Indole *N*-alkylation of tryptamines via dianion and phthalimido intermediates. New potential indolealkylamine haptens

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Tryptamine derivatives **3***a–c* and **4***a*, **4***b*, **4***d* have been converted into the indole *N-p*-carbomethoxybenzyl derivatives **1***a*, **1***b*, **1***g*, and **2***a*, **2***b*, **2***c*, respectively, using dianion and phase-transfer catalytic methodologies. Treatment of these compounds with lithium iodide and sodium cyanide in refluxing dimethylformamide gave the corresponding carboxylic acids **1***d*, **1***e*, **1***h*, and **2***d*, **2***e*, **2***f*. The serotonin analogue **1***f* was obtained by catalytic debenzylation of **1***h*. These products may be useful haptens for eliciting specific antibodies to indolealkylamines.

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Faisant appel à des méthodes impliquant des dianions et une catalyse par transfert de phase, on a pu transformer les dérivés de la tryptamine **3***a–c*, **4***a*, **4***b* et **4***d* en leurs dérivés respectifs *N-p*-carbométhoxybenzyle indoles (**1***a*, **1***b*, **1***g* et **2***a*, **2***b*, **2***c*). La réaction de ces composés avec l'iodure de lithium et le cyanure de sodium dans la diméthylformamide à reflux conduit aux acides carboxyliques correspondants **1***d*, **1***e*, **1***h* et **2***d*, **2***e* et **2***f*. On a obtenu l'analogue de la sérotonine **1***f* par une débenzylation catalytique de **1***h*. Ces composés peuvent être des haptènes utiles pour découvrir des anticorps spécifiques aux indolealkylamines.

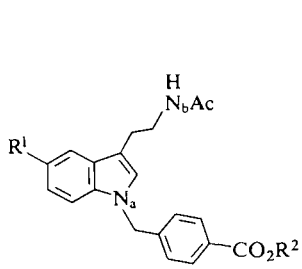
[Traduit par le journal]

Introduction

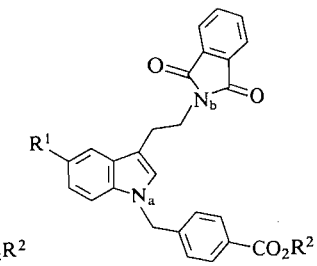
In connection with a problem concerning production of antibodies to tryptamines (1), it was of interest to prepare a series of indole *N*-substituted compounds of the types **1** and **2**. These compounds would possess a free carboxylic acid function (R^2 = H) which would serve as a handle for coupling to protein to afford potential antigens which in turn would be used directly (**1**) or after suitable demasking of the side-chain amino group (**2**) in attempts to elicit specific antibodies (2).

It may be envisaged that compounds **1** and **2** would be most conveniently available by N_a-*p*-carboalkoxybenzylation of either commercially or synthetically (3) available tryptamine derivatives. Although a number of excellent methods have been developed (4), particularly in recent years (5), for *N*-alkylation of simple indole derivatives, this reaction appears not to have been extensively explored (4) for tryptamines. This situation may be explained in part by the observation that relatively few complex indole alkaloids possess N_a-substitution (6) and, since tryptamines are common building blocks for these natural products, a general synthetic need for N_a-alkylated tryptamines has not arisen.

Herein we report on (*i*) the regioselective N_a-*p*-carbomethoxybenzylation of dianions from N_b-acyl tryptamines **3** generated using sodium hydride in DMF (7) or phase-transfer conditions (8) to give **1**, R^2 = Me; (*ii*) similar N_a-benzylation of monoanions of N_b-phthaloyl tryptamines **4**, available using

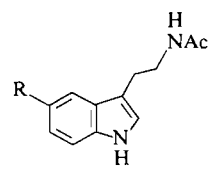


1

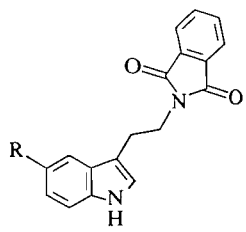


2

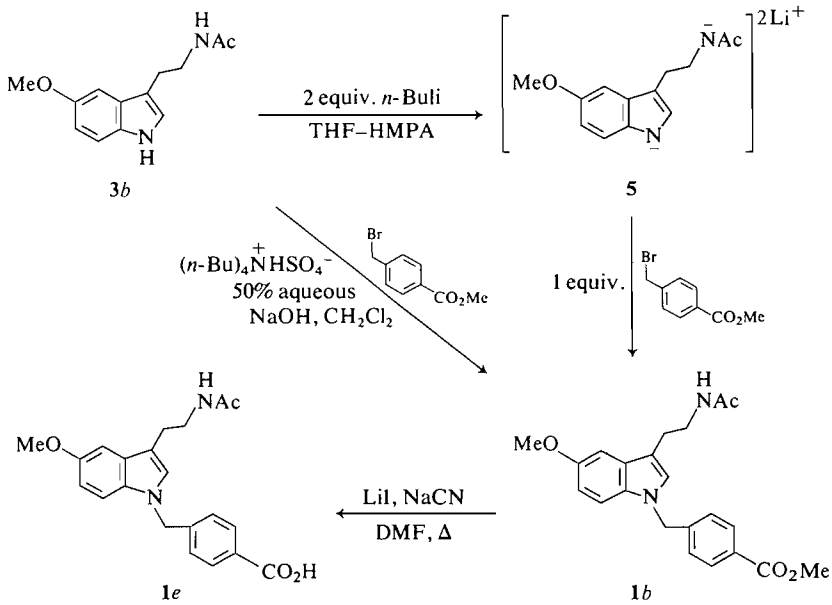
a R^1 = H, R^2 = Me
b R^1 = OMe, R^2 = Me
c R^1 = OAc, R^2 = Me
d R^1 = R^2 = H
e R^1 = OMe, R^2 = H
f R^1 = OH, R^2 = H
g R^1 = OCH_2Ph, R^2 = Me
h R^1 = OCH_2Ph, R^2 = H



3
a R = H
b R = OMe
c R = OCH_2Ph



4
a R = H
b R = OMe
c R = OH
d R = OAc



SCHEME 1

Nefkens' reagent **6** (9), to give **2**, R^2 = Me; and (*iii*) selective ester hydrolysis of **1** and **2** (R^2 = Me) to the carboxylic acids, **1** and **2** (R^2 = H) by the nonaqueous procedure of McMurry and Wong (10).

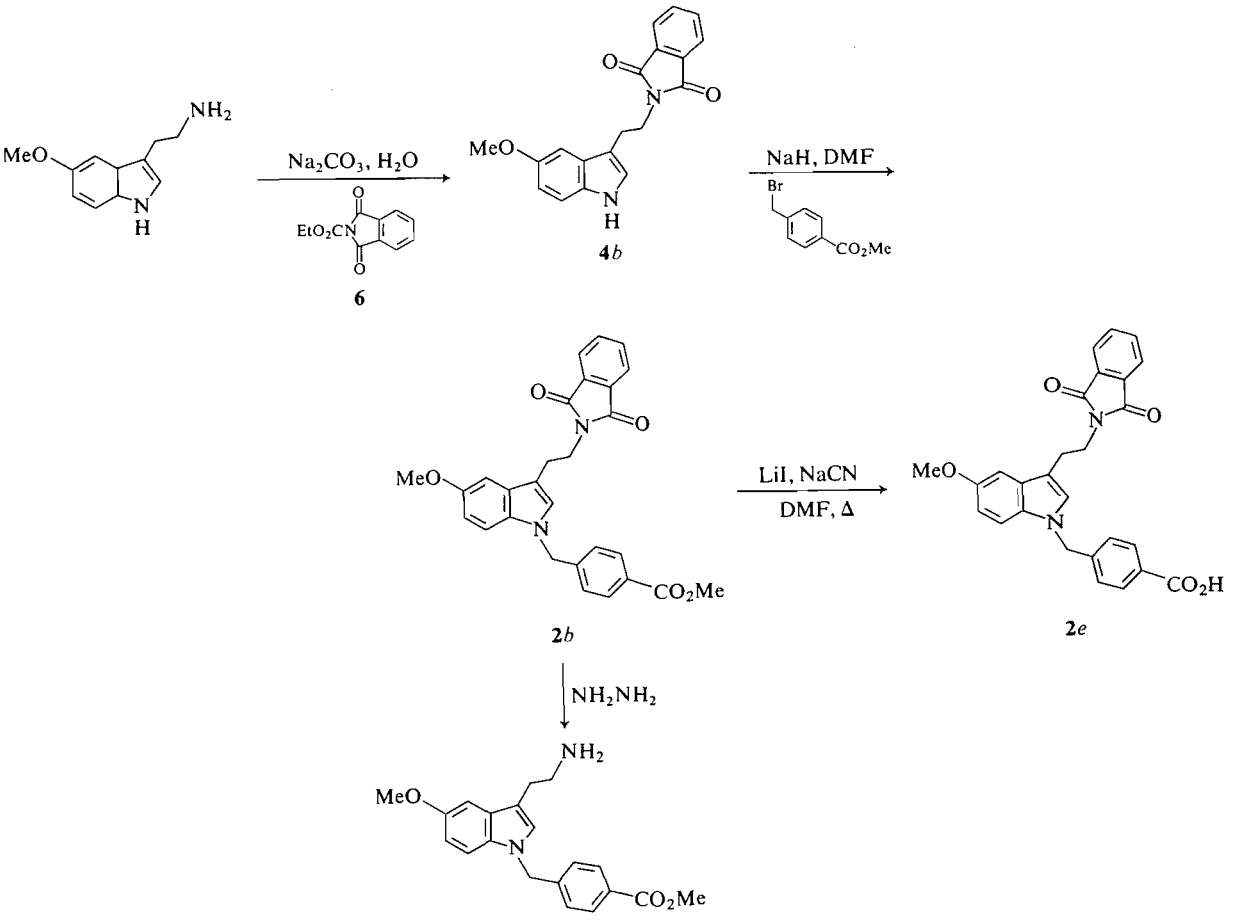
Results and Discussion

It was anticipated that treatment of melatonin (**3***b*) with 2 equiv. of base would generate the dianion **5** which upon reaction with 1 equiv. of *p*-carbomethoxybenzyl bromide would undergo alkylation at the more reactive N_a-anion to provide, after work-up, compound **1***b*.[1] In the event, when this reaction was conducted in a THF–HMPA mixture using *n*-butyllithium as base, the desired product (**1***b*) was formed in 60% yield (Scheme 1). When the N_a-alkylation was carried out in a two-phase system (8) consisting of methylene chloride and concentrated aqueous sodium hydroxide with a phase-transfer catalyst (tetra-*n*-butylammonium hydrogen sulfate), a significant improvement in efficiency and yield was noticed with the added advantage of avoiding the anhydrous conditions that are essential for the procedure using *n*-butyllithium. That the alkylation had occurred in the indole rather than the side-chain nitrogen was ascertained from examination of the ir and nmr spectra which showed absence of characteristic indole NH absorption and presence of a two-proton singlet at τ 4.83 typical of benzylic protons of 1-benzylindole (*vide infra*). For the final stage of the synthesis, **1***b* → **1***e*, it was necessary to use conditions which would selectively hydrolyze the ester without affecting the amide function. The nonaqueous procedure of McMurry and Wong (10) proved suitable for this purpose and provided **1***e* in 50% yield.

Following the route delineated in Scheme 1, compounds **1***d*, **1***f*, and **1***h* were also synthesized (see Tables 1 and 2). In the case of the serotonin analogue **1***f*, the protected *O*-benzylacetylserotonin **3***c* was alkylated with *p*-carbomethoxybenzyl bromide. The resulting product **1***c* underwent deesterification when subjected to reaction with lithium iodide and sodium cyanide in refluxing DMF to give **1***h*. Debenzylation of the blocked phenol to obtain **1***f* was achieved by catalytic hydrogenation.

The N_b-phthaloyl derivatives **2***d–f* were prepared by adaptation of N_a-alkylation conditions extensively used previously in our laboratories (7). The general route is shown in Scheme 2 for the preparation of **2***e* and the results are summarized in Tables 1 and 2. The starting phthaloyl derivatives **4***a–c* were readily prepared from commercially available tryptamines by treatment with phthalic anhydride or, preferably, by application of Nefkens' excellent *N*-carbethoxyphthalimide (**6**) reagent (9) which enjoys moderate use in peptide synthesis (13) but which appears not to be widely employed by organic chemists, e.g., in the Gabriel synthesis. Alkylations were carried out at room temperature using sodium hydride in DMF; as in the case of **3***c*, the protected *O*-acetyl phthaloylserotonin (**4***d*) was used for the base-catalyzed alkylation reaction. The phase transfer method applied to **4***a* gave only low yields of **2***a* and was

[1]For indole *N*-alkylation of tryptophan dianion, see ref. 11; for other synthetic work with indole compounds using dianion intermediates, see ref. 12.



SCHEME 2

therefore not pursued. The nmr spectra of the alkylated products **2***a–c* all showed a two-proton singlet at $\tau \sim 4.8$ which can be unambiguously assigned to the N_a-benzylic hydrogens by analogy with the data obtained in the N_b-acetyl series (**1***a–c*). Finally, deesterifications of **2***a–c* were effected using the LiI–NaCN reagent to give compounds **2***d–f*. The LiI–NaCN reaction on **2***c* gave directly the deesterified-deacetylated product **2***f*. Deacetylation occurs owing to the basic conditions that prevail during aqueous work-up of the reaction mixture.

To test the dephthaloylation step[2] required for antibody generation studies after coupling to protein (1), compound **2***b* was subjected to the standard conditions of hydrazinolysis at room temperature (13). The expected product, **7**, was obtained in good yield.

In conclusion, this work provides ready access to N_a-*p*-carboxybenzyl tryptamine derivatives **1***d–f* and **2***d–f*. These may be useful in radioimmunoassay, immunohistochemical and related studies which are in progress elsewhere.[3]

Experimental

Melting points were measured on a Mel-Temp apparatus and are uncorrected. Microanalyses were performed by A. B. Gygli, Toronto. Infrared spectra were determined with a Beckman IR-5A instrument. Nuclear magnetic resonance spectra were obtained on Varian T-60 and Perkin-Elmer R-12 spectrometers. Thin-layer chromatography was carried out with Merck silica gel GF 254 and column chromatography with Merck silica gel (0.05–0.2 mm) obtained from Brinkmann (Canada) Ltd. THF was dried by refluxing over sodium and benzophenone until a deep blue color persisted in solution. Dry DMF was prepared by refluxing over calcium hydride followed by distillation. HMPA was dried by allowing it to stand over Linde molecular sieves (Type 4A) followed by distillation.

n-Butyllithium was purchased as a solution in *n*-hexane from Alfa Ventron Crop. Tryptamine hydrochloride, 5-methoxytryptamine hydrochloride, and 5-benzyloxytryptamine

[2]For an example of its application in penicillin synthesis see the recent work of Kukolja and Lammert (13).

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TABLE 1. N_a-*p*-Carboxybenzyl derivatives of tryptamines and N_b-phthaloyltryptamines (**1** and **2**)

Compound	Starting material	Method[a]	Yield[b] (%)	Melting point[c] (°C)
1*a*	**3***a*	*B*	>95	136 (PhH – 2% EtOH)
1*b*	**3***b*	*A*	60	116 (PhH–*n*-hexane)
		B	98	
1*d*	**1***a*	*C*	69[d]	155 (EtOH)
1*e*	**1***b*	*C*	66	173 ($CHCl_3$ – 2% EtOH)
1*f*	**1***h*	*D*	96	204 (EtOH)
1*g*	**3***c*	*B*	97	Oil[e]
1*h*	**1***g*	*C*	60	141 (EtOH – 10% H_2O)
4*a*	Tryptamine·HCl	*E*	94	165 (EtOH)
		F	90	
4*b*	5-MeO-Tryptamine·HCl	*E*	91	158 (EtOH)
4*c*	Serotonin–creatinine sulfate	*E*	84[f]	210 (EtOH)
		G	69	
4*d*	**4***c*	*H*	99	Foam
2*a*	**4***a*	*A*	48[g]	139 (MeOH – 20% PhH)
2*b*	**4***b*	*A*	54[g]	143 (EtOH)
2*c*	**4***d*	*A*	79	209 (EtOH – 10% CH_2Cl_2)
2*d*	**2***a*	*C*	60[d]	192–193 (EtOH – 10% H_2O)
2*e*	**2***b*	*C*	48[g]	227 (EtOH – 5% $CHCl_3$)
2*f*	**2***c*	*C*	35	193 (EtOH – 20% H_2O)

[a]See Experimental.
[b]Yield of homogeneous product after chromatography (if necessary).
[c]Recrystallization solvent given in parentheses.
[d]Starting material (25–30%) was recovered.
[e]After chromatography (silica gel PhH–Me_2CO–MeOH 8:1:1) homogeneous by tlc.
[f]Yield improved to 96% if **6** is added portionwise to an aqueous mixture of serotonin salt and Na_2CO_3.
[g]Starting material (30–50%) was recovered.

hydrochloride were purchased from Aldrich Chemical Co. Melatonin and serotonin–creatinine sulfate were procured from Sigma Chemical Co. All of these compounds were used without further purification.

*1-(*p*-Carbomethoxy)benzylmelatonin (**1**b)*

Method A

To a solution of melatonin (**3***b*) (0.116 g, 0.5 mmol) in a mixture of dry THF (30 ml) – HMPA[4] (0.5 ml) maintained under an atmosphere of dry nitrogen and cooled in an ice-bath was added via a syringe through a septum cap a solution of *n*-butyllithium (2.4 *M*, 0.42 ml (1 mmol)) in *n*-hexane. Over a period of 4 h stirring at room temperature there accumulated a colorless, gelatinous precipitate. A solution of methyl α-bromo-*p*-toluate (ref. 14 and footnote 5) (0.114 g, 0.5 mmol) in dry THF (5 ml) was introduced dropwise and stirring was continued for a further 4 h. The clear yellow solution was treated with 0.1 *N* hydrochloric acid solution (5 ml) and the resulting mixture was evaporated to dryness *in vacuo*. The residue was suspended in water (50 ml) and extracted with methylene chloride (2 × 50 ml). The organic extract was dried (sodium sulfate) and evaporated to dryness. The residue on chromatography (silica gel, benzene–acetone–methanol eluent, 8:1:1) gave a yellow gum (0.115 g, 60%) which was crystallized from a 1:3 mixture of benzene – petroleum ether (60–80°C) to give **1***b* as a colorless solid.

Method B

A solution of melatonin (**3***b*) (0.232 g, 1 mmol) in methylene chloride (30 ml) was mixed with an aqueous solution (20 ml 50% w/v) of sodium hydroxide. Solid methyl α-bromo-*p*-toluate (0.250 g, 1.09 mmol) and a solution of tetra-*n*-butylammonium hydroxide (a few drops of 40% aqueous solution) were successively introduced and the mixture was stirred at 30–33°C for 3 h. Heating was discontinued and the mixture was stirred at room temperature overnight (~14 h). The reaction mixture was cooled in ice and carefully acidified (litmus paper) with a dilute solution of hydrochloric acid. The organic layer was separated, washed with a saturated solution of sodium carbonate and then with water. Drying (sodium sulfate) of the organic extract followed by evaporation to dryness *in vacuo* gave a gummy material which was purified by column chromatography as in method *A*. Crystallization of the purified product (0.37 g, 98%) from a mixture of benzene–*n*-hexane (1:1) gave a colorless solid. This compound was found to be identical with a sample of **1***b* prepared by method *A*.

*1-(*p*-Carboxy)benzylmelatonin (**1**e)*

Method C

A mixture of 1-(*p*-carbomethoxy)benzylmelatonin (**1***b*) (0.223 g, 0.587 mmol), anhydrous lithium iodide (0.804 g, 6 mmol), and sodium cyanide (0.050 g, 1 mmol) in dry DMF (50 ml) under a blanket of dry nitrogen was heated in an oil bath at 140–145°C (external temperature) for 50 h. Most of the solvent was removed *in vacuo* and the residual gum was suspended in water (25 ml) and extracted with chloroform (2 × 20 ml). The organic extract was dried (Na_2SO_4) and evaporated to dryness to give 0.062 g (28%) of recovered starting material (**1***b*). The aqueous layer was acidified with concentrated hydrochloric acid. Cooling in ice resulted in formation of a gum. The water layer was decanted, ethanol was added and the whole was evaporated to dryness. There was obtained 0.142 g (66%) of **1***e* as a yellow solid.

[4]Dictated by solubility problems. In all other cases of method *A*, DMF was used as the sole solvent.

[5]This compound was prepared by the method of Julia and Chastrette (14).

TABLE 2. Spectral and analytical data of compounds **1**, **2**, and **4**

Compound	ν_{max} (KBr) (cm^{-1})	τ ($CDCl_3$) (*J* in Hz)	Molecular formula	Elemental analysis (%) C Calcd.	C Obs.	H Calcd.	H Obs.	N Calcd.	N Obs.
1*a*	1720 1645	2.0 (d, 2H, *J* = 10), 2.2–3.1 (m, 7H), 3.86 (br s, 1H), 4.72 (s, 2H), 6.13 (s, 3H), 6.47 (q, 2H, *J* = 8), 7.04 (t, 2H, *J* = 8), 8.10 (s, 3H)	$C_{21}H_{22}N_2O_3$	71.98	71.90	6.33	6.29	7.99	7.96
1*b*	1720 1645	2.0 (d, 2H, *J* = 10), 2.5–3.3 (m, 6H), 4.0 (br s, 1H), 4.83 (br s, 2H), 6.23 (s, 3H), 6.27 (s, 3H), 6.47 (q, 2H, *J* = 8), 7.06 (t, 2H, *J* = 8), 8.1 (s, 3H)	$C_{22}H_{24}N_2O_4$	69.46	69.50	6.36	6.38	7.36	7.34
1*d*[a]	3400 1700 1645 1600	2.0 (d, 2H, *J* = 10), 2.35–3.0 (m, 9H), 4.63 (br s, 2H), 6.53 (q, 2H, *J* = 7), 7.03 (t, 2H, *J* = 7), 8.07 (s, 3H)	$C_{20}H_{20}N_2O_3$	71.41	71.46	5.99	5.97	8.33	8.28
1*e*	3400 (br) 1700 1645 1600	2.04 (d, 2H, *J* = 10), 2.7–3.4 (m, 6H), 4.8 (br s, 2H), 6.1 (s, 3H), 6.38 (q, 2H, *J* = 7), 7.08 (t, 2H, *J* = 7), 8.05 (s, 3H)	$C_{21}H_{22}N_2O_4$	68.84	68.81	6.05	6.07	7.65	7.69
1*f*[b]	3500 (v br) 1700 1645 1600	2.02 (d, 2H, *J* = 10), 2.4–3.6 (m, 6H), 4.60 (br s, 2H), 5.30 (m, 3H), 6.46 (2 × t, 2H, *J* = 7), 7.21 (t, 2H, *J* = 7), 8.15 (s, 3H)	$C_{20}H_{20}N_2O_4$	68.17	68.08	5.72	5.77	7.95	7.99
1*g*[c]	1720 1645	2.05 (d, 2H, *J* = 10), 2.3–3.2 (m, 11H), 4.03 (br s, 1H), 4.85 (s, 2H), 4.95 (s, 2H), 6.15 (s, 3H), 6.53 (q, 2H, *J* = 8), 7.13 (t, 2H, *J* = 8), 8.15 (s, 3H)	$C_{28}H_{28}N_2O_4$	Not determined					
1*h*[a]	3400 (br) 1700 1645 1600	2.0 (d, 2H, *J* = 10), 2.4–3.23 (m, 13H), 4.62 (s, 2H), 4.87 (s, 2H), 6.55 (q, 2H, *J* = 8), 7.08 (t, 2H, *J* = 8), 8.10 (s, 3H)	$C_{27}H_{26}N_2O_4$	73.29	73.31	5.92	5.90	6.33	6.29
4*a*[c]	1775 1712	1.7–3.0 (m, 9H), 5.08 (2 × t, 2H, *J* = 8), 6.75 (t, 2H, *J* = 8)	$C_{18}H_{14}N_2O_2$	74.47	74.49	4.86	4.90	9.65	9.63
4*b*[c]	1775 1715	1.7–3.2 (m, 8H), 5.08 (2 × t, 2H, *J* = 8), 6.75 (t, 2H, *J* = 8)	$C_{19}H_{16}N_2O_3$	71.24	71.26	5.03	5.07	8.74	8.79
4*c*[b]	3400 1770 1705	1.95–3.3 (m, 8H), 6.1 (2 × t, 2H, *J* = 8), 7.07 (t, 2H, *J* = 8)	$C_{18}H_{14}N_2O_3$	70.58	70.60	4.61	4.63	9.15	9.17
4*d*[c]	3500 1775 1768 1715	1.4 (br s, 1H), 2.0–3.3 (m, 8H), 6.1 (t, 2H, *J* = 8), 6.97 (t, 2H, *J* = 8), 7.7 (s, 3H)	$C_{20}H_{16}N_2O_4$	Not determined					
2*a*[c]	1775 1715	1.9–3.2 (m, 13H), 4.8 (br s, 2H), 6.0 (2 × t, 2H, *J* = 8), 6.23 (s, 3H), 6.85 (t, 2H, *J* = 8)	$C_{27}H_{22}N_2O_4$	73.96	73.98	5.06	5.03	6.39	6.37
2*b*[c]	1775 1715 (br)	1.82–3.22 (m, 12H), 4.72 (br s, 2H), 5.82 (2 × t, 2H, *J* = 8), 6.08 (s, 3H), 6.12 (s, 3H), 6.88 (t, 2H, *J* = 8)	$C_{28}H_{24}N_2O_5$	71.78	71.80	5.16	5.14	5.98	5.94

TABLE 2 (*Concluded*)

Compound	ν_{max} (KBr) (cm^{-1})	τ ($CDCl_3$) (*J* in Hz)	Molecular formula	Elemental analysis (%) C Calcd.	C Obs.	H Calcd.	H Obs.	N Calcd.	N Obs.
2*c*	1775 1715 (br)	1.56–3.1 (m, 12H), 4.8 (s, 2H), 5.96 (t, 2H, J = 8), 6.08 (s, 3H), 6.94 (t, 2H, J = 8), 7.04 (s, 3H)	$C_{29}H_{24}N_2O_6$	70.15	70.16	4.87	4.90	5.64	5.68
2*d*	3500 (br) 1780 1720 1715	1.92 (d, 2H, J = 10), 2.0–3.0 (m, 11H), 4.0 (br s, 1H), 4.65 (s, 2H), 5.9 (t, 2H), J = 8), 6.8 (t, 2H, J = 8)	$C_{26}H_{20}N_2O_4$	73.57	73.61	4.75	4.97	6.60	6.62
2*e*[b]	3600 (br) 1780 1715 1700	2.0–3.32 (m, 12H), 4.8 (br s, 2H), 6.05 (t, 2H, J = 8), 6.25 (s, 3H), 6.99 (t, 2H, J = 8)	$C_{27}H_{22}N_2O_5$	71.36	71.39	4.88	4.87	6.16	6.19
2*f*[b]	3600 (v br) 1780 1715 1700	1.70 (br s, 1H), 2.0 (d, 2H, J = 10), 2.20–3.80 (m, 11H), 4.90 (br s, 2H), 6.50 (t, 2H, J = 8), 7.0 (t, 2H, J = 8)	$C_{26}H_{20}N_2O_5$	70.90	70.87	4.54	4.50	6.36	6.40

[a]Nuclear magnetic resonance recorded in DMSO-d_6–$CDCl_3$.
[b]Nuclear magnetic resonance recorded in DMSO-d_6.
[c]Infrared determined in $CHCl_3$.

*1-(p-Carboxy)benzyl-N-acetylserotonin (**1**f)*

Method D

A solution of **1***h* (0.161 g, 0.36 mmol) in absolute ethanol (150 ml) containing a suspension of 10% palladium-on-charcoal (0.175 g) was hydrogenated in a Parr apparatus at 45 psi for 18 h. Filtration of the reaction mixture followed by evaporation to dryness and recrystallization gave **1***f* as an off-white crystalline solid (0.123 g, 96%).

*Phthaloyltryptamine (**4**a)*

Method E

Nefkens' method (9) was adapted. Tryptamine hydrochloride (1.967 g, 1 mmol) and *N*-carbethoxyphthalimide (2.41 g, 1.1 mmol) were suspended in water (50 ml) and sodium carbonate decahydrate (5.72 g, 2 mmol) was added with stirring. After 0.5 h at room temperature, an additional amount of *N*-carbethoxyphthalimide (0.48 g, 0.2 mmol) was added and stirring was continued for another 0.5 h. The yellowish-white solid was collected by filtration and recrystallized to give yellow crystals of **4***a* in three crops, 2.74 g (94%).

Method F

A mixture of tryptamine hydrochloride (0.393 g, 2 mmol), phthalic anhydride (0.312 g, 2.02 mmol), anhydrous sodium carbonate (0.110 g, 1.02 mmol) and dry benzene (50 ml) was refluxed under a Dean–Stark water separator. After 20 h, the solvent was removed *in vacuo* and then the residue was pyrolyzed for 15 min in an oil bath preheated to 210°C. The brownish solid residue was allowed to cool to about 80°C and hot water (200 ml) was added with vigorous trituration. The mixture was extracted with methylene chloride (200 ml) and the organic extract was successively washed with a 5% aqueous solution of sodium hydroxide (100 ml) and water (200 ml). The organic layer was treated with decolorizing carbon, filtered, dried (sodium sulfate), and evaporated to dryness. The residual solid was recrystallized from ethanol to give **4***a* (0.523 g, 90%), identical with a sample obtained by method *E*.

*Phthaloyl-5-hydroxytryptamine (**4**c)*

Method G

A mixture of serotonin–creatinine sulfate (0.388 g, 1 mmol), phthalic anhydride (0.5 g, 3.37 mmol), and anhydrous pyridine (20 ml) was heated in an oil bath at 100°C for 20 h. Evaporation to dryness followed by azeotropic distillation with absolute ethanol gave a residual solid which was pyrolyzed in a preheated oil bath at 200°C. The melt was allowed to cool and was then triturated with hot ethanol (30 ml). The mixture was cooled to 0°C. The resulting solid was collected by filtration and was washed successively with water (40 ml), a saturated aqueous solution of sodium carbonate (50 ml), and water (40 ml). The solid was air dried and recrystallized to give a yellow crystalline material (0.210 g, 69%), shown to be identical with a sample of **4***c* prepared by method *E*.

O-*Acetylphthaloylserotonin (**4**d)*

Method H

A stirred solution of **4***c* (0.306 g, 1 mmol) in dry THF (75 ml) maintained at room temperature under an atmosphere of dry nitrogen was treated with sodium hydride (0.060 g, 1.2 mmol, 50% dispersion in mineral oil). Over a period of 0.5 h, a reddish-brown color developed. Acetic anhydride (0.3 ml, 3 mmol) was added to the mixture and stirring was continued for 12 h. The mixture was treated with aqueous hydrochloric acid (0.1 *N*, 5 ml) and most of the THF was removed *in vacuo*. The aqueous solution was diluted with water (200 ml) and the resulting brownish gum was retained by decanting the supernatant aqueous layer. The gummy material was suspended in absolute ethanol and the whole was taken to dryness *in vacuo*. This process was repeated several times. The gum was washed with hot petroleum ether (60–80°C, 50 ml) and dried *in vacuo* to give **4***d* as a cream-colored foam, 0.342 g (99%) which was used without further purification for the preparation of **2***c*.

N-*Acetyltryptamine (3a)*

Tryptamine hydrochloride (0.200 g, 1.02 mmol) suspended in a mixture of dry pyridine (10 ml), benzene (20 ml), and acetic anhydride (3 ml) was stirred at room temperature for 6 h. The mixture was evaporated to dryness *in vacuo* and the residue was suspended in water (200 ml) and extracted with methylene chloride (2 × 100 ml). Successive washing of the organic extract with 10% aqueous sodium carbonate solution, water, 10% hydrochloric acid, and water followed by drying (sodium sulfate) and removal of solvent *in vacuo* gave a colorless gummy material. This compound was crystallized from a mixture of ether – benzene – petroleum ether (60–80°C) (10:10:1) to give **3***a* as a white crystalline solid (0.192 g, 93%), mp 75°C (lit. (15) mp 75–76°C).

5-Benzyloxy-N-*acetyltryptamine (3c)*

The procedure described for the preparation of **3***a* was employed. From 0.950 g (3.14 mmol) of 5-benzyloxytryptamine hydrochloride and 10 ml of acetic anhydride in a mixture of dry pyridine (40 ml) and benzene (5 ml) there was obtained a gummy product which was crystallized from a mixture of benzene–*n*-hexane (10:1) to give **3***c* as a cream-colored solid (0.943 g, 97%), mp 123°C (lit. (16) mp not recorded); ir ν_{max} (KBr): 1645 cm^{-1}; nmr ($CDCl_3$) τ: 1.30 (br s, 1H, indole NH), 2.3–3.2 (m, 9H, aromatic H), 4.10 (br s, 1H, amide NH), 4.86 (s, 2H, $PhCH_2$), 6.45 (two overlapping triplets, J = 7 Hz, 2H, $N—CH_2$), 7.12 (t, 2H, J = 7 Hz, $—CH_2$), 7.85 (s, 3H, $COCH_3$). *Anal.* calcd for $C_{19}H_{20}N_2O_2$: C 74.00, H 6.54, N 9.08; found: C 73.78, H 6.31, N 8.89.

N-*Carbethoxyphthalimide (6)*

Nefkens' method (9) for the preparation of this compound was modified. A solution of phthalimide (14.7 g, 100 mmol) in dry DMF (100 ml) was added dropwise into a stirred suspension of sodium hydride (5.0 g, 105 mmol, a 50% dispersion in mineral oil, oil removed by washing with dry petroleum ether) kept at room temperature. After 3 h, the evolution of hydrogen had ceased. The mixture was cooled to 5°C and freshly distilled ethyl chloroformate (10 ml, 130 mmol) was added dropwise keeping the temperature below 40°C. The mixture was stirred at 35°C for 3 h and then poured into ice-cold water (1 L) with vigorous stirring. The resulting white solid was collected by filtration and recrystallized from ethanol to give 20 g (91%) of product, mp 80°C (lit. (9) mp 80°C).

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