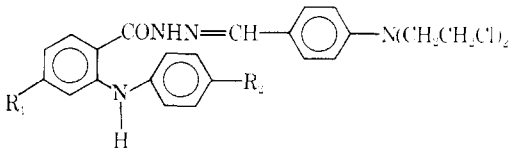
Table I



Cmpd[a]	R_1	R_2	% Yield	Mp, °C	Formula[c]
1	Cl	Cl	70	196–198	$C_{24}H_{22}Cl_4N_4O$
2	H	OCH_3	80	215–217	$C_{25}H_{26}Cl_2N_4O_2$
3	H	Cl	80	194–196	$C_{24}H_{23}Cl_3N_4O$
4[b]	H	Br	85	198–199.5	$C_{24}H_{23}BrCl_2N_4O$

[a] All compounds were recrystallized from EtOH unless otherwise noted. [b] Recrystallization from MeCN. [c] All compounds were analyzed for C, H, N.

idene Hydrazides.—In a typical reaction, 3.06 g (0.01 mol) of *N*-(4-bromophenyl)anthranilic acid hydrazide, 2.46 g (0.01 mol) of *p*-*N*,*N*-bis(2-chloroethyl)aminobenzaldehyde in 40 ml of EtOH containing 1 drop of HOAc were refluxed for 4 hr. The reaction mixture was cooled, the precipitate filtered to yield 5.1 g of crude material, mp 195–199°. Recrystallization from MeCN raised the melting point to 198–199.5°.

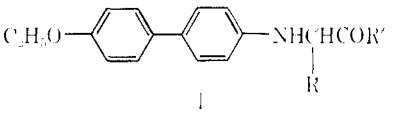
Some Substituted [*p*-(*p*-Ethoxyphenyl)anilino]acetamides

G. Brancaccio, G. Lettieri, A. Larizza, R. Viterbo, and G. C. Perri

Research Laboratories, Richardson–Merrell S.p.A., Naples, Italy

Received November 24, 1969

In further search for pharmacologically active arylaminoacylamide derivatives[1] we have synthesized a series of compounds of the general formula I. However, none of the compounds described here (see Table I) was active when screened for analgetic or antiinflammatory activity.



I

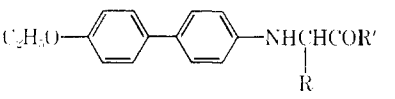
Experimental Section[2]

General Procedure.—A solution of 0.1 mol of *p*-(*p*-ethoxyphenyl)aniline and 0.1 mol of the appropriate halogenoacylamide in 200 ml of *n*-PrOH was refluxed in the presence of an excess of $NaHCO_3$ for 3–4 days. The cooled reaction mixture was concentrated, diluted (H_2O), and filtered. The solid obtained was recrystallized till the compound was chromatographically pure.

Ethyl Ester of *N*-[*p*-(*p*-Ethoxyphenyl)phenyl]glycine.—*p*-(*p*-Ethoxyphenyl)aniline (30 g), 24 g (16 ml) of ethyl bromoacetate, and 15 g of $NaHCO_3$ in 200 ml of *n*-PrOH, were refluxed for 4 days. The cooled reaction mixture was filtered and the solid residue was partitioned (Et_2O–H_2O). The Et_2O layer was separated, dried (Na_2SO_4), and concentrated to dryness (26 g, yield 58%). A sample recrystallized from EtOH had mp 137–139°. *Anal.* ($C_{18}H_{21}NO_3$) C, H, N.

[*p*-(*p*-Ethoxyphenyl)anilino]acetyl(*N*-methyl)piperazide.—A mixture of 5.5 g of *N*-[*p*-(*p*-ethoxyphenyl)phenyl]glycine ethyl ester and 4.4 ml of freshly distilled *N*-methylpiperazine was refluxed for 4 days. The reaction mixture was then treated with EtOAc and filtered (see Table I).

Table I



R	R′	Mp, °C	Recrystn solvent[a]	Formula[b]
H	EtNH	152–154	A	$C_{18}H_{22}N_2O_2$
H	*n*-PrNH	159–161	A	$C_{19}H_{24}N_2O_2$
H	*i*-PrNH	150–151	A	$C_{19}H_{24}N_2O_2$
H	*n*-BuNH	153–155	B	$C_{20}H_{26}N_2O_2$
H	*sec*-BuNH	113–115	A + D	$C_{20}H_{26}N_2O_2$
H	*i*-BuNH	165–167	A	$C_{20}H_{26}N_2O_2$
H	*t*-BuNH	129–131	A + D	$C_{20}H_{26}N_2O_2$
CH_3	*n*-PrNH	124–126	B	$C_{20}H_{26}N_2O_2$
H	Et_2N	151	C	$C_{20}H_{26}N_2O_2$
H	*n*-Pr_2N	124–125	C	$C_{22}H_{30}N_2O_2$[c]
H	Pyrrolidino	176–178	E	$C_{20}H_{24}N_2O_2$
H	Piperidino	169–171	A	$C_{21}H_{26}N_2O_2$
H	Morpholino	145–147	A	$C_{20}H_{24}N_2O_3$
H	*N*-Methylpiperazino	166–168	F	$C_{21}H_{27}N_3O_2$

[a] A, EtOAc; B, EtOH; C, 95° EtOH; D, petr ether (bp 40–68°); E, MeCN; F, dioxane. [b] All compounds were analyzed for C, H, N. The analytical results obtained are within ±0.3% of the theoretical values. [c] C: calcd, 74.54; found, 74.11.

Acknowledgment.—We are indebted to Dr. A. De Leonibus for the microanalyses and to Dr. M. L. Reviglio for the tlc.

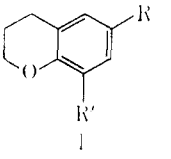
Substituted Chroman-6-ylureas and Thioureas

G. Lettieri, G. Brancaccio, A. Larizza, and R. Viterbo

Research Laboratories, Richardson–Merrell S.p.A., Naples, Italy

Received November 24, 1969

In connection with our interest in pharmacological properties of 6-aminochroman derivatives[1] we have synthesized compounds of structure I where R represents an alkyl or arylurea, or thiourea moiety; and



I

R′ can be H, Cl or Me. These compounds are related to the pharmacologically active 2,3-dihydro-2-methylbenzofuranyl analogs.[2]

Experimental Section[3]

***N*-Methyl-6-aminochromane.**—A mixture of 6-aminochroman[4] (9 g) and 90% HCO_2H (3 ml) was boiled for 90 min.

(1) A. Larizza and G. Brancaccio, U.S. Patent 3,264,349; G. Brancaccio, A. Larizza, G. Lettieri, and R. Viterbo, *Farmaco Ed. Sci.*, **22**, 930 (1967); and the references indicated therein.

(2) Melting points were determined in capillary tubes in a heated copper block and are uncorrected. Tlc was carried out on silica gel using PhH–MeAc–petr ether (1:1:1) as the solvent system.

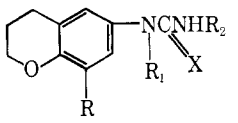
(1) G. Lettieri, G. Brancaccio, A. Larizza, R. Viterbo, and G. C. Perri, *Farmaco Ed. Sci.*, **24**, (1970), in press.

(2) David R. Herbst, U. S. 3,252,999 [*Chem. Abstr.*, **65**, 3835 (1966)].

(3) Melting points were determined in open capillary tubes and are uncorrected.

(4) V. Hach, *Collect. Czech. Chem. Commun.*, **24**, 3136 (1959).

Table I



	R	R_1	X	R_2	Mp, °C	Crystn[a] solvent	Formula	Analyses[b]
1	H	H	O	C_6H_5	209–210	A1	$C_{16}H_{16}N_2O_2$	C, H, N
2	H	H	O	4-ClC_6H_4	226–227	A1	$C_{16}H_{15}ClN_2O_2$	C, H, N
3	H	H	O	$(CH_2)_3CH_3$	125–126	Ac–Petr	$C_{14}H_{20}N_2O_2$	C, H, N
4	H	H	S	C_6H_5	125–126	B–Petr	$C_{16}H_{16}N_2OS$	C, H, N, S
5	CH_3	H	S	C_6H_5	146–148	B–Petr	$C_{17}H_{18}N_2OS$	C, H, N, S
6	CH_3	H	O	C_6H_5	204	A1	$C_{17}H_{18}N_2O_2$	C, H, N
7	H	H	O	3-$O_2NC_6H_4$	236–238	D–W	$C_{16}H_{15}N_3O_4$	C, H, N
8	H	H	O	4-$C_2H_5OC_6H_4$	190–192	A1	$C_{18}H_{20}N_2O_3$	C, H, N
9	H	H	O	2-$CH_3OC_6H_4$	175–176	A1	$C_{17}H_{18}N_2O_3$	C, H, N
10	Cl	H	O	C_6H_5	204–206	B–Petr	$C_{16}H_{15}ClN_2O_2$	C, H, Cl, N
11	H	CH_3	O	C_6H_5	146–148	A1–W	$C_{17}H_{18}N_2O_2$	C, H, N

[a] A1, EtOH; Ac, AcMe; Petr, petr ether (bp 40–70°); B, PhH; D, DMSO; W, H_2O. [b] The analytical results obtained for the indicated elements are within ±0.3% of the theoretical values.

After cooling, the reaction mixture was diluted (H_2O); the precipitated *N*-(6-chromanyl)formamide, was filtered, washed (H_2O), and then crystallized from EtOH–H_2O: yield 8.2 g (77%); mp 95–98°. An analytical sample was recrystallized from the same solvents, mp 98–100°. *Anal.* ($C_{10}H_{11}NO_2$) C, H, N.

A solution of 8.2 g of *N*-(6-chromanyl)formamide in 200 ml of anhyd PhH was added dropwise with stirring to a slurry of 2 g of LAH in Et_2O. After the addition was completed stirring was continued at room temperature for 2 hr and then the mixture was refluxed for an additional 5 hr. The unreacted LAH and the formed complex were carefully decomposed with Et_2O saturated with H_2O. The inorganic salts were filtered off. The evaporated ethereal solution left an oily residue which was distilled, bp 115° (0.001 mm), yield 5.2 g (60%). To avoid autooxidation the compound was used immediately for the subsequent steps. The picrate melted at 135–137°. *Anal.* ($C_{16}H_{16}N_4O_8$) C, H, N.

General Procedure for Compounds in Table I.—A PhH solution of the isocyanate or isothiocyanate was added dropwise with stirring to an equimolar amount of the appropriate chromanylamine dissolved in the same solvent and cooled at 5°. After the addition was completed, the reaction mixture was diluted with petr ether (bp 60–68°). The precipitated solid was filtered and crystallized from appropriate solvent or solvent mixture.

Acknowledgments.—We thank Dr. A. De Leonibus for the microanalyses.

Book Reviews

Two Books on Psychotropic Drugs.

I. **Neurophysiological and Behavioral Aspects of Psychotropic Drugs.** Edited by A. G. Karczmar and W. P. Koella. Charles C Thomas, Springfield, Illinois. 1969. xviii + 199 pp. 18 × 25 cm. $12.50.

II. **Drugs and Youth. Proceedings of the Rutgers Symposium on Drug Abuse.** Edited by J. R. Wittenborn, H. Brill, J. P. Smith, and S. A. Wittenborn. Charles C Thomas, Springfield, Illinois. 1969. xiv + 485 pp. 18 × 26 cm. $22.75.

The two symposia covered in these books complement each other. Book I is concerned with EEG patterns elicited by LSD, cyclazocine, and Ditran, with physiological responses to such drugs and to schizophrenic thinking, and with experimental studies of acquisition, retention, and other learning and memory patterns. Book II gives an overview of drug abuse in middle class youth and the social problems involved in coping with drug dependence. Special chapters are devoted to morphine, heroin, and cocaine, to the amphetamines and barbiturates, and to marijuana and LSD. For each of these agents every psychiatric aspect is considered, and possibilities of therapy are discussed to break dependence and treat pharmacologic side effects. Obviously, the appearance of dependence and of many side effects is dose-related, and the doses leading to these conditions are incredible and appalling. No simple solutions, either sociologic or punitive, are proposed, but seven papers deal with drug abuse and the law and take, on the whole, an enlightened and generous attitude, especially for marijuana which is misclassified by current legal regulations. Other research articles concern themselves with drug abuse specifically among teenagers and college students, and unfold the many unfinished agenda, the implamantation of which baffles sociologists, law enforcement officers, the families of drug abusers, and last but not least, the physicians who see the abusers usually when it is too late to reverse the trend which has led to physiologic and psychiatric disaster.

Through these pages one gets a glimpse at the "now generation" which comprises so many members opposed to regular work and jobs, at the youths who purposely seek to substitute hallucination for "normal" thought processes, and who drift without aim into ever increasing abuse of single and combined drugs. The task for chemists should be to follow the pattern set by nonaddicting narcotics, and to search for more selective agents which could slowly supplant at least those compounds which must be manufactured for therapeutic purposes but which at high doses lead to the array of dependence and abuse potential for which they have become notorious. It has been the rule rather than the exception that the pharmaceutical industry has turned off their research programs on such drugs as soon as the public image of the drug and its originators has become endangered. Continued research in just these areas should ultimately give the physician those weapons with which he could begin to combat the abuse and the ensuing physiologic damage caused by at least some of the drugs discussed in these two volumes.

University of Virginia Alfred Burger
Charlottesville, Virginia