Synthesis of 6-Substituted Nicotinic Acid Derivatives as Analogs of Ergot Alkaloids[1a,b]

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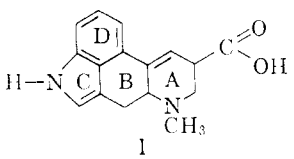
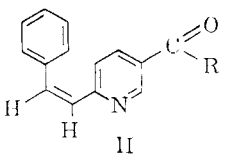
A number of derivatives of 6-phenethylnicotinic acid, *trans*-6-styrylnicotinic acid, *cis*-6-styrylnicotinic acid, 6-phenethynylnicotinic acid, and the three isomeric 6-aminophenethylnicotinic acids were prepared and screened for pharmacological activity. Several of these compounds abolished ergonovine-induced spasms in isolated uterine muscle.

Structural resemblances of derivatives of 6-phenethylnicotinic acid, *trans*-6-styrylnicotinic acid, *cis*-6-styrylnicotinic acid, and 6-phenethynylnicotinic acid to the naturally occurring ergot alkaloids prompted their synthesis and biological evaluation. These derivatives, containing rings A and D of the lysergic acid molecule (I), a portion of ring C, and a carboxamide group, might be considered to be analogs of ergonovine.



I

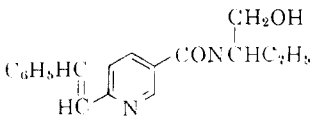


II

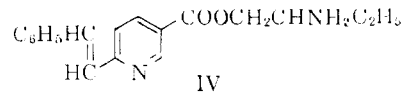
They differ from each other not only in the degree of unsaturation in the aliphatic carbon to carbon bond but in the spatial relationship of the phenyl group to the heterocyclic ring. It would be expected that compounds of the *cis* styryl series (II) would most closely approximate the spatial configuration found in lysergic acid, while the phenyl group in the *trans*-6-styrylnicotinic acid and 6-phenethynylnicotinic acid derivatives would possess markedly different spatial relationships to the heterocyclic ring. In the phenethyl series it might be assumed that because of free rotation of the carbon to carbon bond of the ethylene group, the two aromatic rings can assume the same spatial configuration found in the lysergic acid molecule; however, steric interaction between the two rings would probably prevent this from becoming their preferred configuration.

Ethyl *trans*-6-styrylnicotinate was prepared by the condensation of benzaldehyde with ethyl 6-methylnicotinate and on hydrolysis yielded the previously reported 6-styrylnicotinic acid.[3] Attempts to prepare *trans*-6-styrylnicotinic acid by the condensation of benzaldehyde and 6-methylnicotinic acid following the directions of Plieniger[3] failed to yield this compound.

Ethyl *trans*-6-styrylnicotinate, when treated with ammonia, methylamine, and pyrrolidine, yielded the expected amides (Table I). These amines, however, failed to add to the double bond. Treatment of ethyl *trans*-6-styrylnicotinate with hydrazine hydrate gave the hydrazide. When the ester was boiled with an excess of 2-aminobutanol, a 75% yield of N-2-(1-hydroxybutyl)-*trans*-6-styrylnicotinamide (III) was isolated. Since it was possible that the 2-aminobutyl ester of *trans*-6-styrylnicotinic acid (IV) might have resulted



III



IV

from this reaction, the infrared spectrum of the product was examined. The presence of a strong absorption band at 1641 cm.$^{-1}$ indicated that the product was the amide, since absorption in this area is usually attributed to the C=O stretching of a secondary amide.[4] Furthermore, the spectra showed a band at 1543 cm.$^{-1}$, which can be attributed to N–H deformation of a secondary amide.[4]

Reaction of ethyl *trans*-6-styrylnicotinate with morpholine failed to yield the desired amide. This compound was finally prepared by the reaction of *trans*-6-styrylnicotinyl chloride with morpholine.

The amide, N-methylamide, pyrrolidide, morpholide, N-2-(1-hydroxybutyl)amide, and hydrazide of 6-phenethylnicotinic acid were prepared by low pressure catalytic hydrogenation of the corresponding derivatives of *trans*-6-styrylnicotinic acid (Table II).

6-Phenethynylnicotinic acid was synthesized by the dehydrohalogenation of ethyl 6-(α,β-dibromophenethyl)nicotinate. Elemental analysis and a strong absorption band at 2215 cm.$^{-1}$ in the infrared spectrum indicated that the material isolated was actually 6-phenethynylnicotinic acid.[4] The dibromo product resulted from the addition of bromine to a chloroform solution of ethyl *trans*-6-styrylnicotinate. Attempts to prepare the acid chloride of 6-phenethynylnicotinic acid were unsuccessful. Consequently, the amides of this compound were prepared from the mixed anhydride resulting from the reaction of 6-phenethynylnicotinic acid and ethyl chloroformate. When ammonia, methylamine, or pyrrolidine was added to the mixed anhydride, the corresponding amides were obtained in yields of over 50%. However, only a 25% yield could be obtained when the mixed anhydride was allowed to react with morpholine (Table III).

Catalytic hydrogenation of 6-phenethynylnicotinic acid yielded *cis*-6-styrylnicotinic acid. The amide,

(1) (a) A portion of this paper was presented at the Frederick F. Blicke Symposium of the Division of Medicinal Chemistry at the 138th National Meeting of the American Chemical Society, New York, N. Y., September 1960; (b) This paper comprises a portion of a thesis presented by Jacob Lehrfeld in partial fulfillment of the requirements for the Ph.D. degree at the University of Illinois.

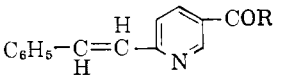
(2) Fellow, American Foundation for Pharmaceutical Education.

(3) H. Plieniger, *Ber.*, **87**, 92 (1954).

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, New York, N. Y., 1958, pp. 205, 58, and 99.

Table I

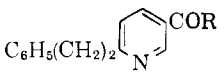
Hydrazide and Amides of *trans*-6-Styrylnicotinic Acid



R	Solvent	Time, hr.	M.p., °C.	% yield	% carbon Calcd.	% carbon Found	% hydrogen Calcd.	% hydrogen Found	% nitrogen Calcd.	% nitrogen Found
$NHNH_2$	Ethanol	2	194–195	59	70.28	70.45	5.48	5.55	17.56	17.50
NH_2	Ethanol	10	234–236	41	74.98	74.80	5.40	5.21	12.49	12.68
$NHCH_3$	*p*-Dioxane	288	177–178	68	75.60	75.67	5.92	5.92	11.76	11.80
C_4H_8N	Benzene	84	142–144	39	77.67	77.64	6.52	6.45	10.07	10.13
$CH_2OHCHNHCH_2CH_3$		20	146–148	76	72.94	72.87	6.80	6.76	9.46	9.37

Table II

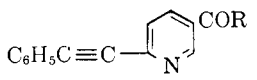
Derivatives of 6-Phenethynylnicotinic Acid



R	M.p., °C.	% yield	% carbon Calcd.	% carbon Found	% hydrogen Calcd.	% hydrogen Found	% nitrogen Calcd.	% nitrogen Found
NH_2	184–186	47	74.31	73.91	6.25	6.35	12.38	12.45
$NHNH_2$	132–134	96	69.69	69.72	6.27	6.39	17.42	17.59
$NHCH_3$	118–120	70	74.97	74.73	6.71	6.68	11.66	11.50
Pyrrolidino	86–88	72	77.07	77.45	7.19	7.08	10.04	9.75
Morpholino	63–65	33	72.94	72.57	6.80	6.83	9.46	9.55
$CH_3CH_2CHNHCH_2OH$	128–130	88	72.45	72.47	7.43	7.47	9.39	9.36

Table III

Amides of 6-Phenethynylnicotinic Acid



R	M.p., °C.	% yield	% carbon Calcd.	% carbon Found	% hydrogen Calcd.	% hydrogen Found	% nitrogen Calcd.	% nitrogen Found
NH_2	253–255	81	75.66	75.55	4.54	4.53	12.61	12.45
CH_3NH	162–164	51	76.25	76.01	5.12	5.31	11.66	11.75
Pyrrolidino	128–130	55	78.23	77.90	5.84	5.92	10.14	9.98
Morpholino	122–123	26	73.95	74.09	5.52	5.63	9.38	9.67

N-methylamide, and morpholide of this product were most conveniently prepared by a similar reduction of the corresponding derivative of 6-phenethynylnicotinic acid (Table IV). Maximum yields were obtained when a palladium catalyst deactivated by lead acetate and quinoline was employed.

Unfortunately, salts of most of the compounds synthesized were readily hydrolyzed by water. Only two of the compounds were sufficiently soluble to permit testing for oxytocic activity. Therefore, it seemed desirable to prepare the three possible ethyl 6-(aminophenethyl)nicotinates and to submit them for pharmacological testing. They were prepared by the catalytic reduction of ethyl *o*-, *m*-, and *p*-nitrostyrylnicotinates (Table VI). The nitrostyrylnicotinic acid esters were obtained by the condensation of the properly substituted nitrobenzaldehyde with ethyl 6-methylnicotinate (Table V).

The assignment of structure to the *cis*- and *trans*-styrylnicotinic acids was based upon analogy and physical measurements. For example, Katsumoto has shown that the *trans* isomer usually results when benzaldehyde is condensed with 2-picoline.[5]

Further evidence for the assignment of structure was obtained from the ultraviolet spectra of the two 6-styrylnicotinic acids which were obtained by the hydrolysis of the reported derivatives. The compound assigned the *trans* structure had a λ_{max} at 323 mμ and an ϵ_{max} of 32,520, while the compound assigned the *cis* structure had a λ_{max} at 509 mμ and an ϵ_{max} of 12,960. Our assignment of structure followed the observation of Gilliam and Stern[6] that the more elongated isomer (in this case the *trans* isomer) absorbs with greater intensity at a somewhat longer wave length than the corresponding *cis* isomer. Similar observations have been reported by Williams,[7] Curtin and Koehl,[8] and Katsumoto.[5] Furthermore, the infrared spectra of the *trans* isomer showed a strong absorption band at 975 cm.$^{-1}$. A band in this region is usually assigned to the C–H deformation of a *trans* double bond.[4] No such band was present in the spectra of the *cis* isomer.

Biological Activity.—The compounds whose synthesis has been described were screened for pharmacological activity. No appreciable activity was detected. In addition, however, the *o*-, *m*-, and *p*- isomers of ethyl 6-aminophenethylnicotinate, N-2-(1-hydroxybutyl) 6-phenethylnicotinamide, and 6-phenethylnicotinylpyrolidide were examined for smooth muscle activity on both uterus and ileum muscle of the rat and guinea

(5) T. Katsumoto, *Bull. Chem. Soc. Japan*, **33**, 242 (1960).

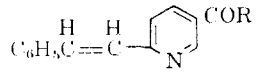
(6) A. E. Gilliam and E. S. Stern, "Electronic Absorption Spectroscopy," 2nd Ed., 1957, p. 267.

(7) J. L. R. Williams, *J. Am. Chem. Soc.*, **84**, 1323 (1962); J. L. R. Williams, S. K. Webster, and J. A. VanAllan, *J. Org. Chem.*, **26**, 4893 (1961).

(8) D. Y. Curtin and W. J. Koehl, Jr., *ibid.*, **84**, 1967 (1962).

TABLE IV

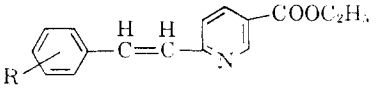
AMIDES OF *cis*-6-STYRYLNICOTINIC ACID



R	M.p., °C.	% yield	% carbon		% hydrogen		% nitrogen	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
NH_2	146–148	50	75.66	75.55	4.54	4.53	12.61	12.45
CH_3NH	116–118	53	75.67	75.62	5.92	6.05	11.76	11.52
Morpholino	87–88	40	73.45	73.18	6.16	6.26	9.52	9.37

TABLE V

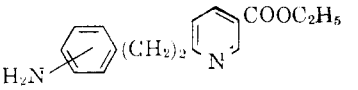
ETHYL 6-(NITROSTYRYL)NICOTINATES



R	M.p., °C.	% yield	% carbon		% hydrogen		% nitrogen	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
o-NO_2	129–131	78	64.42	64.59	4.73	4.97	9.39	9.27
m-NO_2	133–135	89	64.42	64.34	4.73	4.58	9.39	9.45
p-NO_2	186–188	73	64.42	64.46	4.73	4.85	9.39	9.44

TABLE VI

ETHYL 6-(*o*, *m* and *p*-AMINOPHENETHYL)NICOTINATES



NH_2 position	M.p., °C.	% yield	% carbon		% hydrogen		% nitrogen	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
o	72–74	79[a]						
m (HCl)	212–213	70	55.98	55.93	5.87	6.11	8.16	8.05
p	74–76	90	71.08	71.06	6.71	6.63	10.37	10.38

[a] Lit.[3] m.p. 70°.

pig. Of the compounds prepared only these five were sufficiently soluble in dilute hydrochloric acid to permit such testing. Responses were compared against those elicited by an ergonovine maleate standard. The Magnus method[9] for recording *in vitro* contractile responses of isolated tissues was employed and the organ segments were maintained in a bath of Tyrode's medium.[10]

Rat and guinea pig tissues exhibited virtually identical reactions to the test compounds, thus this report on biological activity makes no distinction between species' responses. Doses are expressed as milligrams of drug contained in 100 ml. of bath medium and represent the concentration to which the excised tissue was exposed. Single uterine horns exposed to 0.1–0.2 mg./100 ml. of ergonovine maleate exhibited characteristic increases in rhythmic clonic contractility gradually developing into a tonic spasm that was relieved only after a lapse of about 15 min. following repeated washing of the tissue. These concentrations elicited no effect upon excised gut segments and thus the standard drug exhibits a demonstrable selectivity for uterine smooth muscle.

The substances to be tested were dissolved in water acidified with hydrochloric acid to pH 3. This solvent, when administered alone in volumes equivalent to those subsequently administered along with a test drug, produced no observable effect on the tissues. The addition of this solvent did not influence the pH of the buffered Tyrode's medium. The results of these experiments may be summarized as follows:

(a).—Ethyl 6-(*o*-aminophenethyl)nicotinate, in concentrations of 0.1–5 mg./100 ml., elicited no response from normal uterus or gut. In concentrations of 5 mg./100 ml., however, this substance abolished the uterine spasms previously induced by 0.2 mg./100 ml. of ergonovine maleate.

(b).—Ethyl 6-(*p*-aminophenethyl)nicotinate, in concentrations of 0.1–5 mg./100, ml. produced no effect upon uterus but caused a progressively increasing degree of relaxation in gut in doses of 1–5 mg./100 ml. In concentrations of 5 mg./100 ml., the compound failed to influence the ergonovine-induced uterine spasms.

(c).—N-2-(1-Hydroxybutyl)-6-phenethylnicotinate was similar in effect to ethyl 6-(*o*-aminophenethyl-nicotinate) in that it exerted no influence upon normal uteri when exposed to concentrations up to 10 mg./100 ml.; however, at 1.25 mg./100 ml. and higher, the gut was increasingly depressed. This compound failed to influence ergonovine-induced uterine spasms. While the structure of N-2-(1-hydroxybutyl)nicotinate was established from its infrared spectra, it seemed possible that during testing an acyl rearrangement might have occurred with the result that the compound tested was actually the 2-aminobutyl ester of 6-phenethylnicotinic acid. In order to establish the structure of the compound subjected to biological testing a sample of N-[1-hydroxybutyl]-6-phenethylnicotinate was dissolved in 0.05 *N* hydrochloric acid and heated on a steam bath

(9) R. Magnus, *J. Physiol.*, **102**, 123 (1904).

(10) T. A. Solmon, "A Manuel of Pharmacology," 8th Ed., W. B. Saunders Co., Philadelphia, Pa., 1957, p. 1005.

for 3 min. The solvent was lyophilized and a Nujol mull was prepared from the residue. The spectra contained a band of 1640 cm.$^{-1}$ characteristic of the amide band.

Ethyl 6-(*m*-aminophenethyl)nicotinate, like N-2-(hydroxybutyl)nicotinate and ethyl 6-(*p*-aminophenethyl)nicotinate had no effect on normal uterine activity when given in doses up to 4 mg./100 ml. and failed to influence the uterine spasms induced by ergonovine. Gut depression, however, was evident at doses of 5 and 10 mg./100 ml.

(**d**).—6-Phenethylnicotinyl pyrrolidide exhibited a mild increase in uterine activity at 5 and 10 mg./100 ml., but as the concentration was further increased to 20 mg./100 ml. this response gradually reversed itself. The higher doses produced an overriding depression. The gut responded with a transient increase in contractivity lasting approximately 1 min. This was observed following administration of 2–4 mg./100 ml.

Experimental[11]

Ethyl *trans*-6-Styrylnicotinate.—A solution of 16.5 g. (0.10 mole) of ethyl 6-methylnicotinate,[12] 32 g. (0.30 mole) of freshly distilled benzaldehyde, and 30 ml. of acetic anhydride in 80 ml. of xylene was heated for 72 hr. at 150°. The dark brown solution was then steam distilled. The oily residue which remained after removal of the volatile components solidified upon cooling and was removed by filtration. The solid was dissolved in 250 ml. of benzene, and the resulting solution was washed with cold 0.5% potassium hydroxide until the wash water remained basic. It was then dried over anhydrous sodium sulfate and chromatographed on a 12 × 25.4 cm. alumina (Alcoa activated alumina, grade F-20) column. The product was eluted from the column with 400 ml. of benzene. After evaporation of the benzene a tan solid remained. Recrystallization from 95% ethanol gave 18.0 g. (71%) of a solid melting at 98–100°.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.86; H, 5.97; N, 5.53. Found: C, 75.77; H, 5.65; N, 5.57.

Amides and Hydrazide of *trans*-6-Styrylnicotinic Acid.—Ethyl *trans*-6-styrylnicotinate was dissolved in the proper solvent and treated with the desired amine (Table I). All reactions were carried out at reflux temperature except for the reaction with methylamine which was performed at room temperature and the reaction with 2-aminobutanol in which the reactants were heated to 120°. The hydrazide and unsubstituted amide were recrystallized from ethanol and the pyrrolidide from ethanol by dilution with water. The N-methylamide and the 2-butanolamide were purified by recrystallization from a solution of equal parts water and dioxane.

***trans*-6-Styrylnicotinylmorpholide.**—A mixture of 10 g. (0.04 mole) of *trans*-6-styrylnicotinic acid (m.p. 223–225°),[3] prepared by the alkaline hydrolysis of ethyl *trans*-6-nicotinate, and 100 ml. of thionyl chloride was allowed to react at room temperature for 18 hr., after which the thionyl chloride was removed under reduced pressure. To the cooled residue was added a cold solution of 40 ml. of morpholine and 115 ml. of 5% potassium hydroxide solution, and the mixture was shaken at room temperature for 45 min. The resulting precipitate was filtered and dissolved in benzene. The benzene layer was separated, filtered, and evaporated to dryness. The residue was recrystallized twice from ethanol–water to give 5.55 g. (47%) of a white solid melting at 156–158°.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.29; H, 6.34; N, 9.43.

Ethyl 6-(*o*-, *m*-, and *p*-Nitrostyryl)nicotinates.—These compounds were prepared by the condensation of ethyl 6-methylnicotinate with *o*-, *m*-, and *p*-nitrobenzaldehydes. For example, the following is a procedure employed for the preparation of ethyl 6-(*o*-nitrostyryl)nicotinate. A mixture of 8.0 g. (0.053 mole) of *o*-nitrobenzaldehyde, 8.75 g. (0.053 mole) of ethyl 6-methylnicotinate, 16 ml. of acetic anhydride, and 90 ml. of xylene was heated at 150° for 72 hr. The solution was cooled and the bright yellow precipitate which formed was filtered and washed with a cold solution of 4 parts of xylene to 1 part of ligroin. After drying, the yellow solid weighed 8.9 g. Evaporation of the filtrate yielded a dark brown solid which was dissolved in 200 ml. of benzene and chromatographed on a 12 × 100 mm. alumina (Alcoa activated alumina grade F-20) column using 300 ml. of benzene as the eluting solvent. The benzene was evaporated to about 0.1 its original volume and then a 5-fold excess of ligroin (30–60°) was added. An additional 3.5 g. of product was obtained to bring the total yield to 12.4 g. (79%). The product was dissolved in benzene and ligroin was added until the solution became cloudy. Upon cooling, a yellow solid melting at 129–131° was obtained.

While the optimum yield was obtained in the case of ethyl 6-(*m*-nitrostyryl)nicotinate when the reactant was refluxed for 72 hr., the optimum yield in the case of ethyl 6-(*p*-nitrostyryl)-nicotinate was obtained after only 24 hr. Both of these products were purified by recrystallization from ethanol.

Derivatives of 6-Phenethylnicotinic Acid.—This series of compounds was prepared by the catalytic hydrogenation of the corresponding derivatives of *trans*-6-styrylnicotinic acid. The preparation of ethyl 6-phenethylnicotinate will serve as an example of the procedure. A solution of 11.8 g. (0.046 mole) of ethyl *trans*-6-styrylnicotinate in 200 ml. of absolute ethanol was hydrogenated at a pressure of 3 atm. using 5 g. of wet Raney nickel catalyst (W-5) until the absorption of hydrogen ceased. This required about 3 hr. The catalyst was removed by filtration and the filtrate distilled. The fraction distilling at 146–150° (0.2 mm.) was collected. It weighed 9.4 g. (81%). The hydrobromide, formed by treatment of an ether solution of this oil with anhydrous hydrogen bromide, melted at 133–135° after recrystallization from absolute ethanol by the addition of anhydrous ether and cooling.

Anal. Calcd. for $C_{16}H_{18}BrNO_2$: C, 57.14; H, 5.38; N, 4.16. Found: C, 57.44; H, 5.56; N, 3.84.

Ethyl 6-(*o*-, *m*-, and *p*-Aminophenethyl)nicotinates.—Hydrogenation of the isomeric ethyl 6-(*o*-, *m*-, and *p*-nitrophenethyl)-nicotinates following the procedure outlined for the ethyl 6-phenethylnicotinate yielded the ethyl esters of 6-(*o*-, *m*-, and *p*-aminophenethyl)nicotinate. The *o*-isomer was recrystallized from a benzene–ligroin (60–90°) solution, the *m*- isomer from absolute alcohol by the addition of ether, while the *p*- isomer was recrystallized from water.

Ethyl 6-(α,β-Dibromophenethyl)nicotinate.—A solution of 16.0 g. (0.1 mole) of bromine in 75 ml. of chloroform was added to 33.4 g. (0.093 mole) of ethyl *trans*-6-styrylnicotinate which had been dissolved in 200 ml. of chloroform. The solution was allowed to stand at room temperature for 20 hr. After removal of the chloroform and excess bromine, the residue was triturated with 100 ml. of 95% ethanol and filtered to give 32.6 g. (85%) of a product decomposing at 161–163°. This product was used without further purification. For analysis a sample was recrystallized from 95% ethanol.

Anal. Calcd. for $C_{16}H_{15}Br_2NO_2$: C, 46.63; H, 3.67; Br, 38.78; N, 3.40. Found: C, 47.04; H, 3.59; Br, 38.45; N, 3.17.

6-Phenethynylnicotinic Acid.—To a stirred suspension of 24.85 g. (0.065 mole) of ethyl 6-(α,β-dibromophenethyl)nicotinate in 450 ml. of 2-propanol, which was heated to boiling, was added 24 g. of potassium hydroxide pellets. After refluxing for 21 hr. the solvent was removed by distillation and the residue was dissolved in 800 ml. of ice–water. The solution was acidified to pH 3 with 1:1 hydrochloric acid. The resulting precipitate was filtered and then washed with water. After recrystallization from a dioxane–water solution 12.5 g. (92%) of product decomposing at 234–237° was obtained.

Anal. Calcd. for $C_{14}H_9NO_2$: C, 75.32; H, 4.06; N, 6.28. Found: C, 75.41; H, 3.96; N, 6.15.

Amides of 6-Phenethynylnicotinic Acid.—These compounds were synthesized by the reaction of the appropriate amine with the mixed anhydride formed from the reaction of 6-phenethynylnicotinic acid with ethyl chloroformate. The following synthesis of 6-phenethynylnicotinamide serves as an example of the procedure employed.

A stirred solution of 2.23 g. (0.01 mole) of 6-phenethynylnicotinic acid and 1.01 g. (0.01 mole) of triethylamine was main-

(11) All melting points are corrected and were determined by the capillary tube method. Microcarbon-hydrogen analyses were performed by Weiler-Strauss Microanalytical Laboratory, Oxford, England. Nitrogen analyses were carried out in this laboratory on a Coleman nitrogen analyzer.

(12) A. Platter, W. Keller, and A. Boller, *Helv. Chim. Acta*, **37**, 1379 (1954).

tained at 12–16° while 1.08 g. (0.01 mole) of ethyl chloroformate was added dropwise. After the addition was completed, the stirred suspension was kept at the same temperature for an additional 15 min. and then a stream of ammonia gas was passed through the solution for 3 min. The suspension was allowed to warm to room temperature and remained there for 4 hr., after which time the solvent was removed by evaporation. The resulting solid residue was recrystallized from hot ethanol by the addition of water until the solution became opalescent and then cooled.

Synthesis of *cis*-6-Styrylnicotinic Acid and Derivatives.—To 0.50 g. (0.002 mole) of 6-phenethynylnicotinic acid suspended in 50 ml. of methanol was added 1 drop of quinoline and 0.1 g. of deactivated 10% palladium-on-charcoal catalyst.[8] The mixture was stirred in an atmosphere of hydrogen until 0.002 mole was taken up. The catalyst was then removed by filtration and the filtrate evaporated *in vacuo*. The residue was recrystallized from hot methanol by the addition of water and cooling to give 0.35 g. (69%) of a crystalline solid which melted at 148–150°. Upon cooling, the liquid in the melting point tube resolidified and remelted at 222–225°, which was the melting point of the *trans* isomer.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.67; H, 5.17; N, 6.24.

Similar hydrogenation of the previously prepared amides of 6-phenethynylnicotinic acid yielded the corresponding amides of *cis*-6-styrylnicotinic acid (see Table IV).

Conclusions

Of those compounds tested, only 6-phenethylnicotinyl pyrrolidide exhibited a stimulant effect upon the uterus; but in order to produce such action, a dose was required that was (on a weight basis) approximately 50 times the dose of ergonovine needed to provoke a vigorous response. It did not display the smooth muscle selectivity characteristic of ergonovine, for at doses somewhat below those required for uterine stimulation, it increased gut motility. Ethyl 6-(*o*-aminophenethyl)-nicotinate, which in itself produces no effects on either uterus or gut, consistently abolished the uterine contractions previously initiated by ergonovine. The nature and specificity of this antagonism remains to be determined. The other compounds affected neither normal uterus nor uterus previously stimulated by ergonovine. These last three compounds all depressed gut activity, however. Under the conditions described, none of the substances examined evoked responses that compare favorably with the uterotropic action of ergonovine.

4-Alkyl- (or Aralkyl) 1-Aryl-2-piperazinones

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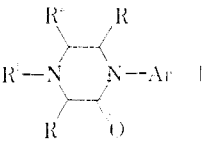
A number of 4-alkyl- (or aralkyl) 1-aryl-2-piperazinones were prepared as potential analgesics. These compounds were prepared either by catalytic debenzylation or pyrolytic debenzylation (or demethylation) of 1,1-dialkyl- (or 1,1-diaralkyl) 3-oxo-4-arylpiperazinium halides.

In the course of our search for new nonnarcotic type analgesics, we have synthesized a group of 4-alkyl- (or aralkyl) 1-aryl-2-piperazinones (I). 1,4-Diaryl-,[1] 1,4-diaralkyl-, and 1,4-dialkyl-2-piperazinones[2] having identical substituents at the 1 and 4 positions, 3-substituted 2-piperazinones,[3] and 3,3-disubstituted-2-piperazinones[4] have been reported. 1-Cyclohexyl-2-piperazinone[5] and 4-alkyl-3-oxo-1-piperazinylalkylphenothiazines[6] have been described. However, no 4-alkyl- (or aralkyl) 1-aryl-2-piperazinones have been recorded in the literature except for six compounds disclosed in our patent.[7] Recently very similar compounds, 1-(2-phenethyl)-4-(lower alkyl)-2-piperazinones,[8] were reported.

The following compounds have been prepared for analgetic screening.



Ar = C_6H_5, 4-$CH_3OC_6H_4$, 3-$CH_3O)C_6H_4$, 4-ClC_6H_4; R = H, CH_3, C_6H_5; R^1 = H, CH_3, $C_6H_5CH_2$, $C_6H_5CH_2CH_2$, $C_6H_5CH_2CH(CH_3)$, 3,4-$(CH_3O)_2C_6H_3CH_2CH(CH_3)$, $(C_2H_5)_2NCH_2CH_2$; R^2 = H, CH_3, C_6H_5; R^3 = H, CH_3

The synthesis of these compounds was carried out as follows with final conversion to the desired piperazinones *via* either catalytic hydrogenolysis or pyrolytic distillation.

The ease of cyclization to form piperazinium halides (III) from the reaction of the diamines (II) and chloroacetyl chloride, α-bromopropionyl chloride, or α-chlorophenylacetyl chloride seems to depend on steric factors. When IIa was treated with chloroacetyl chloride in benzene under Schotten–Baumann conditions, IIIa precipitated from the benzene solution on standing at room temperature. When α-bromopropionyl chloride was used, it was necessary to heat the benzene solution under reflux before cyclization took place. The same

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