Reaction of Tri-*n*-butylphosphine with *n*-Butyl Mercaptan.—The phosphine (20 mmole), mercaptan (20 mmole), diphenyl ether (20 mmole as internal standard) and AIBN (0.1 mmole) were heated for 140 min. at 60° under N_2 in an erlenmeyer flask connected through a condenser and bubble counter to a cold trap. *n*-Butane (0.8 g., 73%) collected in the trap, and gas chromatographic analysis showed 93% reaction of the phosphine and 92% conversion to phosphine sulfide. The tributylphosphine sulfide was identified by comparison of its retention time with known material.

Reaction of Triphenylphosphine with Di-*t*-butyl Peroxide.—The phosphine (20.5 g., 78 mmole) and peroxide (11.0 g., 75 mmole) were heated 95 hours at 130° in a sealed tube. The tube was cooled to −78°, opened, and products separated by first distilling materials boiling below 50°, fraction I, 1.9 g., into a cold trap, transferring the remainder to a distilling flask, and removing materials volatile under reduced pressure; fraction II, 8.2 g., up to the temperature where decomposition of triphenylphosphine oxide became detectable. Triphenylphosphine oxide, 21.4 g., remained as a residue in the flask. Fractions I and II were analyzed by gas chromatography at 25 and 86°, respectively, using phthalate ester and silicone columns in series, with results summarized in Table I. The reaction of the peroxide with triethyl phosphite was carried out in the same manner using 10 mmole of reagents. Material boiling below 80° (0.46 g.) was analyzed separately from the higher boiling fraction using the same techniques as above.

The absence of *t*-butyl ether in the triphenylphosphine experiments (and in a number of similar runs at 130°) was demonstrated by gas chromatography using a 10-ft. Craig polyester succinate column at 120°. This substrate was found to give good separation of authentic ether from the other reaction products and from di-*t*-butyl peroxide. A reaction run for 92 hours at 114° contained much unreacted peroxide, together with the same spectrum of products formed at 130°.

Reactions with CO.—Reactions under pressure were carried out in a glass-lined hydrogenation bomb[9] using 10.0 ml. (52 mmole) of *n*-butyl disulfide, 10.0 ml. (58 mmole) of triethyl phosphite and 80 mg. (0.55 mmole) of di-*t*-butyl peroxide, and heating for 11-16 hours. Gas chromatographic analysis (silicone column, 150°) showed small amounts of low-boiling material (probably butane from the peroxide), triethyl phosphite and *n*-butyl sulfide, but chiefly triethyl phosphorothionate and *n*-butyl thiovalerate. The latter material (which is not reported in the literature) was isolated from the 325-atm. run using a 1-in. diam. silicone column, b.p. 219° (uncor.), n^{25}_D 1.4608. *Anal.* C, 61.63; H, 10.42; S, 18.15. Calcd. for $C_9H_{18}OS$: C, 62.02; H, 10.41; S, 18.39. It showed a carbonyl peak in its infrared spectrum, gave a positive hydroxamic acid test, and a strong odor of mercaptan on hydrolysis. Subsequent runs were analyzed by comparison of the sulfide and thioester peaks.

Photochemical reactions were run in a small flask illuminated by a General Electric RS sunlamp and cooled by a stream of air, and using 10.0 ml. each of disulfide and phosphite. The flask was flushed well with CO before illumination, which was continued for 21–24 hours. In one experiment, the phosphite alone was placed in the flask, and the disulfide added dropwise over 24 hours. *n*-Butyl mercaptan (0.191 mole), triethyl phosphite (0.232 mole), and AIBN (0.0003 mole) were heated for 15 hours at 50° under 184 atm. CO pressure. Gas chromatographic analysis showed a peak corresponding to 1-2% *n*-valeraldehyde. The reaction mixture was distilled giving a forerun of 1 ml., b.p. 30–44° (100 mm.). This fraction showed a strong carbonyl peak in the infrared and gave a positive fuchsin test and precipitate with 2,4-dinitrophenylhydrazine. Two recrystallizations gave the 2,4-dinitrophenylhydrazone of *n*-valeraldehyde, m.p. 104.8–105.7°.

Reaction with Olefins.—Di-*t*-butyl peroxide (5 mmole), triethyl phosphite (10 mmole), 1-hexene (10 mmole) and bromobenzene (10 mmole as internal standard) were heated 20 hours at 140° in a sealed tube. Gas chromatography indicated consumption of almost all of the olefin as well as the other reagents. The experiment was repeated with 10 times the quantities of reagents, but no bromobenzene. The tube was chilled, opened, and 1.9 g. of gaseous products collected in a cold trap. The 29.7 g. of liquid residue was fractionated using a spinning-band column and the individual fractions analyzed by gas chromatography. Low boiling fractions had similar compositions to those obtained in the absence of olefin, and middle fractions were largely triethyl phosphate. Some 5 g. of higher boiling material also was found containing at least six unidentified components, presumably hydrocarbons resulting from radical addition to 1-hexene.

Several triethyl phosphite–butyl mercaptan reactions were carried out in the presence of cyclohexene, 1-hexene and styrene, but the major new products identified were the sulfides arising from mercaptan addition to the olefin. In a typical experiment, 0.1-mole quantities of *n*-butyl mercaptan, triethyl phosphite and cyclohexene were heated under N_2 for 24 hours at 60° in the presence of 0.001 mole of AIBN. Fractional distillation and gas chromatography showed 5.70 g. of unreacted cyclohexene, 2.35 g. of unreacted phosphite, 14.35 g. of triethyl phosphorothionate and 3.10 g. of butyl cyclohexyl sulfide, b.p. 100–108° (10 mm.), lit.[12] 101–103° (10 mm.). *Anal.* C, 69.55; H, 11.57; S, 18.82. Calcd. for $C_{10}H_{20}S$: C, 69.70; H, 11.70; S, 18.60.

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(12) W. E. Bacon and W. M. LeSuer, THIS JOURNAL, **76**, 670 (1954).

NEW YORK 27, N. Y.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

Nuclear Magnetic Resonance Spectra of Indoles

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Examination of the n.m.r. spectra of a series of indole derivatives has revealed the feasibility of using this technique to determine the extent of substitution at the α- and β-positions of the indole nucleus. The existence of measurable indolenine tautomerism in the ground state of indoles or of ring-chain tautomerism in tryptamines is excluded by these spectra. Previous structural assignments to 2-aminoindolenine and 2-bromo-LSD are confirmed by n.m.r. The spectrum of quebrachamine suggests the absence of N-methyl and α-hydrogen functions.

The application of nuclear magnetic resonance spectroscopy (n.m.r.) to the elucidation of organic structural features has been demonstrated repeatedly in recent years. Indeed, n.m.r. is fast becoming a unique tool for providing particular information on the structures of complex synthetic materials and natural products.[1]

In connection with several aspects of indole chemistry under investigation in this Laboratory, the n.m.r. spectra of a number of synthetic and natural indoles have been examined and certain correlations of chemical shift with structure have been derived.

Experimental

Spectra were determined at the Instrument Division Laboratories of Varian Associates, Palo Alto, Calif., on a 4300-C high resolution spectrometer at 60 megacycles per second. Compounds were studied in concentrations of 0.1 to 0.5 *M*

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(1) *Cf.* S. Goodwin, J. N. Shoolery and L. F. Johnson, *Proc. Chem. Soc.*, 306 (1958); H. Conroy, P. R. Brook, M. H. Rout and N. Silverman, THIS JOURNAL, **80**, 5178 (1958); J. N. Shoolery and M. T. Rogers, *ibid.*, **80**, 5121 (1958).

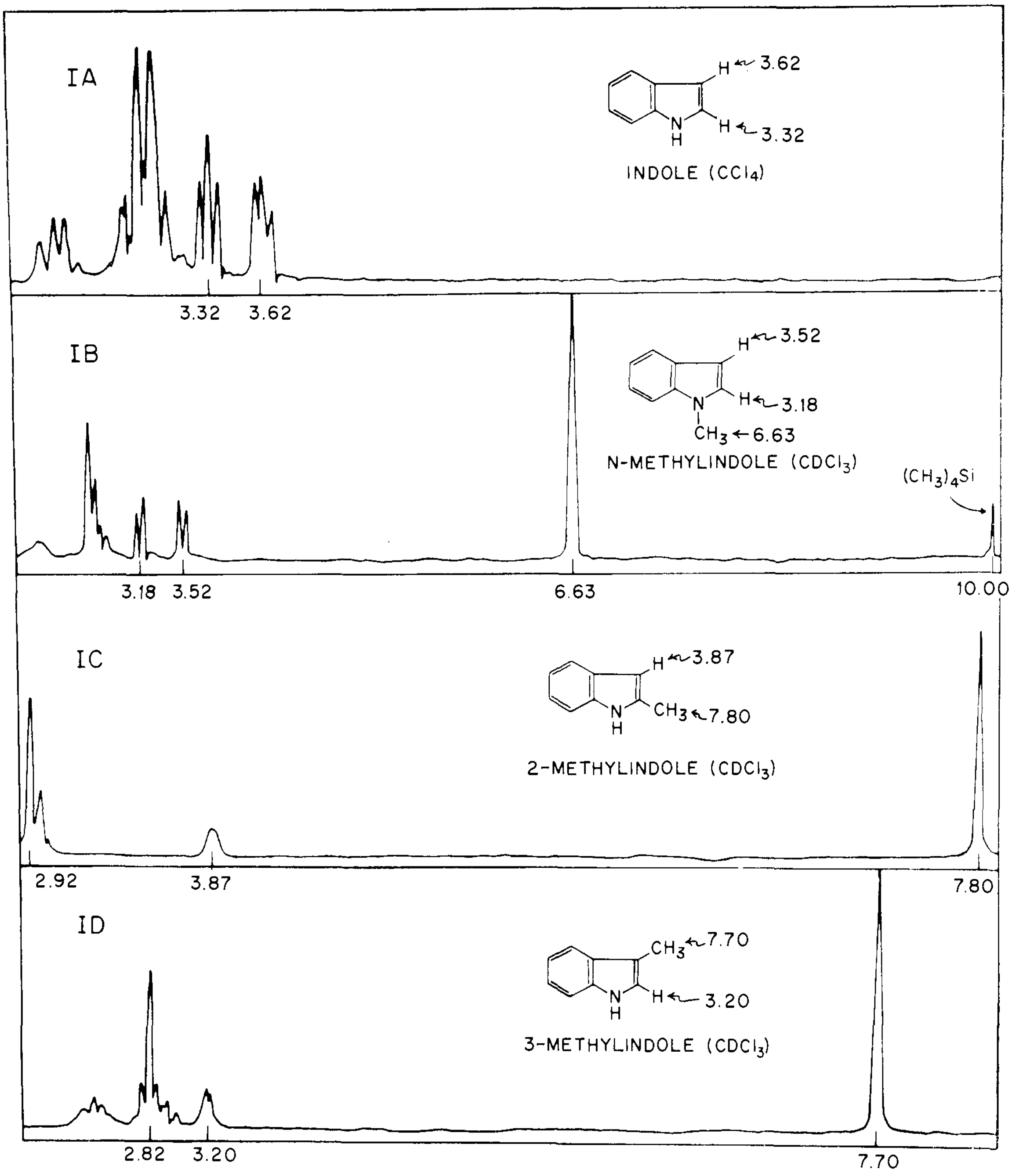

Fig. 1.—Values in τ.

in deuteriochloroform. Shift values of principal peaks were determined by the audio-frequency side-band technique in cycles per second and were reproducible to approximately 1 c.p.s. Minor peaks were determined by linear interpolation from measured peak values. Chemical shifts were measured by reference to internal tetramethylsilane and are expressed in parts per million on the "τ scale" with tetramethylsilane taken as 10.00.[2] Peak values for multiplets are reported for the center of each group.

Deuterated compounds were prepared by dissolving 50 mg. of material in 2 ml. of dioxane, diluting with 2 ml. of deuterium oxide (99.5%) and evaporating the solution to dryness in a desiccator. This procedure was repeated and the dried sample then dissolved in deuteriochloroform.

N_b-Methyltryptamine (*via* **N_b-Formyltryptamine**).—A mixture of 4.5 g. of tryptamine hydrochloride and 1.5 g. of formamide was heated at 140° for 15 minutes. The reaction mixture was cooled, poured into 50 ml. of water and extracted with 2 × 50 ml. of ethyl acetate. The combined extracts were washed with 0.1 *N* hydrochloric acid and with water and dried over sodium sulfate. After removal of the solvent under reduced pressure, 2.4 g. of oil remained. The oil, in 50 ml. of ether, was added slowly to a stirred suspension of 2.0 g. of lithium aluminum hydride in 100 ml. of ether. The mixture was heated at reflux overnight and the excess hydride decomposed with 20% sodium potassium tartrate. The product was extracted with 3 × 75 ml. of ether, the extract dried and concentrated to a solid product. Two recrystallizations from ligroin (90–100°) yielded 1.8 g. (46%) of material melting at 86–87° (lit.[3] 89–90°).

Anal. Calcd. for $C_{11}H_{14}N_2$: N, 16.07. Found: N, 15.81.

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[2] G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

[3] T. Hoshino and K. Shimodaira, *Ann.*, **520**, 19 (1935).

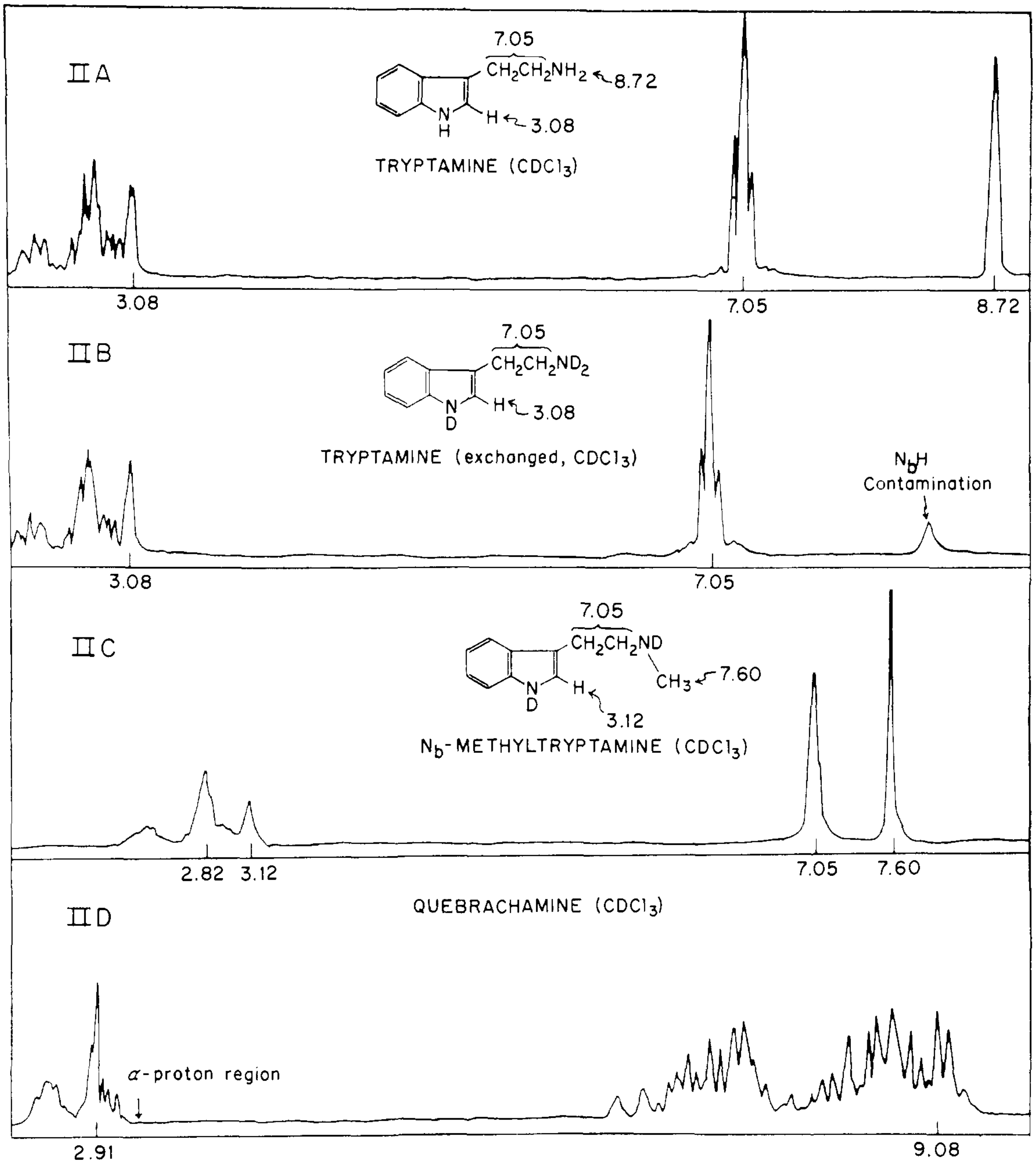

Fig. 2.—Values in τ.

Results

The possibility of detecting α- or β-substitution of the indole nucleus was first explored. In the n.m.r. spectrum of indole (Fig. IA) the α- and β-protons appear as triplets, readily separable from each other and from the aromatic protons. As will be demonstrated below, the peak at 3.32 τ may be assigned to the α-proton and that at 3.62τ to the β-proton. The α- and β-protons are not only split by each other, but also apparently are coupled to the proton on nitrogen, the latter by a 1,3-interaction.[4] This interpretation of the origin of the triplets is supported by the observation that both areas are reduced to doublets in N-methylindole (Fig. IB). Furthermore, in a number of 3-substituted indoles (*cf.* tryptamines below) the α-proton, usually appearing as a doublet, is reduced to a singlet when the indole NH is exchanged with deuterium oxide. The β-proton in 2-methylindole (Fig. IC) shows a poorly resolved doublet at 3.87τ, the shift to higher field resulting from the electronic influence of the 2-methyl group. Principal chemical shifts for a number of substituted indoles are summarized in Table I. Indolenines should differ markedly in spectra from indoles. For example, in 3-methylindole (I) the isomeric form II would show absorption in the vicinity of 8.60τ due to the saturated methyl group. No evidence of tautomerism was observed for the ground state of this compound (Fig. ID) nor for any of the other indoles studied.

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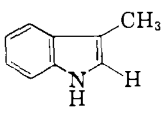
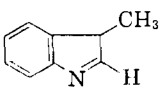
(4) H. S. Gutowsky, C. H. Holm, A. Saika and G. A. Williams, This Journal, **79**, 4596 (1957).



I



II

Examination of a series of N-alkylated tryptamines revealed a consistent difference in chemical shift for N_a and N_b substitution. Thus, N_a-methyl appears at 6.36τ and N_b-methyl at 7.58τ (Table II). In all of these compounds the ring α-proton is readily discernible at 3.08τ to 3.20τ in $CDCl_3$. The change from a doublet to a singlet for the α-proton resulting from replacement of hydrogen by deuterium is evident in the spectrum of tryptamine (Fig. IIA, IIB). As differences in chemical shift and separations due to spin–spin coupling both approach zero, the multiplet usually observed for the side chain methylene groups may approach a singlet and easily could be mistaken for a C–, O– or N–methyl. This rare occurrence is illustrated in the spectrum of N_b-methyltryptamine (Fig. IIC) at 7.05τ. There was no evidence in these spectra of tryptamine and its derivatives for the existence of a cyclic tautomer (III–IV).

TABLE I

PROTON PEAKS IN SUBSTITUTED INDOLES

Indole	Chemical shifts in τ values α-H	β-H	$2\text{-}CH_3$	$3\text{-}CH_3$	$N\text{–}CH_3$	Aryl-H
Indole[a]	3.32	3.62				3.10
2-Methyl-		3.87	7.80			2.92
3-Methyl-	3.20			7.70		2.82
2,3-Dimethyl-			7.95[b]	7.88[b]		2.95
N-Methyl-	3.18	3.52			6.63	2.83
3-Phenyl-	2.97					2.83
N-Methyl-2-phenyl-		3.47			6.43	2.83

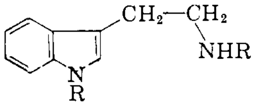
[a] Measured in CCl_4. [b] The order of these assignments is tentative.

TABLE II

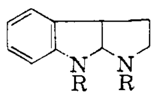
N-SUBSTITUTED TRYPTAMINES[a]

Tryptamine	α-H	N_b–H	N_a–H	N_b–CH_3	N_a–CH_3
Tryptamine	3.08	8.72	1.33		
N_a-Methyl-[b]	3.20	8.65			6.36
N_b-Methyl-	3.12	8.73	0.70	7.58	
$N_{a,b}$-Dimethyl-[c]	3.18	8.03		7.62	6.35
$N_{b,b}$-Dimethyl-[d]	3.13		0.90	7.65	

[a] In deuteriochloroform the aryl peak appeared at 2.78 to 2.83 τ and the four protons of the side chain methylenes at 7.03 to 7.20 τ. [b] K. T. Potts and J. E. Saxton, *J. Chem. Soc.*, 2641 (1954). [c] H. F. Hodson and G. F. Smith, *Chemistry & Industry*, 740 (1956). [d] M. S. Fish, N. M. Johnson and E. C. Horning, THIS JOURNAL, **78**, 3668 (1956).



III



IV

It was of interest to determine the possibility of using n.m.r. to ascertain the size of carbocyclic rings fused to indole. Table III summarizes the pertinent chemical shifts for several such indoles. It may be noted that flexibility in the eight-membered ring of cyclooctindole permits four protons, probably those farthest from the aromatic system, to absorb as high as 8.63τ.

TABLE III

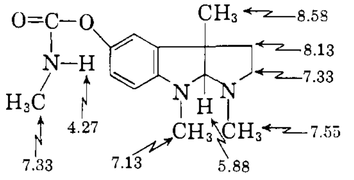
FUSED RING INDOLES

Compound	α,β-CH_2	Satd. C–H
Tetrahydrocarbazole	7.32, 7.45	8.12
Cycloheptindole[a] (CCl_4)	7.32	8.23
Cyclooctindole[b] (CCl_4)	7.35, 7.55	8.45, 8.63

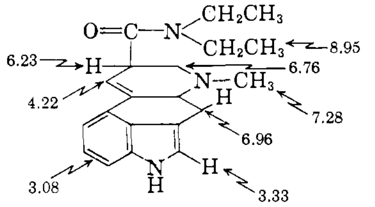
[a] W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, 2583 (1928). [b] B. Witkop, J. B. Patrick and M. Rosenblum, THIS JOURNAL, **73**, 2641 (1951).

A number of indole alkaloids were subjected to n.m.r. analysis to obtain chemical shift data for special types of protons. Chart I summarizes the structural assignments for two compounds of particular interest.

CHART I



eserine (CCl_4)



LSD (D_2O)
(external benzene reference)[5]

The spectrum of bromo-LSD confirms the α-substitution originally assigned,[6] the 3.33τ peak of LSD having been eliminated. The spectrum of 2-aminoindolenine shows three peaks of area ratio 4:2:2, confirming the structure previously assigned on the basis of dissociation constants[7] and spectral data.[8] Despite the complex nature of the spectrum of quebrachamine, both N-methyl and α-hydrogen[9] functions may be excluded with a fair degree of certainty (Fig. IID).

Acknowledgment.—We are indebted to Dr. Edwin Becker of this Institute for valuable discussion and to Mr. Robert Bradley for measuring several n.m.r. spectra.

BETHESDA 14, MD.

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(5) Benzene, when run externally to tetramethylsilane in chloroform, showed a τ value of 3.59. This value was used in order to permit an approximate comparison with other compounds without correcting for differences due to bulk magnetic susceptibility.

(6) F. Troxler and A. Hoffman, *Helv. Chim. Acta*, **40**, 2160 (1957).

(7) J. Kebrle and K. Hoffman, *Helv. Chim. Acta*, **39**, 116 (1956).

(8) B. Witkop, *Experientia*, **10**, 420 (1954).

(9) From an independent analysis of the n.m.r. spectrum of quebrachamine, Prof. H. Conroy has reached the same conclusions regarding α-substitution (personal communication).