Synthesis and Studies of Piperidinone, the Major Metabolite of a New Antidepressant Drug S 3344

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The synthesis of 1-(4-fluorobenzyl)-6-isopropyl-2-piperidinone **7a**, a major metabolite of a new antidepressant S 3344, is described and then substituted with various substituents. The ^1H and ^{13}C nmr provide information on their structure.

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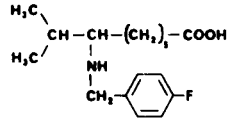
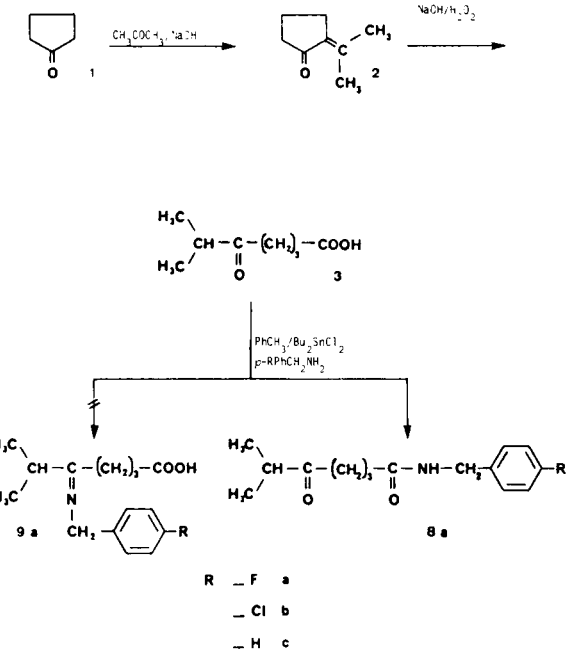
S 3344 is a new antidepressant drug [1,2] whose metabolism leads, through β-oxidation in humans, to its main metabolite **7a**. Subsequent analytical and pharmacological studies [3,4] need an easy synthesis of **7a** on a large scale. The preparation of 100 grams or more was undertaken.

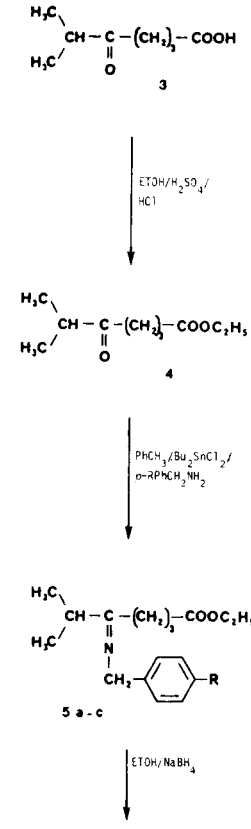


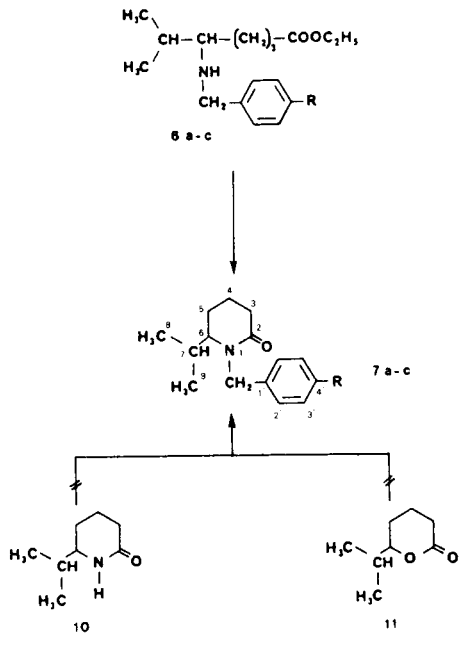
S 3344

Among usual techniques of synthesis for substitution of the lactam **10** [5,6] with *p*-fluorobenzyl chloride or of the lactone **11** [5,6,7] with *p*-fluorobenzylamine failed in our hands. The presence of the isopropyl group with steric and/or electronic hindrance (methyl, ethyl homologues can be obtained in fair yields [8]) may be the reason.



So we synthesised **3** [9,10] from cyclopentanone **1** [9,10]. Attempts to condense *p*-fluorobenzylamine on the keto group of **3** were unsatisfactory. It occurs on the acid group to lead to the keto-amide in spite of the fact that the same reagent reacts on the keto group of the keto-ester **4** to give the desired imino-ester **5a**. We used an efficient catalyst [11] for this type of reaction: azeotropic distillation (toluene) in the presence of 1/20 of the stoechiometric amount of dibutyltin dichloride gave the expected results in good yield. Reduction of **5a** was achieved by its dropwise addition into a suspension of sodium borohydride in absolute alcohol to furnish **6a**. Lactam **7a** was obtained from **6a** by reflux.





This synthetic method was extended to various *p*-phenyl substituents (**b**, X = H; **c**, X = Cl) to test the applicability of this procedure. Compound **7a** is being testing in pharmacology.

The structural assignment was substantiated by mass spectroscopic and ir examinations (Table II).

The ^{1}H nmr data of the compounds are presented in Table III. The signals were assigned using reported chemical shifts. The two protons of the benzyl group (NCH_2) for **5** are shifted towards 3.85 and 4.50 corresponding to two conformers. In compounds **6** an only one singlet is observed at 3.75 which is split in product **7** into two doublets (3.90 and 5.45) corresponding to an AX system. The two methyl groups of the isopropyl substituent are at *ca* 1.10 (d) for **5** 0.90 (d) for **6** and are equivalent, at *ca* 0.85 (t corresponding to a dd) and are nonequivalent for **7**. The ^{13}C nmr experimental chemical shifts are shown in Table IV. The signals of the carbons were assigned unambiguously by single-frequency off-resonance decoupling (SFORD), by J-modulated spin echo and known chemical shift rules in the literature [12-19]. It confirms the nonequivalence of the two methyl groups.

EXPERIMENTAL

Infrared spectra were recorded with a Beckman-Acculab IV. The ^{1}H nmr (80.13 MHz) spectra and the ^{13}C nmr (20.15 MHz) spectra were determined with TMS as the internal standard using a Bruker WP 80 pulsed Fourier transform spectrometer. The ^{13}C nmr spectra were recorded both in the proton-noise decoupled (BB), in the single-frequency-off-resonance decoupled (SFORD) and in the J-modulated spin echo (Pulse Programmer-Aspect 2000-Bruker) modes. Tetramethylsilane was used as the internal standard of chemical shifts (δ in ppm) for deuteriochloroform solutions; coupling constants (absolute values) are expressed in Hz; the proton signals are designed as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; deuterated solvents provided the internal lock signal. Mass spectra were determined on a Ribermag R-10-10 coupled with a Girdel GLC (capillary column CP SIL 5). Combustion analysis were performed by the CNRS (Vernaison).

Table I

Preparation of Compounds **5**, **6**, **7**

Compound	R	Yield %	bp °C/mmHg	Molecular formula	[a]	Analysis Calcd./Found C	H	N
5a	F	41	145/0.05	$C_{17}H_{24}FNO_2$	(293.4)			
5b	Cl	45	155/0.02	$C_{17}H_{24}ClNO_2$	(309.9)			
5c	H	35	135/0.025	$C_{17}H_{25}NO_2$	(275.4)			
6a	F	41	130/0.05	$C_{17}H_{26}FNO_2$	(295.4)	69.12 69.47	8.87 8.84	4.74 5.06
6b	Cl	45	140/0.03	$C_{17}H_{26}ClNO_2$	(311.9)	65.47 65.49	8.40 8.21	4.49 4.49
6c	H	65	135/0.04	$C_{17}H_{27}NO_2$	(277.4)	73.61 73.98	9.81 9.63	5.05 5.12
7a	F	85	110/0.05	$C_{15}H_{20}FNO$	(249.3)	72.26 72.31	8.09 8.02	5.62 5.56
7b	Cl	82	120/0.02	$C_{15}H_{20}ClNO$	(265.8)	67.79 67.79	7.58 7.59	5.27 5.20
7c	H	76	115/0.03	$C_{15}H_{21}NO$	(231.4)	77.88 77.80	9.15 9.13	6.05 6.27

[a] Satisfactory microanalyses were obtained with the exception of compounds **5** which contained traces of tin salts but can be used in the next step without further purification.

Table III
^{1}H NMR Spectral Data of Compounds **5**, **6**, **7**

Compound	R	$CH(CH_3)_2$	N-CH	$N-CH_2$	$NHCH$, $CH(CH_3)_2$, $(CH_2)_3CO$	OCH_2CH_3	OCH_2CH_3	H aromatics
5a	F	1.08 (d, 6H) J = 6 Hz		3.85, (d s, 2H) [b] 4.50	1.50-2.70 (m, 7H)	1.25 (t, 3H) J = 7 Hz	4.12 (q, 2H) J = 7 Hz	6.90-7.50 (m, 4H)
5b	Cl	1.08 (d, 6H) J = 6 Hz		3.80, (d s, 2H) [b] 4.50	1.50-2.75 (m, 7H)	1.25 (t, 3H) J = 7 Hz	4.10 (q, 2H) J = 7 Hz	6.90-7.50 (m, 4H)
5c	H	1.10 (d, 6H) J = 6 Hz		3.88, (d s, 2H) [b] 4.52	1.50-2.75 (m, 7H)	1.30 (t, 3H) J = 7 Hz	4.10 (q, 2H) J = 7 Hz	7.10-7.50 (m, 5H)
6a	F	0.90 (d, 6H) J = 6 Hz		3.75 (s, 2H)	1.40-2.50 (m, 9H)	1.30 (t, 3H) J = 7 Hz	4.15 (q, 2H) J = 7 Hz	6.90-7.50 (m, 4H)
6b	Cl	0.90 (d, 6H) J = 6 Hz		3.70 (s, 2H)	1.00-2.55 (m, 9H)	1.27 (t, 3H) J = 7 Hz	4.15 (q, 2H) J = 7 Hz	6.90-7.50 (m, 4H)
6c	H	0.90 (d, 6H) J = 6 Hz		3.75 (s, 2H)	1.00-2.50 (m, 9H)	1.25 (t, 3H) J = 7 Hz	4.12 (q, 2H) J = 7 Hz	7.10-7.50 (m, 5H)
7a	F	0.85 (t = d d, 6H) J = 6 Hz	3.20 (q = d t, 1H) J = 6 Hz	3.90, 5.45 (d d, 2H) J = 14 Hz	1.30-2.60 (m, 7H)			6.80-7.50 (m, 4H)
7b	Cl	0.85 (t = d d, 6H) J = 6 Hz	3.25 (q, = d t, 1H) J = 6 Hz	3.22, 5.45 (d d, 2H) J = 14 Hz	1.30-2.60 (m, 7H)			7.00-7.30 (m, 4H)
7c	H	0.85 (t = d d, 6H) J = 6 Hz	3.15 (q = d t, 1H) J = 6 Hz	3.85, 5.55 (d d, 2H) J = 14 Hz	1.30-2.60 (m, 7H)			7.30 (s, 5H)

[a] The ^{1}H nmr spectra were recorded for solutions in deuteriochloroform with TMS as the internal standard. [b] The two signals are probably due to two conformers.

Table II

Spectral Properties of the Compounds **5**, **6**, **7**

Compound	R	IR C=O	IR C=N	MS m/e (Relative Intensity, %)
5a	F	1730	1660	293 (M+, 6.9) 248 (M-45, 3.1) 109 (100.0)
5b	Cl	1725	1650	310 (M+, 100.0) 264 (M-46, 81.2)
5c	H	1730	1650	275 (M+, 1) 230 (M-45, 99.1)
6a	F	1730		296 (MH+, 1) 253 (M-43, 38.2)
6b	Cl	1735		311 (M+, 4.8) 270 (M-41, 72.7)
6c	H	1735		277 (M+, 1) 231 (M-46, 13.8)
7a	F	1645		249 (M+, 17.3) 207 (M-43, 62.6) 110 (100.0)
7b	Cl	1630		266 (MH+, 3.8) 222 (M-44, 100.0)
7c	H	1635		231 (M+, 1.1) 188 (M-43, 100.0)

2-Isopropylidene-Cyclopentanone **2**.

Cyclopentanone **1** (50.4 g, 0.6 mole) and acetone (127.6 g, 2.2 moles) were added dropwise and simultaneously to a stirred cooled solution of sodium hydroxyde (30 g, 1000 ml water). The solution was stirred overnight at room temperature, then hydrolyzed (250 ml) and acidified (*p*H 3.5) with acetic acid. The mixture was extrated with benzene (5 x 200 ml). The organic layer was washed with a diluted solution of sodium bicarbonate and with water, dried over sodium sulfate and evaporated. The residual crude product **2** was distilled under vacuum, yield 37.5 g (61%), bp 80-82°/16 mm Hg (lit [9] 80-82°/12 mm Hg).

6-Methyl-5-oxoheptanoic Acid **3**.

A solution a sodium hydroxyde (4*N*, 12 g, 0.3 mole, 75 ml) and a solution of hydrogen peroxyde (15 vol, 0.3 mole, 120 ml) were added dropwise and simultaneously to a stirred, cooled (−10°) solution of 2-isopropylidenecyclopentanone **2** (30 g, 0.24 mole) in methanol (150 ml). When the addition was complete, the mixture was allowed to stand at ambient temperature and stirred overnight. The solvent (methanol) was removed under vacuum and the aqueous layer was washed with diethyl ether (2 x 100 ml), acidified (*p*H 3.5) with diluted sulfuric acid and extracted with diethyl ether (2 x 300 ml). The organic phase was isolated, dried over sodium sulfate and evaporated *in vacuo*. The crude acid thus obtained was pure enough to be used in the next step without further purification. An analytical sample was distillated, bp 100°/0.06 mm Hg, yield 12.6 g (28%) (lit [9] 135-140°/4 mm Hg); ir (neat): 1700 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.05 (d, 6H, $(CH_3)_2CH$, J = 6 Hz), 1.20-3.00 (m, 7H, $CH(CH_3)_2$, $(CH_2)_3CO$), 9.70 (s, 1H, COOH).

Ethyl 6-Methyl-5-oxoheptanoate **4**.

A solution of keto-acid **3** (31.6 g, 0.2 mole) in absolute alcohol with con-

Table IV

^{13}C NMR Spectral Data of Compounds **7**

Compound	R	C2	C3	C4	C5	C6	C7	C8	C9	C10	C1'	C2'	C3'	C4'
7a	F	171.0	31.9	18.2	22.6	59.8	28.7	(18.7) [b]	(15.4) [b]	46.0	133.2 $^4J_{CF}$ = 0	129.1 $^3J_{CF}$ = 8	114.7 $^2J_{CF}$ = 21	161.5 $^1J_{CF}$ = 245
7b	Cl	171.1	31.7	18.0	22.3	59.7	28.4	(18.6) [b]	(15.2) [b]	45.8	135.7	(128.7) [c]	(127.9) [c]	127.8
7c	H	171.8	32.1	18.3	22.7	59.6	28.7	(19.1) [b]	(15.6) [b]	46.6	137.1	(128.3) [c]	(127.6) [c]	126.9

[a] The ^{13}C nmr spectra were recorded for solutions in deuteriochloroform with TMS as the internal standard. [b] Values in parentheses indicate a possible assignment interchange. [c] Values in parentheses indicate a possible assignment interchange.

centrated sulfuric acid (0.3 ml), satured with hydrochloric gas, was refluxed during twelve hours. The solvent was evaporated. The crude residue was distillated in vacuum, yield 27.9 g (74%) bp 130°/17 mm Hg, (lit [10] 121-123°/23 mm Hg); ir (neat): 1710, 1730 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.07 (d, 6H, $(CH_3)_2CH$, J = 6 Hz), 1.25 (t, 3H, O-CH_2-CH_3, J = 7 Hz), 1.50-3.00 (m, 7H, $CH(CH_3)_2$, $(CH_2)_3CO$), 4.17 (q, 2H, O-CH_2-CH_3, J = 7 Hz).

Ethyl 5-(4-Fluorobenzylimino)-6-methylheptanoate **5a**, Ethyl 5-(4-Chlorobenzylimino)-6-methylheptanoate **5b**, and Ethyl 5-Benzylimino-6-methylheptanoate **5c**.

General Procedure.

A mixture of keto-ester **4** (12.15 g, 0.065 mole) and of 4-fluorobenzylamine (8.12 g, 0.065 mole) in dry toluene (200 ml) was refluxed (azeotropic distillation) overnight in the presence of 5% of the stoechiometric amount of dibutyltin dichloride (0.99 g, 0.00325 mole). The precipitate was removed by filtration and the solvent evaporated. The oily residue was distilled in vacuum to give **5a**.

Ethyl 5-(4-Fluorobenzylamino)-6-methylheptanoate **6a**, Ethyl 5-(4-Chlorobenzylamino)-6-methylheptanoate **6b**, and Ethyl 5-Benzylamino-6-methylheptanoate **6c**.

General Procedure.

A solution of imino-ester **5a** (18.5 g, 0.06 mole) in absolute alcohol (100 ml) was added dropwise to a stirred suspension of sodium borohydride (2.75 g, 0.072 mole) in absolute alcohol (500 ml). The mixture was allowed to stand at ambient temperature for 1 hour, hydrolyzed (600 ml) and acidified (*p*H 6-7) with diluted hydrochloric acid (*N*). Alcohol was evaporated under reduced pressure. The aqueous layer was basified (*p*H 10) with sodium bicarbonate, and extracted with diethyl ether (2 x 100 ml). The organic phase was isolated, dried over sodium sulfate and evaporated. The residual crude product **6a** was distilled *in vacuo*.

1-(4-Fluorobenzyl)-6-isopropyl-2-piperidinone **7a**, 1-(4-Chlorobenzyl)-6-isopropyl-2-piperidinone **7b**, and 1-Benzyl-6-isopropyl-2-piperidinone **7c**.

General Procedure.

Pure amino-ester **6a** (2.95 g, 0.01 mole) was refluxed 3 hours at 300° (metallic-bath). The crude oil was distilled under reduced pressure.

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