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Hypoglycaemic activity of 1,1′-biadamantylaryl sulphonylureas

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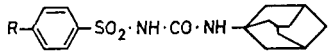
Replacement of the 1-adamantyl group with a 1,1′-biadamantyl group in the *N*-adamant-1-yl-*N*′-arylsulphonylureas leads to compounds having the same or a doubled hypoglycaemic activity. The new biadamantyl derivatives exert a delayed onset of action compared with that of the corresponding adamantane derivatives. The most promising, 3,3′-di(*N*′-*p*-toluenesulphonylureido)-1,1′-biadamantyl (Compd No. 1) and 3,3′-di(*N*′-*p*-methoxybenzenesulphonylureido)-1,1′-biadamantyl (Compd No. 3) are only slightly toxic and appear not to have other pharmacological activity.

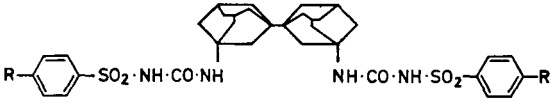
THE interesting hypoglycaemic properties of a number of *N*-adamant-1-yl-*N*′-arylsulphonylureas (I) have recently been reported by Gerzon,



I

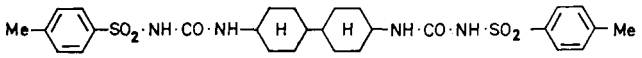
Krumkalns & others (1963). The pharmacological comparison with the corresponding known *N*-alkyl- and *N*-cycloalkyl-*N*′-arylsulphonylureas showed that replacement of either the alkyl or the cycloalkyl group with a 1-adamantyl group yields in certain cases compounds having an equal or greater and more sustained hypoglycaemic action. In particular, *N*-adamant-1-yl-*N*′-*p*-toluenesulphonylurea (Compd No. 2, I; R = Me) has been found to be approximately 15 times more potent than tolbutamide (*N*-butyl-*N*′-*p*-toluenesulphonylurea) and at the same time to have a greatly superior duration of action. All the above compounds are characterized by a rapid onset of action which causes a sudden fall in the blood-sugar level.

Since it is known that polymerization of drugs may lead to an increased or prolonged activity compared to that of the unpolymerized substances, we decided to synthesize three arylsulphonylureas derived from 1,1′-biadamantyl (II) in order to investigate their hypoglycaemic activity and



II

to compare it with that of the corresponding 1-adamantyl derivatives. For the same reasons, but especially for correlation, we have also synthesized an arylsulphonylurea derived from bi(cyclohexyl) (III) comparing



III

its hypoglycaemic activity with that of the corresponding cyclohexyl derivative (glycyclamide; Tolcyclamide).

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Further studies on the more active compounds included toxicity, central nervous system activity and determination of the anticonvulsant, parasympathicolytic, diuretic, antipyretic, choleretic, anticoagulant, anti-infarction, antibacterial, antifungal, and antiparasitic activity.

Chemistry

The compounds in Table 1 were prepared by condensation of *N*-sulphonylcarbamates with amines in boiling toluene. 3,3′-Diamino-1,1′-biadamantyl was obtained from 3,3′-dibromo-1,1′-biadamantyl according to the method, slightly modified, used by Stetter, Mayer & others (1960) to prepare 1-aminoadamantane from 1-bromoadamantane. 4,4′-Diaminobi(cyclohexyl) was prepared by reduction of bi(cyclohexyl)-4,4′-dione dioxime (Wild, Shunk & Hoffman, 1954).

EXPERIMENTAL

3,3′-*Diacetamido*-1,1′-*biadamantyl.* Concentrated sulphuric acid (390 ml) was slowly added to a stirred suspension of 3,3′-dibromo-1,1′-biadamantyl (254 g; Reinhardt, 1962) in acetonitrile (1·9 litres). The suspension was gradually heated to boiling and refluxed for 5 hr, then cooled and poured into ice/water (10 litres). The solid was filtered off, washed repeatedly with water, then with 8% sodium bicarbonate solution, and again with water. After drying, the product was washed with boiling ethanol to give 3,3′-diacetamido-1,1′-biadamantyl (220 g), m.p. 329–330°. Found: C, 74·6; H, 9·3; N, 7·3; $C_{24}H_{36}N_2O_2$ requires C, 74·95; H, 9·4; N, 7·3%.

3,3′-*Diamino*-1,1′-*biadamantyl.* A mixture of 3,3′-diacetamido-1,1′-biadamantyl (164 g) and sodium hydroxide (164 g) in ethylene glycol (2·4 litres) was refluxed with stirring for 5 hr. The resulting solution was poured into water (11 litres), and the precipitate was filtered off and dissolved in chloroform. After drying (Na_2SO_4), the chloroform solution was evaporated and the residue was crystallized from ethanol to give 3,3′-diamino-1,1′-biadamantyl (76 g), m.p. 187–191°. Found: C, 79·9; H, 10·7; N, 9·4; $C_{20}H_{32}N_2$ requires C, 79·9; H, 10·7; N, 9·3%.

Bi(cyclohexyl)-4,4′-*dione dioxime.* A boiling solution of bi(cyclohexyl)-4,4′-dione (24 g) and hydroxylamine hydrochloride (17 g) in ethanol (250 ml) was treated with pyridine (20 g). The resulting suspension was heated under reflux for 30 min, then cooled and filtered. Bi(cyclohexyl)-4,4′-dione dioxime (27 g), m.p. 287–288°, was obtained. Found: C, 64·25; H, 8·9; N, 12·4; $C_{12}H_{20}N_2O_2$ requires C, 64·25; H, 9·0; N, 12·5%.

4,4′-*Diaminobi*(*cyclohexyl*). Platinum oxide (3 g) was added to a solution of the above dioxime (10 g) in glacial acetic acid (350 ml), and the suspension shaken for 15 hr with hydrogen at 20 atmos. pressure. The catalyst was then filtered off, and the solution evaporated to dryness. The residue was dissolved in water, and the solution made alkaline and extracted with ether. The ethereal layer was washed, dried (Na_2SO_4) and evaporated to give 4,4′-diaminobi(cyclohexyl) (5·4 g), m.p. 77–80° unsharp. Found: C, 73·15; H, 12·6; N, 14·0; $C_{12}H_{24}N_2$ requires C, 73·4; H, 12·3; N, 14·3%.

Preparation of the sulphonylureas. The appropriate sulphonylcarbamate (0·12 mole) and amine (0·05 mole) were refluxed in toluene (250 ml) for 5 hr. The hot suspension was filtered and the solid product washed repeatedly with ether and then dried at 130° for 20 hr.

Pharmacology

In all the experiments the blood-sugar level was determined according to Ceriotti (1963).

EFFECT ON THE BLOOD-SUGAR LEVELS IN RATS AND RABBITS

Male Sprague-Dawley rats, 140–160 g, and rabbits, 2·5 kg, all fasted for 18 hr, were used. The drugs were administered orally, suspended in a 5% acacia mucilage. The blood-glucose was determined each hour for 7 hr after administration. The tests were made with 3 doses between 5 and 100 mg/kg and each dose was given to 21 rats and 2 rabbits. The relative hypoglycaemic potency of the drugs was calculated according to Root, Sigal & Anderson (1959). The given relative potency value has been expressed in relation to the hypoglycaemic activity of *N*-adamant-1-yl-*N'*-*p*-toluenesulphonylurea (Compd No. 2), which has been assigned the potency of 1·0.

An analogous experiment was made also on adrenalectomized rats used 18 hr after the operation. Each drug was tested on 21 rats at the single dose of 25 mg/kg, orally. The blood-sugar was determined every 2 hr for 14 hr after administration.

ACTION ON LIVER GLYCOGEN LEVEL IN RATS

Male Sprague-Dawley rats, 200–230 g, fed normally up to the start of the experiment, were used. The animals received 0·71 mmole/kg of compound No. 1 and 3; the liver glycogen (Clementi, 1960) was determined 6 hr later (5 animals/group).

Results

Table 1 shows that compounds Nos. 1 and 3 are approximately just as active, at equal weight doses, as the corresponding adamantane derivatives (compounds Nos 2 and 4), whereas the activity of compound No. 5 is approximately half that of the corresponding adamantane derivative (compound No. 6), all at equal weight. The duration of action was roughly equal for the above compounds. Compound No. 7 was found to be practically inactive.

Fig. 1 shows that when administered to adrenalectomized rats, the new biadamantyl derivatives displayed a hypoglycaemic activity and a total duration of action comparable to that of the corresponding adamantane compounds. The onset of action, however, was different; compounds Nos 1 and 3 brought about the greatest lowering of the blood-sugar level at the 6th hr, whereas compounds Nos 2 and 4 exerted their highest activity at the 2nd hr.

Compounds Nos 1 and 3 significantly increased the liver glycogen in the

TABLE 1. ARYLSULPHONYLUREAS: CHEMICAL CHARACTERISTICS AND HYPOGLYCAEMIC POTENCIES

Compd No.	R	Yield (%)	M.p. °C	Formula	Analyses								Relative potency	
					Found %				Required %					
					C	H	N	S	C	H	N	S	Rat	Rabbit
1[a] II	*p*-Me	91[b]	325–327	$C_{36}H_{46}N_4O_6S_2$	62·3	6·8	8·1	9·3	62·2	6·7	8·1	9·2	1·05	0·92
2[c] I	*p*-Me	54	173–174	$C_{18}H_{24}N_2O_3S$	62·0	6·9	8·0	9·2	62·0	6·8	8·2	9·4	1·00	1·00
3[a] II	*p*-MeO	89[b]	323–327	$C_{36}H_{46}N_4O_8S_2$	59·4	6·4	7·8	8·7	59·5	6·4	7·7	8·8	0·98	0·95
4 I	*p*-MeO	60[d]	158–159	$C_{18}H_{24}N_2O_4S$	59·7	6·8	7·6	8·6	59·3	6·6	7·7	8·8	0·98	0·96
5[a] II	*p*-Cl	90[b]	336–338	$C_{34}H_{40}Cl_2N_4O_6S_2$	55·7	5·5	7·7	8·7	55·5	5·5	7·6	8·7	0·17	0·15
6[c] I	*p*-Cl	59	149–151	$C_{17}H_{21}ClN_2O_3S$	55·4	5·7	7·6	8·7	55·3	5·6	7·6	8·7	0·35	0·32
7 III	*p*-Me	85[b]	214–217	$C_{28}H_{38}N_4O_6S_2$	56·7	6·2	9·5	10·7	56·9	6·5	9·5	10·9	0·06	0·04
Glycyclamide													0·98	1·03

[a] De Angeli S.p.A. (1966). British Patent Application, 66/48.122.
[b] Crude product.
[c] See Gerzon & others (1963).
[d] Purified according to Gerzon & others (1963).

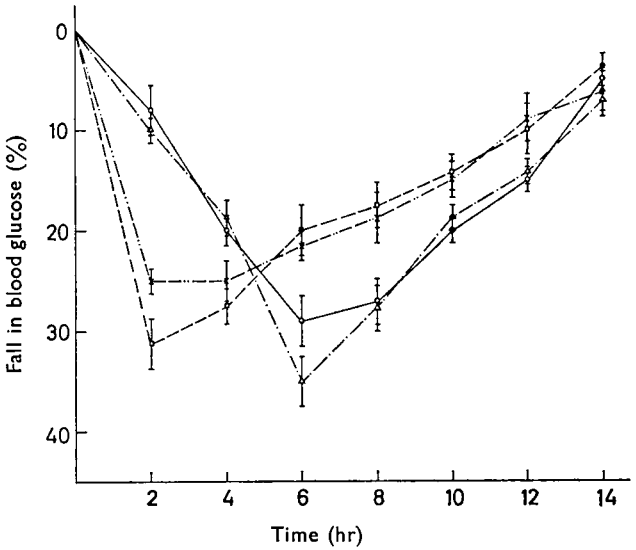

FIG. 1. Hypoglycaemic activity at a dose of 25 mg/kg orally in adrenalectomized rats 3,3′-di(*N′-p*-toluene sulphonylureido)-1,1′-biadamantyl (Compd No. 1, ○——○), 3,3′-di(*N′-p*-methoxybenzenesulphonylureido)-1,1′-biadamantyl (Compd No. 3, △ — · — · △), *N*-adamant-1-yl *N′-p*-toluenesulphonylurea (Compd No. 2, □ — — — □), and *N*-adamant-1-yl-*N′-p*-methoxybenzenesulphonylurea (Compd No. 4, ×– – · · · – – – · · · ×). The individual points show the mean glucose levels, while the bars represent the stand errors.

rat (mucilage 35·28 ±0·25 liver glycogen mg/g ±s.e. wet tissue; compd 1, 53·60 ±0·93, P <0·001; compd 2, 49·32 ±1·84, P <0·001). When administered intraperitoneally to groups of adult male white mice (10 animals/group), these substances were well tolerated, even at a dose of 1·6 g/kg.

After examination of the compounds for the other pharmacological activities listed, it was apparent that no other action was worthy of note.

Discussion

The hypoglycaemic activity data for the arylsulphonylureas agreed well with those of Gerzon & others (1963). In view of this, and in the light of the results, it may be stated that in *N*-adamant-1-yl-*N*′-arylsulphonylureas, replacement of the 1-adamantyl group with a 1,1′-biadamantyl group leads to compounds having the same or an approximately doubled hypoglycaemic activity. If the pharmacological data are evaluated by the molar proportions instead of by weight, 3,3′-di(*N*′-*p*-toluenesulphonylureido)-1,1′-biadamantyl (Compd No. 1) and 3,3′-di(*N*′-*p*-methoxybenzenesulphonylureido)-1,1′-biadamantyl (Compd No. 3) are twice as potent as the corresponding 1-adamantyl derivatives while the less active 3,3′-di(*N*′-*p*-chlorobenzenesulphonylureido)-1,1′-biadamantyl (Compd No. 5) displays similar hypoglycaemic potency to the corresponding 1-adamantyl derivative. But the onset of action of the biadamantyl derivatives is distinctly delayed compared to that of the adamantane derivatives. Compounds Nos 1, 3 and 5 exert the maximum activity at the 6th hr, gradually and gently lowering the blood-glucose level while the corresponding adamantane derivatives act much more rapidly, reaching the maximum fall at the 2nd hr. This agrees with our expectations based on the fact that a greater molecular bulk would have been able to cause a marked reduction in the absorption rate.

Dimerization does not appear to influence the total duration of the hypoglycaemic action, which is almost the same for both series. Our substances increase the liver glycogen in the rat, as do the other well-known sulphonylureas. The most interesting compounds, Nos 1 and 3, are only slightly toxic, and apparently are free from any other noticeable pharmacological activity.

The almost complete lack of activity of 4,4′-di(*N*′-*p*-toluenesulphonylureido)bi(cyclohexyl) (Compd No. 7), particularly when compared with the high activity of the corresponding *N*-cyclohexyl-*N*′-*p*-toluenesulphonylurea(glycyclamide), indicates that the above monomer-dimer correlations must be limited, at present, in the sphere of the arylsulphonylureas, only to the *N*-adamant-1-yl-*N*′-arylsulphonylureas.

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