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The indolyl sulfide compounds (**5,6,7,8**) gave 3-3'-diindole methane derivatives by a double decomposition-displacement reaction. These same compounds when reacted with alkoxides yielded 3-alkoxy-methylindole derivatives (**9-14**).

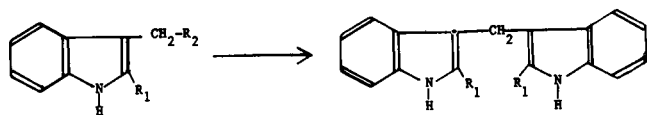
J. Heterocyclic Chem., **18**, 391 (1981).

There has been a continued interest in the synthesis of plant growth regulators, especially in the 3-substituted indole compounds. In the search for biologically active compounds (4-8) a series of indol-3-ylmethyl-S-alkanoic acid derivatives, such as indol-3-ylmethyl-S-acetic acid (**5**), indol-3-ylmethyl-S-propionic acid (**6**), (2-methylindol-3-yl)methyl-S-acetic acid (**7**) and (2-methylindol-3-yl)methyl-S-propionic acid (**8**), have been prepared. The ease of formation of the 3,3'-diindole methanes and their derivatives (**3** and **4**), from the gramine derivatives and of their quarternary salts (**15** and **16**) by a double decomposition-displacement reaction on itself is well known (9-10). However, we have observed a new but similar type of displacement reaction with indolyl sulfide compounds, which occurs with greater ease (Scheme I).

Indol-3-ylmethyl-S-acetic acid (**5**) was synthesized according to Licari and Dougherty's procedure (11). In a like manner indol-3-ylmethyl-S-propionic acid (**6**) was obtained. The starting intermediate gramine (**1**), in both the above cases, was synthesized according to Kuhn and Stein's method (12).

To prepare (2-methylindol-3-yl)methyl-S-acetic acid (**7**), 2-methylgramine (**2**) was treated with the sodium salt of mercaptoacetic acid. A yield of 80% was obtained. Similarly (2-methylindol-3-yl)methyl-S-propionic acid (**8**) was synthesized in 82% yield. The starting intermediate,

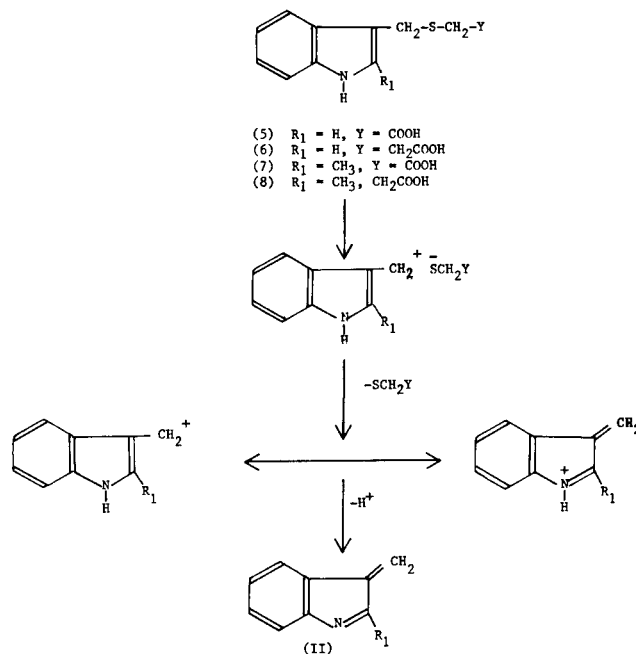
SCHEME I



- (1) R₁ = H, R₂ = N(CH₃)₂
 (2) R₁ = CH₃, R₂ = N(CH₃)₂
 (15) R₁ = H, R₂ = N(CH₃)₃⁺
 (16) R₁ = CH₃, R₂ = N(CH₃)₃⁺
 (5) R₁ = H, R₂ = SCH₂COOH
 (6) R₁ = H, R₂ = SCH₂CH₂COOH
 (7) R₁ = CH₃, R₂ = SCH₂COOH
 (8) R₁ = CH₃, R₂ = SCH₂CH₂COOH

- (3) R₁ = H
 (4) R₁ = CH₃

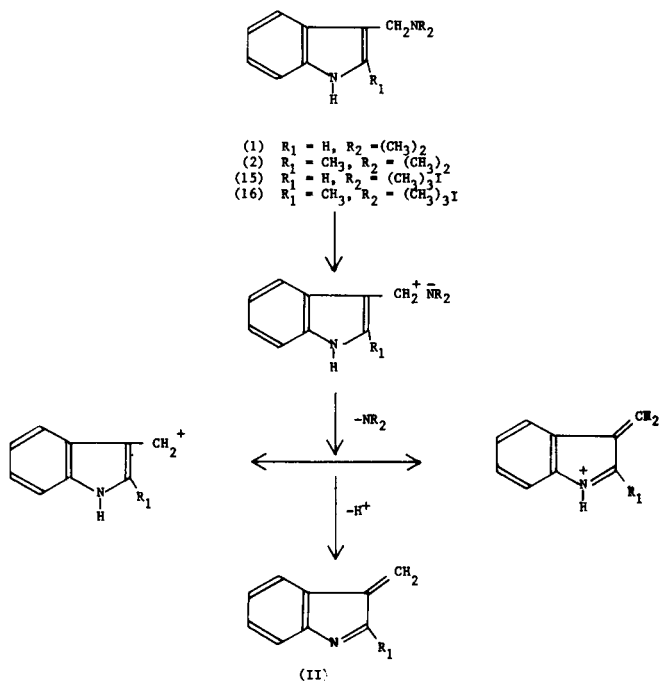
SCHEME II



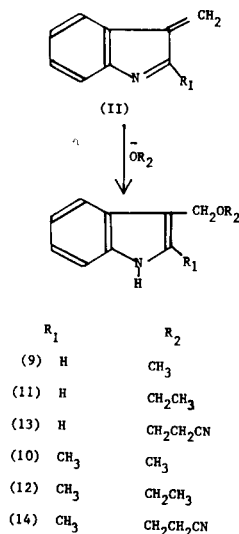
2-methylgramine (**2**) was prepared according to Supniewski and Serafin's procedure (13) *via* the Mannich reaction. The 2-methylindole used in the preparation of 2-methylgramine was prepared in 90% yield, which is greater than that suggested by Fitzpatrick and Hiser (17). The indol-3-ylmethyl-S-alkanoic acid (**5** or **6**) was refluxed in 50% sodium hydroxide solution to yield **3**. Similarly, **7** or **8** were also refluxed in 50% sodium hydroxide solution to yield **4**.

All four compounds **5**, **6**, **7** and **8** were treated with sodium methoxide, in methanol:pyridine (40:50) solution, to yield their respective 3-methoxymethylindole derivatives (**9** and **10**). Similarly, 3-ethoxymethylindole derivatives (**11** and **12**) were synthesized by treating the above intermediates (**5**, **6**, **7** and **8**) with sodium ethoxide in ethanol:pyridine (60:40) solution. These results suggested a possible mechanistic route (Scheme II) which generated the species (II) from the indol-3-ylmethyl-S-

SCHEME III

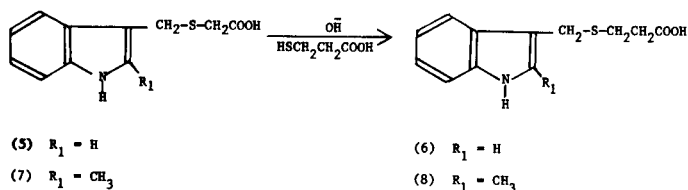


SCHEME IV



alkanoic acid derivative linkage similar to that suggested (Scheme III) for gramine derivatives (14). It has been suggested (14) that the initial step in the displacement addition reaction is the displacement of the leaving group catalyzed by the basic medium generating the species II. The nucleophilic alkoxide then immediately attacks the species II to yield 3-alkoxymethylindole derivatives (Scheme IV). Although unlikely, the direct displacement of the leaving group by alkoxide is possible. Therefore, an elimination addition reaction is suggested for this type of

SCHEME V



nucleophilic substitution reaction.

Employing the above rationale, 3-hydroxypropionitrile was treated with **5**, **6**, **7** and **8**, to give the respective indol-3-ylmethoxypropionitrile derivatives (**13** and **14**). Utilizing this easy sulfide displacement reaction, we were able to synthesize indol-3-ylmethyl-S-propionic acid (**6**) by displacing the S-acetic acid group from indol-3-ylmethyl-S-acetic acid (**5**). Similarly, (2-methylindol-3-yl)methyl-S-propionic acid (**8**) was obtained from (2-methylindol-3-yl)methyl-S-acetic acid (**7**) (Scheme V).

EXPERIMENTAL

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

2-Methylgramine (2).

Acetic acid (50 ml., 0.83 mole), 50 ml. (0.57 mole) of dioxane, 13.3 ml. (0.15 mole) of dimethylamine and 10.5 ml. (0.14 mole) of formaldehyde were stirred for 30 minutes. 2-methylindole (**1**) (13.2 g., 0.100 moles), dissolved in 150 ml. (1.70 moles) of dioxane was added to the above solution and the mixture was stirred overnight. The solution was then diluted with 300 ml. of water and filtered. The filtrate was neutralized with concentrated sodium hydroxide solution. The yellow precipitate which was obtained was filtered and washed with water. The yield was 80%, m.p. 119-121° [lit. (13) m.p. 120-121°]; ir (potassium bromide): 3460, 3420, 3150, 3060, 2960, 1470, 2930, 2840, 1490, 1600, 1590, 1520, 1500, 1635, 750 cm^{-1} .

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.60; H, 8.51; N, 14.90. Found: C, 76.45; H, 8.51; N, 14.76.

3,3'-Diindolylmethane (3).

Sodium hydroxide solution, (50 ml., 50%) was refluxed with 2.5 g. (0.01 mole) of **5** or 0.01 moles of **6** for 2 hours. The undissolved white precipitate which was obtained was filtered, washed with water, dried in the oven and recrystallized from benzene. The experimental yield was 90%, m.p. 166-167° [lit. (9) m.p. 164-165°]; ir (potassium bromide): 3450, 3050, 2960, 2870, 1625, 1600, 1540, 1520, 1470, 750 cm^{-1} .

Anal. Calcd. for $C_{12}H_{14}N_2$: C, 82.92; H, 5.69; N, 11.38. Found: C, 82.90; H, 5.67; N, 11.30.

2,2'-Dimethyl-3,3'-diindolylmethane (4).

Compound **7** (2.5 g., 0.01 mole) or 0.01 moles of **8** were refluxed with 50 ml. (50%) sodium hydroxide solution for 2 hours. The white precipitate which was obtained was filtered, washed, dried in a vacuum oven and recrystallized from benzene. The final product yielded was 92% with m.p. 235-237° [lit. (16) m.p. 237-238°]; ir (potassium bromide): 3420, 3050, 3000, 2960, 1490, 1360, 1630, 1580, 1570, 1470,

1450, 750 cm^{-1} .

Anal. Calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_2$: C, 83.22; H, 6.50; N, 10.22. Found: C, 83.08; H, 6.72; N, 10.08.

Indol-3-ylmethyl-S-acetic Acid (5).

Sodium hydroxide (1 g.), dissolved in 10 ml. of water, was refluxed for 15 minutes under a nitrogen atmosphere. To this, 4 g. (0.022 mole) of gramine and 2.6 g. (0.028 mole) of mercaptoacetic acid were added and refluxed for an additional 50 minutes. The reaction mixture was cooled and acidified with acetic acid. The white precipitate obtained was filtered, washed and recrystallized from benzene. A 90% yield was obtained, m.p. 107-109° [lit. (11) m.p. 106-108°]; ir (potassium bromide): 3420, 3150, 3100, 3050, 1490, 1620, 1590, 1540, 1440, 1720, 1295, 750 cm^{-1} .

Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{NO}_2\text{S}$: C, 59.72; H, 4.97; N, 6.33. Found: C, 59.85; H, 5.00; N, 6.29.

Indol-3-ylmethyl-S-propionic Acid (6).

In 10.0 ml. of water, 1.0 g. of sodium hydroxide was dissolved and refluxed for 15 minutes under a nitrogen atmosphere. To this, 4.0 g. (0.022 mole) of gramine and 2.9 g. (0.027 mole) of mercaptopropionic acid were added and refluxed for 50 minutes. The reaction mixture was cooled to 0-5° and acidified with acetic acid. The pinkish precipitate which was obtained was filtered, washed and recrystallized from benzene. The yield was 85%. Compound 6 could also be synthesized from 5 under the following conditions: 2.0 g. of sodium hydroxide in 10.0 ml. of water were refluxed for 15 minutes under nitrogen and cooled to 70-80°. Then, 2.6 g. (0.011 moles) of 5 and 2.9 g. (0.027 moles) of mercaptopropionic acid were added and the mixture was stirred for 45 minutes at 70-80°. The reaction mixture was cooled, filtered and acidified with acetic acid. The 74% yield of 6 was obtained after recrystallization from benzene, m.p. 115-117°; ir (potassium bromide): 3410, 3150, 3100, 3050, 1490, 1630, 1580, 1530, 1460, 1730, 1280, 780 cm^{-1} .

Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{NO}_2\text{S}$: C, 61.40; H, 5.60; N, 6.00. Found: C, 61.50; H, 5.70; N, 5.88.

(2-Methylindol-3-yl)methyl-S-acetic Acid (7).

Sodium hydroxide (1 g.) dissolved in 10.0 ml. of water was refluxed for 15 minutes under nitrogen atmosphere. To this, 4.2 g. (0.022 mole) of 2 and 2.9 g. (0.027 mole) of mercaptoacetic acid were added and the mixture was refluxed for 50 minutes. The cooled mixture was acidified with acetic acid and the precipitate which was obtained was filtered, dried and recrystallized from benzene. A yield of 89% was obtained, m.p. 105-107°; ir (potassium bromide): 3420, 2190, 3140, 3000, 2960, 2860, 1720, 1030, 1530, 1480, 1460, 1380, 1300, 1220, 1145, 1070, 750 cm^{-1} .

Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{NO}_2\text{S}$: C, 61.26; H, 5.53; N, 5.95. Found: C, 61.29; H, 5.60; N, 5.94.

(2-Methylindol-3-yl)methyl-S-propionic Acid (8).

Sodium hydroxide (1 g.) dissolved in 10 ml. of water was refluxed for 15 minutes under nitrogen atmosphere. To this, 4.2 g. (0.022 mole) of 2 and 2.9 g. (0.027 mole) of mercaptopropionic acid were added and the mixture was refluxed for 50 minutes. The cooled mixture was acidified with acetic acid and the precipitate which was obtained was filtered, dried and recrystallized from benzene. A yield of 89% was obtained. Compound 8 could also be synthesized from 7 under the following conditions: 2.0 g. of sodium hydroxide in 10.0 ml. of water were refluxed for 15 minutes under nitrogen and cooled to 70-80°. Then 2.5 g. (0.010 mole) of 7 and 2.9 g. (0.027 moles) of mercaptopropionic acid were added and the mixture was stirred for 45 minutes at 70-80°. The reaction mixture was cooled, filtered, acidified with acetic acid and recrystallized from benzene. A yield of 70% was obtained, m.p. 115-117°; ir (potassium bromide): 3425, 3185, 3150, 3080, 3020, 3000, 2970, 2850, 1730, 1630, 1475, 1460, 1360, 1300, 1230, 1130, 1070, 750 cm^{-1} .

Anal. Calcd. for $\text{C}_{13}\text{H}_{15}\text{NO}_2\text{S}$: C, 62.51; H, 6.03; N, 5.68. Found: C, 62.62; H, 6.15; N, 5.57.

3-Methoxymethylindole (9).

Compound 5 (1.5 g., 0.006 mole) or 0.006 mole of 6, 0.6 g. of sodium methoxide, 40 ml. of methanol and 50 ml. of pyridine were refluxed for 50 minutes. The reaction mixture was cooled, and methanol and pyridine were removed under reduced pressure over a period of 2 hours. The solid thus obtained was dried and recrystallized from benzene. The yield was 72%, m.p. 90-91°; ir (potassium bromide): 3420, 3230, 3180, 3140, 3090, 3020, 2990, 2860, 1620, 1470, 1480, 1300, 1240, 1140, 1100, 750 cm^{-1} .

Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{NO}$: C, 74.53; H, 6.83; N, 8.69. Found: C, 74.70; H, 6.81; N, 8.75.

3-Methoxymethyl-2-methylindole (10).

Compound 7 (1.7 g., 0.007 mole) or 0.007 mole of 8, 1.9 g. of sodium methoxide, 40 ml. of methanol and 50 ml. of pyridine were refluxed for 50 minutes. The reaction mixture was cooled and methanol and pyridine were pulled off under reduced pressure. The solid which was obtained was recrystallized from benzene. The yield was 80%, m.p. 110-112°; ir (potassium bromide): 3420, 3230, 3190, 3145, 3080, 3030, 2990, 2860, 1620, 1480, 1490, 1300, 1400, 1150, 1100, 750 cm^{-1} .

Anal. Calcd. for $\text{C}_{11}\text{H}_{13}\text{NO}$: C, 75.43; H, 7.43; N, 8.00. Found: C, 75.72; H, 7.54; N, 7.77.

3-Ethoxymethylindole (11).

Compound 5 (1.8 g. 0.008 mole) of 0.008 mole of 6, 0.9 g. of sodium ethoxide, 60 ml. of ethanol and 40 ml. of pyridine were refluxed for 50 minutes. The reaction mixture was cooled and evaporated to dryness. The solid obtained was recrystallized from benzene. The yield was 78% m.p. 67-68°; ir (potassium bromide): 3435, 3260, 3150, 3120, 3050, 3010, 2970, 2880, 1620, 1450, 1430, 1310, 1260, 1120, 1090, 750 cm^{-1} .

Anal. Calcd. for $\text{C}_{11}\text{H}_{13}\text{NO}$: C, 75.43; H, 7.43; N, 8.00. Found: C, 75.23, H, 7.39; N, 7.98.

3-Ethoxymethyl-2-methylindole (12).

The mixture of 2.1 g. (0.008 mole) of 7 or 0.008 mole of 8, 1.1 g. of sodium ethoxide, 60 ml. of ethanol and 40 ml. of pyridine was refluxed for 70 minutes. The reaction was cooled and ethanol and pyridine were removed under vacuum to dryness. The solid which was obtained was recrystallized from benzene. The yield was 68%, m.p. 79-80°; ir (potassium bromide): 3440, 3280, 3120, 3110, 3050, 2960, 2870, 1625, 1440, 1420, 1300, 1250, 1140, 1100, 1080, 750 cm^{-1} .

Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{NO}$: C, 76.19; H, 7.93; N, 7.40. Found: C, 76.00; H, 7.86; N, 7.40.

Indol-3-ylmethoxypropionitrile (13).

Compound 5 (2.3 g., 0.008 mole) or 0.008 mole of 6, 70 ml. of 3-hydroxypropionitrile and 40 ml. of pyridine were refluxed for 50 minutes. The reaction mixture was cooled and dropped into cold water (150 ml.) with constant stirring. The solid was recrystallized from ethanol. The yield was 60%, m.p. 85-89°; ir (potassium bromide): 3400, 3050, 3000, 2850, 2250, 1460, 1625, 1560, 1540, 1440, 1100, 750 cm^{-1} .

Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}$: C, 72.00; H, 6.00; N, 14.00. Found: C, 71.90, H, 6.00; N, 13.85.

(2-Methylindol-3-yl)methoxypropionitrile (14).

A mixture of 2.6 g. (0.0085 mole) of 7 or 0.0085 mole of 8, 80 ml. of 3-hydroxypropionitrile and 40 ml. of pyridine were refluxed for 50 minutes. The reaction mixture was cooled and dropped into cold 200 ml. of water with constant stirring. The solid obtained was recrystallized from ethanol. The yield was 54%, m.p. 109-111° ir (potassium bromide): 3410, 3130, 3050, 3000, 2920, 2860, 2250, 1630, 1470, 1550, 1440, 1110, 750 cm^{-1} .

Anal. Calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}$: C, 72.80; H, 6.54; N, 13.08. Found: C, 72.72; H, 6.80. N, 12.97.

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- (2) To whom inquiries should be addressed.
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- (8) A preliminary report of this work was presented at the 1978 Research Symposium of the Historical Black Land Grant Colleges and State Universities, St. Louis, Missouri, November 8-10, 1978.
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