J. Indian Chem. Soc.,
Vol. LI, October 1974, pp. 898-899

Potential Anticonvulsant Drugs—I
Synthesis of Substituted-γ-Aminobutyrophenones

VINAY S. MISRA and SHIVA PRAKASH

Department of Chemistry, Lucknow University, Lucknow

Manuscript received 20 *February* 1973; *revised* 1 *July* 1974; *accepted* 1 *July* 1974

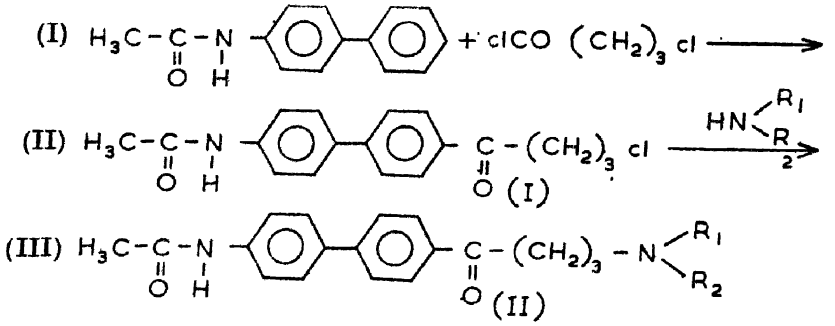
A number of 4-(4'-Acetamidophenyl)-γ-substituted butyrophenones has been synthesised and their anticonvulsant properties evaluated. Some of them have shown promising effects.

ν-PIPERIDINO butyrophenones have been reported to exhibit various pharmacological properties[1-6]. 4[1]-fluoro-ν-piperidino butyrophenone(I) has been shown to demonstrate sedative, antispasmodic and sympholytic activity[1] and it also inhibited the enzyme monoamine Oxidase (MAO)[7]. Antidepressant, antispasmodic and tranquillising effects have been observed in 4[1]-fluoro-4-(4-methyl)-piperidyl butyrophenone[4].

In view of these varied observations it was considered worthwhile to synthesise various butyrophenones (III) with basic substituents.

The compounds (III), have been prepared by treating 4-(4'-Acetamidophenyl)-ν-chloro-butyrophenone (II) with various primary and secondary amines. (II) was obtained by the Friedel-Crafts reaction of 4-Acetamido diphenyl with -ν-chlorobutyryl chloride.

The steps involved in the synthesis are :



Experimental

Melting points were taken in open capillary tubes and are uncorrected.

(a) *4-(4'-Acetamidophenyl)-ν-chlorobutyrophenone (II)*

In a 500 ml round bottomed flask fitted with a reflux condenser and a calcium chloride guard tube, were placed 4-Acetamidodiphenyl[10] (16 g), carbon disulfide (40 ml) and anhydrous aluminium chloride (30 g), and ν-chlorobutyryl chloride[8,9] (25 g) added dropwise to this mixture. During the addition of the acid chloride copious evolution of hydrogen chloride occurred. The reaction mixture was then heated on a water-bath for 30 mins. The carbon-disulfide was distilled off and the resulting thick brown pasty mass decomposed by the addition of crushed ice and dilute hydrochloric acid. The solid substance thus obtained was filtered and recrystallised from 40% ethanol, m.p. 140°, yield 15 g (70%). Found : C, 68.67%; H, 5.52%, N, 4.32%. $C_{18}H_{18}NO_2Cl$ requires, C, 68.57%; H, 5.71; N, 4.44%. I.R. 1642 cm^{-1} (Carbonyl of Butyrophenone); 3300 cm^{-1} (-NH)

(b) *Substituted-4-(4'-Acetamidophenyl)-ν-Aminobutyrophenone (III)* :

A mixture of 0.63 g. (0.002 mole) 4-(4'-Acetamidophenyl)-ν-chlorobutyrophenone, 0.22 g of anhydrous potassium carbonate, 10 ml of absolute ethanol and 0.002 mole of the appropriate amine was heated under reflux for 10 hrs. At the end of this period the solvent was distilled off and the residue extracted with hot water, dilute hydrochloric acid and hot water successively. The solid product was recrystallised from 40% ethanol.

The analysis, m.p. and other data are recorded in Table 1 and 2.

Bioassay :

Eight compounds (Nos. 1, 3, 4, 5, 7, 9, 10 and 11) were tested against pentylenetetrazole induced con-

TABLE 1

	R_1	R_2	M.P. °C	Yield %	Mol. formula	% Nitrogen Calcd.	% Nitrogen Found
(1)	H	Ph	120	70	$C_{24}H_{24}N_2O_2$	7.52	7.38
(2)	H	*p*-Tolyl	176	75	$C_{25}H_{26}N_2O_2$	7.25	6.92
(3)	H	*o*-Tolyl	125	73	$C_{25}H_{26}N_2O_2$	7.25	6.95
(4)	H	*m*-Tolyl	130	75	$C_{25}H_{26}N_2O_2$	7.25	6.93
(5)	H	*o*-Anisyl	280	72	$C_{26}H_{26}N_2O_3$	6.96	6.84
(6)	H	*p*-Anisyl	260	70	$C_{25}H_{26}N_2O_3$	6.96	6.72
(7)	H	*m*-Anisyl	265	71	$C_{25}H_{26}N_2O_3$	6.96	6.92
(8)	H	*o*-chlorophenyl	125	68	$C_{24}H_{23}N_2O_2Cl$	6.88	6.53
(9)	H	*p*-chlorophenyl	135	75	$C_{24}H_{23}N_2O_2Cl$	6.88	6.45
(10)	H	*o*-Nitrophenyl	115	70	$C_{24}H_{23}N_3O_4$	10.07	9.52
(11)	H	*p*-Nitrophenyl	120	70	$C_{24}H_{23}N_3O_4$	10.07	9.54
(12)	H	*n*-Butyl	120	70	$C_{22}H_{28}N_2O_2$	7.95	6.54
(13)	Et.	Et.	160	70	$C_{22}H_{28}N_2O_2$	7.95	7.53
(14)	H	Cyclohexyl	145	70	$C_{24}H_{31}O_2N_2$	7.36	6.48
(15)	H	Cycloheptyl	130	70	$C_{25}H_{33}O_2N_2$	7.12	7.54

TABLE 2

	R	M.P. °C	Yield %	Mo.l formula	% Nitrogen Calcd.	% Nitrogen Found
a	Morpholino	160	70	$C_{22}H_{26}N_2O_3$	7.65	7.54
b	Piperidino	154	70	$C_{23}H_{28}N_2O_2$	7.65	7.48
c	Pyrrolidino	172	70	$C_{22}H_{26}N_2O_2$	8.00	7.94

vulsions in mice[11]. Compound No. 10 afforded greatest protection (50%) against the deaths and convulsive seizures caused by metrazole. ALD_{50} (approximate lethal dose 50%) ranged from 650 to 1000 mg/kg.

Acknowledgement

The authors are indebted to Prof. S. S. Parmar of K, G.'s Medical College, Lucknow for the bioassay work. One of them (S.P.) is indebted to the U.P., S.C.S.I.R. for a junior fellowship. The authors are thankful to Prof. Ram Gopal, Head of the Department of Chemistry, Lucknow University for providing the departmental facilities.

References

1. MEIR, E. FREED, *U.S. Patent*, 3,248,402 (1966); *Chem. Abs.*, 1966, 65, 2223b.
2. RICHARD F. SQUIRES and JOERGEN BUUS LASSEN, *Biochem. Pharmacol.*, 1968, 17, 369.
3. J. A. CHRISTENSEN, S. HERHESTAM, J. B. LASSEN and N. STERNER, *Acta. Pharmacol. Toxicol.*, 1965, 23, 109; *Chem. Abs.*, 1966, 64, 10252g.
4. AKTIEBOLAG FERROSAN, *Neth. Patent*, 6,408,661, 1965; *Chem. Abs.*, 1965, 63, 4263g.
5. S. A. BIOFARMA, *Fr. Patent*, CAM 74, 1964; *Chem. Abs.*, 1965, 63, 12978g.
6. JERZY MAH, HALINA SZURSKA and TDERISZ OSTASZ, *Dissertationes Pharm.*, 1965, 17, 277; *Chem. Abs.*, 1966, 64, 11720e.
7. AKTIEBOLAG FERROSAN, *Fr. Patent*, M 3543, 1965; *Chem. Abs.*, 1966, 64, 5051b.
8. A. M. CLOVES, *Annalen*, 319, 360.
9. F. F. BLICKE, W. B. WRIGHT and M. F. ZEINTY JR., *J. Amer. Chem. Soc.*, 1941, 63, 2489.
10. FR. HEUSLER, *Annalen*, 1890, 260, 234.
11. R. KUMAR, T. K. GUPTA and S. S. PARMAR, *J. Fur. Prakt. Chemie.*, 1970, 312, 201.