increase was greatest in *P. vulgaris*-infected eggs and least in *S. dysenteriae*-infected eggs. These findings appear to correlate with the esterase activity of the packed cells.

REFERENCES

(1) Lewis, P. A., *J. Exptl. Med.*, **23**, 660(1916).
(2) Greig, M. E., and Holland, W. C., *Science*, **110**, 237 (1949).
(3) Greig, M. E., and Mayberry, T. C., *J. Pharmacol. Exptl. Therap.*, **102**, 1(1951).
(4) Green, V. A., Steber, M., McKenna, G. F., Davis, J. E., and Taylor, A., *Texas J. Sci.*, **9**, 89(1957).
(5) Green, V. A., and Davis, J. E., THIS JOURNAL, **50**, 64 (1961).
(6) McKenna, G. F., and Taylor, A., *Texas Repts. Biol. and Med.*, **11**, 283(1951).
(7) Hall, G. E., and Lucas, C. C., *J. Pharmacol. Exptl. Therap.*, **59**, 34(1937).
(8) Nachmansohn, D., and Rothenberg, M. A., *J. Biol. Chem.*, **168**, 223(1947).
(9) Schwartz, B. S., Warren, M. R., Barkley, F. A., and Landis, L., *Antibiotics Ann.*, **1959/60**, 44(1960).

Synthesis of Compounds Containing the Isoindoline Ring System

By ABOO SHOEB and JAMES E. GEARIEN

In an attempt to gain further knowledge concerning the pharmacological properties inherent in the isoindoline ring system, a number of compounds containing this ring system were synthesized and screened for biological activity. These compounds are analogs of biologically active compounds. Only the amide of N-[3-(2-isoindolinyl)propyl]-beta-alanine demonstrated appreciable biological activity. The carbon-hydrogen absorption bands present in the infrared spectra of these compounds were related to their chemical structure.

ALTHOUGH isoindoline is a relatively unstable compound, N-substituted isoindolines are quite stable, easily prepared, and provide convenient intermediates for synthesis. The ganglionic blocking action of 4,5,6,7-tetrachloro-2-(dimethylaminoethyl)isoindoline dimethochloride (1) and the hypertensive action of a series of the quaternary salts of hydrogenated bis-(2-isoindolinyl)alkanes (2) have been extensively studied. Few other compounds containing the isoindoline ring system have been reported to contain biological activity. It therefore appeared desirable to synthesize a number of analogs of biologically active compounds in which the isoindoline ring system is substituted for the amino or substituted amino group.

Three esters which contain the isoindoline ring system and which are analogs of procaine, Trasentine, and eucatropine were synthesized. These esters were 2-isoindolinylethyl 4-aminobenzoate hydrobromide, 2-isoindolinylethyl diphenylacetate hydrochloride, and 2-isoindolinylethyl *dl*-mandelate hydrochloride. The first of these esters was prepared by reacting 2-(2-hydroxyethyl)isoindoline with *p*-nitrobenzoyl chloride. The resulting 2-isoindolinylethyl *p*-nitrobenzoate was catalytically reduced to 2-isoindolinylethyl *p*-aminobenzoate. 2-Isoindolinylethyl diphenylacetate hydrochloride was similarly synthesized by the reaction of 2-(2-hydroxyethyl)isoindoline with diphenylacetyl chloride. 2-Isoindolinylethyl *dl*-mandelate was prepared by reacting silver mandelate with 2-(2-chloroethyl)-isoindoline.

In order to introduce the isoindoline ring system into a molecule having the prerequisites for antihistamine activity, 2-(2-isoindolinyl)ethyl benzhydryl ether was synthesized by reacting benzhydryl bromide with 2-(2-hydroxyethyl)-isoindoline in the presence of metallic sodium. It was isolated as its hydrochloride.

1,6-Bis-(2-isoindolinyl)hexane was prepared by the lithium aluminum hydride reduction of 1,6-hexane diphthalimide.

It also appeared desirable to introduce this ring system into compounds which might possess antitumor activity. 2-[2-Bis-(2-chloroethyl)-aminoethyl]isoindoline was synthesized by first reacting 2-(2-chloroethyl)isoindoline with diethanolamine to yield crude 2-[2-bis-(2-hydroxyethyl)aminoethyl]isoindoline which was then converted to the nitrogen mustard analog by treatment with thionyl chloride. The second possible antitumor agent, 1-[3-(2-isoindolinyl)-propyl]dihydrouracil, was prepared by the following series of reactions

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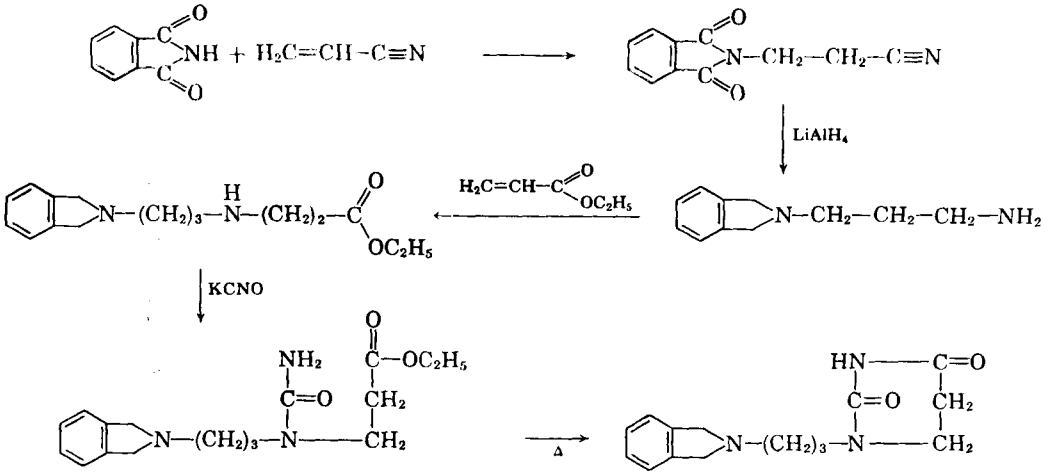

It was found that 2-(3-aminopropyl)isoindoline could be added to acrylamide as well as to ethyl acrylate. The addition of 2-(3-aminopropyl)-isoindoline to acrylamide produced the amide of N-[3-(2-isoindolinyl)propyl]-beta-alanine. This compound is analogous to a number of compounds (3) which possess oxytocic activity.

N^1 - [4 - (2 - Phenylisoindolinyl)]sulfanilamide was prepared by the usual synthesis employed for N^1-substituted sulfanilamides.

The compounds prepared in this study were screened for biological activity. Only the amide of N - [3 - (2 - isoindolinyl)propyl] - beta - alanine showed appreciable activity. This compound stimulated the contractions of isolated uterine muscles.

Most of the compounds prepared were found to contain three carbon-hydrogen absorption bands in the 2700–3200 cm.$^{-1}$ region of their infrared spectra. Since absorption in this area of the spectrum is usually the result of the absorption by carbon-hydrogen bonds and since there was present in these molecules three distinct types of carbon-hydrogen bonds, it was felt that with the aid of several simple model compounds, analysis of this region of their spectra would be possible. From a study of the spectra of the compounds listed in Table I it appeared that the three bands were the result of absorption by the carbon-hydrogen bonds of the aromatic ring, the carbon-hydrogen bonds of the heterocyclic ring, and the carbon-hydrogen bonds of the alkyl chain attached to the nitrogen atom.

The bands appearing at 3025–3050 cm.$^{-1}$ result from absorption by aromatic carbon hydrogen bonds. When only a single aromatic ring is present in the compound, the band occurs at 3025 as a shoulder on the stronger peak at 2940 cm.$^{-1}$. However, the addition of a second phenyl group as in 2 phenylisoindoline, 2-phenyl-4-aminoisoindoline, or 1,6-bis(2-isoindolinyl)hexane, increases the intensity of this band and it occurs as a separate peak. The absorption bands at 2940 to 2975 cm.$^{-1}$ were definitely established. These appeared to be due to absorption of the carbon-hydrogen bonds of the alkyl groups connected to the heterocyclic nitrogen atom. Substitution of a phenyl group for the alkyl group, 2-phenylisoindoline and 2-phenyl-4-amino-isoindoline, resulted in the loss of absorption peaks in this area. Furthermore, the substitution of an ethyl group for the methyl group of 2-methylisoindoline gave rise to a doublet rather than a single peak.

It appeared likely that the absorption bands occurring in the portion of the infrared spectra 2720 and 2800 cm.$^{-1}$ might be caused by the absorption of carbon-hydrogen bonds of the methylene group of the heterocyclic ring. It was, therefore, desirable to obtain the spectra of an isoindoline ring system that did not contain carbon-hydrogen bonds in that ring. Since it was difficult to obtain a 1,1,3,3 tetra-substituted isoindoline, the spectra of the compounds previously synthesized were compared to the spectra of N-methylphthalimide. While the previously identified peaks at 3050 and 2975 cm.$^{-1}$ were pres-

TABLE I.—STUDY OF THE SPECTRA

Compound	C—H Bond Aromatic Ring	C—H Bond Hetero-cyclic Ring	C-Bond Alkyl Chain
2-Methylisoindoline	3025[a]	2775	2940
2-Ethylisoindoline	3025[a]	2800	2940–2975
2-Phenylisoindoline	3050	2750	...
2-Phenyl-3-amino-isoindoline	3040	2720	...
1,6-Bis-(2-isoindo-linyl)hexane	3050	2780	2940
N-Methylphthalim-ide	3050	...	2975

[a] Occurs as a shoulder on the peak at 2940 cm.$^{-1}$.

ent, the peak at 2720 to 2800 was missing. This indicates that the peak usually occurring in this area is due to absorption of the methylene group of the heterocyclic ring.

EXPERIMENTAL[1]

2-(2-Hydroxyethyl)isoindoline.—A solution of 9.0 Gm. (0.047 mole) of N-(2-hydroxyethyl)phthalimide (4) in 25 ml. of tetrahydrofuran was slowly added to a previously cooled slurry of 5.4 Gm. (0.047 mole) of lithium aluminum hydride in 100 ml. of anhydrous ether. After the addition was completed, the cold reaction mixture was decomposed with absolute alcohol. Water was then added until the aluminum oxide was completely precipitated. The resulting suspension was filtered and the clear filtrate dried over anhydrous sodium sulfate. After the removal of the ether, the residue was distilled. It boiled at 167–169°/15 mm. The distillate weighed 4.6 Gm. (60%).

von Braun and co-workers (5) prepared 2-(2-hydroxyethyl)isoindoline by the reaction of ethylene oxide on isoindoline. They reported the isolation of an oil boiling at 162–164°/12 mm.

2-Isoindolinylethyl *p*-Nitrobenzoate.—To a stirred solution of 6.5 Gm. (0.04 mole) of 2-(2-hydroxyethyl)isoindoline in 50 ml. of dry benzene was added, dropwise, a solution of 7.5 Gm. (0.04 mole) of *p*-nitrobenzoyl chloride in 25 ml. of dry benzene. The reaction mixture was refluxed for 2 hours and the solvent removed. The remaining oil was neutralized with 10% sodium hydroxide and then extracted with benzene. After evaporation of the solvent, 9.3 Gm. (75%) of yellow crystals was obtained. These were recrystallized from an alcohol-water mixture.

Anal.—Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.18; H, 4.96; N, 8.78.

2-Isoindolinylethyl *p*-Aminobenzoate Hydrobromide.—The reduction of 2-isoindolinylethyl *p*-nitrobenzoate to 2-isoindolinylethyl 4-aminobenzoate was carried out by shaking a solution of 3.0 Gm. (0.009 mole) of the nitro compound in 75 ml. of ether with 0.3 Gm. of Raney nickel catalyst at 15 pounds of hydrogen pressure. When the theoretical quantity of hydrogen had been absorbed, the hydrogenation was discontinued and the catalyst removed by filtration. The filtrate was treated with anhydrous hydrogen bromide. The precipitated hydrobromide salt was filtered and recrystallized from absolute alcohol by precipitation with anhydrous ether. The pure compound weighed 1.2 Gm. (42%) and melted at 239–240°.

Anal.—Calcd. for $C_{17}H_{19}BrN_2O_2$: C, 56.21; H, 5.26; N, 7.70. Found: C, 56.00; H, 5.26; N, 7.80.

2-(2-Chloroethyl)isoindoline Hydrochloride.—To 8.6 Gm. (0.053 mole) of 2-(2-hydroxyethyl)isoindoline dissolved in 20 ml. of chloroform was added slowly a solution of 8 ml. of thionyl chloride in 15 ml. of chloroform. The reaction mixture, after being refluxed for approximately 15 minutes, crystallized. After cooling in ice, the reaction mixture was filtered and the resulting crystalline solid washed with chloroform and then with ether. After recrystallization from absolute alcohol by the addition of a few drops of anhydrous ether, a yield of 10.6 Gm. (91%) of a white crystalline solid was obtained. It melted at 191–192°.

Anal.—Calcd. for $C_{10}H_{13}Cl_2N$: C, 55.06; H, 6.00; Cl, 32.51. Found: C, 55.21; H, 5.87; Cl, 32.43.

This compound has been previously reported by Gump, *et al.* (6). Its preparation and physical constants were not reported.

2-Isoindolinylethyl *dl*-Mandelate Hydrochloride.—Silver mandelate was prepared by neutralizing 10.0 Gm. of *dl*-mandelic acid with dilute ammonium hydroxide and adding a 10% solution of silver nitrate until the precipitation of the silver salt was complete. The silver mandelate was removed by filtration, washed with water, alcohol, and finally ether.

A mixture of 4.2 Gm. (0.016 mole) of silver mandelate, 3.5 Gm. (0.020 mole) of 2-(2-chloroethyl)isoindoline hydrochloride, and 20 ml. of dry benzene was refluxed for 8 hours. During this time the solution was protected from light. The resulting silver chloride was removed by filtration. Ether was added to the filtrate to produce a gummy mass which solidified upon standing in the refrigerator overnight. The solvent was decanted and the residue dissolved in absolute alcohol. The hydrochloride precipitated upon the addition of anhydrous hydrogen chloride. After recrystallization from isopropyl alcohol, 3.0 Gm. (58%) of a white solid melting at 151–152° was obtained.

Anal.—Calcd. for $C_{18}H_{20}ClNO_3$: C, 64.75; H, 6.00; Cl, 10.64; N, 4.20. Found: C, 64.27; H, 6.09; Cl, 10.28; N, 4.37.

2-Isoindolinylethyl Diphenylacetate Hydrochloride.—To a stirred solution of 7.0 Gm. (0.043 mole) of 2-(2-hydroxyethyl)isoindoline in 25 ml. of dry benzene was added slowly a solution of 10.0 Gm. (0.043 mole) of diphenylacetyl chloride (7) in 15 ml. of dry benzene. The reaction mixture was refluxed on a steam bath for 2 hours. After removal of the solvent on a flash evaporator, the residue was recrystallized from isopropyl alcohol. The pure compound melted at 194–195° and weighed 15 Gm. (92%).

Anal.—Calcd. for $C_{24}H_{24}ClNO_2$: C, 73.18; H, 6.14; Cl, 9.02; N, 3.56. Found: C, 73.16; H, 6.21; Cl, 9.00; N, 3.70.

2-(2-Isoindolinyl)ethyl Benzhydryl Ether Hydrochloride.—2-(2-Hydroxyethyl)isoindoline (8.0 Gm., 0.049 mole) was dissolved in 20 ml. of dry benzene. To this solution was added 1.3 Gm. (0.055 mole) of sodium cut in very small pieces. After the mixture was refluxed for 1 hour, a solution of 13.7 Gm. (0.055 mole) of benzhydryl bromide (8) was added and the resulting solution refluxed for 4 hours. The reaction mixture was filtered to remove the precipitated sodium bromide. After evaporation of the solvent in a flash evaporator, the residue was distilled. It boiled at 195°/0.35 mm. The viscous reddish-brown distillate was dissolved in the least possible amount of benzene and the solution was allowed to stand overnight. A small amount of tetraphenylethane (m.p. 200°) crystallized and was removed by filtration. An equal volume of ether was added to the filtrate and the resulting solution was saturated with anhydrous hydrogen chloride.

[1] Melting points are uncorrected. Microanalyses are by Weiler and Strauss, Oxford, England.

The hydrochloride precipitated and was removed by filtration. After recrystallization from absolute ethanol, 0.7 Gm. (38%) of a white solid melting at 204–204.5° was obtained.

Anal.—Calcd. for $C_{23}H_{29}ClNO$: C, 75.51; H, 6.56; Cl, 9.71. Found: C, 75.66; H, 6.72; Cl, 9.86.

1,6-Hexamethylenediphthalimide.—To 10.0 Gm. (0.085 mole) of 1,6-hexamethylenediamine in a round bottomed flask was added 25.5 Gm. (0.17 mole) of phthalic anhydride. After the vigorous reaction had subsided, the mixture was heated for 45 minutes at 100°, after which the temperature was increased to 160° for 10 minutes. The solid residue was treated with boiling 50% alcohol and the insoluble precipitate was removed by filtration. After recrystallization from tetrahydrofuran the crystals melted at 178–179°. It weighed 30.0 Gm. (97%).

Anal.—Calcd. for $C_{22}H_{20}N_2O_4$: C, 70.21; H, 5.32; N, 7.44. Found: C, 70.13; H, 5.31; N, 7.65.

1,6-Bis-(2-isoindolinyl)hexane Dihydrochloride.—A solution of 6.6 Gm. (0.018 mole) in 20 ml. of tetrahydrofuran was added, dropwise, to a slurry of 4.0 Gm. of lithium aluminum hydride in 75 ml. of anhydrous ether. The reaction mixture was refluxed for 15 minutes and then the reagent was decomposed by the addition of ethanol. Water was carefully added to precipitate the alumina which was filtered. The clear filtrate was evaporated to dryness and the resulting solid dissolved in benzene and treated with an equivalent of an alcoholic solution of hydrogen chloride. The precipitated hydrochloride, after recrystallization from methanol, melted at 297–298°. The crystals weighed 3.5 Gm. (50%).

Anal.—Calcd. for $C_{22}H_{30}Cl_2N_2$: C, 67.17; H, 7.63; N, 7.12. Found: C, 66.85; H, 7.13; N, 6.81.

2-[2-Bis(2-chloroethyl)aminoethyl]isoindoline Dihydrochloride.—To a 100-ml. mixture of equal parts alcohol and benzene was added 7.5 Gm. (0.034 moles) of 2-(2-chloroethyl)isoindoline hydrochloride and 4.6 Gm. (0.034 mole) of diethanolamine. The resulting solution was refluxed for 4 hours, after which the solvents were removed on a flash evaporator. The residue dissolved in 10 ml. of chloroform was added, dropwise, to a solution of 15 ml. of thionyl chloride in 15 ml. of chloroform. When the addition was completed the mixture was heated under reflux for 20 minutes and then cooled in an ice bath until crystallization was complete. The solid reaction product after filtration and recrystallization from a mixture of equal parts acetone and alcohol weighed 11.0 Gm. (90%) and melted at 270° (decompn.).

Anal.—Calcd. for $C_{14}H_{22}Cl_4N_2$: C, 46.66; H, 6.12; Cl, 39.45; N, 7.78. Found: C, 46.52; H, 6.26; Cl, 39.51; N, 7.85.

2-(3-Aminopropyl)isoindoline.—2-Cyanoethylphthalimide (9) (15.0 Gm. 0.087 mole) was placed in a Soxhlet thimble and extracted into a slurry of 10.6 Gm. of lithium aluminum hydride in 200 ml. of anhydrous ether. After the reaction was completed, the reaction mixture was cooled to 5°, decomposed first with absolute alcohol, and finally with sufficient water to precipitate the aluminum oxide. The suspension was filtered and the clear filtrate was dried over anhydrous sodium sulfate. The mixture was filtered and the solvent removed by distillation. The resulting oil was distilled under vacuum. The fraction distilling at 94–96°/0.6 mm. was collected. It weighed 9.8 Gm. (60%).

Anal.—Calcd. for $C_{11}H_{16}N_2$: C, 74.95; H, 9.15; N, 15.90. Found: C, 74.82; H, 9.34; N, 15.92.

The pure oil rapidly absorbed carbon dioxide from the air to form a solid carbonate. The free base was regenerated upon the addition of strong alkali.

N-[3-(2-Isoindolinyl)propyl]-beta-alanine Amide Dihydrochloride.—A solution of 1.8 Gm. (0.01 mole) acrylamide in 20 ml. of absolute ethanol was slowly added to a stirred solution of 2.1 Gm. (0.02 mole) of 2-(3-aminopropyl)isoindoline in 10 ml. of absolute ethanol. The mixture was allowed to stand for 1 week. After removal of the solvent in a flash evaporator, the dark residue was washed with anhydrous ether and then dissolved in absolute alcohol. The hydrochloride was precipitated by the addition of anhydrous hydrogen chloride. The resulting precipitate was recrystallized from a mixture of equal parts of isopropanol and 95% alcohol. The recrystallization gave 2.7 Gm. (85%) of a white crystalline precipitate that melted at 173–174°.

Anal.—Calcd. for $C_{14}H_{23}Cl_2N_3O$: C, 52.50; H, 7.24; Cl, 22.14; N, 13.13. Found: C, 52.43; H, 6.97; Cl, 22.31; N, 12.98.

N-[3-(2-Isoindolinyl)propyl]-beta-alanine Ethyl Ester.—A solution of 5.7 Gm. (0.057 mole) of ethyl acrylate in 10 ml. of absolute alcohol was added dropwise, with stirring, to a cooled solution of 10.0 Gm. (0.057 mole) of 2-(3-aminopropyl)isoindoline in 20 ml. of absolute alcohol. The mixture was allowed to stand at room temperature for 4 days, at which time the solvent was removed on a steam bath under *vacuum*. The residue distilled and a fraction weighing 14.2 Gm. (90%) and distilling at 156–158°/0.6 mm. was collected.

Anal.—Calcd. for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.15. Found: C, 69.28; H, 8.52; N, 10.11.

1-[3-(2-Isoindolinyl)propyl]dihydrouracil.—To a stirred solution of 8.8 Gm. (0.032 mole) of N-[3-(2-isoindolinyl)propyl]-beta-alanine ethyl ester in a mixture of 3 ml. of hydrochloric acid and 10 ml. of water was added, dropwise, a solution of 3.4 Gm. (0.042 mole) of potassium cyanate in 10 ml. of water. The resulting solution was stirred for 1 hour and then allowed to stand overnight at room temperature. During this time a second layer formed. The upper layer was separated and treated with sufficient alcohol to precipitate the potassium cyanate present completely. After filtration of the solid, the filtrate was evaporated to dryness. A solid remained which, after recrystallization from absolute alcohol, gave 2.2 Gm. (25%) of a white crystalline solid melting at 184–185°.

Anal.—Calcd. for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.00; N, 15.38. Found: C, 65.63; H, 7.29; N, 15.38.

N-Phenyl-3-nitrophthalimide.—To 3-nitrophthalic anhydride (10) (66.0 Gm., 0.45 mole) was added, dropwise, 42.0 Gm. (0.45 mole) of redistilled aniline. After the addition was completed and the reaction had subsided, the reaction mixture was heated at 210° for 20 minutes. The resulting orange liquid solidified on cooling and was recrystallized from a mixture of equal parts of acetone and ethanol. It

yielded a yellow crystalline solid which melted at 136–138°. The yield was 107.0 Gm. (82%).

Anal.—Calcd. for $C_{14}H_8N_2O_4$: C, 62.68; H, 3.01; N, 10.52. Found: C, 62.43; H, 2.89; N, 10.32.

N-Phenyl-3-aminophthalimide.—N-Phenyl-3-nitrophthalimide (10.0 Gm., 0.037 mole) dissolved in 100 ml. of equal parts tetrahydrofuran and ethanol, was reduced over Raney nickel catalyst in a Parr hydrogenator at 30 pounds of hydrogen pressure. After approximately 8 hours of shaking, the theoretical quantity of hydrogen had been absorbed. The solvent was then removed on a flash evaporator and the solid residue was recrystallized from benzene to yield 7.5 Gm. (85%) of a white crystalline solid. It melted at 185–187°.

Anal.—Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.63; H, 4.02; N, 11.88.

2-Phenyl-4-aminoisoindoline.—A solution of 13.0 Gm. (0.054 mole) of N-phenyl-3-aminophthalimide in 100 ml. of tetrahydrofuran was added, dropwise, to a suspension of 6.2 Gm. of lithium aluminum hydride in 75 ml. of tetrahydrofuran. The addition required 45 minutes. The reaction mixture was then refluxed for an additional 10 minutes, cooled in an ice bath, and the excess lithium aluminum hydride decomposed with absolute alcohol. The alumina was precipitated by the careful addition of water and the reaction mixture was filtered. The filtrate was dried over anhydrous sodium sulfate. After removal of the solvent, a greenish solid remained. After recrystallization from ethanol it weighed 10.0 Gm. (87%) and melted at 123–124°.

Anal.—Calcd. for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71; N, 13.33. Found: C, 79.72; H, 6.83; N, 13.55.

N^1-[4-(2-Phenylisoindolinyl)]-N^4-acetylsulfanilamide.—To a refluxing solution of 2.1 Gm. (0.010 mole) of 2-phenyl-4-aminoisoindoline and 0.8 Gm. (0.010 mole) of pyridine in 30 ml. of benzene was added, dropwise, a solution of 2.6 Gm. (0.011 mole) of 4-acetamidobenzenesulfonyl chloride in 20 ml. of equal parts benzene and acetone. After the addition was completed, the resulting solution was refluxed for 10 minutes. Upon cooling, an oil settled to the bottom of the flask. The supernatant liquid was decanted and the oil was washed with ether and finally with cold water. Upon standing it solidified and was recrystallized from 50% isopropanol to give 3.3 Gm. (81%) of a white crystalline solid. The solid melted at 230–231°.

Anal.—Calcd. for $C_{22}H_{21}N_3O_3S$: C, 64.84; H, 5.19; N, 10.31; S, 7.86. Found: C, 64.78; H, 5.55; N, 10.41; S, 7.51.

N^1-[4-(2-Phenylisoindolinyl)]sulfanilamide.—N^1-[4-(2-Phenylisoindolinyl)]-N^4-acetylsulfanilamide (2.8 Gm., 0.007 mole) was refluxed for 1 hour with a solution of 2 ml. of hydrochloric acid in 4 ml. of water. The reaction mixture was then neutralized with sodium carbonate and the precipitated product collected on a Buchner funnel. After recrystallization from isopropanol to which a few drops of acetone was added, 1.8 Gm. (69%) of a white crystalline solid was obtained. It melted at 234–236°.

Anal.—Calcd. for $C_{20}H_{19}N_3O_2S$: C, 65.73; H, 5.25; N, 11.49; S, 8.77. Found: C, 65.50; H, 5.51; N, 11.22; S, 8.68.

2-Methylisoindoline.—2-Methylisoindoline was prepared by the lithium aluminum hydride reduction of N-methylphthalimide, following the procedure employed for the preparation of 2-(2-hydroxyethyl)isoindoline. It distilled at 85–86°/15 mm. [lit. (11) b.p. 81–82°/13 mm.].

2-Ethylisoindoline.—The compound was prepared by the lithium aluminum hydride reduction of N-acetylphthalimide, following the procedure of Rabjohn, Drumm, and Elliott (12). A fraction distilling at 217–220° was collected [lit. (12) b.p. 219–220°].

2-Phenylisoindoline.—N-Phenylphthalimide was reduced with lithium aluminum hydride as described by Wittig, Closs, and Mindermann. It melted at 168–169° [lit. (13) b.p. 169–170°].

SUMMARY

A series of compounds containing the isoindoline ring system, which are analogs of biologically active compounds, were prepared and screened for pharmacological activity. Only the amide of N-[3-(2-isoindolinyl)propyl]-beta-alanine showed appreciable biological activity. This compound increased the contractions of the isolated guinea pig uterus.

The carbon-hydrogen absorption bands occurring in 2700–3200 $cm.^{-1}$ region of their infrared spectra were examined and related to their molecular structure. The absorption bands occurring from 3025 to 3050 were the result of absorption of carbon-hydrogen bonds in the aromatic ring. Those occurring in the 2940–2975 region were the results of absorption of carbon-hydrogen bonds in the alkyl chain attached to the heterocyclic nitrogen atom. The band occurring at 2750 to 2780 was caused by absorption of the methylene group in the heterocyclic ring.

REFERENCES

(1) Plummer, A. J., Trapold, J. H., Schneider, J. A., Maxwell, R. A., and Earl, A. E., *J. Pharmacol. Exptl. Therap.*, **115**, 172(1955).
(2) Rice, L. M., Grogan, C. H., and Reid, E. E., *J. Am. Chem. Soc.*, **77**, 616(1955).
(3) Gearien, J. E., and Liska, K. J., *ibid.*, **76**, 3554 (1954).
(4) Arnold, A. T., "Organic Syntheses," Vol. **32**, John Wiley & Sons, Inc., New York, N. Y., 1952, p. 19.
(5) von Braun, J., Braunsdorf, O., and Rath, K., *Ber.*, **55**, 1677(1922).
(6) Nikerson, M., and Gump, W. S., *J. Pharmacol. Exptl. Therap.*, **97**, 25(1949).
(7) Stolle, R., and Wolf, F., *Ber.*, **46**, 2249(1913).
(8) Buu-Hoï, N., *Ann.*, **556**, 1(1944).
(9) Buc, S. R., *J. Am. Chem. Soc.*, **69**, 254(1947).
(10) Lawrence, W. S., *ibid.*, **42**, 1872(1920).
(11) von Braun, N., and Kohler, Z., *Ber.*, **51**, 103(1918).
(12) Rabjohn, N., Drumm, M. F., and Elliott, R. L., *J. Am. Chem. Soc.*, **78**, 1634(1956).
(13) Wittig, G., Closs, G., and Mindermann, F., *Ann.*, **594**, 89(1955).