) was washed, filtered, air dried and dissolved in 40 ml. ethanol. Ten ml. of potassium hydroxide (16.0 g., 0.29 moles) was added to the mixture, refluxed for 1 hour, cooled and the ethanol removed. The product was dissolved in water (100 ml.) and filtered. The filtrate was acidified with acetic acid (50%) and the brown crystalline product (5a) was collected, air dried and recrystallized from ethanol. A yield of 70% was obtained, m.p. 93—95°; IR (potassium bromide): 3850, 3430, 3030, 2460, 2900, 1700, 1600, 1580, 1540, 1480, 1450, 1400, 1340, 1280, 1240, 1200, 1110, 1080, 1060, 930, 750 cm⁻¹. ¹H NMR; [(CD₃)₂CO, δ, ppm]: 2.52 (3H,

—CH₃); 1.75 (2H, C—CH₂—C); 2.44, (2H, C—C—CH₂COOH); 2.67, (2H, —S—CH₂—); 6.99—7.65 (4H, indole ring); 10.35 (1H, N—H).

Anal. Calcd. for C₁₃H₁₅O₂NS: C, 62.62; H, 6.06; N, 5.62. Found: C, 62.63; H, 6.00; N, 5.59.

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REFERENCES AND NOTES

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SAŽETAK

Sinteza 2-metilindol-3-S-kiselinskih derivata

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Opisana je sinteza i tumačenje C-13 NMR spektara od 2-metilindol-3-S-alkalnosa kiselina.