Research Laboratories, The National Drug Company

2,3-Dimethyl-3*H*-indole-3-acetic Acid (1)

Paul D. Rosenstock (2)

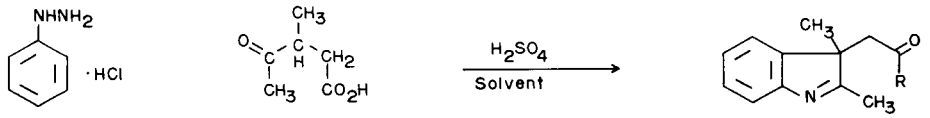
The synthesis of the plant-growth hormone, 2-methyl-3-indoleacetic acid (I), by means of the Fischer ring closure of levulinic acid phenylhydrazone has been reported in several communications (3-7). However, the analogous cyclization of 3-methyllevulinic acid phenylhydrazone to yield 2,3-dimethyl-3*H*-indole-3-acetic acid (II), the simplest indolenine analogue of acid I, has not previously been investigated. A simple one-step synthesis of acid (II) which involves the reaction of 3-methyllevulinic acid (III) with phenylhydrazine hydrochloride in acid medium is described herein.

Fischer cyclization of suitably substituted phenylhydrazone derivatives is a useful synthetic route to the indolenine nucleus. For example, Plancher (8) synthesized 2,3,4-trimethyl-3*H*-indole, the first reported indolenine compound, by ring closure of 3-methyl-2-butanone phenylhydrazone with zinc chloride. Similarly, 2,3,4-trimethyl-4-nitro-3*H*-indole was obtained by cyclization of 3-methyl-2-butanone *p*-nitrophenylhydrazone in glacial acetic acid solution (9), while 3,3-dimethyl-5-methoxy-3*H*-indole-2-carboxylic acid was obtained by treatment of 2-oxo-3-methylbutyric acid *p*-methoxyphenylhydrazone with hydrochloric acid (10).

2,3-Dimethyl-3*H*-indole-3-acetic acid (II) was readily prepared in good yield by heating an aqueous solution of 3-methyllevulinic acid (III) and phenylhydrazine hydrochloride in the presence of a sulfuric acid catalyst. With methanol as the solvent, a mixture containing 52% of methyl 2,3-dimethyl-3*H*-indole-2-acetate (IV) and 18% of indolenine-acid (II) was obtained. This ester-to-acid ratio was not significantly altered by changing the experimental conditions. When higher boiling alcohols were employed as solvents, materials were obtained which appeared to be polymeric on a basis of molecular weight determinations. These substances were not further investigated.

Methyl 2,3-dimethyl-3*H*-indole-3-acetate (IV) is a colorless to pale yellow viscous liquid which is air and light sensitive. It readily forms hydrochloride (V) and hydrobromide (VI) salts which are white solids, but these derivatives also have a tendency to darken on heating or on exposure to light or air. Reaction of the ester with hydrazine hydrate gave an almost quantitative yield of the corresponding hydrazide derivative (VII) while transesterification with 3-pyridylcarbinol led to the formation of 3'-pyridylmethyl 2,3-dimethyl-3*H*-indole-3-acetate (VIII).

2,3-Dimethyl-3*H*-indole-3-acetic acid (II) is a white crystalline solid which, in contrast to the instability of its methyl ester (IV), is surprisingly stable. However, the acid does not form stable salt derivatives nor does it give an acid chloride on treatment with the standard reagents. For the preparation of amide derivatives it was necessary to use a mixed anhydride procedure which provided stable amide derivatives in good yields.



(III)

II R = -OH

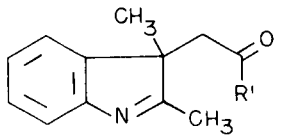
IV R = $-OCH_3$

VII R = $-NHNH_2$

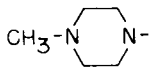
VIII R = $-O-CH_2$-(pyridyl)

TABLE I

2,3-Dimethyl-3*H*-indole-3-acetamide Derivatives



(IX)

R'	°C M.P.(cor.)	% Yield	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$-NH_2$	170-172 (a)	65	$C_{12}H_{14}N_2O$	71.26	71.36	6.98	7.18	13.85	13.65
$-N(CH_3)_2$	131-132 (b)	61	$C_{14}H_{18}N_2O$	73.01	73.01	7.88	7.62	12.17	12.43
$-NH-CH(CH_3)_2$	145-147 (b)	76	$C_{15}H_{20}N_2O$	73.73	73.49	8.25	8.20	11.47	11.55
$-NHC_6H_{11}$	173-175 (a)	81	$C_{18}H_{24}N_2O$	76.02	75.94	8.51	8.50	9.85	9.86
	143-145 (c)	42	$C_{16}H_{20}N_2O_2$	70.56	70.62	7.40	7.52	10.29	10.18
	144-146 (b)	52	$C_{17}H_{23}N_3O$	71.54	71.59	8.12	8.08	14.73	14.78

Crystallization solvents: (a) Benzene-hexane. (b) Ether-hexane. (c) Ether.

EXPERIMENTAL (11)

Diethyl 2-Acetyl-2-methylsuccinate.

Ethyl α-methylacetoacetate (792 g., 6 moles) was added to a well stirred suspension of 144 g. (6 moles) of sodium hydride in 8 liters of toluene over a 2 hour period. The resulting solution was heated under reflux for 2 hours, cooled slightly, and treated with 735 g. (6 moles) of ethyl chloroacetate over a 1 hour period. The suspension was then heated under reflux for 12 hours, cooled, filtered and the solvent evaporated under reduced pressure. The residue was distilled *in vacuo* to yield 836 g. (58%) of colorless liquid, b.p. 70-74° (0.2 mm.). The analytical sample had a boiling point of 72° (0.2 mm.), n_D^{25} 1.5437.

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.56; H, 7.77.

3-Methyllevulinic Acid (12) (III).

Hydrolysis of diethyl 2-acetyl-2-methylsuccinate with concentrated hydrochloric acid on a steam bath until the gas evolution ceased gave a 94% yield of 3-methyllevulinic acid (III) as a colorless oily liquid, b.p. 105-110° (1 mm.), n_D^{25} 1.4416; lit. (13), b.p. 115-118° (3 mm.), n_D^{17} 1.4446.

2,3-Dimethyl-3*H*-indole-3-acetic Acid (II).

Method A.i.

A solution of 98 g. (0.75 mole) of 3-methyllevulinic acid; 110 g. (0.75 mole) of phenylhydrazine hydrochloride and 75 ml. of sulfuric acid in 1100 ml. of absolute methanol was heated under reflux for 3 hours. During the course of the reaction, the solution changed from colorless to a wine-red. At the end of the reaction period, the methanol was evaporated under reduced pressure, the deep red oily residue dissolved in 400 ml. of water and extracted with ether until the ether was colorless. The ether extracts were discarded, the solution made basic with 50% sodium hydroxide, and the oil which separated was extracted with three 300 ml. portions of ether. The combined ether extracts were dried over anhydrous sodium sulfate, filtered, the ether evaporated and the residue distilled *in vacuo*. The fraction b.p. 92-96° (0.15 mm.) was collected to yield 84 g. (52%) of methyl 2,3-dimethyl-3*H*-indole-3-acetate (IV) as a pale yellow oil, n_D^{25} 1.5397. This material was sufficiently pure for preparative purposes. The analytical sample was obtained as a colorless oil by redistillation of an aliquot, b.p. 95-97° (0.15 mm.), n_D^{25} 1.5403.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.40; H, 7.09; N, 6.41.

Treatment of methyl 2,3-dimethyl-3*H*-indole-3-acetate (IV) with anhydrous hydrogen chloride gas yielded the corresponding hydrochloride derivative (V) as a white solid, m.p. 186-189°. Two recrystallizations from acetonitrile gave an analytical sample, m.p. 194-196°.

Anal. Calcd. for $C_{13}H_{16}NO_2Cl$: C, 61.54; H, 6.36; N, 5.52. Found: C, 61.52; H, 6.32; N, 5.52.

Similarly, treatment of amino-ester (IV) with aqueous hydrobromic acid resulted in formation of methyl 2,3-dimethyl-3*H*-indole-3-acetate hydrobromide (VI), m.p. 187-189° dec. Three recrystallizations from acetonitrile gave a white crystalline analytical sample, m.p. 190-193° dec.

Anal. Calcd. for $C_{13}H_{16}NO_2Br$: C, 52.36; H, 5.41; N, 4.70. Found: C, 52.39; H, 5.60; N, 4.66.

Method A.ii.

The basic water layer from the above extraction of the amino-ester IV was cautiously neutralized to *p*H 6.9 with hydrochloric acid and the oil that separated was extracted into three 500 ml. portions of chloroform. The combined extracts were dried over anhydrous sodium sulfate, filtered, the solvent evaporated under reduced pressure, the orange oily residue dissolved in 200 ml. of hot ether. The solid which separated was filtered to yield 28 g. (18%) of pale yellow crystalline 2,3-dimethyl-3*H*-indole-3-acetic acid (II), m.p. 104-106°.

This material was sufficiently pure for preparative purposes. Two recrystallizations of an aliquot from 50% methanol-ether yielded a white crystalline analytical sample, m.p. 105-107°.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.65; H, 6.45; N, 6.80.

Method B.

A solution of 26 g. (0.2 mole) of 3-methyllevulinic acid (III), 29 g. (0.2 mole) of phenylhydrazine hydrochloride and 25 ml. of sulfuric acid in 450 ml. of water was heated under reflux for 5 hours. During the course of the reaction, the color of the solution changed from pale yellow to deep red and there was some charring. At the end of the reflux period, the solution was cooled, made basic with 50% sodium hydroxide solution and extracted with three 300 ml. portions of chloroform. The chloroform extracts were discarded and the water layer was worked-up by the procedure described above in Method A.ii to yield 26 g. (62%) of 2,3-dimethyl-3*H*-indole-3-acetic acid (II) as a cream colored solid, m.p. 104-106°.

Method C.

A solution of 60 g. (0.28 mole) of methyl 2,3-dimethyl-3*H*-indole-3-acetate (IV) in 600 ml. of 10% methanolic potassium hydroxide was heated under reflux for 4 hours. At the end of this period, the methanol was evaporated under reduced pressure and the residue dissolved in 400 ml. of water. The resulting solution was worked-up as in Method B to yield 52 g. (91%) of acid (II) as a cream colored solid, m.p. 104-106°.

2,3-Dimethyl-3*H*-indole-3-acethydrazide (VII).

A solution of 11 g. (0.05 mole) of methyl 2,3-dimethyl-3*H*-indole-3-acetate (IV) and 5.9 g. (0.1 mole) of 85% hydrazine hydrate in 15 ml. of methanol was heated under reflux for one day. The solvent was evaporated under reduced pressure, the yellow solid residue triturated with 70 ml. of ether, filtered, and air dried to yield 10.3 g. (95%) of white solid, m.p. 146-149°. Two recrystallizations from acetone-hexane gave an analytical sample, m.p. 148-149°.

Anal. Calcd. for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.41; H, 7.00; N, 19.36.

3'-Pyridylmethyl 2,3-Dimethyl-3*H*-indole-3-acetate (VIII).

A solution of 11 g. (0.05 mole) of methyl 2,3-dimethyl-3*H*-indole-3-acetate (IV) and 6.5 g. (0.05 mole) of 3-pyridylcarbinol in 200 ml. of heptane and 200 ml. of toluene was heated under reflux under a Dean-Stark Trap for 18 hours. During the first 8 hours of the heating period, a trace of clean sodium was added every hour. At the end of the reaction period, the solution was washed with 100 ml. of water, the solvents evaporated under reduced pressure, and the residue distilled *in vacuo*. The fraction boiling at 170-174° (0.1 mm.) was collected to yield 9.5 g. (66%) of pale yellow oil which solidified in the receiver to a white solid, m.p. 93-95°. One recrystallization from 2% methanol-ether yielded an analytical sample, m.p. 98-100°.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.58; H, 6.18; N, 9.60.

2,3-Dimethyl-3*H*-indole-3-acetamide Derivatives (IX).

A cold solution of 20 ml. (0.1 mole) of 2,3-dimethyl-3*H*-indole-3-acetic acid (II) and 10 g. (0.1 mole) of triethylamine in 200 ml. of chloroform was added dropwise and with stirring, over a period of 2 hours to a solution of 11 g. (0.1 mole) of ethyl chloroformate in 200 ml. of chloroform. The reaction mixture was maintained at from -30° to -15° during the course of the addition. When the addition was complete, the resulting clear solution was stirred for 1 hour at -15° after which time a solution of 0.2 mole of amine in 100 ml. of chloroform was added in one portion. The reaction was exothermic and generally caused a rapid temperature rise of about twenty degrees. Stirring was continued and the solution was allowed to warm slowly to room temperature. The cloudy reaction mixture was then transferred to a separatory funnel and extracted with 200 ml. portions of water, 5% sodium hydroxide, 5% hydrochloric acid and water. The organic layer was dried over anhydrous sodium sulfate, filtered, the solvent evaporated and the residue dissolved in 100 ml. of dry ether. The ether solution was cooled, the crude amide filtered, and purified by recrystallization from benzene-hexane (see Table I).

REFERENCES

(1) All communications concerning this paper should be addressed to Frank P. Palopoli; The National Drug Company; Division of Richardson-Merrell Inc.; Haines and McCallum Streets; Philadelphia, Pennsylvania 19144.

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