These values are in very good agreement for the symmetric (8.73–8.77 μ) and antisymmetric (7.46–7.58 μ) SO_2 vibration reported by Vandi, et al.,[15] for some sulfamide derivatives.

(15) A. Vandi, T. Moeller, and L. F. Audrieth, *J. Org. Chem.*, **26**, 3478 (1961).

Acknowledgments.—The authors wish to thank Dr. Edward Takesue for carrying out preliminary pharmacology studies in this series. They are also indebted to Messrs. Phillip Eden, George Leslie, Roger Riedlin, and Urs Stoeckli for technical assistance.

Synthesis of Some Dibenzo[*b*,*f*][1,5]diazocines and Dibenzo[*b*,*f*][1,4]diazocines

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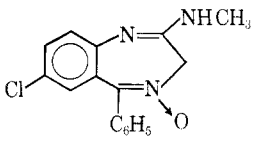
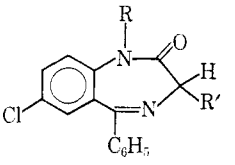
Some dibenzo[*b*,*f*][1,5]diazocines and dibenzo[*b*,*f*][1,4]diazocines, with a number of structural features in common with diazepam, have been synthesized. The pharmacological properties of the compounds were evaluated, and it was shown that they do not have activity profiles comparable to those of diazepam, oxazepam, or chlordiazepoxide. One compound was found to have pronounced antitremorine activity.

Chlordiazepoxide (I), diazepam (II, R = CH_3; R′ = H), and oxazepam (II, R = H; R′ = OH) exhibit sedative, muscle relaxant, and anticonvulsant properties in animals and clinically have application as antianxiety agents.[1]

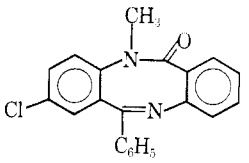


I

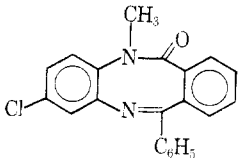


II

We were interested in ascertaining whether the pharmacological properties of appropriately substituted dibenzo[*b*,*f*][1,5]diazocines and dibenzo[*b*,*f*][1,4]diazocines in any way resembled those of 1,4-benzodiazepines such as diazepam. Accordingly, 2-chloro-5,6-dihydro-5-methyl-6-oxo-12-phenyldibenzo[*b*,*f*][1,5]diazocine (III) and 2-chloro-5,6-dihydro-5-methyl-6-oxo-11-phenyldibenzo[*b*,*f*][1,4]diazocine (IV) were selected as



III



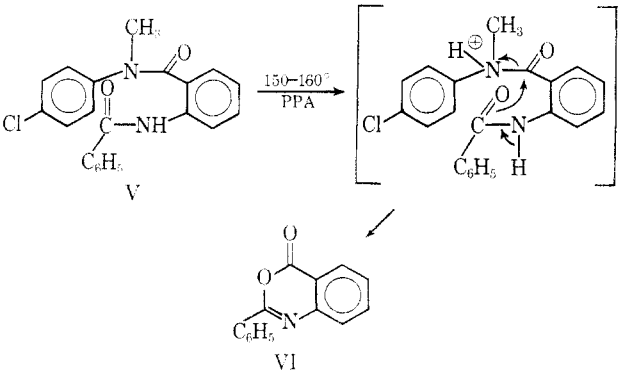
IV

primary synthetic targets.

An initial attempt to obtain III by Bischler–Napieralski closure of V in the presence of polyphosphoric acid gave the benzoxazone (VI) (Scheme I). The successful route, outlined in Scheme II, utilized VII which was reduced to III directly.

When the reactions were repeated using 2-amino-5-chlorobenzophenone, reduction of the intermediate VIII afforded the amino compound IX (Scheme III). Attempted crystallization of IX from acetone gave the quinazolinone X which could be readily reconverted to IX by acid hydrolysis. Cyclization of IX furnished XI. Compounds XII and XIII, containing the dimethylaminoethyl and dimethylaminopropyl side chains, respectively, were obtained by alkylation of XI.

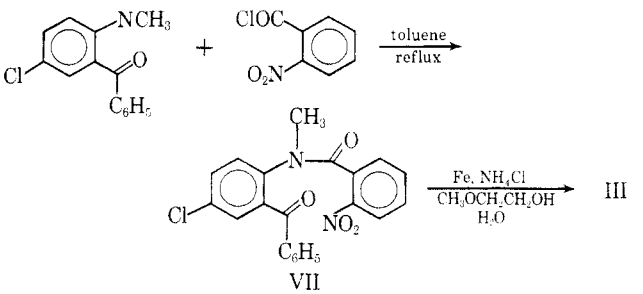
Scheme I



V

VI

Scheme II



VII

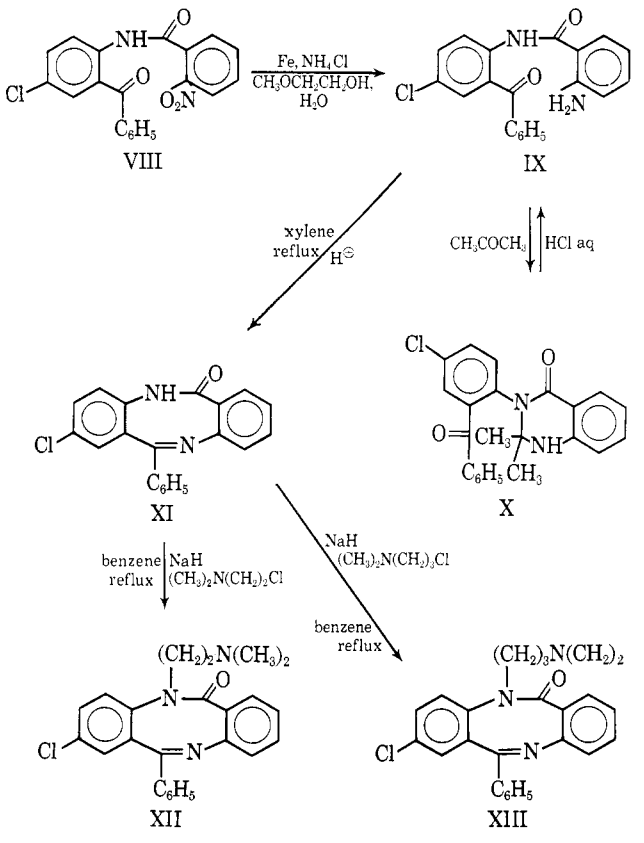
Reduction of VII using a palladium catalyst furnished the cyclic compound XIV (Scheme IV). Under different conditions XV could be isolated from the catalytic reduction products. XIV was also formed on reduction of III with PtO_2 in acetic acid. The N-acetyl derivative XVI was obtained by acetylation of XIV with acetic anhydride.

Reduction of III with $LiAlH_4$ gave XVII which was readily acetylated to give XVIII (Scheme V).

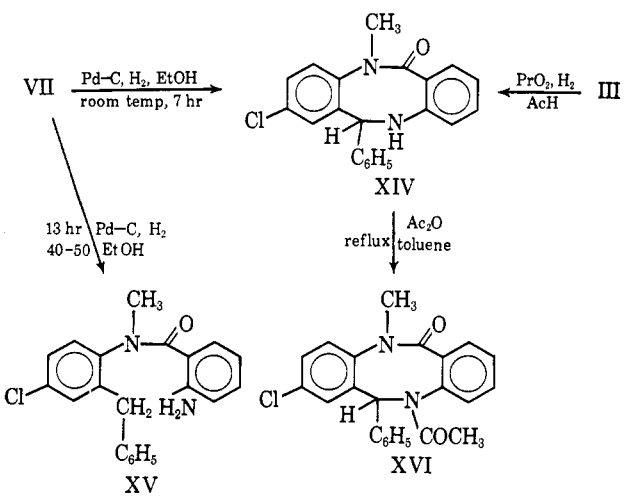
For the dibenzo[*b*,*f*][1,4]diazocine system the intermediate XIX was required (Scheme VI). Reaction of *p*-chloro-*N*-methylaniline and the acid chloride (pseudo-form) of *o*-benzoylbenzoic acid gave a readily separable mixture of the amide (XX) and the phthalide (XXI). Nitration of XX afforded XIX, the structure of which

(1) (a) L. H. Sternbach, L. O. Randall, and S. R. Gustafson in "Psychopharmacological Agents," M. Gordon, Ed., Academic Press Inc., New York, N. Y., 1964, Chapter 5; (b) S. J. Childress and M. I. Gluckman, *J. Pharm. Sci.*, **53**, 577 (1964); (c) J. Le Gassike and F. M. McPherson *Brit. J. Psychiat.* **111**, 521 (1965).

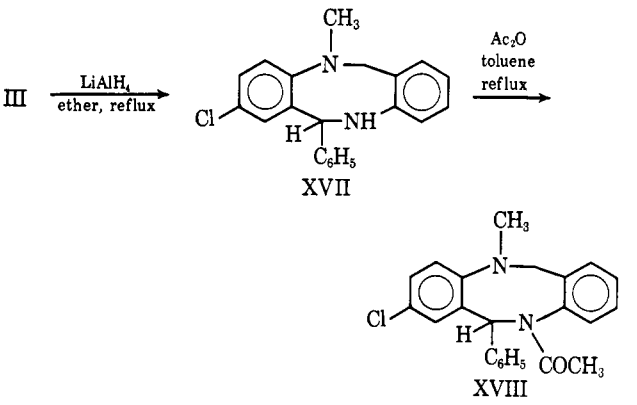
SCHEME III



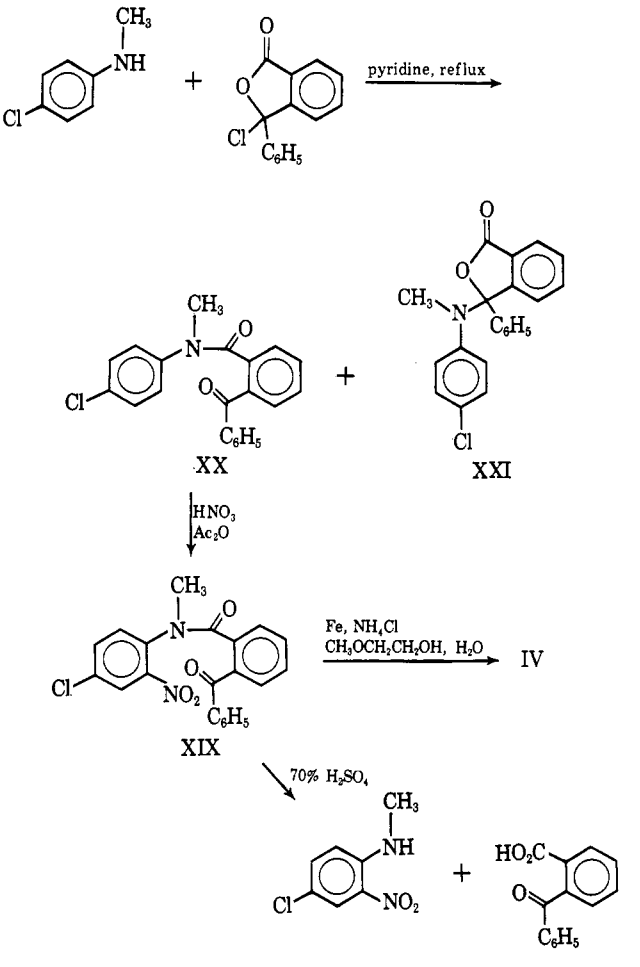
SCHEME IV



SCHEME V



SCHEME VI



was established by acid hydrolysis to give 4-chloro-2-nitro-N-methylaniline and *o*-benzoylbenzoic acid. Conversion of XIX to the desired dibenzo[*b*,*f*][1,4]-diazocine (IV) was effected by reductive cyclization in poor yield.

Pharmacological Results.—It is apparent from the test data listed in Table I that the compounds synthesized do not have activity profiles comparable to chlordiazepoxide, diazepam, and oxazepam. There is no indication from the tetrabenazine reversal test results that the compounds might be interesting as potential antidepressants. Compound XII shows antitremorine potency comparable to trihexylphenidyl but is not active *vs.* oxotremorine indicating that it may be acting by blocking the metabolism of tremorine.

Experimental Section[2]

2-Benzamido-N-(4-chlorophenyl)-N-methylbenzamide (V).—A mixture of *p*-chloro-N-methylaniline[3] (25.0 g) and isatoic anhydride (28.8 g) was heated at 160–170° for 5 hr. After cooling, the highly viscous crude product was triturated in 2:1 benzene–hexane (300 ml). Solid material (8.3 g) was removed by

(2) All melting points (uncorrected) were determined on a Thomas–Hoover capillary melting point apparatus, ultraviolet absorption spectra in methanol solution, and infrared spectra as Nujol mulls. The nmr spectra were recorded on a Varian Associates A-60 spectrometer at 60 Mc/sec with Me_4Si as internal standard.

(3) L. E. Mills, U. S. Patent 1,935,575 (1933).

TABLE I
PHARMACOLOGICAL ACTIVITY OF SOME DIBENZODIAZOCINES[a]

Compd	Locomotor depress.[b,c]	Muscle relax.[b,c]	Ataxia[b,c]	Lethality[b,c]	Max electroshock[d]	Antipentylenetetrazole[e]	Tetrabenazine antagonism	Antitremorine
I	10	30	10	>300	ED_{50} = 7.86	ED_{50} = 0.89		
II								
R = CH_3, R^1 = H	3	30	30	300	ED_{50} = 5.47	ED_{50} = 0.23		
R = H, R^1 = OH	3	10	10	>300		ED_{50} = 0.22		
III	300 (30 ip)	300 (300 ip)	1000	>1000		Inactive at 100	Inactive at 30	
XI	Slight stim at 100	>300	300	>300		Inactive at 100	Inactive at 30	
IV	400	>400	400	>400	Inactive at 36	Inactive at 100	Inactive at 30	
XIV	>400 (36 ip)	>400 (>36 ip)	>400 (>36 ip)			Inactive at 100	V. slight act. at 30; inactive at 10	
XVI	>300	>300	>300	>300		Inactive at 100		Inactive at 10
XVII	>300	>300	>300	>300	Inactive at 30	Inactive at 100	Inactive at 30	Inactive at 10
XVIII	>300 (30 ip)	>300 (30 ip)	>300	>300	Inactive at 30		Inactive at 10	Inactive at 10
XII	100	>300	300	>300		Inactive at 100	Inactive at 30	Complete protect. at 40; some act. at 10
XIII	100	>300	300	>300	Inactive at 30	Inactive at 100		Inactive at 10

[a] All tests were carried out using CF 1 male mice (18–22 g). Doses are oral in milligrams per kilogram unless otherwise indicated. [b] Lowest dose producing significant effect. [c] S. Irwin in "Animal and Clinical Pharmacological Techniques in Drug Evaluation," J. H. Nodine and P. E. Siegler, Ed., Yearbook Medical Publishers, Chicago, Ill., 1964, p 317. [d] E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exptl. Therap.*, **106**, 319 (1952). [e] G. M. Everett and R. K. Richards, *ibid.*, **81**, 402 (1944).

filtration and the filtrate was concentrated to an orange oil (35 g). The oil was dissolved in benzene (70 ml) and chromatographed on alumina (500 g). The column was eluted with benzene followed by $CHCl_3$ (400-ml fractions). The $CHCl_3$ eluates were combined (17 g), pyridine (75 ml) and benzoyl chloride (12.0 g) were added, and the mixture was refluxed for 4 hr. The cooled reaction mixture was poured over a mixture of ice and concentrated HCl (50 ml), the resultant orange gum was extracted with ether, and the ether solution was washed with water, dried (Na_2SO_4), and evaporated yielding a yellow viscous oil (14.4 g). The oil in benzene (40 ml) was chromatographed on alumina (200 g) and the column was eluted with benzene followed by $CHCl_3$ (200-ml fractions). The benzene eluates were crystallized from acetone–petroleum ether (bp 30–60°) to give V (3.1 g), mp 151–152°. The analytical sample, obtained by recrystallization from the same solvent system, had mp 153–154°; λ_{max} 6.01 (s), 6.15 (vs) μ.

Anal. Calcd for $C_{21}H_{17}ClN_2O_2$: Cl, 9.72; N, 7.68. Found: Cl, 9.78; N, 7.63.

Attempted Cyclization of V.—A mixture of V (0.9 g) and polyphosphoric acid (9.0 g) was heated with stirring at 150–160° for 3 hr. The cooled reaction mixture was stirred into cold water (50 ml) resulting in the formation of a white solid which was collected, washed with water, and air dried: 0.5 g, mp 102–107° dec. On recrystallization from acetone–water separation was effected into 2-phenyl-3,1,4H-benzoxaz-4-one[4] (0.15 g) and N-benzoylanthranilic acid[5] (0.16 g), both identified by comparison with authentic samples.

N-(2-Benzoyl-4-chlorophenyl)-N-methyl-2-nitrobenzamide (VII).—A solution of 5-chloro-2-methylaminobenzophenone[6] (12.5 g) and *o*-nitrobenzoyl chloride (10.0 g) in toluene (100 ml) was refluxed overnight. The solution was concentrated until precipitation began then diluted with petroleum ether. On cooling, the crude product separated and was filtered off, washed with petroleum ether, and air dried; yield 20.1 g, mp 136–140°. The analytical sample was obtained on recrystallization from ethyl acetate: mp 142–143°, λ_{max} 6.03 (s) μ.

Anal. Calcd for $C_{21}H_{15}ClN_2O_4$: C, 63.88; H, 3.83; N, 7.10. Found: C, 63.83; H, 3.90; N, 7.18.

2-Chloro-5,6-dihydro-5-methyl-6-oxo-12-phenyldibenzo[*b*,*f*]-[1,5]diazocine (III).—To a stirred refluxing solution of VII (2.0 g) and NH_4Cl (1.6 g) in 2-methoxyethanol (20 ml) and water (5 ml), iron filings (1.6 g) were added, portionwise, over 1.5 hr. After an additional reflux period of 1.5 hr the reaction mixture was filtered, the filter cake was washed well with boiling methanol, and the combined filtrates were evaporated to dryness. Recrystallization of the residue from CH_2Cl_2–hexane afforded 1.2 g of product, mp 206–210°. Further recrystallization from acetone–petroleum ether raised the melting point to 213–214°; λ_{max} 6.00 (vs), 6.16 (sh) μ; nmr ($CDCl_3$), δ = 3.24 (NCH_3, 3 H, sharp band) ppm.

Anal. Calcd for $C_{21}H_{15}ClN_2O$: C, 72.72; H, 4.36; Cl, 10.22; N, 8.08. Found: C, 73.00; H, 4.57; Cl, 9.99; N, 8.04.

N-(2-Benzoyl-4-chlorophenyl)-2-nitrobenzamide (VIII).—A solution of 2-amino-5-chlorobenzophenone (45.2 g) and *o*-nitrobenzoyl chloride (38.9 g) in toluene (300 ml) was refluxed overnight, concentrated *ca.* 50%, cooled, and diluted with petroleum ether (300 ml). The crude product was collected by filtration, washed with petroleum ether, and air dried: yield 74.4 g, mp 142–145°. Recrystallization from methanol afforded 61.4 g, mp 159–162°. Further recrystallization from the same solvent afforded the analytical sample as pale yellow needles: mp 162–163°; λ_{max} 3.06 (m), 5.92 (m), 6.05 (m–w) μ.

Anal. Calcd for $C_{24}H_{13}ClN_2O_4$: C, 63.09; H, 3.44; N, 7.36. Found: C, 62.91; H, 3.30; N, 7.54.

2-Amino-N-(2-benzoyl-4-chlorophenyl)benzamide (IX).—Following the procedure described in the preparation of III using VIII (26.9 g), NH_4Cl (23.7 g), methoxyethanol (220 ml), water (55 ml), and iron filings (23.7 g), there was obtained 16.9 g of product, mp 151–153°, after recrystallization from CH_2Cl_2–hexane. Further recrystallization gave the analytical sample: mp 153–154°; λ_{max} 2.90 (s), 3.00 (s), 6.03 (m–s), 6.13 (s) μ.

Anal. Calcd for $C_{20}H_{15}ClN_2O_2$: C, 68.43; H, 4.31; Cl, 10.11. Found: C, 68.33; H, 4.28; Cl, 9.98.

3-(2-Benzoyl-4-chlorophenyl)-2,2-dimethyl-1,2,3,4-tetrahydro-4-quinazolinone (X).—The procedure for the preparation of IX

(4) D. T. Zentmyer and E. C. Wagner, *J. Org. Chem.*, **14**, 967 (1949).
(5) R. E. Steiger, *ibid.*, **9**, 396 (1944).
(6) L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *ibid.*, **27**, 3781 (1962).

in the preceding experiment was followed, except that the crude product was dissolved in boiling acetone and the solution was filtered free of insoluble salts and then diluted with petroleum ether until precipitation began. The crude product was collected (11.0 g, mp 177–185° from 18.1 g of VIII) and recrystallized from acetone yielding X (8.9 g), mp 214–215°. Further recrystallization from the same solvent gave the analytical sample; mp 217–218°; λ_{max} 3.03 (m-s), 5.97 (s), 6.14 (vs) μ.

Anal. Calcd for $C_{23}H_{19}ClN_2O_2$: C, 70.65; H, 4.90; N, 7.17; Cl, 9.07. Found: C, 70.52; H, 5.15; N, 7.17; Cl, 9.01.

Hydrolysis of X.—A solution of X (3.0 g) in concentrated HCl (100 ml) was refluxed for 3.5 hr. A yellow solid precipitated during this time. The reaction mixture was evaporated to dryness and the residual powder was warmed in 10% Na_2CO_3 (40 ml) for 20 min. The product (IX) was collected by filtration, washed with water, and air dried; yield 2.7 g, mp 148–151°.

2-Chloro-5,6-dihydro-6-oxo-12-phenyldibenzo[b,f][1,5]diazocine (XI).—A stirred solution of IX (16.9 g) in xylene (1700 ml) containing *p*-toluenesulfonic acid (1.7 g) was refluxed for 6.5 hr. During this period a total of 900 ml of solvent was removed dropwise *via* a Dean–Stark separator. The remaining solution was refluxed overnight and concentrated to about 200 ml, and hexane was added. The crude product was collected, washed with hexane, and air dried; yield 17.2 g, mp 160–174°. Recrystallization from CH_2Cl_2–hexane afforded a CH_2Cl_2 solvate of the product (8.7 g), mp 217–220°. Further recrystallization from the same solvent system raised the melting point to 218–220°. The analytical sample was dried *in vacuo* at 140° overnight; mp 220–221°; λ_{max} 3.15 (m-w), 5.98 (s), 6.10 (m) μ.

Anal. Calcd for $C_{20}H_{13}ClN_2O$: C, 72.20; H, 3.94; Cl, 10.66; N, 8.42. Found: C, 72.09; H, 4.15; Cl, 10.83; N, 8.43.

2-Chloro-5,6-dihydro-5-(2-dimethylaminoethyl)-6-oxo-12-phenyldibenzo[b,f][1,5]diazocine (XII).—A stirred mixture of XI (2.4 g), NaH (0.43 g of a 53.3% dispersion in mineral oil), and benzene (100 ml) was refluxed for 1 hr and cooled. A solution of 2-dimethylaminoethyl chloride (1.0 g) in benzene (10 ml) was added and the reaction mixture was refluxed overnight and cooled, and water (50 ml) was added dropwise. The benzene layer was separated and the aqueous layer was reextracted with benzene. The combined benzene layers were extracted with 10% HCl and the extracts were basified with concentrated NH_4OH. The crude product, isolated by extraction with $CHCl_3$, amounted to 2.3 g, mp 115–158°. Recrystallization from ether-petroleum ether afforded 1.13 g of XII, mp 169–171°. The analytical sample was obtained by recrystallization from acetone–ether–petroleum ether; mp 172–173°, λ_{max} 6.10 (s) μ.

Anal. Calcd for $C_{24}H_{22}ClN_3O$: C, 71.35; H, 5.49; Cl, 8.78; N, 10.40. Found: C, 71.48; H, 5.37; Cl, 8.81; N, 10.43.

2-Chloro-5,6-dihydro-5-(3-dimethylaminopropyl)-6-oxo-12-phenyldibenzo[b,f][1,5]diazocine (XIII).—From XI (5.4 g), NaH (0.96 g of a 53.3% dispersion in mineral oil), and γ-dimethylaminopropyl chloride (2.6 g), following essentially the procedure described for the preparation of XII, there was obtained 3.9 g of crude product in the form of a highly viscous yellow oil. The free base (1.7 g) was dissolved in the minimum volume of warm acetone and treated with maleic acid (0.48 g) in acetone solution. The crude maleate was isolated and recrystallized ethyl acetate–acetone affording yellow crystals, mp 188–189°, yield 0.87 g.

Anal. Calcd for $C_{25}H_{24}ClN_3O \cdot C_4H_4O_4$: C, 65.24; H, 5.28; N, 7.87. Found: C, 65.11; H, 5.40; N, 7.80.

2-Chloro-5-methyl-6-oxo-12-phenyl-5,6,11,12-tetrahydrodibenzo[b,f][1,5]diazocine (XIV).—Compound VII (4.5 g) was dissolved in ethanol (150 ml) and reduction was effected at room temperature and a pressure of 4.2 kg/cm² of hydrogen in the presence of a 5% Pd-C catalyst (0.2 g) over a period of 7 hr. The solutions from two such runs were combined, the catalyst was filtered off, and the ethanol was evaporated yielding an oily solid. This solid was treated with boiling benzene (5 ml/g of solid) and the insoluble portion was filtered off giving product (2.6 g), mp 244–248°. Recrystallization from CH_2Cl_2–hexane furnished XIV (1.9 g), mp 249–251°. The analytical sample, obtained by recrystallization from the same solvent system had mp 251–253°; λ_{max} 3.04 (m), 6.13 (vs) μ.

Anal. Calcd for $C_{21}H_{17}ClN_2O$: C, 72.30; H, 4.91; Cl, 10.17; N, 8.03. Found: C, 72.00; H, 5.55; Cl, 10.54; N, 7.89.

Compound III (1.0 g) was dissolved in glacial acetic acid (150 ml) and reduced at room temperature and a hydrogen pressure of 4.2 kg/cm² in the presence of PtO_2 (0.01 g) as catalyst over a period of 2 hr. The catalyst was filtered off and the filtrate was evaporated to dryness. Crystallization of the residue from CH_2Cl_2–hexane afforded crude product (0.26 g), mp 240–250°. Further recrystallization from acetone–petroleum ether raised the melting point to 244–246°. This product was shown to be XIV by mixture melting point determination and by comparison of infrared spectra.

2-(2-Amino-N-methylbenzamido)-5-chlorodiphenylmethane (XV).—A solution of VII (7.2 g) in ethanol (150 ml) was hydrogenated at room temperature and a pressure of 4.2 kg/cm² hydrogen in the presence of a 5% Pd-C catalyst (0.35 g) for 4 hr and at 46–50° for 9 hr. The catalyst was filtered off and the filtrate was evaporated to give a viscous oil (6.5 g) which was dissolved in benzene (35 ml) and chromatographed on a column of alumina (65 g). Elution with 1:2 $CHCl_3$–benzene and with 2:1 $CHCl_3$–benzene gave colorless and amber oils which were crystallized from ether-hexane affording crude product (2.8 g), mp 111–115°. Recrystallization from CH_2Cl_2–hexane yielded XV (1.2 g): mp 117–119°; λ_{max} 2.85 (m), 2.92 (m), 6.10 (s) μ; nmr ($CDCl_3$), δ = 3.03 (NCH_3, 3 H, sharp band), 3.73 (CH_2, 2 H), 4.59–4.68 (NH_2, 2 H, broad band) ppm.

Anal. Calcd for $C_{21}H_{19}ClN_2O$; C, 71.88; H, 5.46; N, 7.99. Found: C, 71.95; H, 5.62; N, 8.06.

11-Acetyl-2-chloro-5-methyl-6-oxo-12-phenyl-5,6,11,12-tetrahydrodibenzo[b,f][1,5]diazocine (XVI).—A solution of XIV (3.2 g) and acetic anhydride (1.9 g) in toluene (100 ml) was refluxed for 7 hr and then evaporated to dryness. Recrystallization of the solid residue from ethyl acetate–hexane afforded the product (1.1 g), mp 229–230°. Further recrystallization from the same solvent system raised the melting point to 230–231°, λ_{max} 6.03 (vs) μ.

Anal. Calcd for $C_{23}H_{29}ClN_2O_2$: C, 70.66; H, 4.91; Cl, 9.07. Found: C, 70.52; H, 5.00; Cl, 9.37.

2-Chloro-5-methyl-12-phenyl-5,6,11,12-tetrahydrodibenzo-[b,f][1,5]diazocine (XVII).—To a stirred suspension of $LiAlH_4$ (1.65 g) in anhydrous ether (400 ml) III (3.9 g) was added, and the mixture was refluxed for 18 hr, cooled, and treated with successive portions of water (1.48 ml), 15% NaOH (1.48 ml), and water (4.44 ml). After stirring the mixture for 0.5 hr, the salts were filtered off and washed thoroughly with ether. The combined ether filtrates were evaporated to a yellow oil, which was crystallized from hexane to give the crude product (2.8 g), mp 129–134°. Recrystallization from acetone-petroleum ether furnished XVII (2.0 g); mp 132–133°; nmr (DMSO-d_6), δ = 2.80 (NCH_3, 3 H, sharp band), 4.05, 4.24 (CH_2, 2 H, AB quartet, J = 15.5 cps), 5.90 (>CH, 1 H, singlet) ppm.

Anal. Calcd for $C_{21}H_{19}ClN_2$: C, 75.34; H, 5.72; N, 8.37. Found: C, 75.01; H, 5.46; N, 8.38.

11-Acetyl-2-chloro-5-methyl-12-phenyl-5,6,11,12-tetrahydrodibenzo[b,f][1,5]diazocine (XVIII).—A solution of XVII (1.0 g) and acetic anhydride (0.76 g) in toluene (50 ml) was refluxed for 6.5 hr, concentrated to *ca.* 25 ml, diluted with petroleum ether until cloudy, and chilled. The crystalline solid which separated was collected by filtration and air dried; yield 0.67 g, mp 152–154°. Recrystallization from CH_2Cl_2–hexane gave the analytical sample: mp 155–156°; λ_{max} 6.0 (s) μ; nmr (DMSO-d_6), δ = 1.70 (CH_3CO, 3 H, sharp band), 2.93 (NCH_3, 3 H, sharp band), 3.73, 4.39 (CH_2, 2 H, AB quartet, J = 13.5 cps), 6.39 (>CH, 1 H) ppm.

Anal. Calcd for $C_{23}H_{21}ClN_2O$: C, 73.28, H, 5.62; Cl, 9.41. Found: C, 72.83; H, 5.77; Cl, 9.10.

2-Benzoyl-N-(4-chlorophenyl)-N-methylbenzamide (XX).—A solution of *o*-benzoylbenzoic acid (104.5 g) and oxalyl chloride (70.2 g) in benzene (50 ml) was heated on a steam bath for 1.5 hr. Solvent and excess oxalyl chloride were evaporated and the chilled residue was treated with a solution of *p*-chloro-N-methylaniline[3] (50 g) in pyridine (250 ml). The reaction mixture was refluxed overnight, cooled, diluted with water (250 ml), and acidified with concentrated HCl (200 ml). The acidic mixture was extracted first with ether (total of 1300 ml) and then with $CHCl_3$ (total of 600 ml). Evaporation of the dried (Na_2SO_4) $CHCl_3$ solution yielded an oily solid which was recrystallized from CH_2Cl_2–hexane to give XX (30.0 g), mp 139–141°. Further recrystallization from the same solvent system raised the melting point to 142–143°; λ_{max} 6.02 (s), 6.08 (vs) μ.

Anal. Calcd for $C_{21}H_{16}ClNO_2$: Cl, 10.14; N, 4.01. Found: Cl, 9.94, N, 4.08.

Evaporation of the dried (Na_2SO_4) ether layer yielded an oil which was dissolved in warm benzene (3–4 ml/g of oil) and chromatographed on a column of alumina (10 g of alumina/g of oil).

Elution with benzene yielded a yellow oily solid which was recrystallized from acetone–hexane to give the phthalide (XXI) (24.8 g), mp 132–133°. Recrystallization from the same solvent system afforded the analytical sample, mp 133–134°, λ_{max} 5.67 (vs) μ.

Anal. Calcd for $C_{21}H_{16}ClNO_2$: Cl, 10.14; N, 4.01. Found: Cl, 10.06; N, 4.01.

Further elution with 1:1 $CHCl_3$–benzene followed by $CHCl_3$ afforded additional XX: 21.0 g, mp 140–143°. Total yield of the benzamide (XX) was 42% and that of the phthalide (XXI) was 20%.

2-Benzoyl-N-(4-chloro-2-nitrophenyl)-N-methylbenzamide (XIX).—Concentrated HNO_3 (10.0 g) was added dropwise to a stirred suspension of XX (10.0 g) in acetic anhydride (100 ml) at 5–10°. The reaction mixture was cautiously heated to reflux and maintained in that state for 4 hr. Most of the solvent was evaporated and the residual oil poured into 10% Na_2CO_3 (*ca.* 400 ml). After 3 days the crude solid product was filtered off and recrystallized from 1:1 methanol–acetone affording a yellow crystalline solid (7.6 g), mp 138–141°. Further recrystallization from the same solvent system raised the melting point to 140–141°.

Anal. Calcd for $C_{21}H_{15}ClN_2O_4$: C, 63.88; H, 3.83; N, 7.10. Found: C, 63.83; H, 3.88; N, 7.02.

Hydrolysis of XIX.—Compound XIX (0.6 g) was added to 70% H_2SO_4 (12 ml) heated to 105°, and the resultant solution was heated to 145° in 8 min and then poured over ice (55 g). The orange gummy solid which formed was extracted with $CHCl_3$ (two 50-ml portions) and the $CHCl_3$ extracts were extracted with 5% NaOH (two 25-ml portions) and then washed with water (two 10-ml portions) and dried (Na_2SO_4). The dried $CHCl_3$ solution was concentrated to a very low volume, diluted with petroleum ether, and chilled. An orange crystalline solid formed which was filtered off and dried: 0.18 g, mp 104–105°, shown by mixture melting point determination and infrared spectra comparison with an authentic sample[7] to be 4-chloro-*N*-methyl-2-nitroaniline. The alkali extracts were acidified with 10% HCl and chilled. A tan solid was filtered off, washed with water, and dried, 0.30 g, mp 92–95°. Recrystallization from $CHCl_3$–petroleum ether gave 0.2 g of solid, mp 125–127°, shown to be identical with an authentic sample of *o*-benzoylbenzoic acid by mixture melting point determination and comparison of infrared spectra.

2-Chloro-5,6-dihydro-5-methyl-6-oxo-11-phenyldibenzo[*b*,*f*][1,4]diazocine (IV).—From XIX (2.0 g), NH_4Cl (1.6 g), and iron filings (1.6 g) following essentially the procedure described for the preparation of III, there was obtained an oily crude product (1.8 g). This was dissolved in benzene (15 ml) and chromatographed on a column of alumina (30 g). Elution with benzene gave a yellow oil (0.7 g) which after long standing afforded yellow crystals (0.25 g), mp 131–152°. Recrystallization from CH_2Cl_2–hexane furnished 0.12 g, mp 154–155°. Further recrystallization from the same solvent system gave the analytical sample: mp 157–158°; λ_{max} 6.00 (vs), 6.14 (s) μ; nmr ($CDCl_3$), δ = 3.18 (NCH_3, 3 H, sharp band) ppm.

Anal. Calcd for $C_{21}H_{15}ClN_2O$: C, 72.72; H, 4.36; Cl, 10.22. Found: C, 72.66; H, 4.36; Cl, 10.25.

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(7) J. J. Blanksma, *Rec. Trav. Chim.*, **21**, 273 (1902).

Synthesis and Biological Activity of Some Ring-Substituted Tryptamines

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The synthesis of tryptamines having a hydroxy, methoxy, or benzyloxy substituent in the 5, 6, or 7 positions is reported. Eight of the nine compounds examined showed activity in modifying the open-field behavior of rats. With two exceptions all of the compounds evoked a hyperthermia in rabbits; the more active compounds in this respect were also lethal to rabbits. The tentative conclusion is made that substitution in the 5 position of the indole nucleus conferred higher biological activity than did substitution by the same group in either the 6 or 7 positions.

The tryptamine nucleus is present in many naturally occurring and synthetic compounds which show psychotomimetic activity. Brimblecombe and coworkers[2] have reported the synthesis and pharmacological properties of a number of tryptamines which were unsubstituted in the benzene ring of the indole nucleus. The present paper describes the effect on biological activity of the introduction of selected substituents in the 5, 6, and 7 positions of the benzene ring.

Chemistry.—3-(2-Dimethylaminoethyl)-5-hydroxyindole bioxalate (bufotenin dioxalate, I) was purchased from Koch-Light Laboratories Ltd. 3-(2-Diethylaminoethyl)-5-benzyloxyindole oxalate (II), 3-(2-pyrrolidinoethylindole hydrochloride (IV), 3-(2-pyrrolidinoethyl)-5-benzyloxyindole hydrochloride (V), 3-(2-pyrrolidinoethyl)-5-methoxyindole hydrochloride (VII), 3-(2-pyrrolidinoethyl)-6-methoxyindole (VIII), and 3-(2-pyrrolidinoethyl)-7-methoxyindole (IX) were all prepared from the appropriate indole by reduction of the corresponding intermediate glyoxylamides (Table I) with $LiAlH_4$ in dioxane according to the method of Speeter and Anthony.[3] 3-(2-Diethylaminoethyl)-5-hydroxyindole (III) and 3-(2-pyrrolidinoethyl)-5-hydroxyindole (VI) were obtained from the respective benzyloxytryptamines (II and V) by catalytic debenzylation with hydrogen over 10% Pd–C in methanol. The physical properties of these tryptamines are recorded in Table II.

Experimental Section

Pharmacology. Methods. (a) Toxicity.—Using a suitable solvent, see Table III, the compounds were injected subcutaneously into male 190–210-g albino rats. The animals were observed over a period of 7 days for overt changes in behavior, signs of poisoning, or deaths and, in addition, were tested for their ability to climb a pair of inclined rods. Two animals were used at each dose level, the highest dose being 50 mg/kg; progressively smaller doses were administered to additional pairs of rats until a dose was reached which had no effect. Control animals were injected with the solvent alone to confirm that no toxic effects followed solvent administration.

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(2) R. W. Brimblecombe, D. F. Downing, D. M. Green, and R. R. Hunt, *Brit. J. Pharmacol.*, **23**, 43 (1964).

(3) M. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6208 (1954).