latter administered alone, using the criteria of the behavioral method employed.

Tables I and II show the responses obtained with animals subjected to septal and amygdaloid lesions, respectively. It can be seen that small lesions in these areas produced no consistent change in behavior or in the responses to the administration of the drugs used. Similar results were obtained with the other areas investigated. The only behavioral change noted was a slight hyperexcitability; but since sham operated animals also showed this reaction, it was attributed to the operating procedure rather than to the presence of a lesion.

The results of this study indicate that investigations of behavior involving the production of lesions require a great deal of caution in the interpretation of behavioral changes that are seen. Lesion size may be one of the factors that has contributed to the many conflicting reports appearing in this field.

SUMMARY

Small lesions within the limbic system of the rat produced no consistent behavioral defects or altered responses to chlorpromazine and/or pentobarbital as measured by a new behavioral scoring method. Lesion size may be one of the factors that has contributed to the many conflicting reports appearing in this field.

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Facile Synthesis of Isoindoline and Substituted Isoindolines

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The preparation of isoindoline and several derivatives bearing nuclear substituents by methods previously employed successfully only for *N*-substituted derivatives is described. The method involves the preparation and hydrogenolysis of *N*-benzyl isoindolines.

WHILE A considerable amount of work has been reported on the synthesis of *N*-substituted isoindolines and hydrogenated isoindolines by a variety of methods, difficulty was experienced by several workers (including the author) in obtaining isoindoline (VI*a*) in good yields and in a pure form. Isoindoline derivatives have been obtained by the reaction of amines with *o*-xylylene dibromide (1, 2). Bornstein (3) prepared isoindoline (VI*a*) by the hydrolytic cleavage of 2-(*p*-tolylsulfonyl)-isoindoline (prepared from *o*-xylylene dibromide and *p*-toluenesulfonamide) with phenol and hydrobromic acid in propionic acid. The reduction of *N*-substituted phthalimides with lithium aluminum hydride was a generally satisfactory method for obtaining *N*-substituted isoindolines (4, 5) and was utilized also for the preparation of tetrahydro and hexahydroisondoline (4), but failed when applied to the reduction of phthalimide. As a result, we have devised a method for the preparation of isoindoline and substituted isoindolines which was based on the lithium aluminum hydride reduction of *N*-benzylphthalimides of their corresponding isoindolines, followed by the hydrogenolysis of the benzyl moiety with palladium-on-charcoal. This route was satisfactory also for the preparation of 5-methylisoindoline (VI*b*) and 4-aminoisoindoline (VI*d*), but failed to yield 4-chloroisoindoline from the hydrogenolysis of *N*-benzyl-4-chloroisoindoline (V*c*). Treatment of V*c* with hydrogen and palladium caused the hydrogenolysis of the chlorine and the benzyl group; isoindoline (VI*a*) was the isolated product.

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EXPERIMENTAL[1]

N-Benzylphthalimide.—This was prepared from potassium phthalimide (0.5 mole) and benzyl chloride (0.5 mole) in *N*,*N*-dimethylformamide in 75% yield by the method of Billman and Cash (6), crude, m.p. 111–112°. The compound was used in subsequent reactions without further purification. [Lit. (6) m.p. 115–116°.]

N-Benzyl-4-methylphthalimide (IIb).—This was obtained from potassium 4-methylphthalimide (I*b*) and benzyl chloride; yield: 72%, m.p. 122.5 to 123.5°.

Anal.—Calcd. for $C_{16}H_{13}NO_2$: C, 73.99; H, 5.77; N, 5.57. Found: C, 73.87; H, 5.82; N, 5.63.

N-Benzyl-3-chlorophthalimide (IIc).—This was obtained from potassium 3-chlorophthalimide (I*c*) and benzyl chloride; yield: 98%, m.p. 137 to 138.5° (recrystallized from *n*-butanol).

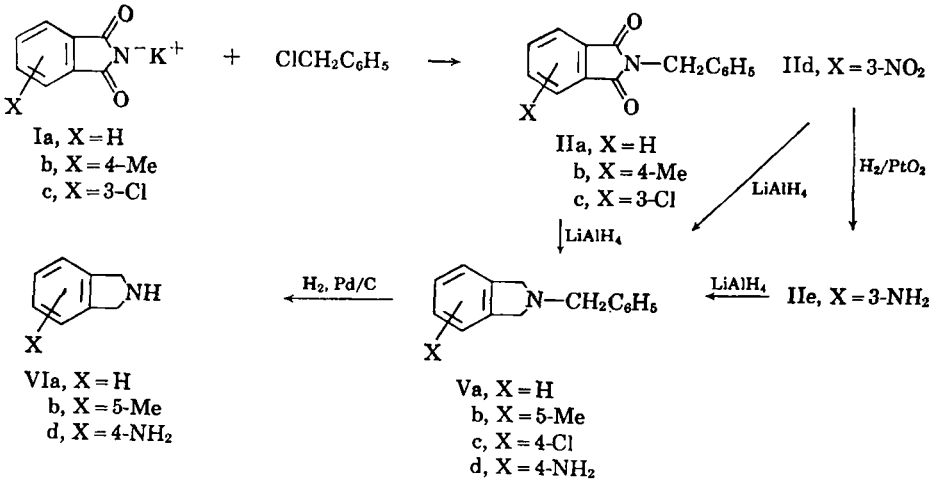
Anal.—Calcd. for $C_{15}H_{10}NO_2Cl$: C, 66.30; H, 3.71. Found: C, 66.29; H, 3.71.

N-Benzyl-3-nitrophthalimide (IId).—A mixture of 19.3 Gm. (0.1 mole) of 3-nitrophthalic anhydride and 10.7 Gm. (0.1 mole) of benzylamine was fused at 200–250° and the mixture allowed to cool. Upon recrystallization from isopropyl alcohol, 23 Gm. (83%) of yellow flakes, m.p. 140–141°, were obtained.

Anal.—Calcd. for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N, 9.93. Found: C, 63.68; H, 3.74; N, 9.90.

N-Benzyl-3-aminophthalimide (IIe).—A solution of 25 Gm. (0.089 mole) of *N*-benzyl-3-nitrophthalimide in 290 ml. of benzene was hydrogenated in a Parr hydrogenator at room temperature using 0.5 Gm. of platinum oxide until the hydrogen uptake

[1] Both the melting points and the boiling points were uncorrected. All melting points were obtained in a Thomas Hoover silicone oil filled capillary melting point apparatus. The assistance of Mr. R. C. Pharo with a number of the experiments reported herein, of Mr. J. E. Zarembo and his staff in carrying out the analyses, and of Mr. H. Adelman in the interpretation of infrared spectra is gratefully acknowledged.



had ceased (30 minutes). The catalyst and benzene were removed yielding 19.0 Gm. (85%) of yellow needles, m.p. 148.5 to 149.5°.

Anal.—Calcd. for $C_{15}H_{12}N_2O_2$: N, 11.11. Found: N, 11.35.

N-(Benzyl)isoindoline (Va).—The procedure for the reduction of the imide to the isoindoline was similar to the method previously described (4). To 1000 ml. of ether (dried over sodium) in a 2-L. flask fitted with a stirrer, Soxhlet extractor, and a thermometer was added 23 Gm. (0.6 mole) of lithium aluminum hydride. The thimble of the Soxhlet extractor was charged with 70 Gm. (0.3 mole) of *N*-benzylphthalimide and continuously extracted for 24 hours. With stirring, 100 ml. of 10% sodium sulfate was slowly added to the ether mixture while the reaction flask was cooled in an ice bath. The precipitate was filtered off and washed two times with 200 ml. of ether; the combined ether extracts were dried over magnesium sulfate, the ether was eliminated, and the residue distilled, yielding 37.5 Gm. (60%) of an oil, b.p. 180° (0.35 mm.), n_D^{25} 1.5897. This oil solidified on standing (m.p. 36–37°) and darkened when exposed to light and air. [Lit. (2) m.p. 41° recrystallized from alcohol.]

N-(Benzyl)-4-chloroisoindoline (Vc).—This was obtained from II*c* in 66% yield; b.p. 144° (0.5 mm.), n_D^{25} 1.5945. The compound darkens on standing.

Anal.—Calcd. for $C_{15}H_{14}ClN$: C, 73.91; H, 5.79; N, 5.75. Found: C, 73.69; H, 5.47; N, 5.62.

N-(Benzyl-5-methylisoindoline (Vb).—This was obtained from II*b*, b. p. 126–130° (0.04 mm.), m.p. 47–49°. The analytical sample, m.p. 57–58°, was recrystallized from ethanol-water.

Anal.—Calcd. for $C_{16}H_{17}N$: C, 86.05; H, 7.68; N, 6.27. Found: C, 85.67; H, 7.53; N, 6.31.

N-(Benzyl)-4-aminoisoindoline (Vd).—This was obtained from II*e* in 45% yield; b.p. 152–157° (0.001 mm.), m.p. 64–65°. The compound was characterized as the phenylurea derivative, prepared from phenyl isocyanate in ether, m.p. 178–179°.

Anal.—Calcd. for $C_{22}H_{21}N_3O$: C, 76.94; H, 6.16; N, 12.24. Found: C, 77.25; H, 6.37; N, 12.06.

The reduction of *N*-benzyl-3-nitrophthalimide (II*d*) (0.07 mole) with lithium aluminum hydride (0.21 mole) by the aforementioned procedure also yielded 27% of V*d*.

Isoindoline (VIa).—Hydrogenolysis of 9.5 Gm. (0.043 mole) *N*-(benzyl)isoindoline (V*a*) in 100 ml. of ethanol was carried out by shaking the solution in a Parr apparatus for 16 hours with 2 Gm. of 5% palladium-on-carbon under an initial pressure of 50 p.s.i. hydrogen at 50°. Distillation of the product gave 3.8 Gm. (75%) of VI*a* b.p. 105° (20 mm.), n_D^{25} 1.5650, a clear oil which solidifies on standing in the refrigerator, m.p. 17°. [Lit. (2) b.p. 115° (30 mm.), n_D^{25} 1.5698, m.p. 16.0 to 16.5°.] The *p*-toluenesulfonyl derivative was prepared by treating 0.5 Gm. of isoindoline (VI*a*) with 0.6 Gm. of *p*-toluenesulfonyl chloride in 3 ml. of pyridine. The mixture was warmed for 30 minutes, allowed to cool, and poured over ice. The yellow crystals which precipitated were filtered and recrystallized from ethanol, m.p. 175 to 175.5°. [Lit. (3) 175–176° prepared from *o*-xylylene dibromide and *p*-toluenesulfonamide.]

5-Methylisoindoline (VIb).—This was prepared by the hydrogenolysis of V*b* in the aforementioned manner in 76% yield, b.p. 111° (14 mm.), m.p. 43–44°.

Anal.—Calcd. for $C_9H_{11}N$: C, 81.16; H, 8.38; N, 10.52. Found: C, 80.91; H, 8.05; N, 10.30.

This compound was further characterized by preparing the phenylurea derivative, m.p. 160–161°.

Anal.—Calcd. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.41; H, 6.33; N, 11.21.

4-Aminoisoindoline (VId).—This was obtained by the hydrogenolysis of V*d* in the aforementioned manner (80% yield); b.p. 137–140° (0.1 mm.), m.p. 86–87°.

Anal.—Calcd. for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88. Found : C, 71.35; H, 7.60; N, 20.61.

The dihydrochloride of VI*d* was prepared from methanol and hydrogen chloride and recrystallized from methanol-ether, m.p. 283–284°.

Anal.—Calcd. for $C_8H_{10}N_2 \cdot 2HCl$: C, 46.35; H, 5.84; N, 13.53. Found: C, 46.24; H, 5.80; N, 13.61.

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