Journal of Medicinal Chemistry, 1971, Vol. 14, No. 10 1017

New Compounds

Synthesis of New Urethans. p-Cyclohexylsulfamoyl and p-Piperidinosulfonylcarbanilic Acid Esters

I. Lalezari* and H. Golgolab

Department of Chemistry, Faculty of Pharmacy, University of Tehran, Tehran, Iran

Received March 19, 1971

In continuation of our search for new anticancer compounds,[1] new urethans listed in Table I were prepared by Curtius degradation of appropriate benzoyl azides.

Table I

R	R'	Mp, °C	Yield, %	Formula[a]
Cy[b]	Et	187	68	$C_{15}H_{22}N_2O_4S$
Cy	*i*-Pr	188	77	$C_{16}H_{24}N_2O_4S$
Cy	*tert*-Bu	182	61	$C_{17}H_{26}N_2O_4S$
Cy	*n*-Am	142	76	$C_{18}H_{28}N_2O_4S$
Cy	*n*-Hex	130	72	$C_{19}H_{30}N_2O_4S$
Cy	*n*-Oct	135	73	$C_{21}H_{34}N_2O_4S$
Cy	Allyl	172	64	$C_{16}H_{22}N_2O_4S$
Cy	Benzyl	180	71	$C_{20}H_{24}N_2O_4S$
Cy	Cholesteryl	225	40	$C_{40}H_{61}N_2O_4S$
Cy	Cyclopentyl	200	87	$C_{18}H_{26}N_2O_4S$
Cy	Cyclohexyl	176	82	$C_{19}H_{28}N_2O_4S$
Cy	Cycloheptyl	194	62	$C_{20}H_{30}N_2O_4S$
Cy	Cyclooctyl	178	86	$C_{21}H_{32}N_2O_4S$
Cy	*o*-Methoxyphenyl	160	54	$C_{20}H_{24}N_2O_5S$
Cy	*p*-Nitrophenyl	187	40	$C_{19}H_{21}N_3O_6S$
Cy	Ethylfurfuryl	154	97	$C_{20}H_{26}N_2O_5S$
Cy	α-Cyclohexyl-α-methylbenzyl	198	30	$C_{27}H_{36}N_2O_4S$
Cy	Ph_2CH	209	63	$C_{26}H_{28}N_2O_4S$
Pip[c]	Thymyl	178	85	$C_{22}H_{28}N_2O_4S$
Pip	*o*-Carboxyphenyl	141.5	92	$C_{19}H_{20}N_2O_6S$
Pip	Trityl	110	82	$C_{31}H_{30}N_2O_4S$

[a] All compounds were analyzed for C, H, and the results were satisfactory. Similarly ir and nmr spectra were as expected. [b] Cyclohexylamino. [c] Piperidino.

The compounds proved to be inactive[2] (T/C = 89–103% at 400 mg/kg) against the L 1210 lymphoid leukemia in BDF_1 mice, and the Walker carcinosarcoma 256 in random-bred albino rats.

Experimental Section[3]

p-Cyclohexylsulfamoylbenzoyl Azide.—*p*-Cyclohexylsulfamoylbenzoic acid ethyl ester (mp 100) was prepd by known methods from *p*-cyclohexylsulfamoylbenzoic acid[4] and transformed to *p*-cyclohexylsulfamoylbenzhydrazide (mp 174°). The hydrazide (2.97 g, 0.01 mole) in 20 ml of 50% AcOH was stirred at ice bath temp with 20 ml of a 5% aq $NaNO_2$ to give 2.56 g of azide (80%), mp 110° dec. *Anal.* ($C_{13}H_{16}N_4O_3S$) C, H.

p-Piperidinosulfonylbenzoyl azide was prepd similarly. *p*-Piperidinosulfonylbenzoic acid[5] was transformed to the corresponding ester (mp 100°) then to hydrazide (mp 205°). This treated as above gave 1.8 g of azide (90%), mp 115° dec. *Anal.* ($C_{12}H_{14}N_4O_3S$) C, H.

General Preparation of Urethans.—The benzoyl azides (0.01 mole) and 0.02 mole of appropriate alcohol or phenol were refluxed for 1 hr in 20 ml of dry PhMe. The solvent was evapd and the residue was recrystd from dil EtOH. Et esters were also prepd by 5-hr refluxing of the azide in 10 times its wt of abs EtOH.

(1) N. Sharghi, I. Lalezari, Gh. Niloufari, and F. Ghabgharan, *J. Med. Chem.*, **13**, 1248 (1970).

(2) Screening results were supplied by CCNCS of the National Institutes of Health, Bethesda, Md.

(3) Melting points were taken on a Leitz hot stage microscope and were uncorrected. The ir spectra were determined with a Leitz Model III spectrograph. Nmr spectra were obtained on a Varian A60A instrument.

(4) C. S. Miller, U. S. Patent 2,608,512 (1953); *Chem. Abstr.*, **47**, 5440*d* (1953).

(5) Fujio Nagasawa, Japanese Patent 278 (1954); *Chem. Abstr.*, **49**, 11024*e* (1955).

Aldehyde Disubstituted Aminoacethydrazones as Potential Hypertensive Agents

A. Tajana* and R. Pozzi

Research Division, Recordati s.a.s., Milan, Italy

Received March 27, 1971

In the course of our research on new nitrofuran derivatives, the usual pharmacological screening showed a hypertensive activity for 5-nitrofuran-2-aldehyde diethylaminoacethydrazone, 5-nitrofuran-2-aldehyde *N*-pyrrolidinoacethydrazone, and 5-nitrofuran-2-aldehyde *N*-piperidinoacethydrazone.[1]

This observation prompted us to synthesize a series of disubstituted acethydrazones. No activity on arterial pressure was found except for compds **1**, **8**, **15**, **16**, **33**, and **44** which exhibited a light hypotensive activity. Some derivatives of naphthaldehydes, of 2,3,5,6-tetramethylbenzaldehyde, of 2-methylbenzofuran-3-aldehyde and of *p*-chlorobenzaldehyde (**10**, **11**, **13**, **21**, **30**, **32**, **37**, **48**, **50**, and **56**) were found active ip in mice at 30–50 mg/kg (corresponding to about 0.2 LD_{50}) as anticonvulsants in electroshock.[2]

Experimental Section[3]

2-Formylbenzofuran.[4]—A mixt of 48.6 g (0.03 mole) of benzofuran-2-carboxylic acid and 178.47 g (1.5 moles) of $SOCl_2$ was refluxed for 2 hr. The $SOCl_2$ was distd at reduced pressure. The residue, dissolved in 450 ml of PhMe, was reduced by the procedure of Rosenmund. The catalyst was filtered, and the solvent was evapd *in vacuo* at 40° under N_2. The crude oil distd at 98° (0.5 mm), yield 31 g (72%). *Anal.* ($C_9H_6O_2$) C, H.

Aminoacethydrazones. Method A.—A mixt of 0.01 mole of aldehyde, 0.01 mole of aminoacethydrazide, and 3 ml of EtOH was refluxed for 2 hr. When the products crystd, they were collected

(1) E. Massarani, D. Nardi, A. Tajana, and L. Degen, *J. Med. Chem.*, **14**, 633 (1971).

(2) E. Massarani, D. Nardi, and M. J. Magistretti, *ibid.*, **9**, 617 (1966).

(3) Melting points are uncorrected and were determined in a capillary tube. Analyses are indicated only by the symbols of the elements. The anal. results were within ±0.4% of theor values.

(4) Other authors synthesized this compound with other methods [T. Reichstein and I. Reichstein, *Helv. Chim. Acta*, **13**, 1275 (1930); H. Normont, *C. R. Acad. Sci.*, **218**, 683 (1944); M. Bisagni, *J. Chem. Soc.*, 3688 (1955)].