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3-*Indolylacetaldehyde and* 3-*Indolylacetone.*

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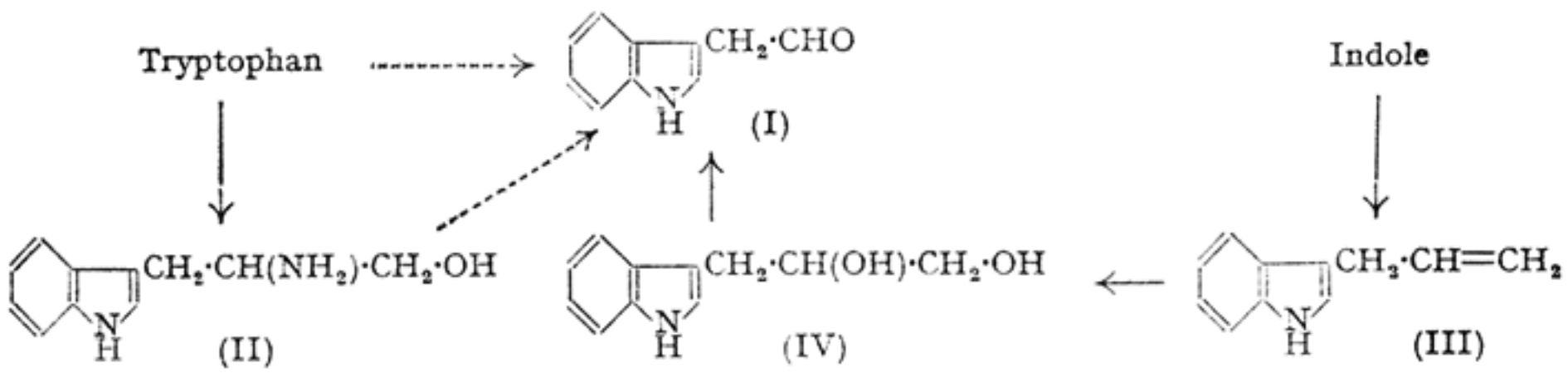
3-Indolylacetaldehyde (I), the aldehyde corresponding with heteroauxin, which has been claimed to have been detected in some plant sources, has been prepared for the first time, and has been fully characterized. The related 3-indolylacetone (VI) has also been prepared.

The tissues of several plant species have been reported to contain a neutral compound, believed by many workers to be 3-indolylacetaldehyde (I), the aldehyde related to heteroauxin; however, recent work by Bentley, Henbest, Jones, and Smith (*Nature*, 1952, **169**, 485) has shown that the neutral hormone present in cabbage and brussels sprouts is 3-indolylacetonitrile. The chief evidence for the presence of 3-indolylacetaldehyde in plants (for a comprehensive review see Larsen, *Ann. Rev. Plant Physiol.*, 1951, **2**, 176) has been the conversion of part of a neutral ether-soluble fraction into a growth-promoting acidic material (presumed to be heteroauxin) by enzymic action, although Gordon and Nieva (*Arch. Biochem.*, 1949, **20**, 356, 367) have reported that the neutral substance can be extracted by aqueous solutions of dimedone and sodium hydrogen sulphite, regeneration being possible in the latter case to yield a material again convertible into a physiologically active acid. The isolation of the aldehyde itself (or any derivatives thereof) has not been described, but Larsen has prepared a material containing about 2% of this substance (estimated by bioassay of the auxin produced by soil treatment) by treating tryptophan with ninhydrin (or isatin) in aqueous solution.

3-Indolylacetaldehyde is also of interest because it has been postulated as a possible intermediate in the conversion *in vivo* of tryptophan into heteroauxin.

In the first place the ninhydrin oxidation of tryptophan was re-investigated, but it soon became clear that a very heterogeneous product was invariably formed. In view of the probable instability of the aldehyde, attention was then directed towards milder synthetical methods, in particular, to the possibility of oxidising tryptophanol (II) (Karrer and Portmann, *Helv. Chim. Acta*, 1949, **32**, 1034) by means of periodic acid—this reagent has been employed to split *vic.*-amino-alcohols (Jackson, "Organic Reactions," Vol. 2, p. 341). Periodate oxidation of tryptophanol was conducted in water at pH ~6 in the presence of ether to remove the sensitive aldehyde as formed. However, the reaction proceeded only slowly at 20° producing much insoluble material, and the heterogeneous ether-soluble portion yielded a complex mixture of 2 : 4-dinitrophenylhydrazones.

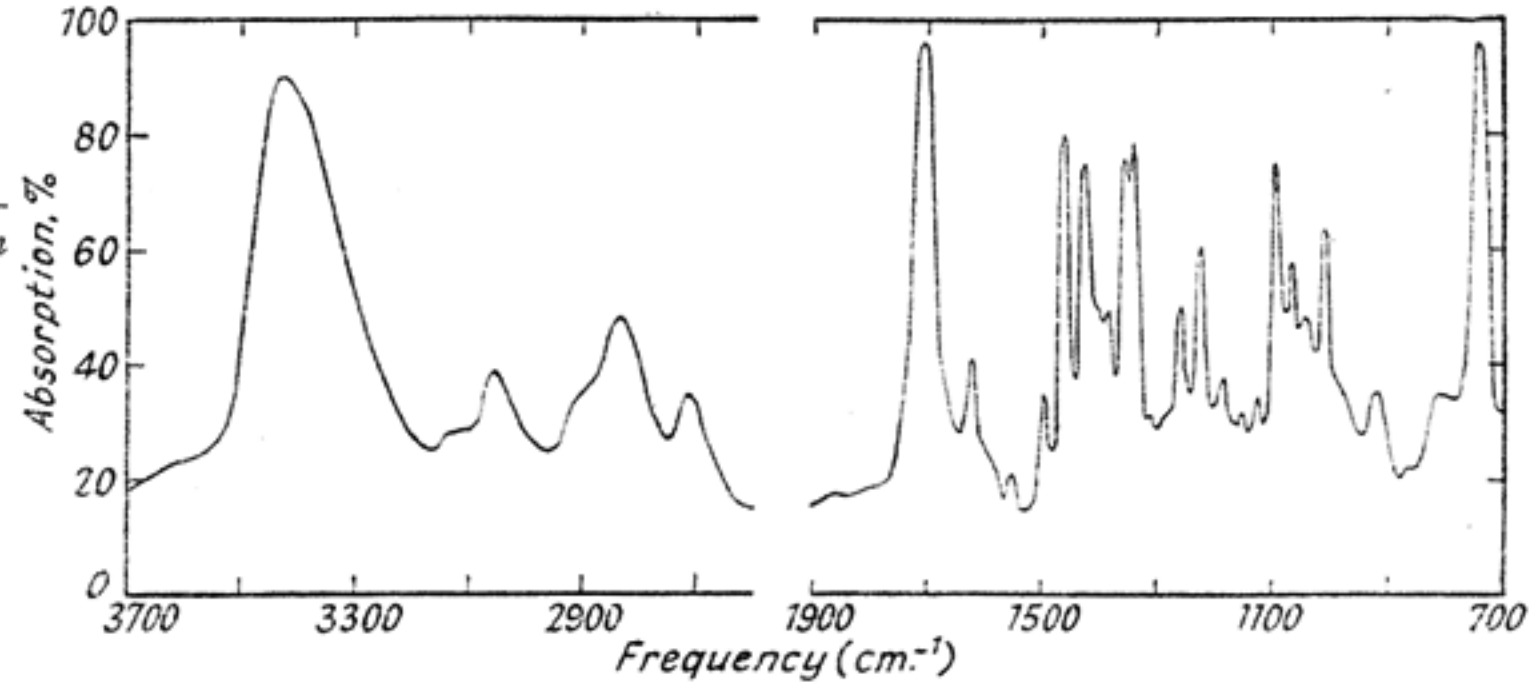


Periodate fission of the *vic.*-glycol (IV) should take place more rapidly than that of tryptophanol. This glycol was prepared from indole, by first treating the Grignard derivative of the latter with allyl bromide, producing 3-allylindole (III) in good yield. Analogy with other reactions of indolyl Grignard reagents would indicate that the allyl group is attached at the 3-position, and this was confirmed by infra-red measurements (see Experimental). Treatment of 3-allylindole with osmium tetroxide below 0° readily led to the crystalline glycol (IV). An attempt to prepared the glycol from (III) and performic acid was unsuccessful, intractable tars being obtained.

Oxidation of the glycol with periodate was conducted in the presence of ether–light petroleum in which only 3% of the glycol dissolved. The reaction proceeded rapidly at 20°, and 3-indolylacetaldehyde could be isolated readily from the organic phase. Distilla-

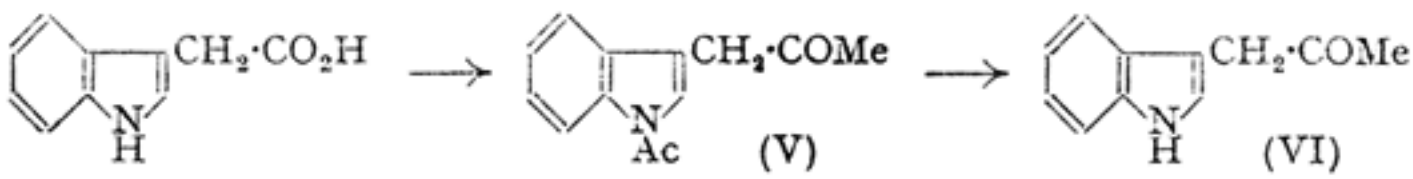
tion (attended by some material loss) gave the pure aldehyde, which was quite stable when stored at −60°. A determination of its molecular weight in benzene solution showed that it was monomeric—it was necessary to check this as phenylacetaldehyde can exist as a fairly stable trimer. The infra-red absorption spectrum is shown in the accompanying Figure. The aldehyde was further characterized as the semicarbazone, 2 : 4-dinitrophenylhydrazone, and the dimedone derivative.

From previously reported work with crude 3-indolylacetaldehyde, it is uncertain whether this compound functions as a plant-growth hormone. We are indebted to Dr. J. Bentley and Mr. S. Housley, of the Botany Department of this University, for the following preliminary report of the activity of the pure compound in the *Avena* straight-growth test (Bentley, *J. Exptl. Bot.*, 1950, **1**, 201). 3-Indolylacetaldehyde itself appears to be either inactive or inhibitory in this test. Solutions of the aldehyde cause some growth of *Avena* coleoptile sections, but an acidic substance has been shown to be produced during the test, which, assuming that this is heteroauxin, would account for all (and sometimes even more of) the activity shown by the aldehyde test solution. The amount of acid produced was determined by extracting the final test solution with ether, followed by separation into an acidic and a neutral fraction in the usual way, and evaluation of the acid by the straight-growth test. It was noteworthy that the amount of acid formed was greater in the presence of coleoptile sections than in their absence.



3-Indolylacetaldehyde—infra-red absorption spectrum.

It was of chemical and possible biological interest to prepare the related compound, 3-indolylacetone (VI). It was hoped that hydration of the triple bond of 3-propargylindole would give this ketone, but an attempt to prepare the propargyl compound by treating indolylmagnesium bromide with propargyl bromide failed, chiefly because the Grignard reagent reacted first with the active acetylenic hydrogen atom to regenerate indole.



Phenylacetone has been prepared by heating phenylacetic acid with acetic anhydride in the presence of sodium acetate (this reaction has been recently reviewed by King and McMillan, *J. Amer. Chem. Soc.*, 1951, **73**, 4911). Application of the method to 3-indolylacetic acid gave a 45% yield of a ketonic product, analysis and infra-red examination of which showed that it was *N*-acetyl-3-indolylacetone (V). This compound could be hydrolysed readily to (crystalline) 3-indolylacetone (VI), which was virtually inactive in the *Avena* straight-growth test.

Experimental

M. p.s were taken on a Kofler block and are corrected. Ultra-violet light-absorption spectra were determined with a Unicam SP 500 spectrophotometer, ethanolic solutions being used, and infra-red spectral measurements were made with a Perkin-Elmer double-beam instrument (sodium chloride prism), either a liquid or a supercooled melt being used.

3-*Allylindole* (III).—Ethylmagnesium bromide (representing a 20% excess over the indole

to be used) was prepared from magnesium (6·5 g.) in ether (80 c.c.) and ethyl bromide (30 g.) in ether (30 c.c.). Redistilled indole (25·8 g.) in benzene (50 c.c.) was then added slowly with stirring. The indolylmagnesium bromide solution was stirred for a further 20 minutes, and redistilled allyl bromide (29·2 g.) in benzene (20 c.c.) was then added slowly, a mild exothermic reaction taking place. After the mixture had been stirred at 20° overnight, the product was isolated with ether. Distillation gave 3-allylindole (22·7 g., 70%) (together with a little unchanged indole), b. p. 94—98°/0·03 mm., n_D^{19} 1·5998. Completely satisfactory analytical data could not be obtained with this compound, carbon values being somewhat high and hydrogen values low. Light absorption: Maxima, 2200, 2740, and 2860 Å; ε = 35,000, 6400, and 5300, respectively.

For hydrogenation, a solution of 3-allylindole (1·71 g.) in ethanol (50 c.c.) was shaken with Adams's catalyst (0·1 g.) in an atmosphere of hydrogen. Hydrogenation was rapid and ceased after 273 c.c. had been absorbed (theoretical for 1 mole, 276 c.c.). Filtration and evaporation of the solution gave 3-propylindole (1·72 g.). Light absorption: Maxima, 2230, 2820, and 2900 Å; ε = 33,800, 5900, and 5000, respectively.

Infra-red absorption (main bands only).

(s = strong; m = medium; w = weak, are given as approximate indications of intensity.)

Spectrum region, cm.$^{-1}$	Indole	2-Methylindole	3-Methylindole	3-*n*-Propylindole	3-Allylindole	3-Indolylacetaldehyde
3100—3000	3050m	3060m	3065mw	3055mw	3080ms 2900ms (vinyl, CH stretching)	3065mw
3000—2900		2950m	2940m	2970ms		2830m
2900—1600					1625s (aliphatic C : C stretching) 1620ms	1705s (C = O stretching)
1600—1400		1550ms * 1410s *				
	1420m			1425m	1425s	1425s
1400—1200		1390m				
			1345m	1335m		1355s
		1290ms	1300m			1340s
	1250ms	1240m	1250m		1260ms	1255m
		1220ms		1225m		1225ms
1200—1000		1150m			1130m	
	1090ms		1090s *	1090ms *	1090s	1095s
						1070ms
		1035m			1050ms	1040m
1000—700					995s 914s (vinyl, CH bending)	
			975m			
	935m	925m	925m			
			802m		810ms	
	770s	780vs *			770s	
		750vs	755m			

All the above compounds showed strong bands at 3400—3450 cm.$^{-1}$ (NH stretching) and ~1460 cm.$^{-1}$, medium to strong bands at ~1350 cm.$^{-1}$, very strong bands at ~740 cm.$^{-1}$ (resolved into two bands at 730 and 750 with indole), and all except indole showed medium to strong bands at ~1010 cm.$^{-1}$

* Strong intensity bands differentiating 2- and 3-alkylindoles.

3-3′-*Indolylpropan*-1 : 2-*diol* (IV).—A solution of 3-allylindole (1·3 g.) and pyridine (2 c.c.) in ether (20 c.c.) was cooled to *ca.* −30° and added to a solution of osmium tetroxide (2 g.) in ether (200 c.c.) also at −30°. The solution was then allowed to warm to 15° during 1 hour, during which time the addition complex (4·3 g.) separated as a light brown solid. This was dissolved in chloroform (35 c.c.) and shaken with mannitol (30 g.) in water (300 c.c.) containing potassium hydroxide (3 g.) for 10 minutes. The chloroform layer was rejected and the aqueous phase was extracted continuously with ether for 6 hours. Evaporation of this extract yielded a gum which readily solidified. This was triturated twice with ether–light petroleum (b. p. 40—60°) (1 : 1; 10 c.c. portions) to give a slightly coloured granular solid (1·35 g.), m. p. 93—97°. Recrystallization of this from benzene gave the pure *glycol* as plates, m. p. 97·5—98° (Found: C, 69·0; H, 7·1. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·85%). Light absorption: Maxima, 2240, 2820, and 2900 Å; ε = 33,800, 5900, and 5000, respectively. When a solution of the glycol

(50 mg.) in water (30 c.c.) was shaken with an equal volume of ether, 40% of the glycol went into the ethereal layer; when a 1 : 1 mixture of ether–light petroleum (b. p. 40—60°) was used only 5% was extracted (cf. following experiment).

3-*Indolylacetaldehyde* (I) *and Derivatives.*—Before the reaction was begun, a high-vacuum line was evacuated to 10^{-5} mm. and an air-bath warmed to 120°. Aqueous sodium metaperiodate solution (0·1N; 26 c.c.) was stirred with ether–light petroleum (b. p. 40—60°) (1 : 1; 30 c.c.) in an atmosphere of nitrogen in a flask with a side-arm fused in at the level of the interface between the two layers of reaction solution. A solution of the foregoing glycol (0·5 g.) in water (30 c.c.) was added, the temperature of the stirred mixture rising from 14° to 18°. Stirring was continued for 5 minutes, and the organic layer was then removed *via* the side-arm, two portions of ether (30 c.c.) being added to the stirred aqueous phase to remove the remainder of the product. The combined extract was dried (Na_2SO_4) and evaporated under reduced pressure to leave substantially pure aldehyde (0·29 g.) as a colourless syrup. The pure compound was obtained by distillation [at 120° (bath temp.)] from a short-path still, but much polymerization appeared to take place during this operation, even when it was conducted as rapidly as possible, for the yield of distillate was only 0·09 g. (from 0·29 g.). Pure 3-*indolylacetaldehyde* had n_D^{18} 1·6178 (Found: C, 75·15; H, 5·3. $C_{10}H_9ON$ requires C, 75·4; H, 5·7%). Light absorption: Maxima, 2220, 2800, and 2890 Å; ε = 32,600, 6000, and 5000, respectively.

The 2 : 4-*dinitrophenylhydrazone* formed readily, but crystallized only slowly from supersaturated solutions in aqueous dioxan as yellow-brown plates, m. p. 196—202° (Found: C, 56·75; H, 4·0. $C_{16}H_{13}O_4N_5$ requires C, 56·6; H, 3·85%). Light absorption: Maxima, 2680 and 3580 Å; ε = 16,800 and 23,600, respectively.

The *semicarbazone* was prepared with semicarbazide acetate in aqueous methanol solution. Recrystallization from aqueous methanol gave long needles, m. p. 142—155° unchanged on further recrystallization (Found: C, 61·1; H, 6·0. $C_{11}H_{12}ON_4$ requires C, 61·1; H, 5·6%). Light absorption: Maxima, 2210, 2730, 2800, and 2900 Å; ε = 42,900, 6900, 6950, and 5650, respectively.

A saturated solution of dimedone in aqueous methanol (1 : 1) containing the aldehyde was set aside at 20° overnight; the *dimedone* derivative separated (dilution with water increased the yield) and after crystallization from aqueous methanol or chloroform formed needles. To obtain consistent m. p. values, the material was dried at 120°/20 mm.; it then had m. p. 148—152° (Found: C, 73·7; H, 7·45; N, 3·2. $C_{26}H_{31}O_4N$ requires C, 74·1; H, 7·4; N, 3·3%).

N-*Acetyl*-3-*indolylacetone* (V).—A mixture of 3-indolylacetic acid (2 g.), freshly fused sodium acetate (1·55 g.), and acetic anhydride (5 c.c.) was heated at 135—140° (oil-bath temp.) for 18 hours. The cooled mixture was treated with water and chloroform–ether (1 : 4). The organic layer was washed with saturated aqueous potassium hydrogen carbonate (3 × 20 c.c.), and then dried (Na_2SO_4) and evaporated under reduced pressure. Distillation from a short-path still gave the *ketone* (1·1 g.) as a pale yellow viscous syrup, b. p. 120° (bath temp.)/10^{-5} mm., n_D^{19} 1·5953 (Found: C, 72·05; H, 6·25. $C_{13}H_{13}O_2N$ requires C, 72·55; H, 6·1%). Light absorption: Maxima, 2380, 2910, and 3000 Å; ε = 16,800, 6500, and 6700, respectively (cf. light absorption of *N*-acetyl-2 : 3-dimethylindole: Maxima, 2450, 2940, and 2990 Å; ε = 17,300, 5200, and 5100, respectively). This distilled product, which may have contained a little of the enol-acetate, was used for the next stage (hydrolysis to 3-indolylacetone) without further purification.

The *N*-acetyl ketone was characterized by the formation of a 2 : 4-*dinitrophenylhydrazone*, which crystallized from ethyl acetate as orange-yellow needles, m. p. 194—195° (Found: C, 57·75; H, 4·6. $C_{19}H_{17}O_5N_5$ requires C, 57·7; H, 4·35%). The *semicarbazone* crystallized slowly from "Methyl Cellosolve" as a granular solid, m. p. 208—211° (Found: C, 61·75; H, 6·0. $C_{14}H_{16}O_2N_4$ requires C, 61·75; H, 5·9%).

3-*Indolylacetone* (VI).—N-Methanolic sodium methoxide (0·8 c.c.) was added to a solution of *N*-acetyl-3-indolylacetone (0·93 g.) in dry methanol (60 c.c.). After being kept at 40° for 10 minutes, the solution was acidified with dilute hydrochloric acid and extracted with ether. The ethereal extract was processed in the usual way to yield a solid product which after one recrystallization from aqueous methanol (1 : 1) weighed 0·41 g. and had m. p. 113—115°. Further recrystallisation from the same solvent gave the *ketone* as needles, m. p. 115—117·5° (Found: C, 76·0; H, 6·45. $C_{11}H_{11}ON$ requires C, 76·3; H, 6·4%). Light absorption: Maxima, 2210, 2800, and 2890 Å; ε = 35,100, 6400, and 5300, respectively. Infra-red spectrum: 3380 cm.$^{-1}$ (strong) (NH stretching); 1706 cm.$^{-1}$ (strong) (C:O stretching). The 2 : 4-*dinitrophenylhydrazone* crystallized from methanol–ethyl acetate as orange-red prisms, m. p. 161—163° (Found: C, 58·1; H, 4·2. $C_{17}H_{15}O_4N_5$ requires C, 57·8; H, 4·3%).