added until its *p*H was about 6. The hot solution was filtered through Kieselguhr and the clear filtrate and washings were added to an alcoholic solution of picric acid. On cooling, the amine picrate separated out, which was recrystallized from methanol. The yield of the picrate in almost all cases ranged from 60 to 70%.

Two grams of the above picrate was boiled with 14 ml. of concentrated hydrochloric acid. After cooling, the precipitated picric acid was filtered. The filtrate was extracted with nitrobenzene and then with ether. The aqueous layer was evaporated to dryness under vacuum. The dark hydrochloride thus obtained was recrystallized from a mixture of methanol and ethyl acetate.

2,6-Dihydroxybenzaldehyde. A mixture of 3 g. of 3-carboxy-2,6-dihydroxybenzaldehyde and 200 ml. of water was refluxed for about 4 hrs. The resulting solution was filtered and the clear filtrate repeatedly extracted with ether. The ether extract was washed with a saturated solution of sodium bicarbonate, and then with water. Evaporation of ether afforded the aldehyde, which was crystallized from water as 1.1 g. of pale yellow needles, m.p. 154°–155°.

Anal. Calcd. for $C_7H_6O_3$: C, 60.9; H, 4.3. Found: C, 60.8; H, 4.2.

Anil of 3-carboxy-2-hydroxy-6-methoxybenzaldehyde. The anil of 3-carboxy-2-hydroxy-6-methoxybenzaldehyde was prepared according to the general method described by Weijlard *et al.*[9] It was crystallized from alcohol in orange colored needles of m.p. 203–205° (dec.).

Anal. Calcd. for $C_{15}H_{13}NO_4$: N, 5.1. Found: N, 5.5.

Anil of 3-carboxy-2,5-dihydroxy-6-methoxybenzaldehyde. The anil was crystallized from alcohol in red needles, of m.p. 223–225° (dec.).

Anal. Calcd. for: $C_{15}H_{13}NO_5$: N, 4.9. Found: 5.0.

3-Methoxycarbonyl-2,5,6-trimethoxybenzaldehyde. A mixture of 1 g. of 3-carboxy-2,5-dihydroxy-6-methoxybenzaldehyde, 2 g. of anhydrous potassium carbonate, 2 ml. of dimethyl sulfate, and 55 ml. of dry acetone was gently refluxed for 12 hr. Filtration and removal of acetone left an oil which was washed with dilute sodium hydroxide and extracted with ether. Evaporation of the ether gave 3-methoxycarbonyl-2,5,6-trimethoxybenzaldehyde as an oil.

Its *2,4-dinitrophenylhydrazone* crystallized from alcohol in tiny needles, m.p. 169°.

Anal. Calcd. for $C_{18}H_{18}N_4O_9$: N, 12.5. Found: 12.0.

Attempted hydrolysis of 3-methoxycarbonyl-2,5,6-trimethoxybenzaldehyde. One gram of 3-methoxycarbonyl-2,5,6-trimethoxybenzaldehyde and 50 ml. of 5% sodium carbonate was heated on a water bath for 1 hr., when the oil slowly went into solution. On cooling, and acidification with hydrochloric acid, a pale yellow compound was obtained, which was crystallized from alcohol in needles, m.p. 225°.

It did not give a coloration with alcoholic ferric chloride solution, but dissolved in sodium bicarbonate; nor did it form a 2,4-dinitrophenylhydrazone or an "anil."

Anal. Found: C, 58.1; 58.4; H, 5.4; 5.8.

No definite structure could be assigned to it from the analytical data.

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Synthesis of 3-Indoleacetamides[1,2]

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The enhancement of activity for parthenocarpic fruit development in the tomato by changes in the ring structure and side chain of 3-indoleacetic acid[4,5] has prompted the preparation of several 3-indoleacetamides.

Various 3-indoleacetyl amino acids have been prepared by using the mixed anhydride procedure[6,7] and the carbodiimide method.[8–10] The classical method of amide formation, Schotten-Baumann reaction, was not used by these investigators since this procedure is contingent upon the preparation of 3-indoleacetyl chloride. This was generally assumed not possible until reported by Shaw and Woolley.[11] The Schotten-Baumann reaction has been used in this laboratory for the preparation of 3-indoleacetamides.

The properties of various 3-indoleacetamides are given in Table 1. All of the compounds exhibited ultraviolet absorption characteristic of the indole nucleus except the *p*-aminobenzoic acid derivative where the strong absorption of the *N*-substituted *p*-aminobenzoic acid moiety masked completely the typical indole ultraviolet absorption (280 to 300 mμ).

EXPERIMENTAL

3-Indoleacetyl chloride.[11] This compound was prepared in 60–70% yields by the reaction of 3-indoleacetic acid with phosphorus pentachloride in anhydrous ether solution at 0°. The product was recrystallized from a mixture of ether and petroleum ether to yield colorless to pink crystals, m.p. 68–70°, trinitrobenzene adduct[12] m.p. 88°.

3-Indoleacetyl derivatives. 3-Indoleacetyl derivatives were synthesized by a method similar to the one used by Wood and Fontaine[13] for the preparation of substituted phenoxyacetyl derivatives. The following description illustrates the general procedure for the synthesis of all of the amino acid derivatives of 3-indoleacetic acid.

Glycine (0.75 g., 0.01 mole) was dissolved in 30 ml. of *N* sodium hydroxide (0.03 mole) and the solution cooled in an ice bath to 0–5°. 3-Indoleacetyl chloride (1.93 g., 0.01 mole) was dissolved in 10 ml. of anhydrous ether, cooled to 0°, and added dropwise with efficient mechanical stirring to the alkaline glycine solution. After 0.5 hr. the ice bath was removed to permit the solution to reach room temperature, and stirring was continued for an additional hour. The alkaline mixture was then thoroughly extracted with ether, the aqueous fraction cooled to 0°, and acidified to *p*H 2 with

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TABLE 1

PROPERTIES OF 3-INDOLEACETAMIDES

3-Indoleacetamides	Formula	M.p.	$[\alpha]_D^{27}$	Yield %	Nitrogen % Calcd.	Nitrogen % Found	Neutralization Equivalent Calcd.	Neutralization Equivalent Found
N-(3-Indoleacetyl)-glycine	$C_{12}H_{12}N_2O_3$	86–87[a]		17	12.1	12.1	232	232
N-(3-Indoleacetyl)-DL-isoleucine	$C_{16}H_{20}N_2O_3$	102		34	9.7	9.9	288	290
N-(3-Indoleacetyl)-DL-methionine	$C_{15}H_{18}N_2O_3S$	169–171d		19	9.1	9.2	306	302
N-(3-Indoleacetyl)-L-tryptophan	$C_{21}H_{19}N_3O_3$	181–183	+14.56	9	11.6	11.7	361	358
N-(3-Indoleacetyl)-L-aspartic acid	$C_{14}H_{14}N_2O_5$	164.5d	−4.51	29	9.7	9.4	145	144
N-(3-Indoleacetyl)-L-glutamic acid	$C_{15}H_{16}N_2O_5$	162.5d	−10.57	20	9.3	9.3	151	152
N-(3-Indoleacetyl)-6-aminopurine	$C_{15}H_{12}N_6O$	242–244		30	28.8	28.5		
N-(3-Indoleacetyl)-*p*-aminobenzoic acid	$C_{17}H_{14}N_2O_3$	253–255d		45	9.5	9.6	294	296
N-(3-Indoleacetyl)-*m*-aminobenzoic acid	$C_{17}H_{14}N_2O_3$	246d		37	9.5	9.7	294	297

[a] *Cf.* reference 6.

dilute phosphoric acid. After standing for 1 hr. in the cold, the precipitate was collected by filtration. The product was further purified by recrystallizations from water coupled with carbon decolorizations. The yield of the recrystallized product was 380 mg., m.p. 86–87°.

Those 3-indoleacetamides, which possessed limited water solubility, were recrystallized from dilute ethanol or ethanol alone (adenine derivative). The yield of the recrystallized products was usually 25–30%.

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Structural Studies of the Isoximes of Weygand and Bauer

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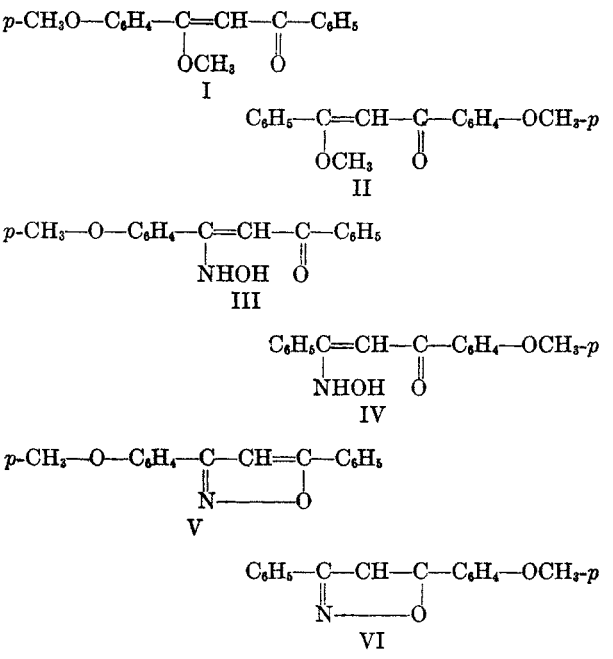
The infrared and ultraviolet spectra of the isoximes of Weygand and Bauer indicate that these substances are represented best as the more stable of the configurational isomers of the oximes. Chemical evidence points to facile rearrangement of the more stable isomers to the less stable forms which undergo ring closure with formation of isoxazoles.

Weygand and Bauer[2] reported that on treating the "A-ether" (I) and the "B-ether" (II) with hydroxylamine, they isolated compounds III and IV, respectively, which they called isoxime A and isoxime B. They showed that they obtained isoxazoles V and VI when they treated the isoximes with acids.



It is common knowledge that β-diketones yield isoxazoles when treated with hydroxylamine. Blatt[3] showed that methoxyamine hydrochloride, in contrast to the free base, adds to the ketonic carbonyl group. Barnes and Pinkney[4] showed that the free base, hydroxylamine, adds 1,4 to α,β-unsaturated ketones, and that in isoxazoline formation, nitrogen is found on the carbon atoms that was previously the carbonyl carbon. Blatt[3] showed that acetylenic ketones also add the free base, methoxyamine.

We believe that the structural formula III and IV should be designated as oximes with the following configurational formulas VII and VIII, and that these anti forms, on acidification, rearrange to the syn forms which then enolize and undergo

(1) In partial fulfillment of the requirements for the Master's degree.

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