New Compounds

Synthesis of an Allylic Alcohol and Chloride in the Nortriptyline Series

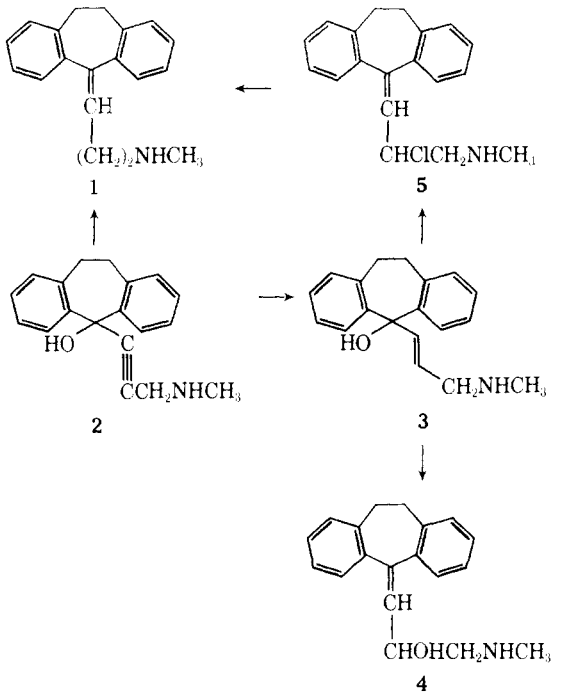
WILLIAM B. LACEFIELD

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206

Received June 22, 1970

The conventional synthesis of nortriptyline (**1**) from the acetylenic carbinol **2** by catalytic reduction and dehydration has been described.[1] Partial hydrogenation of **2** yields the vinyl carbinol **3**.[1] I wish to report the rearrangement of **3** to the allylic alcohol **4** and to the chloride **5** and the hydrogenolysis of **5** to **1**.

The tertiary vinyl carbinol **3** undergoes a very facile rearrangement in the presence of acid. The product of this rearrangement with aq HCl is **4**, whereas with dry HCl in $CHCl_3$ the product is **5**. Catalytic hydrogenolysis of **5** affords **1** in good yield. Compound **4** and the corresponding ketone **6**, have been described as antidepressant and anxiolytic agents.[2]



Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points were taken in an open capillary and are uncorrected.

5-(2-Hydroxy-3-methylaminopropylidenyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (4).—A soln of 5-hydroxy-5-(3-methylaminopropenyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (**3**) (27.9 g, 100 mmoles) in 100 ml of 3 *N* HCl was prepared by warming the mixture gently. After 1 hr at room temp the mixture was made basic with 50% NaOH. The product was extracted into 1 l. of Et_2O, washed with H_2O, dried (Na_2SO_3), filtered, and evaporated *in vacuo*. Two recryst from C_6H_6–Skelly B (1:5) afforded **4** (20 g of yellow rosettes): mp 110–112°; uv max (95% EtOH) 242 mμ (ε 14,500). *Anal.* ($C_{19}H_{21}NO$) C, H, O.

An attempt to prepare **5** from **4** with HCl in $CHCl_3$ under the same conditions which gave **5** from **3** afforded only **4** as the HCl salt. Thus, a soln of **4** (2.8 g, 10 mmoles) in $CHCl_3$ (100 ml) was treated with anhyd HCl. The resultant ppt was collected by filtration, washed with Et_2O, dried (Na_2SO_3), and recrystd from EtOH–$(CH_3)_2CO$–Et_2O (1:1:10). The product was **4**·HCl (2.0 g), mp 166–167°. *Anal.* ($C_{19}H_{22}ClNO$) C, H, N.

5-(2-Chloro-3-methylaminopropylidenyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene·HCl (5).—A soln of 5 g (18 mmoles) of **3** in 200 ml of warm (40°) $CHCl_3$ was satd with HCl gas. The reaction mixture was concd *in vacuo* to *ca.* 0.5 vol and was poured into 400 ml of dry Et_2O. Crude **5** was collected by filtration. Two recrystn from $CHCl_3$–Et_2O (1:5) gave **5** (5.2 g, 87%): mp 141–143° dec; uv max (95% EtOH) 243 mμ (ε 15,000). *Anal.* ($C_{19}H_{21}Cl_2N$) C, H, Cl.

Nortriptyline·HCl (1).—A 3.4-g (10 mmoles) sample of **5** was added to a prereduced mixture of NaOAc (3.3 g, 40 mmoles), PtO_2 (0.1 g), and glacial AcOH (200 ml). The reaction mixture was shaken with H_2 at 3.16 kg/cm² until 10 mmoles had been consumed. Pt was removed by filtration, and AcOH was distilled *in vacuo*. The residue was treated with 10 ml of 50% NaOH soln. The pptd **1** (free base) was extd into 500 ml of Et_2O, washed twice with 25-ml portions of H_2O, dried (Na_2SO_4), and filtered. The filtrate was treated with HCl gas until pptn of **1**·HCl was complete. The product was collected by filtration and recrystd twice from EtOH–Et_2O (1:10) giving pure **1**·HCl, mp 206–208°, identical with an authentic sample of nortriptyline·HCl by mmp and by ir, uv, and nmr spectra. *Anal.* ($C_{19}H_{22}ClN$) C, H, Cl, N.

Acknowledgments.—The author is grateful for helpful discussions with Dr. Jack Mills and Dr. Winston S. Marshall and for the assistance of Mrs. Wilma Mills which was instrumental in the successful completion of this work. Special thanks are due to Dr. Harold E. Boaz and Mr. D. O. Woolf for the spectral data and to Mr. George Maciak for microanalyses.

(1) L. R. Peters and G. F. Hennion, *J. Med Chem.*, **7**, 390 (1964).

(2) Soc. Ind. pour la Fab. des Antibiotiques, Belgium Patent 730,094 (1969) (Derwent 39,820).

Acylthiazolidines

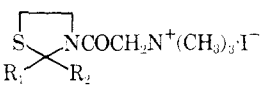
F. BANCI

Research Department, Dott. R. Ravasini and Co., Rome, Italy

Received June 29, 1970

In a search for lipotropic agents based on the thiazolidine ring[1a,b] we have synthesized a series of new compounds of the general formulas in Tables I and II. The

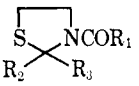
TABLE I



No.	R_1	R_2	Mp, °C	Formula	—Analyses for I⁻— Calcd	Found
1	H	H	dec	$C_8H_{17}INOS$	40.38	39.45
2	H	C_6H_5	dec	$C_{14}H_{21}INOS$	33.54	32.98
3	H	$CH_3(CH_2)_6$	dec	$C_{15}H_{31}INOS$	31.69	31.10
4	H	4-ClC_6H_4	dec	$C_{14}H_{20}ClINOS$	30.74	30.15
5	H	4-$CH_3OC_6H_4$	dec	$C_{15}H_{23}INO_2S$	31.07	30.20

(1) (a) P. Maitre and A. Cier, *Sem. Hop.*, **39**, 2173 (1963). (b) D. A. Carneiro Filho and D. P. Brandao Egidio, *Hospital (Rio de Janeiro)*, **75**, 1187 (1969); *Chem. Abstr.*, **72**, 11312 (1970).

TABLE II



No.	R_1	R_2	R_3	Mp, C°	Crystn solvent	Formula[b]
1	3-Py[c]	H	H	194–196[a]	EtOH	$C_{15}H_{13}N_5O_3S$[a]
2	3-Py	Me	Et	170–172[a]	EtOH	$C_{18}H_{19}N_5O_3S$[a]
3	3-Py	Et	Et	183–184[a]	EtOH	$C_{19}H_{21}N_5O_3S$[a]
4	3-Py	H	*n*-Pr	134–136[a]	EtOH	$C_{18}H_{19}N_5O_3S$[a]
5	3-Py	H	$CH_3(CH_2)_6$	159–161[a]	EtOH	$C_{22}H_{27}N_5O_3S$[a]
6	3-Py	H	C_6H_5	99–100	EtOH	$C_{15}H_{14}N_2OS$
7	3-Py	H	4-ClC_6H_4	192–193[a]	EtOH	$C_{21}H_{16}ClN_5O_3S$[a,d]
8	3-Py	H	4-$CH_3OC_6H_4$	130–134[a]	EtOH	$C_{22}H_{19}N_5O_3S$[a]
9	$CH_3(CH_2)_3$	H	C_6H_5	68–69	Ligroin	$C_{14}H_{19}NOS$
10	$(CH_3)_2CHCH_2$	H	C_6H_5	64–65	Ligroin	$C_{14}H_{19}NOS$
11	$CH_3(CH_2)_{10}$	H	C_6H_5	55–56	EtOH–H_2O	$C_{21}H_{33}NOS$

[a] As picrate. [b] Elemental analyses were performed by A. Bernhardt, West Germany. The analytical results were within ±0.4% of the theoretical values. All compounds were analyzed for C, H, N, S. [c] Py = pyridyl. [d] Cl anal. also.

thiazolidines in Table I were unstable and too toxic for pharmacological test. None of the thiazolidines described in Table II showed significant activity in mice kept on a hyperlipidic diet in comparison with choline.

Experimental Section

All melting points were obtained in open capillary tubes and are uncorrected.

General Procedure for Compounds in Table I.—The 3-dimethylaminoacetylthiazolidines were prepared according to the literature[2a] and were converted into quaternary salts by treating their ethereal soln with an equimolar amount of MeI for 12 hr at room temp. The ppt was washed with Et_2O, dried *in vacuo*, and immediately analyzed for I^-.

General Procedure for Compounds in Table II.—The thiazolidines used for acylation were known products; they were synthesized according to described methods.[2a,b] The nicotinyl derivatives were prepared by adding nicotinyl chloride·HCl (0.02 mole) portionwise to a soln of the appropriate thiazolidine (0.02 mole) and Et_3N (0.04 mol) in CH_2Cl_2 (100 ml). After 20 hr at room temp the soln was concentrated *in vacuo* to dryness and washed (H_2O); the residue was dissolved in EtOH and purified by dilution (H_2O) and the sepd oil was crystd as the picrate in the usual way (EtOH).

For the preparation of the other acyl derivatives, Et_2O, and K_2CO_3 were used instead of CH_2Cl_2 and Et_3N, respectively.

Acknowledgment.—We thank Mr. A. Clerico for helpful assistance in synthetic work.

(2) (a) R. Tondeur, R. Sion and E. Deray, *Bull Soc. Chim. Fr.*, 2493 (1964). (b) E. D. Bergmann and A. Kaluszyner, *Recl. Trav. Chim. Pays-Bas*, **78**, 289 (1959).

Some Amides of 2-Hydroxy- (or Alkoxy-) 3-methoxybenzoic Acid

E. COSTAKIS AND G. TSATSAS*

Laboratory of Pharmaceutical Chemistry, University of Athens, Athens 144, Greece

Received July 6, 1970

The fact that amides of vanillic acid and their derivatives show various biological activities, notably analeptic,[1-3] antibacterial, and antifungal,[4] prompted us to perform the synthesis and pharmacological evaluation of the title amides. The standard methods of synthesis are given in the Experimental Section.

All of the amides listed in Table I were tested for antibacterial and antifungal actions,[5] and some of them were examined for CNS activity in mice,[6-8] for anti-inflammatory activity in rats and guinea pigs,[9-12] and analeptic activity in mice and rats.[13-15] None of the compounds in these tests showed anything worthy of note.

Experimental Section[16]

Amides were purified by recrystn or distn under reduced pressure. The 2-alkoxy- (methoxy-, ethoxy-, or isopropoxy-) 3-methoxy benzoic acids and their corresponding chlorides were prepared as reported previously.[17] 2-Acetoxy-3-methoxybenzoyl chloride was obtained in 88% yield, by treating the corresponding acid with $SOCl_2$. Low yields (25–30%) were encountered when 2-hydroxy-3-methoxybenzoyl chloride was prepared by refluxing *o*-vanillic acid with excess $SOCl_2$ in C_6H_6 for 1.5 hr.[18]

Amides of 2-Alkoxy-3-methoxybenzoic Acid.—A soln of the 2-alkoxy-3-methoxybenzoyl chloride (0.05 mole) in 20 ml of anhyd Et_2O was added dropwise with vigorous stirring to a soln of the amine (0.05 mole) in 40 ml of 1 *N* NaOH. Stirring was continued 30 min after completion of the addition. The mixture was extd with Et_2O. The combined exts were dried (Na_2SO_4) and evapd (see Table I).

2-Hydroxy-3-methoxybenzamides.—To a cooled soln of 2-acetoxy-3-methoxybenzoyl chloride (0.05 mole) in 50 ml of dry C_6H_6 was added dropwise with stirring a soln of amine (0.05 mole) and Et_3N (0.05 mole) in 30 ml of dry C_6H_6. Stirring was

* To whom correspondence should be addressed.

(1) K. Kratzl and E. Kvasnicka, *Monatsh. Chem.*, **83**, 18 (1952).
(2) K. Kratzl, K. H. Ginzel, E. Kvasnicka and M. Nelböck-Hochsteher, *Proc. Int. Congr. Biochem., 2nd*, **1952**, 437 (1953).
(3) B. Botta, L. Canonica, and E. Pavanati, *Atti. Soc. Lomb. Sci. Med. Biol.*, **9**, 22 (1954).
(4) I. A. Pearl and D. L. Beyer, *J. Amer. Chem. Soc.*, **75**, 2627 (1953).
(5) G. Coppi, A. Maselli, and C. Ciani-Bonardi, *Farmaco Ed. Sci.*, **20**, 203 (1965).
(6) F. M. Berger, *J. Pharmacol. Exp. Ther.*, **93**, 470 (1948).
(7) J. R. Boissier, *Actual. Pharmacol.*, **12**, 7 (1959).
(8) C. Bianchi, *Arch. Int. Pharmacodyn. Ther.*, **111**, 227 (1957).
(9) C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954).
(10) L. O. Randall and J. T. Selitto, *Arch. Int. Pharmacodyn. Ther.*, **111**, 409 (1957).
(11) J. Reinhart and E. de Beer in "Biological Standardization," J. Burn, D. Finney, and L. Goodwin, Ed., 2nd ed, Oxford University Press, London, 1950, p 316.
(12) E. Adami and E. Marazzi, *Arch. Int. Pharmacodyn. Ther.*, **107**, 322 (1956).
(13) P. Siegmund and M. Wolf, *Arch. Exp. Pathol. Pharmakol.*, **216**, 323 (1952).
(14) G. Chen and B. Bohner, *J. Pharmacol. Exp. Ther.*, **131**, 179 (1961).
(15) R. Rushton and H. Steinberg, *Nature (London)*, **197**, 1017 (1963).
(16) Melting points and boiling points are not corrected.
(17) G. Tsatsas and E. Costakis, *J. Med. Chem.*, **12**, 870 (1969).
(18) M. A. El-F. Ibrahim, H. A. El-Mangouri, aud Y. M. Abou-Zeid, *Congr. Sci. Farm. Conf. Comun., 21st*, **1961**, 468 (1962).