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 Et_2O 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°, α_{589}^{20} +17.2 (0.154 g in 10 ml of $CHCl_3$). The (−) isomer had mp 60–62, α_{589}^{26} −17.3 (0.1209 g in 10 ml of $CHCl_3$).

The HCl salts of both enantiomorphs were prepd by passing HCl gas through their Et_2O soln. (+)-Phenyl-2-pyridylcarbinol·HCl had mp 179–180°. *Anal.* ($C_{12}H_{12}ClNO$) C, H, N, Cl. (−)-Phenyl-2-pyridylcarbinol·HCl had a mp of 174–176°. *Anal.* ($C_{12}H_{12}ClNO$), 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 H_2O, the reaction mixt was chilled to 10° and neutralized with solid K_2CO_3. The resulting ppt, after recrystn from H_2O and then cyclohexane–PhH (1:1), melted at 103–104°; yield 1.0 g (53%). *Anal.* ($C_{12}H_9NO_2$) C, H, N.

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

Central Nervous System Depressive Activity of Some Amides of Tryptamine[1]

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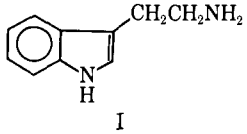
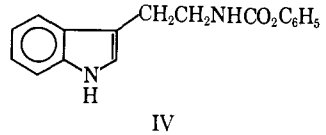
During our investigation of the inhibitory activity of a series of *N*-acyltryptamines on hydroxyindole-*O*-methyltransferase (HIOMT),[2] several compounds were found to cause sedation in rats. This led us to synthesize other substituted amides, benzenesulfonamide, and ureido derivatives of tryptamine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

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



I

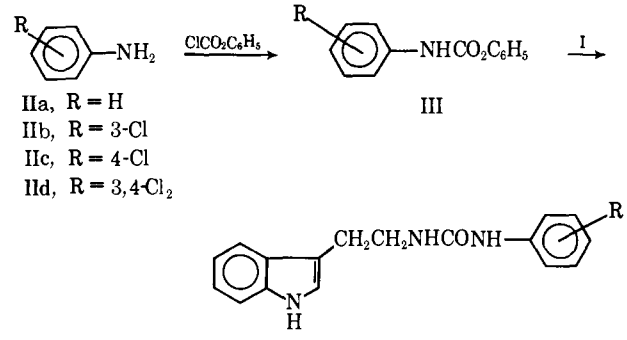


IV

$CHCl_3$ or CH_2Cl_2 with the appropriate acid chloride in the presence of Et_3N (in the case of **13** pyridine was used). Compound **10** was obtained by Schotten–Baumann reaction between I and $PhSO_2Cl$.

The general route (Scheme I) for the synthesis of

SCHEME I



IIa, R = H
IIb, R = 3-Cl
IIc, R = 4-Cl
IId, R = 3,4-Cl_2

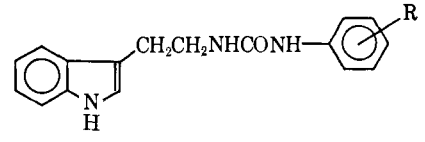
III

6–9

urea derivatives **6–9** started with the reaction of phenyl chloroformate with aniline (IIa) or substituted anilines (IIb–IId) 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 previous attempt to prepare the ureas by the treatment of $PhNH_2$ 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.

TABLE I

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



Compd[a]	R	Yield, %	Recrystn solvent	Mp, °C	Formula
6	H	75	MeOH	185–187	$C_{17}H_{17}N_3O$
7	3-Cl	83	MeOH–H_2O	148.5–150.5	$C_{17}H_{16}ClN_3O$
8	4-Cl	82	EtOH–H_2O	198–200	$C_{17}H_{16}ClN_3O$
9	3,4-Cl_2	84	50% MeOH	150–151.5	$C_{17}H_{15}Cl_2N_3O$

[a] The corresponding starting materials, substituted phenyl phenylcarbamates, were prepared by treating aniline or substituted $PhNH_2$ with $ClCO_2Ph$, 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° (C_6H_6); substituted phenyl phenylcarbamates, 3-Cl, 74–76° (C_6H_6); 4-Cl, 150–152° (C_6H_6); 3,4-Cl_2, 131–133° (C_6H_6).

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 ED_{50} 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 Section[3]

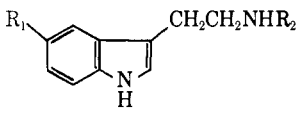
***N*-β-3-Indolylethyl-*m*-nitrobenzenesulfonamide (11).**—To a soln of 6.4 g (40 mmoles) of tryptamine (I) and 4.04 g (40 mmoles) of Et_3N in 100 ml of CH_2Cl_2 was added with cooling a soln of 8.86 g (40 mmoles) of *m*-nitrobenzenesulfonyl chloride in 25 ml of CH_2Cl_2. The mixt was stirred for 3 hr and then washed successively with H_2O (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 (1960); (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] Accum counts (mean ± S.D.)	% decrease	$p<$
1[b]	H	C_6H_5CO	531 ± 73		NS
2	H	$C_{10}H_7CO$	500 ± 98		NS
3[b]	H	$C_6H_5CH_2CO$	310 ± 53	38.6	0.01
4[c]	H	$3,4\text{-}Cl_2C_6H_3CO$	462 ± 57	16.2	0.05
5[c]	Br	$3,4\text{-}Cl_2C_6H_3CO$	158 ± 73	64.5	0.001
6	H	C_6H_5NHCO	544 ± 45		NS
7	H	$3\text{-}ClC_6H_4NHCO$	443 ± 126		NS
8	H	$4\text{-}ClC_6H_4NHCO$	462 ± 63	15.3	0.1
9	H	$3,4\text{-}Cl_2C_6H_3NHCO$	613 ± 95		NS
10[b]	H	$C_6H_5SO_2$	488 ± 99		NS
11	H	$3\text{-}NO_2C_6H_4SO_2$	608 ± 40		NS
12	H	$3\text{-}NH_2C_6H_4SO_2$	648 ± 50		NS
13	H	$C_6H_5CH{=}CHSO_2$	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), H_2O (100-ml), satd $NaHCO_3$ (two 100-ml portions), and again H_2O (100 ml). The CH_2Cl_2 phase was dried (Na_2SO_4) 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.* ($C_{16}H_{15}N_3O_4S$) C, H, N.

N-β-3-Indolylethyl-*m*-aminobenzenesulfonamide (12).—A suspension of 9.2 g (27 mmoles) of N-β-3-indolylethyl *m*-nitrobenzenesulfonamide (**11**) and 0.5 g of 10% Pd/C in 150 ml of EtOH was shaken with H_2 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.* ($C_{16}H_{17}N_3O_2S$) C, H, N.

N-β-3-Indolylethyl-2-naphthamide (2).—In a similar manner as described for the prepn of **11**, tryptamine (**I**) in $CHCl_3$ was treated with $C_{10}H_7COCl$ in the presence of Et_3N. After stirring at ambient temp for 15 hr, a solid product was filtered and washed first with H_2O then with Et_2O; yield, 3.8 g (80%), mp 188–191.5°. Recrystn from $C_6H_5CH_3$ gave 3.0 g (63%), mp 192–194°. *Anal.* ($C_{21}H_{18}N_2O$) C, H, N.

N-β-3-Indolylethyl-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 $CHCl_3$ 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 $CHCl_3$ filtrate was washed successively with 10-ml portions of H_2O, 2 N HCl, 2 N NaOH, and again H_2O, dried (Na_2SO_4), treated with charcoal, filtered, and then evapd *in vacuo*. The oily residue was dissolved in C_6H_6, 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.* ($C_{18}H_{18}N_2O_2S$) C, H, N.

Phenyl N-β-Indolylethylcarbamate (IV).—To a stirred suspension of 3.2 g (20 mmoles) of tryptamine (**I**) in a mixt of 100 ml of Et_2O and 20 ml of H_2O was added at ice temp one-half of 3.2 g (20 mmoles) of $ClCO_2C_6H_5$. The remaining half of $ClCO_2C_6H_5$ 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 H_2O, dried (Na_2SO_4), treated with charcoal, and then concd *in vacuo* to about 50 ml. Petr ether was added to the Et_2O soln to cloudiness, and chilling brought down 3.5 g (64%) of pale pink plates, mp 66–69°. Three recrystns from Et_2O–petr ether gave an anal. sample as small, pale yellow crystals, mp 70–71.5°. *Anal.* ($C_{17}H_{16}N_2O_2$) C, H, N.

N-β-3-Indolylethyl-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 supension. (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 ED_{50}.—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. ED_{50} was determined by plotting dose *vs.* per cent of animals affected by the compd at a given dose (method of Miller and Tainter[4]).

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-pyridyl 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).