Indoles and auxins. VII. Active esters and anhydrides of 3-indoleacetic acid[1]

JUDITH C. HART,[2] EILEEN M. MATHESON,[3] AND O. HUTZINGER
Atlantic Regional Laboratory, National Research Council of Canada, Halifax, Nova Scotia

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The synthesis of activated esters and anhydrides of 3-indoleacetic acid is described. Their usefulness for the preparation of amino acid derivatives is shown by reaction with glycine methyl ester.

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3-Indoleacetic acid (IAA) is frequently found in conjugated and bound forms. For the preparation of these compounds and for introducing IAA into natural polymers, an "active" form of IAA is needed. 3-Indoleacetyl chloride is not convenient for this purpose. It has been prepared by standard methods (1–5) but it hydrolyzes and polymerizes readily and is therefore difficult to handle and store.

We have now investigated derivatives of IAA with groups normally used for carboxyl activation of amino acids in peptide synthesis: esters of IAA with *p*-nitrophenol, 2,4-dinitrophenol, pentachlorophenol, 8-hydroxyquinoline, and *N*-hydroxysuccinimide; mixed anhydrides of IAA and 3-indoleacetic anhydride. The mixed anhydride of IAA and ethyl chloroformate has been synthesized and used before (6–8). It is reactive but unstable and is prepared immediately before use. We found that the anhydride with isobutyl chloroformate (reported to give better yields in peptide synthesis (9)) has similar properties. The active esters were prepared by the dicyclohexylcarbodiimide or mixed anhydride methods. They are stable compounds, can be used for reactions in aqueous solutions and are hydrolyzed only slowly by *N*/10 sodium hydroxide at temperatures below 0°. 3-Indoleacetic anhydride is also stable on storage, it is slowly decomposed by moisture.

To show the usefulness of these derivatives for the synthesis of amino acid and peptide derivatives of IAA, the activated esters and 3-indoleacetic anhydride were allowed to react with glycine methyl ester (no racemization is expected in the amino component during this reaction; cf. 10). With exception of the 8-hydroxyquinoline derivative the reaction is complete after 10 h. The short reaction times required for completion of the reaction with 3-indoleacetic anhydride (30 min) and the 2,4-dinitrophenyl ester of IAA (1 h) are noteworthy.

The active forms of IAA mentioned above may also be useful for binding IAA chemically to proteins (11). 3-Indoleacetic anhydride and the mixed anhydrides react with phenolic hydroxy groups, the mixed anhydrides also provide a convenient route for the preparation of simple amides.

Experimental

Mixed Anhydride Method (A)

IAA (.01 *M*) in anhydrous tetrahydrofuran (THF; 30 ml) and triethylamine (1.4 ml) was treated with isobutyl chloroformate (method *A-1*) or ethyl chloroformate (*A-2*) (10 ml, 1 *M* solution in THF). For best results, the amino component should be added to the mixed anhydride after 3–5 min, or when the white paste becomes slightly yellow.

p-Nitro- or 2,4-dinitrophenol (.01 *M*) was added for the preparation of the activated nitrophenol esters. The mixture was stirred (10 min) at room temperature, ether (150 ml) added, and the solution carefully (to avoid hydrolysis) washed with *N*/10 sodium hydroxide and water. The ether solution was dried (Na_2SO_4), evaporated, and the residue recrystallized.

When ammonia gas was bubbled through the mixed anhydride solution at −10°, some THF removed, and water added, pure 3-indoleacetamide (m.p. 155°, yield 65–70%) precipitated from the reaction mixture.

Dicyclohexylcarbodiimide (DCC) Method (B)
Activated Esters (B-1)

DCC (.0105 *M*) was added to a solution of IAA (.01 *M*) and the hydroxy compound (.0105 *M*) in THF or ethyl acetate (30 ml) at 3°. The mixture was kept for 10 h at 3° and 4 h at 25°, the precipitate was removed, ether (150 ml) was added to the solution, and the ester worked up as before.

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[2]NRCC Summer Student (1968).
[3]NRCC Summer Student (1969).

TABLE 1

Properties of indoleacetic acid derivatives

3-Indoleacetic acid derivative*	Method	Yield (%) (recrystallized material)	Melting point (°C) (cryst. solvent)	Analysis								Time required for conversion into IAA glycine methyl ester†
				Calculated				Found				
				C	H	N	Cl	C	H	N	Cl	
1*a*	*A-1*	65	110 (methanol)	64.86	4.08	9.46	—	65.14	3.98	9.52	—	10 h
	B-1	78										
1*b*	*A-2*	58	150 (benzene)	56.31	3.25	12.31	—	56.24	3.26	11.96	—	1 h
1*c*	*B-1*	63	146 (ethyl acetate–chloroform)	61.76	4.44	10.29	—	62.19	4.46	10.01	—	8 h
1*d*	*B-1*	67	165 (ethanol)	45.37	1.90	3.31	41.86	45.37	1.86	3.27	41.70	5 h
1*e*	*B-1*	86	187 (benzene)	75.48	4.67	9.27	—	75.73	4.58	9.15	—	>2 days‡
1*f*§	*B-2*	88	145 (dioxane)	72.28	4.85	8.43	—	72.16	4.75	8.42	—	30 min

*Recently, the 2,4,5-trichlorophenyl ester of 3-indoleacetic acid has been prepared by a method similar to *B-1* (12).
†At the time indicated >90% of the active IAA derivative had been converted to the glycine methyl ester amide as shown by chromatography. For details see text.
‡Only 60–70% had reacted after 2 days.
§This compound has been mentioned in the literature (13, 14). However, no experimental or physical data were reported.

IAA Anhydride (B-2)

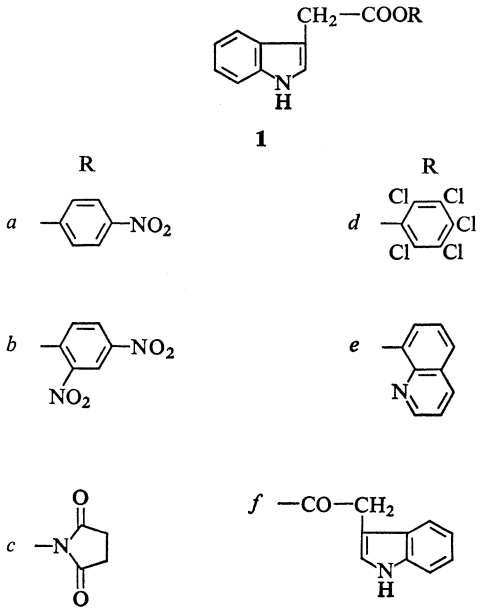
A solution of IAA (.02 *M*) and DCC (.0105 *M*) in anhydrous dioxane (30 ml) was kept at 25° for 3 h. The precipitate was removed, dioxane evaporated, the residue triturated with benzene and the solid recrystallized.

3-Indoleacetylglycine Methyl Ester

A solution of glycine methyl ester hydrochloride, the IAA-derivative (10^{-5} moles each), and triethylamine (0.01 ml) in dioxane (3 ml) was kept at room temperature for the time indicated in Table 1. The progress of the reaction was followed chromatographically using silica thin-layer plates, methanol–chloroform–carbon tetrachloride (1:5:4) as the developing solvent, and Ehrlich's reagent for visualization. For characterizing IAA glycine methyl ester, the combined reaction mixtures were chromatographed on silica thin-layer plates (1 mm thickness) in the same solvent. 3-Indoleacetylglycine methyl ester (R_F = 0.55) appears, after elution with methanol and evaporation of the solvent, as a colorless oil; mass spectrum, *m/e* 246 (M^+; 26%), 247 (4%), 157 (2.5%), 131 (12%), 130 (100%), 129 (5%).

Calcd. for $C_{13}H_{14}N_2O_3$: 246.10044. Found: 246.1000.

Data for all compounds are given in Table 1, their structures were ascertained by infrared (i.r.) and mass spectroscopy.[4]



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[4]The mass spectrometry data are being deposited with the Mass Spectrometry Data Centre, AWRE Aldermaston, Berkshire, U.K.

Single bond radius of trigonal nitrogen and the C(sp^2)—N(sp^2) single bond

Arthur Camerman

Department of Biological Structure, University of Washington, Seattle, Washington 98105

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Estimation of p-π character in nitrogen–carbon bonding is dependent on a knowledge of the trigonal nitrogen – trigonal carbon single bond length. Recent experimental results indicate a value of 1.470 ± 0.005 Å for this bond distance and a value of 0.720 ± 0.010 Å for the trigonal nitrogen single bond radius; these values are suggested as criteria for estimating p-π character in trigonal N – aromatic C bonds.

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Estimations of interaction between p electrons of nitrogen and π electron clouds of aromatic systems, and therefore of the importance of resonance configurations for molecules such as amides, have been often dependent on the value one accepts for the single σ bond length between