Potential Central Nervous System Active Agents. 1. Synthesis of Aromatic *N*-Benzyl Amides

Vincent C. Agwada

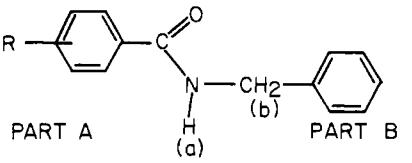
Department of Chemistry, Faculty of Physical Sciences, University of Nigeria, Nsukka, Nigeria

The preparation and spectral properties (IR, MS, NMR) are given for 18 aromatic *N*-benzyl amides, variously substituted on the acyl part, including four new ones and an (*E*)-cinnamamide derivative. The amides were prepared by heating the appropriate *N*-benzylammonium salt in *o*-xylene, or from the reaction of the corresponding acid chloride with benzylamine. The occurrence of an intense peak in their mass spectra, which corresponds to the loss of the *N*-acyl substituent without hydrogen transfer, is reported.

The use of *N*-benzyl amides as standard derivatives for the characterization of carboxylic acids and esters is well-known (*1*). In addition, a number of aliphatic carboxamides which contain the *N*-benzyl residue, such as *N*-benzyl-2-chloropropanamide (Hibicon), possess enhanced anticonvulsant activity. This effect, however, was reported to be lacking in the limited number of aromatic analogues that have been investigated (*2*). As part of a general study of the structure–activity relationship in the central nervous system active compounds, 17 *N*-benzylbenzamides, variously substituted on the acyl part, and an (*E*)-cinnamamide derivative (**18-1**) were synthesized according to the method of Fieser and Jones (*3*) in boiling *o*-xylene.

Compounds **7** and **13** and the (*E*)-cinnamamide derivative **18-2** were synthesized from their respective acid chlorides, and benzylamine was synthesized according to the usual procedure (*2*, *4*). Four of the derivatives, **5**, **9**, **13**, and **15**, are new. The spectroscopic data (IR, MS, NMR) not hitherto described in the literature are reported in this communication.

The experimental data of compounds reported herein are presented in Table I. The IR and NMR spectral data are shown in Table II and those of the mass spectra are given in



no.	R	no.	R
1	H	10	4-OMe
2	2-Me	11	2-Cl
3	3-Me	12	3-Cl
4	4-Me	13	2-Br
5	3-NH_2	14	2-I
6	4-NH_2	15	3-I
7	2-OH	16	3-NO_2
8	3-OH	17	2-$CONHCH_2Ph$
9	3-OMe		

Table III. Satisfactory elemental analyses (±0.4% for C, H, N, and halogen, where present, for new compounds; N, for known ones) were obtained for all compounds.

These amides show a characteristic absorption in the infrared spectrum around 3300 cm^{-1} due to the N–H stretching vibration of the trans isomer (*5–8*). (The molecular models of these substances support this assignment.) Also, the amide I and II bands occur in the ranges 1659–1633 and 1564–1535 cm^{-1}, respectively. The proton NMR spectra show a doublet in the region of 4.43 and 4.60 ppm (J = 6 Hz, 2 H) for the benzylic hydrogens ($PhCH_2NHCO$–). The observed coupling constant for these is in excellent agreement with values reported for amides (*9*). The NH proton occurs as a broad and variable signal in the aromatic region. The cinnamamide prepared thermally from the *E* acid (**18-1**) or from its chloride (**18-2**) differ only in their melting points and IR spectra. Since the vinylic coupling constants of these are the same (15 Hz), no isomerism about the double bond must have occurred. Of the amides prepared by the method reported in this communication, eight have higher

Table I. Experimental Data for *N*-Benzylbenzamides and *N*-Benzyl-(*E*)-cinnamamide (18-1, 18-2)

				mp, °C		
compd	mol formula	$M^{+\cdot}$	yield,[a] %	solvent	sublimed	reported
1	$C_{14}H_{13}NO$	211	29[b]	108–109[a]	106–106.5	105–105.5 (*10*), 106 (*11*)
2	$C_{15}H_{15}NO$	225	78	113–114		104 (*12*)
3	$C_{15}H_{15}NO$	225	60	105–106		74.5–75.5 (*1*), 97 (*11*)
4	$C_{15}H_{15}NO$	225	89	133–134.5	135	133 (*1*, *11*)
5	$C_{14}H_{14}N_2O$	226	77	83–84[a]	85	
6	$C_{14}H_{14}N_2O$	226	55	106–109	112–113	89–90 (*1*)
7	$C_{14}H_{13}NO_2$	227	78	158		136.5–137 (*1*), 135–136 (*13*)
8	$C_{14}H_{13}NO_2$	227	89	139–140.5	140–141.5	141–142.5 (*1*)
9	$C_{15}H_{15}NO_2$	241	100	66.5–69	65–67	60–61 (*11*)
10	$C_{15}H_{15}NO_2$	241	92	147–148		131–132.5 (*1*), 126–131 (*1*), 87–88 (*14*, *15*)
11	$C_{14}H_{12}ClNO$	245/247	84	104.5–105		99–99.5 (*10*)
12	$C_{14}H_{12}ClNO$	245/247	40	97–98	*c*	97–98 (*11*)
13	$C_{14}H_{12}BrNO$	289/291	48	115–117	115–117	
14	$C_{14}H_{12}INO$	377	44	130–131	134–135	109–110 (*1*)
15	$C_{14}H_{12}INO$	337	44	95–98	96–97	
16	$C_{14}H_{12}N_2O_3$	256	42	95–96	*c*	100–101 (*1*), 95 (*11*)
17	$C_{22}H_{20}N_2O_2$	344	98	173–174[d]	*c*	178–179 (*1*), 178 (*16*), 176–178 (*17*)
18-1	$C_{16}H_{15}NO$	237	92	111[e]		94–96.5 (*2*), 103–104 (*18*), 106–107 (*19*)
18-2	$C_{16}H_{15}NO$	237	83	117–119	107–108	

[a] From crude; these are pure for all practical purposes except for the halo and nitro compounds they needed little or no further purification (evidence from thin-layer chromatography). [b] Yield after heating for 1 h neat. [c] Decomposes. [d] From acetone. [e] From ethanol-water.

0021-9568/82/1727-0479$01.25/0

Table II. IR and NMR Spectral Data for the Aromatic *N*-Benzyl Amides[a]

	IR, cm^{-1}				proton NMR δ				
		amide band							
compd	NH, NH_2	I	II	others	aromatic (A and B)	NH (a)	CH_2 (b)	$J_{a,b}$	others
1	3280	1645	1555	1605	7.10–8.00	6.85 br	4.60 d	6	
2	3280	1640	1535	1603	6.80–7.60	6.42 br	4.55 d	6	2.37 (s, $PhCH_3$)
3	3340 sh, 3320	1650	1545	1610 sh, 1589, 1500 sh	7.00–7.80	*b*	4.55 d	6	2.82 (s, $PhCH_3$)
4	3302[c]	1643	1550	1613 sh, 1570 sh, 1510	6.90–7.90	6.75 br	4.57 d	6	2.35 (s, $PhCH_3$)
5	3400, 3220	1649	1555	1635 sh, 1610 sh, 1590	6.40–7.50	*b*	4.54 d	6	3.84 (br, $PhNH_2$)
6	3401,[c] 3305, 3215	1643	1535	1633 sh, 1610 sh, 1605, 1574, 1504	7.25 (m, B), 7.57 (d, 2, J = 8, A, + NH br), 7.65 (d, 2, J = 8, A)		4.54 d	6	3.81 (br, $PhNH_2$)
7	3340[d]	1650	1550	1598	6.30–7.60	*b*	4.58 d	6	
8	3310[d]	1650 sh	1545	1628, 1590, 1500 sh	6.85–7.54[e]	*b*	4.48 d	6	
9	3300 sh, 3270	1650	1555	1600 sh, 1588, 1540 sh	6.80–7.60	*b*	4.54 d	6	3.72 (s, $PhOCH_3$)
10	3305 sh,[c] 3255	1633	1564	1512, 1507	6.40–8.20	*b*	4.57 d	6	3.79 (s, $PhOCH_3$)
11	3260	1650	1560	1600	6.91–7.65	*b*	4.55 d	6	
12	3300	1649	1555	1610 sh, 1570 sh	7.00–7.90	6.80 br	4.56 d	6	
13	3260	1652	1560	1595	6.90–7.70	6.62 br	4.47 d	6	
14	3260	1650	1560	1590	6.75–8.00	6.46 br	4.46 d	6	
15	3292 sh,[c] 3270	1648 sh 1636	1544	1607 sh, 1592 sh, 1563 sh, 1500 sh	6.70–8.20	*b*	4.53 d	6	
16	3280[c]	1634	1547	1607 sh, 1589, 1525	7.37 (m, B),[e] 7.60–9.00 (A)	*b*	4.58 d	6	
17	3268,[c] 3210 sh	1633	1550	1590, 1598, 1576	7.00–7.60[e]	8.52 br	4.43 d	6	
18-1	3288	1657	1562	1618, 1580	6.90–7.60	*b*	4.45 d	6	6.57 (d, 1, J = 15, =CH)
			1555 sh						7.62 (d, 1, J = 15, =CH)
18-2	3268	1659	1557 1538	1615, 1580 sh	6.90–7.60	*b*	4.45 d	6	6.51 (d, 1, J = 15, =CH)
									7.64 (d, 1, J = 15, =CH)

[a] Symbols: br = broad signal; s = singlet; d = doublet; m = multiplet. [b] Signal occurs in the aromatic region. [c] Measured in KBr. [d] OH occurs in the same region. [e] Measured in $(CD_3)_2SO$.

Table III. Relative Intensities of Characteristic Signals in the Mass Spectra of the Aromatic *N*-Benzyl Amides at 70 eV[a]

	relative intensities, %														
	ion					*m/e*[b]									
compd	$M^{+\cdot}$	$M^{+\cdot}$ – 1	$M^{+\cdot}$ – R	R-$PhCO^+$	R-Ph^+	107	106	105	92	91	77	76	65	51	39
1	36	14		100		15	37		1	13	81	5	8	39	14
2	36	6	19	100		10	17	16	8	86	27	4	37	22	26
3	53	16	4	100		2	21	4	6	63	7	1	25	7	10
4	37	11		100		2	16	6	5	45	7	1	21	7	8
5	3			10		7	64	3	26	100	8		18	7	7
6	30	2		100		2	12	3	26	26	8	2	28	7	16
7	27	2	2	19	7	10	21	5	11	100	11	2	22	7	15
8	14	60		100	99.9	3	23	4	87	33	11	2	69	10	26
9	86	17	1	100		42	31	5	26	26	46	5	16	10	9
10	37	6		100		11	12	4	11	19	18	3	9	4	4
11	44/14	12	51	100/35	36/11	44	49	52	7	58	85	18	24	61	37
12	58/19	28	3	100/33	42/14	5	48	7		19	12	6	8	8	
13	66/66	15	94	100/95	35/31	31	43	54	6	61	82	41	28	46	22
14	33	5	28	46	17	40	51	62	6	48	100	44	22	63	37
15	44	10	7	100	41	9	37	53	6	31	62	91	25	40	16
16	100	23	2	77	3	6	49	10	9	49	23	50	47	22	18
17	1		2	33	2	5	27	13	9	100	11	6	12	6	
18-1	76	4		100 (PhCH=CHCO$^+$)	57 (PhCH=CH$^+$)	11	64	4	2	23	48	4	8	19	6
18-2	70	4		100 (PhCH=CHCO$^+$)	58 (PhCH=CH$^+$)	12	65	4	2	22	49	4	8	18	6

[a] Low-resolution spectra; where mass of ion is same as that of *m/e*, the latter is quoted. [b] *m/e* 107 = $PhCH_2NH_2^{+\cdot}$; *m/e* 106 = $PhCH{=}NH_2^+$; *m/e* 105 = $PhCH{=}NH^{+\cdot}$; *m/e* 92 = $C_7H_8^+$; *m/e* 91 = $PhCH_2^+$; *m/e* 77 = Ph^+; *m/e* 76 = $C_6H_4^+$; *m/e* 65 = $C_5H_5^+$; *m/e* 51 = $C_4H_3^+$; *m/e* 39 = $C_3H_3^+$.

melting-point values than those reported for them in the literature (*1*, *2*).

The compounds show unusual mass-spectral behavior. They exhibit a characteristic peak, *m/e* 106 (Table III), which corresponds to the loss of *N*-acyl substituent from the molecular ion without hydrogen transfer as usual (*20*). This phe-

nomenon, now quite well documented in the case of open and cyclic diamine compounds and their derivatives, has been explained on the basis of neighboring group participation of the second nitrogen function (*21*). But an α cleavage of this type, without hydrogen rearrangement, is rare in the monoamine derivatives.

These compounds have been submitted for biological screening, and the results will be reported elsewhere.

Experimental Section

Elemental analyses were performed by Dr. Franz Pascher and Ellen Pascher, Mikroanalytisches Laboratorium, Bonn. Mass spectra (MS) were determined on a CEC 21-110 B spectrometer at 70 eV by Professor Manfred Hesse, University of Zürich, Switzerland (to whom I am grateful for helpful discussions). Unless otherwise mentioned, melting points were determined on a Kofler hot stage and are uncorrected. Infrared (IR) spectra were obtained on a Unicam Model SP 1000 spectrophotometer in Nujol mulls. Nuclear magnetic resonance (NMR) spectra were measured on a Varian Associates T-60 instrument, in $CDCl_3$. All peak positions were measured in ppm relative to tetramethylsilane (Me_4Si) as an internal standard ($\delta_{Me_4Si} = 0$). The J values were recorded in hertz.

***Thermal Method. Typical Procedure. N-Benzyl-4-methylbenzamide* (4).** A mixture of 4-methylbenzoic acid (27.2 g, 0.2 mol), benzylamine (21.4 g, 0.2 mol), and 50 mL of *o*-xylene was placed in a 100-mL round-bottomed flask equipped with a reflux condenser and a Dean-Stark apparatus and heated in an electrical heating mantle for 7.5 h when distillation of water ceased. Xylene was removed by distillation, the reaction mixture cooled to room conditions, 50 mL of ice cold water added, and the slurry filtered. The cake was further washed with two portions of 50 mL of cold water, 50 mL of 2 N cold aqueous hydrochloric acid, 50 mL of saturated aqueous sodium bicarbonate, and finally water, to give 40.0 g of dry crude. Crystallization from ethanol (95%) gave 34.0 g of colorless needles. Further purification was done by sublimation in vacuo.

***Acid Chloride Method. Typical Procedure. N-Benzyl-2-hydroxybenzamide* (7).** A mixture of salicylic acid (13.8 g, 0.1 mol) and 10.5 mL of thionyl chloride was refluxed for 2 h after which excess reagent was distilled off to give a residual glass, which was taken up in 40 mL of dry benzene. To this was added cautiously, with stirring and cooling (ice bath), a mixture of benzylamine (10.7 g, 0.1 mol) and 15.0 g of triethylamine over 0.5 h; the final solution was allowed to stand for 18 h. Benzene was removed in vacuo to give 18.0 g of crude after normal work-up. Crystallization from ethanol gave 14.1 g of colorless prisms.

Treatment of the benzylammonium salt in *o*-xylene at reflux led to extensive decarboxylation to phenol. The same phenomenon was observed with the salt of 2-methoxybenzoic acid, which also yielded a small portion of **7**.

Acknowledgment

I thank Messrs. O. O. Ibe, D. O. Nwankwo, and N. Igwe for the IR and NMR spectra. My thanks also go to Mr. F. U. Ekezie for the construction of the Dean-Stark apparatus used in the experiments.

Literature Cited

(1) Denner, O. C.; King, J. *J. Org. Chem.* **1943**, *8*, 168.
(2) Kuschner, S.; Cassell, R. C.; Morton, L., II; Williams, J. H. *J. Org. Chem.* **1951**, *16*, 1283.
(3) Fieser, L. F.; Jones, J. E. "Organic Synthesis"; Wiley: New York, 1955; Collect. Vol. 3, p 590.
(4) Smith Kline French Laboratories; *Chem. Abstr.* **1969**, *70*, 37497p, 47130c.
(5) Nakanishi, K. "Practical Infrared Absorption Spectroscopy"; Holden-Day: San Francisco, CA, 1962; p 46.
(6) Williams, D. H.; Fleming, I. "Spectroscopic Methods in Organic Chemistry"; McGraw-Hill: London, 1966; p 63.
(7) Homer, R. B.; Johnson, C. D. In Zbicky, J. "The Chemistry of Amides"; Interscience: London, 1970; pp 187-243.
(8) Kotera, A.; Shibata, S.; Sone, K. *J. Am. Chem. Soc.* **1955**, *77*, 6183.
(9) LaPlanche, L. A.; Rogers, M. T. *J. Am. Chem. Soc.* **1964**, *86*, 337.
(10) Boudet, R. *Bull. Soc. Chim. Fr.* **1949**, 172, 174.
(11) Shingaku, T. *Chem. Abstr.* **1961**, *55*, 4408i.
(12) Osieka, H.; Pomer, E.; Kiefer, H. *Chem. Abstr.* **1969**, *71*, P49619p.
(13) VanAllan, J. A. *J. Am. Chem. Soc.* **1947**, *69*, 2913.
(14) Wilson, B.; Glockling, F. *J. Chem. Soc.* **1950**, 2759.
(15) Buck, I. *J. Am. Chem. Soc.* **1931**, *53*, 1536.
(16) Safford, R. W.; Francell, R. J.; Shay, J. F. *Anal. Chem.* **1949**, *21*, 1454.
(17) Barber, H. J.; Wragg, W. R. *J. Chem. Soc.* **1947**, 331.
(18) Kanunjanz, I. L.; Gambarjan, N. P. *Chem. Abstr.* **1956**, *50*, 11277f.
(19) Narasimhan, N. S.; Ranada, A. C. *Tetrahedron Lett.* **1965**, 4145.
(20) Budziklewicz, H.; Djerassi, C.; Williams, D. H. "Mass Spectrometry of Organic Compounds"; Holden-Day: San Francisco, CA, 1968; p 351.
(21) Süess, H.; Hesse, M. *Helv. Chim. Acta* **1979**, *62*, 1040.

Received for review December 21, 1981. Accepted April 27, 1982. I am indebted to the University of Nigeria for the award of Senate Research Grant No. 00343/79.

Potential Central Nervous System Active Agents. 2. Synthesis of *N*-Benzylphenylacetamides

Vincent C. Agwada

Department of Chemistry, Faculty of Physical Sciences, University of Nigeria, Nsukka, Nigeria

Six *N*-benzylphenylacetamides variously substituted on the acyl part with chloro, methyl, or methoxyl groups, including five new ones, were synthesized by heating their corresponding *N*-benzylammonium salts in *o*-xylene. Their IR, NMR, and mass-spectral (MS) data are presented and compared with those of the *N*-benzylbenzamides and *N*-benzylacetamide, respectively.

In the preceding communication (*1*), the synthesis and the spectroscopic data (IR, MS, NMR) of several *N*-benzylbenzamides, substituted on the acyl part and including the (*E*)-cinnamamide derivative, were reported. Presented in the present communication are the synthesis and the spectroscopic data of six *N*-benzylphenylacetamides, variously substituted on the acyl part with chloro, methyl, or methoxyl groups. Data for *N*-benzylacetamide (**7**) are included for comparison. The compounds were synthesized from their corresponding *N*-

0021-9568/82/1727-0481$01.25/0