

washed with petr ether, and recrystd from 2-PrOH-petr ether (bp 30–60°), mp 76–78° (lit.⁶ 82°, 78°).

A column of alumina (200 g in a 2.5 × 61 cm column) was prepared using heptane to form a slurr. It was treated with a soln of (±)-tartaric acid (3 g in 10 ml of MeOH), and the column was washed with an addl liter of heptane. A soln of the racemic carbinol (9.25 g, 0.05 mole) and (+)-tartaric acid (7.5 g, 0.05 mole) in 20 ml of MeOH was applied to the column and eluted with heptane (2 l.). The eluent was collected in 200-ml fractions. Elution was contd with *i*-PrOH (2 l.) in 200-ml fractions. Finally 1 l. of EtOH was passed through and collected in 1 portion. All the fractions were evapd under reduced pressure to give oily residues. The solids were completely sol in anhyd Et₂O indicating the presence of the alcohol as the free base. The opt activities of the different fractions indicated that the (+) isomer was eluted by heptane while the (–) isomer was eluted in *i*-PrOH. Tartaric acid was eluted by EtOH. The (+) isomer had mp 64–65°, $\alpha_{589}^{20} +17.2$ (0.154 g in 10 ml of CHCl₃). The (–) isomer had mp 60–62°, $\alpha_{589}^{26} -17.3$ (0.1209 g in 10 ml of CHCl₃).

The HCl salts of both enantiomorphs were prep'd by passing HCl gas through their Et₂O soln. (+)-Phenyl-2-pyridylcarbinol·HCl had mp 179–180°. Anal. (C₁₂H₁₂ClNO) C, H, N, Cl. (–)-Phenyl-2-pyridylcarbinol·HCl had a mp of 174–176°. Anal. (C₁₂H₁₂ClNO), C, H, N, Cl.

2-(*p*-Hydroxybenzoyl)pyridine.—A soln of 2.0 g (0.0094 mole) of 2-(*p*-methoxybenzoyl)pyridine in 20 ml of 48% HBr was heated at 140° for 4 hr. After cooling and the addn of 20 ml of H₂O, the reaction mixt was chilled to 10° and neutralized with solid K₂CO₃. The resulting ppt, after recrystn from H₂O and then cyclohexane-PhH (1:1), melted at 103–104°; yield 1.0 g (53%). Anal. (C₁₂H₉NO₂) C, H, N.

(6) A. Tschitschibabin, *Ber.*, **37**, 1371 (1904).

Central Nervous System Depressive Activity of Some Amides of Tryptamine¹

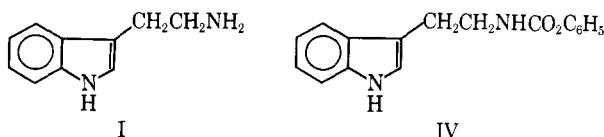
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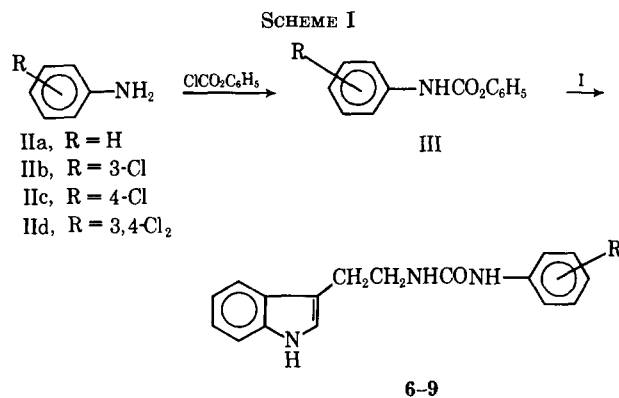
During our investigation of the inhibitory activity of a series of *N*-acetyltryptamines on hydroxyindole-*O*-methyltransferase (HIOMT),² several compounds were found to cause sedation in rats. This led us to synthesize other substituted amides, benzenesulfonamide, and ureido derivatives of tryptamine for evaluation of their CNS-depressive activity.

All the acyl and benzenesulfonyl derivatives of tryptamine (I) except **10** were prepared by treating I in



CHCl₃ or CH₂Cl₂ with the appropriate acid chloride in the presence of Et₃N (in the case of **13** pyridine was used). Compound **10** was obtained by Schotten-Baumann reaction between I and PhSO₂Cl.

The general route (Scheme I) for the synthesis of



urea derivatives **6-9** started with the reaction of phenyl chloroformate with aniline (IIa) or substituted anilines (IIb–IIId) to give *N,O*-diphenylcarbamate (IIIa) or its substituted analogs (IIIb–IIId), followed by replacement of phenoxy group of III by I forming the ureas. Table I lists the physical constants of the 4 ureas. A

TABLE I
SUBSTITUTED *N*-β-3-INDOLYLETHYL-*N'*-PHENYLUREA

Compd ^a	R	Yield, %	Recrystn solvent	Mp, °C	Formula
6	H	75	MeOH	185–187	C ₁₇ H ₁₇ N ₃ O
7	3-Cl	83	MeOH–H ₂ O	148.5–150.5	C ₁₇ H ₁₆ ClN ₃ O
8	4-Cl	82	EtOH–H ₂ O	198–200	C ₁₇ H ₁₆ ClN ₃ O
9	3,4-Cl ₂	84	50% MeOH	150–151.5	C ₁₇ H ₁₅ Cl ₂ N ₃ O

^a The corresponding starting materials, substituted phenyl phenylcarbamates, were prepared by treating aniline or substituted PhNH₂ with ClCO₂Ph, according to the procedure of D. G. Crosby and C. Neimann (*J. Amer. Chem. Soc.*, **76**, 4458 (1954); mp's: *N,O*-diphenyl carbamate, 125–127° (C₆H₆); substituted phenyl phenylcarbamates, 3-Cl, 74–76° (C₆H₆); 4-Cl, 150–152° (C₆H₆); 3,4-Cl₂, 131–133° (C₆H₆).

previous attempt to prepare the ureas by the treatment of PhNH₂ or the substituted anilines with *N*-β-3-indolylethyl phenylcarbamate (IV) in refluxing dioxane was unsuccessful. Compound IV was made from I and phenyl chloroformate in a basic medium.

Of the 13 compounds tested, five (**3**, **4**, **5**, **8**, **13**) have shown a significant effect in reducing the spontaneous motor activity of mice (Table II). The ED₅₀ values of the two most active compounds (**5**, **3**) were 19 ± 3.8 and 12 ± 3.2 mg per kg, respectively. Although **5** is also the best HIOMT inhibitor thus far found,³ no correlation can be established between the enzyme inhibitory activity and the effect on spontaneous motor activity of mice.

Experimental Section³

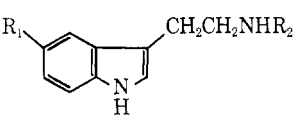
***N*-β-3-Indolylethyl-*m*-nitrobenzenesulfonamide (11).**—To a soln of 6.4 g (40 mmoles) of tryptamine (I) and 4.04 g (40 mmoles) of Et₃N in 100 ml of CH₂Cl₂ was added with cooling a soln of 8.86 g (40 mmoles) of *m*-nitrobenzenesulfonyl chloride in 25 ml of CH₂Cl₂. The mixt was stirred for 3 hr and then washed successively with H₂O (two 100-ml portions), 10% HCl (two 100-ml

(1) This work was supported in part by Grant MH-11168, U. S. Public Health Service, Bethesda, Md.

(2) (a) B. T. Ho, W. M. McIsaac, and L. W. Tansey, *J. Pharm. Sci.*, **58**, 130 (1969); (b) B. T. Ho, W. M. McIsaac, L. W. Tansey, and P. M. Kralik *ibid.*, **57**, 1998 (1968); (c) B. T. Ho, W. M. McIsaac, and L. W. Tansey, *ibid.*, **58**, 563 (1969); (d) B. T. Ho, M. B. Noel, and W. M. McIsaac, *ibid.*, **59**, 573 (1970).

(3) Melting points were taken on a Mel-Temp apparatus and are corrected. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for these elements or functions were within ±0.4% of the theoretical values. Ir spectra of all the compounds were compatible with the assigned structures.

TABLE II



No.	R ₁	R ₂	Spontaneous activity ^a		p <
			Accum counts (mean ± S.D.)	% decrease	
1 ^b	H	C ₆ H ₅ CO	531 ± 73		NS
2	H	C ₁₀ H ₇ CO	500 ± 98		NS
3 ^b	H	C ₆ H ₅ CH ₂ CO	310 ± 53	38.6	0.01
4 ^c	H	3,4-Cl ₂ C ₆ H ₃ CO	462 ± 57	16.2	0.05
5 ^c	Br	3,4-Cl ₂ C ₆ H ₃ CO	158 ± 73	64.5	0.001
6	H	C ₆ H ₅ NHCO	544 ± 45		NS
7	H	3-ClC ₆ H ₄ NHCO	443 ± 126		NS
8	H	4-ClC ₆ H ₄ NHCO	462 ± 63	15.3	0.1
9	H	3,4-Cl ₂ C ₆ H ₃ NHCO	613 ± 95		NS
10 ^b	H	C ₆ H ₅ SO ₂	488 ± 99		NS
11	H	3-NO ₂ C ₆ H ₄ SO ₂	608 ± 40		NS
12	H	3-NH ₂ C ₆ H ₄ SO ₂	648 ± 50		NS
13	H	C ₆ H ₅ CH=CHSO ₂	362 ± 129	29.0	0.1

^a See Experimental Section. ^b For synthesis, see B. T. Ho, W. M. McIsaac, L. W. Tansey, and P. M. Kralik, *J. Pharm. Sci.*, **57**, 1998 (1968). ^c For synthesis, see B. T. Ho, W. M. McIsaac, and L. W. Tansey, *ibid.*, **58**, 563 (1969).

portions), H₂O (100-ml), satd NaHCO₃ (two 100-ml portions), and again H₂O (100 ml). The CH₂Cl₂ phase was dried (Na₂SO₄) and then evapd *in vacuo* to yield 11.5 g (83%) of product, mp 102–103°. Recrystn from EtOH gave 10.2 g (74%), mp 101–102°. *Anal.* (C₁₆H₁₅N₃O₃S) C, H, N.

N-β-3-Indolyethyl-m-aminobenzenesulfonamide (12).—A suspension of 9.2 g (27 mmoles) of N-β-3-indolyethyl m-nitrobenzenesulfonamide (11) and 0.5 g of 10% Pd/C in 150 ml of EtOH was shaken with H₂ at 2–3 atm until the absorption ceased (about 1 hr). The filtered EtOH soln was evapd *in vacuo* to yield 7.9 g (94%) of product, mp 117–118°. Recrystn from EtOH gave 6.7 g (80%), mp 118–119°. *Anal.* (C₁₈H₁₇N₂O₂S) C, H, N.

N-β-3-Indolyethyl-2-naphthamide (2).—In a similar manner as described for the prepn of 11, tryptamine (I) in CHCl₃ was treated with C₁₀H₇COCl in the presence of Et₃N. After stirring at ambient temp for 15 hr, a solid product was filtered and washed first with H₂O then with Et₂O; yield, 3.8 g (80%), mp 188–191.5°. Recrystn from C₆H₅CH₃ gave 3.0 g (63%), mp 192–194°. *Anal.* (C₂₁H₁₈N₂O) C, H, N.

N-β-3-Indolyethyl-styrylsulfonamide (13).—To a chilled soln of 0.8 g (5 mmoles) of tryptamine (I) and 1.0 ml (12.4 mmoles) of pyridine in 15 ml of CHCl₃ was added slowly 1.0 g (5 mmoles) of β-styrenesulfonyl chloride. A green ppt formed instantly and changed to bright yellow in a few min. After the mixt was stirred at room temp for 15 hr, 330 mg (34%) of tryptamine·HCl was removed by filtration. The CHCl₃ filtrate was washed successively with 10-ml portions of H₂O, 2 N HCl, 2 N NaOH, and again H₂O, dried (Na₂SO₄), treated with charcoal, filtered, and then evapd *in vacuo*. The oily residue was dissolved in C₆H₆, and petr ether was added to cloudiness. Chilling of the mixt caused the sedimentation of a pale yellow solid together with a yellow oil. The oily product was sepd by decantn and dissolved in a small amount of petr ether. Crystn took place on chilling to yield 350 mg (22%) of yellow product, mp 135–140°. Addn of more petr ether and chilling gave another 310 g (20%) of less pure product. Subsequent recrystns from MeOH afforded an anal. sample, mp 147.5–149°. *Anal.* (C₁₈H₁₅N₂O₂S) C, H, N.

Phenyl N-β-Indolyethylcarbamate (IV).—To a stirred suspension of 3.2 g (20 mmoles) of tryptamine (I) in a mixt of 100 ml of Et₂O and 20 ml of H₂O was added at ice temp one-half of 3.2 g (20 mmoles) of ClCO₂C₆H₅. The remaining half of ClCO₂C₆H₅ was added dropwise simultaneously with a total of 10 ml of 2 N NaOH in such a manner that the reaction temp was maintained near 5°. After stirring for an addl 45 min at ambient temp, the org layer was sepd, washed successively with 15-ml portions of 5% HCl and H₂O, dried (Na₂SO₄), treated with charcoal, and then coned *in vacuo* to about 50 ml. Petr ether was added to the Et₂O soln to cloudiness, and chilling brought down 3.5 g (64%) of pale pink plates, mp 66–69°. Three recrystns

from Et₂O-petr ether gave an anal. sample as small, pale yellow crystals, mp 70–71.5°. *Anal.* (C₁₇H₁₆N₂O₂) C, H, N.

N-β-3-Indolyethyl-N'-4-chlorophenylurea (8).—A mixt of 1.0 g (4.05 mmoles) of phenyl N-4-chlorophenylcarbamate (IIIc), 0.57 g (4.05 mmoles) of tryptamine (I), and 30 ml of dioxane was refluxed for 2 hr. The cooled soln was poured into 50 g of ice with stirring. The white solid was collected on a filter and recrystd from 75% EtOH; yield, 1.0 g (83%) of shiny white needles, mp 196–198°. One more recrystn from 50% EtOH gave an anal. sample, mp 198–200°.

See Table II for physical constants of 6, 7, and 9 prepd by the same method.

Pharmacology. Effects on Spontaneous Motor Activity.—For each compd in Table I, 15 male Yale-Swiss mice (Texas Inbred Co., Houston, Texas) were used. The animals were divided into 5 groups of 3, and each animal was injected ip with 100 μmoles/kg of the compd in a Tween-80 and saline suspension. (For better suspension each compd was ground before mixing.) Fifteen minutes was allowed between each group injection. After the injection, each group of 3 mice was placed inside an activity cage (Metro Scientific Co.) and counted for 10 min. To allow for the initial curiosity of animals in a new environment, counts in the first 5 min were disregarded, and those in the last 5 min were considered for an actual reading. Injections and readings were timed so that the peak time of the action of the compds (30 min postinjection) fell within the 5 min of actual reading time.

The mean and standard deviation of the scores (5-min net counts) of the 5 experimental groups and those of the 5 control groups were calcd. The values of each compd were compared with those of the controls, and treated statistically, using the Student *t* method. For those values that were significant, the per cent change in spontaneous motor activity was then calcd.

Determination of ED₅₀.—Ten mice were injected ip with a minimum of 6 doses of 3 and 5 in a Tween-80 and saline suspension; 10 control mice were given only the vehicles. Animals were run in the activity cage individually for a total of 10 min. Since the first 6 min was regarded as a stage of curiosity, only the counts in the last 4 min were considered for an actual reading.

Each score (4-min net counts) of individually run, experimental animals was compared to the mean and standard deviation of the scores of the control animals. Those scores of experimental animals falling outside of the range of the control standard deviation were considered to be significant. ED₅₀ was determined by plotting dose vs. per cent of animals affected by the compd at a given dose (method of Miller and Tainter⁴).

Acknowledgment.—The authors wish to thank Miss Karen Kelly for her technical assistance.

(4) L. D. Miller and M. L. Tainter, *Proc. Soc. Exp. Biol. Med.*, **57**, 261 (1944).

Quinuclidine Analogs of Tobacco Alkaloids

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Since quinuclidine possesses a tertiary amino N in a rigid nonplanar ring system and is present in many biologically active alkaloids^{1,2} and other compounds,³ it was of interest to investigate changes in pharmacologic activity that result from the substitution of a 3-quinuclidinyl group for the planar 3-pyridinyl moiety of nicotine and anabasine. This note describes the synthesis and pharmacologic evaluation of 3-(1-methyl-2-pyrrolidinyl)- (1) and 3-(2-piperidinyl)quinuclidine (2).

(1) R. B. Turner and R. B. Woodward, *Alkaloids*, **3**, 1 (1950).

(2) W. I. Taylor, *ibid.*, **11**, 73 (1968).

(3) M. D. Mashkovsky and L. N. Yakhontov, *Fortschr. Arzneimittelforsch.*, **13**, 293 (1969).