Synthesis and Spectral Properties of 6*H*-2,7,7-Trimethyl-4-(*o*,*p*-R-phenylamino)-7,8-dihydrofuro[3,2-*c*]azepines

Eduardo Cortés Cortés* [1], Eduardo Cortés Romero and Alicia Domínguez Taylor

Istituto de Química [2], Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán, 04510, México, D.F.

Received November 5, 1993

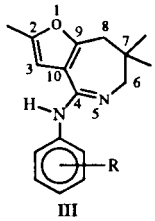
The preparation of nine novel 6*H*-2,7,7-trimethyl-4(*o*-,*p*-R-phenylamino)-7,8-dihydrofuro[3,2-*c*]-azepines with possible pharmacological activity is described. The structure of all products was corroborated by ir, ^{1}H-nmr and ms.

J. Heterocyclic Chem., **31**, 725 (1994).

The furo[3,2-*c*]azepines represent a series of compounds of medicinal interest, mainly as tranquilizing, and antibacterial agents [3-7]. Thus there are only few patents on the preparation of this type of compounds [3,4,6,7].

As a part of a program directed towards the synthesis and spectral property determination of heterocyclic derivatives with possible pharmacological activity, we describe in this report the synthesis of compounds **III**, **1-9** (Scheme 1), following the two steps indicated in Scheme 2.

SCHEME 1



III

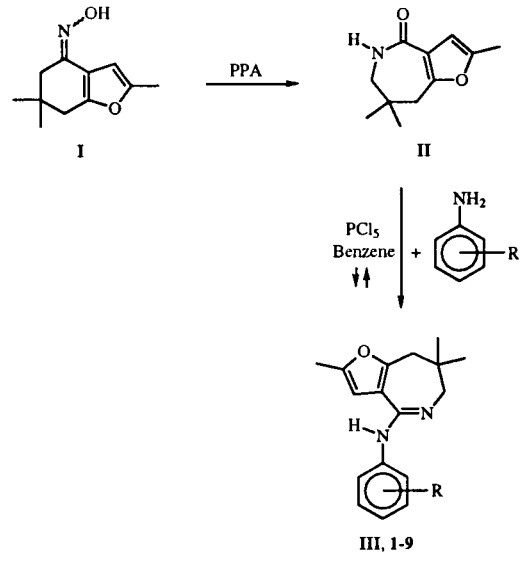
R

1	H
2	*o*-CH_3
3	*o*-OCH_3
4	*o*-Cl
5	*o*-Br
6	*p*-CH_3
7	*p*-OCH_3
8	*p*-Cl
9	*p*-Br

The oxime mixture **I** was converted to the furoazepin-4-one **II** by heating in the presence of polyphosphoric acid in 99% yield [8].

Treatment of furazepin-4-one **II** with the corresponding R-phenylamine in presence of phosphorus pentachloride and refluxing benzene for seventeen hours afforded the compounds **III**, **1-9**. The infrared spectrum of compounds **1-9** displayed absorptions at 3400-3420 cm^{-1} for N-H stretching, at 1635-1638 cm^{-1} for C=N stretching, at 1240-1285 cm^{-1} for C-N stretching; at 1030-1100 cm^{-1} for C-O stretching, and the corresponding absorptions for the R-substituent. In the ^{1}H-nmr spectra of derivatives **1-9** the presence of one-proton broad signal at δ 3.5-5.0, with exchanges with deuterium oxide, was consistent with the presence of an amine group; another one proton singlet at δ 6.2-6.5 was assigned to the methine proton joined to C-3. The two proton signal at δ 2.95-3.0 singlet and δ 2.70-2.77 signelt were assigned to the methylene protons joined to C-6 and C-8. The aromatic compounds appeared as an unresolved multiplet or singlet at δ 6.7-7.6.

SCHEME 2



The mass spectrum of the compounds **1-9** exhibit an abundant molecular ion which probably reflects the stable nature of the 7,8-dihydrofuro[3,2-*c*]azepine ring under electron impact. The relative abundance of the principal fragments ions of compounds **1-9** are given in Table 1. It can be seen that the compounds have some common features, the only difference being in the base peak. The main fragmentation pathways of **1-9** include the elimination of the R-substituent from the molecular ion to produce the base peak $[M-R]^+$ for 1-5; loss of a hydrogen atom occurs in all the mass spectra given rise to the base peak for **6-9**.

Further investigation on the synthesis of novel compounds from furazepin-4-one are presently being carried out.

Table 1

Relative Abundances (%) of Principal Fragments in the Mass Spectra of 6*H*-2,7,7-trimethyl-4(*o*-,*p*-R-phenylamino)-7,8-dihydrofuro[3,2-*c*]azepines

Compound	R	M‡	[M-1]$^+$	[M-R]$^+$	[M-15]$^+$	[M-30]‡	[M-43]$^+$	[M-44]‡	[196+R]$^+$	196	176	120	43
1	H	95	100	100	19	23	12	14	5	6	5	19	18
2	*o*-CH_3	75	68	100	100	18	14	8	10	7	6	71	35
3	*o*-QCH_3	74	40	100	8	25	8	5	5	7	9	54	28
4	*o*-Cl	90	83	100	44	54	15	30	14	15	14	42	53
5	*o*-Br	83	21	100	17	28	8	10	6	9	12	44	33
6	*p*-CH_3	74	100	7	7	13	8	8	7	6	5	19	44
7	*p*-OCH_3	56	100	-	22	12	6	5	5	4	5	57	21
8	*p*-Cl	90	100	-	19	22	13	14	6	8	10	32	15
9	*p*-Br	85	100	-	16	14	10	10	5	9	14	90	52

Table 2

Physical, Analytical and Spectral Data for the 6*H*-2,7,7-Trimethyl-4- (*o*-,*p*-R-phenylamino)-7,8-dihydrofuro[3,2-*c*]azepines

Compound No.	R	Mp °C	Yield %	Molecular Formula	Analyses % Calcd./Found C	H	Spectral Data
1	H	Semisolid	28.0	$C_{17}H_{20}N_2O$	76.08 76.06	7.51 7.50	ir (chloroform): 3406, 1637, 1285, 1110 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.0 (s, 5H), 6.3 (s, 1H), 5.3-4.6 (bs, 1H), 2.95 (s, 2H), 2.72 (s, 2H), 2.25 (s, 3H), 1.05 (s, 6H); ms: M‡ at m/z 268
2	*o*-CH_3	Semisolid	53.8	$C_{18}H_{22}N_2O$	75.56 75.54	7.85 7.84	ir (chloroform): 3407, 1638, 1285, 1112 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.3-6.7 (m, 4H), 6.5 (s, 1H), 5.0-4.0 (bs, 1H), 2.98 (s, 2H), 2.77 (s, 2H), 2.27 (s, 2H), 2.2 (s, 3H), 1.1 (s, 6H); ms: M‡ at m/z 282
3	*o*-OCH_3	Semisolid	26.0	$C_{18}H_{22}N_2O_2$	72.45 72.43	7.43 7.42	ir (chloroform): 3409, 1637, 1285, 1113 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 6.95 (s, 4H), 6.42 (s, 1H), 5.0-4.6 (bs, 1H), 3.80 (s, 3H), 2.95 (s, 2H), 2.72 (s, 2H), 2.25 (s, 3H), 1.07 (s, 6H), ms: M‡ at m/z 298
4	*o*-Cl	Semisolid	60.0	$C_{17}H_{19}ClN_2O$	67.43 67.41	6.33 6.32	ir (chloroform): 3403, 1637, 1286, 1090, 745 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.5-6.8 (m, 4H), 6.27 (s, 1H), 4.5-3.5 (bs, 1H), 3.0 (s, 2H), 2.75 (s, 2H), 2.20 (s, 3H), 1.1 (s, 6H); ms: M‡ at m/z 302, [M+2]‡ at m/z 304
5	*o*-Br	Semisolid	35.0	$C_{17}H_{19}BrN_2O$	58.80 58.78	5.52 5.49	ir (chloroform): 3400, 1635, 1283, 1112, 650 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.6-6.7 (m, 4H), 6.3 (s, 1H), 4.0-3.5 (bs,1H), 3.0 (s, 2H), 2.75 (s, 2H), 2.23 (s, 3H), 1.1 (s, 6H). ms: M‡ at m/z 346, [M+2]‡ at m/z 348
6	*p*-CH_3	Semisolid	39.0	$C_{18}H_{22}N_2O$	75.56 75.53	7.85 7.83	ir (chloroform): 3418, 1635, 1285, 1100 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 6.95 (AA'BB', 4H), 6.25 (s, 1H), 4.0-3.5 (bs, 1H), 2.93 (s, 2H), 2.7 (s, 2H), 2.25 (s, 3H), 2.22 (s, 3H), 1.05 (s, 6H); ms: M‡ at m/z 282
7	*p*-OCH_3	Semisolid	28.0	$C_{18}H_{22}N_2O_2$	72.45 72.42	7.43 7.40	ir (chloroform): 3405, 1637, 1285, 1100 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 6.9 (s, 4H), 6.4 (s, 1H), 4.0-3.5 (bs, 1H), 3.0 (s, 3H), 2.95 (s, 2H), 2.73 (s, 2H), 2.25 (s, 3H) 1.1 (s, 6H); ms: M‡ at m/z 298
8	*p*-Cl	Semisolid	30.0	$C_{17}H_{19}ClN_2O$	67.43 67.40	6.33 6.31	ir (chloroform): 3412, 1635, 1286, 1090, 750 cm^{-1}; ^{1}H-nmr (deuteriochloroform):δ 7.05 (AA'BB', 4H), 6.3 (s, 1H), 4.5-3.5 (bs, 1H), 2.93 (s, 2H), 2.75 (s, 2H), 2.22 (s, 3H), 1.1 (s, 6H); ms: M‡ at m/z 302, [M+2]‡ at m/z 304
9	*p*-Br	65-67	25.0	$C_{17}H_{19}BrN_2O$	58.80 58.77	5.52 5.50	ir (chloroform): 3408, 1638, 1286, 1090, 660 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.1 (AA'BB', 4H), 6.2 (s, 1H) 4.5-3.5 (bs, 1H), 2.96 (s, 2H), 2.75 (s, 2H), 2.2 (s, 3H), 1.05 (s, 6H); ms: M‡ at m/z 346, [M+2]‡ at m/z 348

EXPERIMENTAL

All the final compounds **1-9** are semisolid.

The ir spectra were recorded on a Nicoledt FT-55X spectrophotometer. The ^{1}H-nmr spectra were recorded on a Varian FT-80 spectrometer operating at 80 MHz, in deuteriochloroform solution containing tetramethylsilane as the internal standard with chemical shifts (δ) expressed downfield from TMS. The mass spectra were measured on a Hewlett-Packard Model 5985A quadrupole mass spectrometer using the direct inlet system. The spectra wre recorded at an ionization chamber temperature of 190° and an ionizing electron energy of 70 eV.

Compounds **I** and **II** have been prepared following a reported procedure [8]. The structure of **I** and **II** was supported by ir, ^{1}H-nmr and mass spectral data which are similar to those reported.

Synthesis of 6*H*-2,7,7-Trimethyl-4-(*o*-,*p*-R-phenylamino)-7,8-dihydrofuro[3,2-*c*]azepines **1-9**.

To 15 ml of benzene was added 0.208 g (1 x 10^{-3}mole) of phosphorus pentachloride and the mixture was stirred and heated at reflux for two hours. Subsequently was added 0.203 g (1.0 x 10^{-3}mole) of furoazepin-4-one **II** and the reflux was continued for two hours, subsequently was added 3.6 x 10^{-3} mole of R-aniline and stirring at reflux was continued for seventeen hours. The reaction mixture was cooled with ice-water, filtered and washed with benzene (3 x 5 ml). The solid residue was dissolved in ethanol and ammonium hydroxide was added until basic *p*H. After the addition the solution was extracted with methylene chloride (3 x 15 ml), the organic solution was dried (sodium sulfate) and evaporated to yield a semisolid, compounds **1-9**. Physical, analytical and spectral data for the 6*H*-2,7,7-trimethyl-4-(*o*-,*p*-R-phenylamino)-7,8-dihydrofuro[3,2-*c*]azepines, **1-9**, are given in Table 2.

REFERENCES AND NOTES

[1] Author to whom correspondence should be addressed.

[2] Contribution No. 1217 from Instituto de Química, UNAM.

[3] M. S. Weiss, G. J. Gibs, J. F. Poletto and W. A. Remers, U.S. Patent 3,758,501 (1973); *Chem. Abstr.*, **82**, 576634r (1974).

[4] R. C. Effland, L. Davis, C. G. Helsley; U.S. Patent 3,952,025 (American Hoechst Corp.) (1976).

[5] R. Royer, G. Lamotte, S. P. Bachelet, *Eur. J. Med.*, **11**, 221 (1976).

[6] M. J. Weiss, G. J. Gibs, J. F. Poletto and W. A. Remers, U.S. Patent 3,849,441 (American Cyanamid Co.) (1974).

[7] M. S. Weiss, G. J. Gibs, J. F. Poletto and W. A. Remers, U.S. Patent 3,849,446 (American Cyanamid Co.) (1974).

[8] E. Cortés C., R. Martínez and J. G. Avila Zarraga, *J. Heterocyclic Chem.*, **29**, 1617 (1992).