Discussion and Results

Compounds I, II, and III were chlorinated under a wide variety of conditions and the results are recorded on Tables I, II, and III.

TABLE I
PHENYL ETHER CHLORINATION

Chlorinating system	% 2-	% 4-
No catalyst, Cl_2, CCl_4, R.T.	8.4	91.6
No catalyst, Cl_2, HOAc, 0°	11.0	89.0
$SnCl_4$, Cl_2, CCl_4, 0°	25.2	74.8
$FeCl_3$, Cl_2, CCl_4, 0°	17.0	83.0
$AlBr_3$, Cl_2, CCl_4, 0°	7.7	92.3

TABLE II
2-CHLOROPHENYL ETHER CHLORINATION

Chlorinating system	% 2,6-	% 2,4-	% 2,2'-	% 2,4'-
No catalyst, Cl_2, HOAc, 0°	...	0.9	10.7	88.4
$SnCl_4$, Cl_2, CCl_4, 0°	Trace	1.4	23.1	75.5
$FeCl_3$, Cl_2, CCl_4, 0°	Trace	2.0	22.9	75.1
$AlBr_3$, Cl_2, CCl_4, 0°	1.2	5.4	21.5	72.0

TABLE III
4-CHLOROPHENYL ETHER CHLORINATION

Chlorinating system	% 2,4-	% 2,4'-	% 4,4'-
No catalyst, Cl_2, HOAc, 0°	...	8.8	91.2
$SnCl_4$, Cl_2, CCl_4, 0°	0.3	23.2	76.5
$FeCl_3$, Cl_2, CCl_4, 0°	1.0	20.2	78.8
$AlBr_3$, Cl_2, CCl_4, 0°	3.7	19.6	76.7

Examination of Table I provides some explanation of why II was not found in previously reported noncatalytic chlorinations since it is formed in relatively minor amounts. The most interesting feature of Table I is the manner in which the *ortho/para* ratio rises and falls with increasing activity of the chlorinating species. A possible explanation for this is discussed elsewhere.[2,3] Briefly, we believe the increase in *ortho/para* ratio is due to a decrease in steric interactions in the transition state as more reactive chlorinating species are used. We feel the *ortho/para* ratio passing through a maximum is also correlated with increasing activity of the chlorinating species, since the dipolar interaction between the ether group (-I) and the incoming partially positive chlorine atom increases.

Tables II and III show the same general trend to a lesser extent, which is somewhat puzzling.[4] They also show that some substitution takes place in the already chlorinated nucleus and this increases as the activity of the chlorinating species increases. The data in Table III clearly demonstrate that IV[5] is not formed in measurable amounts nor is any product of meta substitution produced in any of the systems[5] in measurable amounts.

Experimental

General Chlorination Method.—A solution of 0.01 mole of I, II, or III in 10 ml. of solvent (acetic acid or carbon tetrachloride) was prepared and cooled in an ice bath. To this solution was added 0.01 g. of catalyst (stannic chloride, ferric chloride, or aluminum bromide), if any. The resulting mixture was combined with a cold solution of 0.003 mole of chlorine in 4 ml. of solvent. The reaction mixture was allowed to stand in an ice bath for 1 hr. (The noncatalytic chlorination of I in carbon tetrachloride was carried out at room temperature and stored in the dark for 48 hr.) At the end of the reaction period, the mixture was poured into water, carbon tetrachloride added if necessary, the organic layer dried, evaporated, and the oily residue used directly for vapor phase chromatographic analysis.

Analytical Procedure.[6] The analyses were performed on a Barber-Colman Model 20 gas chromatograph equipped with a 200-ft. apiezon "L" capillary column and an argon ionization detector. Although areas were found to be nearly proportional to mole per cent, any deviation from linearity was corrected for by use of calibrated standard samples.

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[2] H. Weingarten, *J. Org. Chem.*, **26**, 4347 (1961).

[3] J. R. Knowles, R. O. C. Norman, and G. K. Radda, *J. Chem. Soc.*, **4885** (1960).

[4] Treatment of II under much more severe conditions (30 min. at 140° with aluminum chloride or aluminum bromide and no solvent) produced no detectable isomerization.

[5] Standard samples of the possible *meta* substituted compounds were prepared for comparison by usual Ullmann methods.

[6] Details of the analytical procedure are identical to those reported by H. Weingarten, W. D. Ross, J. M. Schater, and G. Wheeler, Jr., *Anal. Chim. Acta*, **26**, 391 (1962).

The Synthesis and Properties of N,N-Dialkylaminovinylindoles

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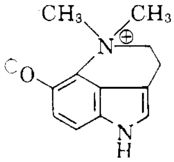
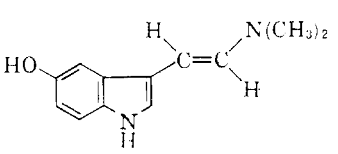
Recently the structure of dehydrobufotenine, isolated from the parotid gland of the South American toad, *Bufo marinus*, has been established as the tricycle I[1,2] superseding the old enamine formula II.[3] Because of interest in the hallucinogenic activity of alkylated tryptamines[4] we are reporting here the synthesis and some properties of enamines of type II.[5,6]



I



II

The starting materials, namely 3-indoleacetaldehyde[7] and 5-benzyloxy-3-indoleacetaldehyde were prepared by the oxidation of the corresponding tryptophans according to the method of Gray.[7]

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[1] F. Märki, A. V. Robertson, and B. Witkop, *J. Am. Chem. Soc.*, **83**, 3341 (1961).

[2] B. Robinson, G. F. Smith, A. H. Jackson, D. Shaw, B. Frydman, and V. Deulofeu, *Proc. Chem. Soc.* (London), 310 (1961).

[3] H. Wieland and T. Wieland, *Ann.*, **528**, 234 (1937).

[4] St. Szara, *Experientia*, **12**, 441 (1956).

The aldehydes were then condensed with secondary amines using the technique of Herr and Heyl.[8]

The two dimethylaminovinylindoles, 3-(2′-dimethylaminovinyl)indole and 5-benzyloxy-3-(2′-dimethylaminovinyl)indole, were isolated as unstable oils of roughly 80% purity as judged from infrared analysis. They hydrolyzed readily to dimethylamine and apparently polymeric material. Piperidinovinylindole likewise was obtained as an unstable oil which was characterized by infrared and ultraviolet spectra. Condensation of the appropriate aldehydes with dibenzylamine afforded the crystalline enamines, 3-(2′-dibenzylaminovinyl)indole and 5-benzyloxy-3-(2′-dibenzylaminovinyl)indole. In addition 3-(2′-diisopropylaminovinyl)indole was obtained as a relatively stable crystalline solid.

These three enamines gave satisfactory n.m.r. spectra[9] whereas the spectra of the N,N-dimethyl analogs were indicative of extensive polymerization and decomposition.

The diisopropylamino compound (III) (Fig. 1) showed the following assignable n.m.r. peaks: a doublet at 1.20 δ (—CH_3) (tetramethylsilane = 0.0 δ), a septet at 3.72 δ (—$NCHR_2$), a doublet (*J* = 14.5 c.p.s.) 5.41 δ (*trans* $\underset{\mathrm{H}}{\mathrm{C}}{=}\overset{\underline{\mathrm{H}}}{\mathrm{C}}{-}\mathrm{N}$) and the corresponding doublet (*J* = 14.5 c.p.s.) at 6.88 δ (*trans* $\underline{\mathrm{H}}{-}\mathrm{C}{=}\overset{\mathrm{H}}{\mathrm{C}}{-}\mathrm{N}$). The data for 3-(2′-dibenzylaminovinyl)indole (IV) and for 5-benzyloxy-3-(2′-dibenzylvinylamino)indole (V) are presented in Fig. 1. The 3-(2-piperidinovinylamine)indole gave less satisfactory n.m.r. spectrum due to polymerization but showed a doublet at 5.53 δ (*J* = 14 c.p.s., *trans* $\underset{\mathrm{H}}{\mathrm{C}}{=}\overset{\underline{\mathrm{H}}}{\mathrm{C}}{-}\mathrm{N}$).

For comparison the data for 3-indole-β-acrylic acid (VI) are presented in Fig. 1 and establish the *trans* relationship of the ethylenic protons.

The infrared spectra of the indolevinyl amines showed a sharp N—H absorption at 2.80 μ and a sharp intense C=C peak at 6.07–6.10 μ which compares well with the enamine absorption reported for N,N-dimethyl-β-methyl-β-phenylvinylamine (6.10 μ vs)[6] and for di-β-β-diphenylvinylamine (6.08 μ vs).[6]

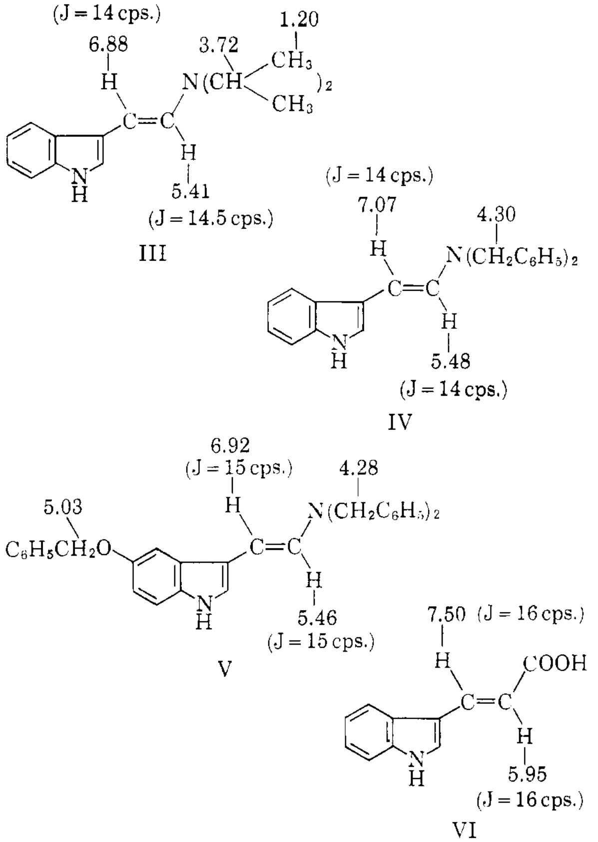
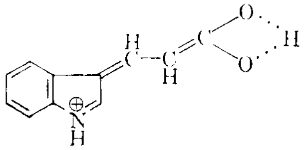


Fig. 1.—N.m.r. data for vinylindoles, expressed in δ units, tetramethylsilane = 0.0 δ. Solvent: deuteriochloroform for III–V, deuteroacetone for VI.

The ultraviolet spectra of the various indolevinylamines showed only end absorption in the 290–340-mμ region in contrast to 3-indole-β-acrylic acid[10] which shows a strong absorption peak (λ_{max}^{EtOH} 3186, ϵ_{max} 12,500) in this region.

This result is due to the fact that in the photoexcited state the two nitrogens oppose or cancel each other's contributions, whereas the excited state VIa of indoleacrylic acid leads to a considerable bathochromic effect. The ultraviolet absorption spectrum of 3(2′-diisopropylvinylamine)indole is shown in Fig. 2.



VIa

3-(2′-Dimethylaminovinyl)indole was converted to a methiodide by treatment of a benzene solution of the enamine with methyl iodide but even after

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(5) The isomeric immonium structure (IIb) has been implied as an intermediate in the degradation of N,N-dimethyltryptamine by monamine oxidase. Tritium studies rule out any tautomerism between the imine and enamine:

$$\underset{\text{IIa}}{\mathrm{R{-}CH{=}CH{-}\overset{\oplus}{N}H(CH_3)_2}} \rightleftharpoons \underset{\text{IIb}}{\mathrm{R{-}CH_2{-}CH{=}\overset{\oplus}{N}(CH_3)_2}}$$

T. E. Smith, H. Weissbach, and S. Udenfriend, *Biochem.*, **1**, 137 (1962).

(6) B. Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956).

(7) R. A. Gray, *Arch. Biochem. Biophys.*, **81**, 480 (1959).

(8) M. E. Herr and F. W. Heyl, *J. Am. Chem. Soc.*, **74**, 3627 (1952).

(9) We thank Mr. Robert Bradley for the n.m.r. spectra obtained with a Varian A-60 instrument.

(10) J. S. Moffatt, *J. Chem. Soc.*, 1442 (1957).

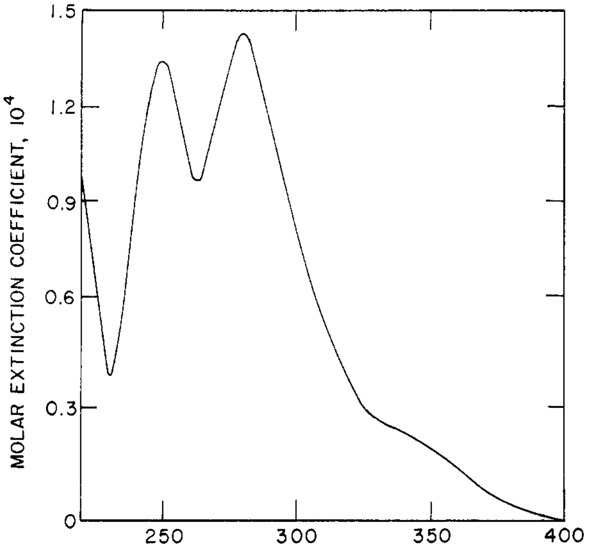

Fig. 2.—Ultraviolet absorption spectra of 3(2′-diisopropylvinylamino)indole in acetonitrile.

recrystallization from methanol–ether and dry acetone, analysis indicated contamination with trimethylammonium iodide and the compound was not investigated further. All other attempts to prepare stable salts from these enamines were unsuccessful.

Attempts to reduce 3-(2′-dimethylaminovinyl)-indole by catalytic hydrogenation to N,N-dimethyltryptamine were unsuccessful, but reduction with sodium borohydride in methanol or with lithium aluminum hydride in ether resulted in the formation of N,N-dimethyltryptamine which was identified by comparison of R_f values on thin layer chromatography (Silica Gel-G), color reaction (Ehrlich's) and infrared spectrum with those of authentic N,N-dimethyltryptamine.

Catalytic debenzylation of 5-benzyloxy-3-(2′-dimethylaminovinyl)indole in benzene with palladium on charcoal and hydrogen did not lead to the desired product (II).

Experimental[11]

5-Benzyloxy-3-indoleacetaldehyde was prepared by the method of Gray[7] from 5-benzyloxytryptophan.[12] A benzene solution of the aldehyde was mixed with a saturated sodium sulfite solution. The resulting bisulfite addition compound was recrystallized from water–ethanol. Liberation of the aldehyde with sodium carbonate solution gave a yellow oil (infrared absorption spectrum (neat): NH 2.85 μ, C=O 5.80 μ) which was characterized as the semicarbazone, m.p. 150–151°, recrystallized from methanol-water.

Anal. Calcd. for $C_{18}H_{18}N_4O_2$: C, 67.05; H, 5.61; N, 17.38. Found: C, 67.07; H, 5.78; N, 16.80.

Preparation of 3-(2-Disubstituted Aminovinyl)indoles.—The free aldehydes were prepared directly before use by liberation from the bisulfite addition compounds with sodium carbonate, and simultaneous extraction into ether. The ether was dried over sodium sulfate and then removed *in vacuo*. To 0.01 mole of aldehyde in 30–50 ml. of dry thiophene-free benzene in a reflux apparatus containing a Bidwell-Sterling moisture trap[7] and magnetic stirrer was added a solution of 0.012–0.02 mole of amine in 15 ml. of benzene. The reaction was warmed slowly and then refluxed for 2–3 hr. The benzene was evaporated and the residue purified as described under the individual amines. The amines were stored in a desiccator, preferably under nitrogen.

3-(2′-Dimethylaminovinyl)indole was obtained as an unstable oil after treatment of a benzene solution of the condensation product with Norit followed by evaporation of the benzene *in vacuo*.

Infrared absorption spectrum ($HCCl_3$): N—H 2.84 μ, C=C 6.07 μ vs. $\lambda_{max}^{acetonitrile}$ 245 mμ, 276 mμ, 325 mμ shoulder; ϵ_{max} 10,000; 9400; 3500.

5-Benzyloxy-3-(2′-dimethylaminovinyl)indole was obtained as an unstable brown oil. Infrared absorption spectrum (neat): N—H 2.78 μ, C=C 6.08 μ vs. $\lambda_{max}^{acetonitrile}$ 248 mμ shoulder, 278 mμ, 315 mμ shoulder; ϵ_{max} 7600; 8100; 3400.

3-(2′-Piperidinovinyl)indole was obtained as an unstable light brown oil. Infrared absorption spectrum (neat): N-H 2.79 μ, C=C 6.09 μ vs. $\lambda_{max}^{acetonitrile}$ 245 mμ shoulder; 278 mμ, 325 mμ shoulder; ϵ_{max} 10,100; 10,800; 3400.

3-(2′Dibenzylaminovinyl)indole was recrystallized from dry ether containing a trace of triethylamine yielding white crystals, m.p. 128.5–130°; yield 12%. The crystals turned tan within a week. Infrared absorption spectrum (KBr): N-H 2.80 μ C=C 6.10 μ vs. $\lambda_{max}^{acetonitrile}$ 246 mμ, 272 μ, 310 mμ shoulder; ϵ_{max} 12,00; 9600; 5030.

Anal. Calcd. for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.06; H, 6.76; N, 7.91.

5-Benzyloxy-3-(2′-dibenzylaminovinyl)indole was recrystallized from ether containing a trace of trimethylamine as white crystals, yield 15%, m.p. 139–141°, which became tan on standing. Infrared absorption spectrum ($CHCl_3$): N-H 2.70 μ C=C 6.10 μ vs. $\lambda_{max}^{acetonitrile}$ 245 mμ, 258 mμ, 279 mμ, 330 mμ shoulder; ϵ_{max} 15,400; 95,400; 16,100; 5100.

Anal. Calcd. for $C_{31}H_{28}N_2O$: C, 83.75; H, 6.36; N, 6.30. Found: C, 83.24; H, 6.53; N, 5.98.

3-(2′-Diisopropylaminovinyl)indole was recrystallized from dry ether containing a trace of triethylamine as light tan crystals, m.p. 129–132°, yield 25%. Infrared absorption spectrum ($HCCl_3$): N-H 2.82 μ. C=C 6.09 μ vs. $\lambda_{max}^{acetonitrile}$ 250 mμ, 280 mμ, 338 shoulder; ϵ_{max} 11,600; 13,200; 2800.

Anal. Calcd. for $C_{16}H_{22}N_2$: C, 79.34; H, 9.09; N, 11.57. Found: C, 78.93; H, 8.45; N, 11.37.

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[11] The skillful cooperation of the Regis Chemical Co. under a Psychopharmacology Service Center Contract is gratefully acknowledged.

[12] A. Ek and B. Witkop, *J. Am. Chem. Soc.*, **75**, 500 (1953).

Photochemical Reactions. XI.

Diphenylacetylene[1–3]

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Photochemical dimerization of substituted olefins represents a convenient method for the preparation of certain cyclobutanes. In analogy, sub-

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