Synthesis and Antiinflammatory Activity of 2,2'-Diaminobiphenyl Derivatives

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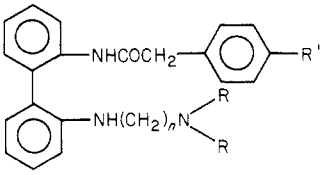
A series of 2,2'-diaminobiphenyl derivatives was prepared and tested for antiinflammatory activity. Several compounds showed antiinflammatory activity, particularly 2-[*N*-[(*p*-nitrophenyl)acetyl]amino]-2'-[*N*-[(diethylamino)ethyl]-amino]biphenyl (**4**), which also displayed analgesic activity. Some preliminary structure–activity relationships are reported.

During a pharmacological investigation we found that some derivatives of 2,2'-diaminobiphenyl showed an interesting antiinflammatory activity in the carrageenan-induced paw edema test.

Among the 2,2'-diaminobiphenyl derivatives prepared and tested for pharmacological activity, the most interesting were those with both amino groups substituted as in formula I.



I

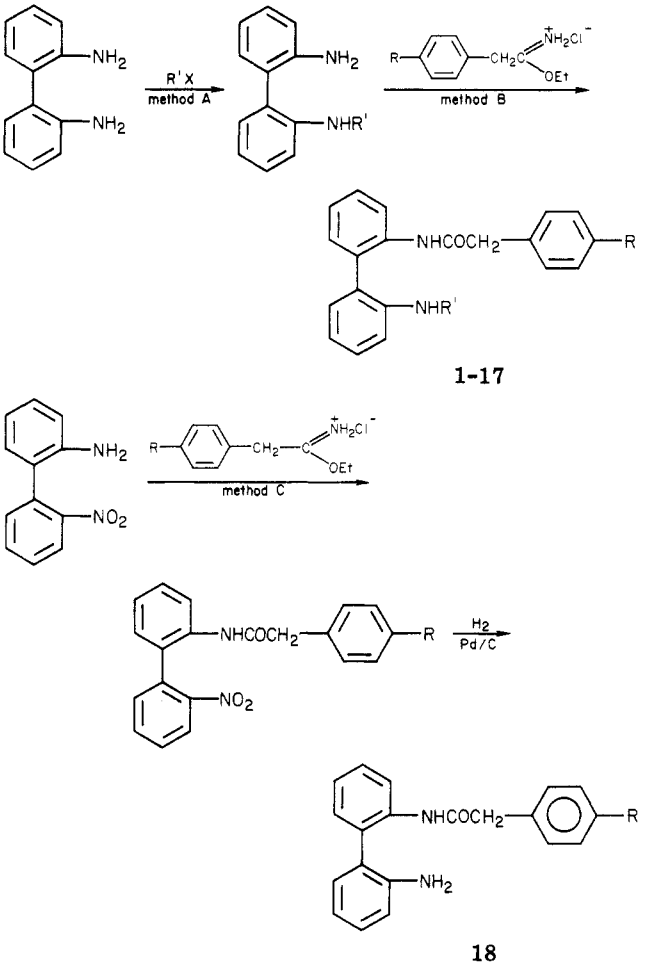
Biological Activity. Several compounds were active in the carrageenan-induced edema test (**1**, **2**, **4**, **6**, **7**, **10-12**, and **14–18**) and in the adjuvant arthritis test (**3–5**, **8**, **9**, **13**, and **14**).

Only compound **4** is active in both these two preliminary pharmacological tests. Both *N*-alkyl and (*N*-alkylamino)alkyl derivatives of 2,2'-diaminobiphenyl are inactive. Also, *N*-acyl derivatives are inactive, but compound **18** of Table I shows a certain activity in the carrageenan edema test. When both amino groups are substituted, activity is mainly related to the presence of a (dialkylamino)ethyl or (dialkylamino)propyl chain (**1–11**) and, to a lesser extent, to an alkyl chain (**12–17**). Substitution of a (dialkylamino)alkyl chain with an ethoxyalkyl group results in the loss of activity. Regarding to the *N*-(phenylacetyl) group in the series of (dialkylamino)alkyl derivatives, substitution of the phenyl ring enhances activity and the best substituents are nitro and methoxy groups.

Compound **4** was further investigated in the carrageenan-induced pleurisy and in the mouse writhing test for analgesic activity; oral LD_{50} in the mouse was also determined (Table II). Because of its interesting antiinflammatory and analgesic activity, as well as its low toxicity, compound **4** will undergo further pharmacological and toxicological investigation. Table I summarizes the structure of active compounds and their activity in the rat paw edema and in the adjuvant arthritis tests.

Chemistry. All the *N*-alkyl-*N'*-acyl-2,2'-diaminobiphenyl compounds (Table I) were prepared by reacting the suitable iminoester hydrochlorides[1] with the required (alkylamino)biphenyl compounds (method B of Scheme

Scheme I



I). Only compounds **10** and **11** were prepared by catalytic hydrogenation (Pd/C; 3 atm of hydrogen) of **2** and **4** in a 4:1 THF–MeOH solvent mixture at room temperature. The *N*-alkyl-2,2'-diaminobiphenyl compounds were obtained by partial alkylation of 2,2'-diaminobiphenyl (method A, Scheme I). The monoacyl derivatives of the 2,2'-diaminobiphenyl were also prepared by reaction of iminoester hydrochlorides and 2-amino-2'-nitrobiphenyl (method C, Scheme I), obtained by partial reduction of 2,2'-dinitrobiphenyl.[2] Good yields of 2-amino-2'-nitrobiphenyl were obtained when this reduction was carried out with NaHS in 3:1 MeOH–toluene solution at refluxing

(1) Pinner, A. "Die Imidoäther und ihre Derivate"; Oppenheim: Berlin, 1892.

(2) Purdie, D. *J. Am. Chem. Soc.* **1941**, *63*, 2276.

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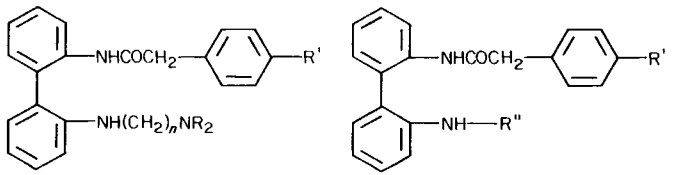
Table I



1-11 12-18

compd	R	R'	R''	n	method[a]	yield, %	mp,[b] °C	crystn solvent[b]	formula	anal.	carrageenan edema, % inhibn[c,e]	adjuvant arthritis, % inhibn[d,e]
1	C_2H_5	H		2	B	44		col	$C_{26}H_{31}N_3O$	C, H, N	17	NSE
2	CH_3	NO_2		2	B	58	131-134	C_2H_5OH	$C_{24}H_{26}N_4O_3$	C, H, N	54*	NSE
3	CH_3	NO_2		3	B	25	86-88	CH_3OH	$C_{25}H_{28}N_4O_3$	C, H, N	NSE	24
4	C_2H_5	NO_2		2	B	53	76-78	C_2H_5OH	$C_{26}H_{30}N_4O_3$	C, H, N	54*	33**
5	C_2H_5	NO_2		3	B	58		col	$C_{27}H_{32}N_4O_3$	C, H, N	NSE	16
6	CH_3	OCH_3		2	B	43		col	$C_{25}H_{29}N_3O_2$	C, H, N	65*	NSE
7	CH_3	OCH_3		3	B			col	$C_{26}H_{31}N_3O_2$	C, H, N	16	NSE
8	CH_3	Cl		3	B	50	59-62	C_2H_5OH	$C_{25}H_{28}ClN_3O$	C, H, Cl, N	NSE	30
9	C_2H_5	Cl		3	B			col	$C_{27}H_{32}ClN_3O$	C, H, Cl, N	NSE	29
10	CH_3	NH_2		2	B	52		col	$C_{24}H_{28}N_4O$	C, H, N	16	NSE
11	C_2H_5	NH_2		2	B	47		col	$C_{26}H_{32}N_4O$	C, H, N	33*	NSE
12		H	C_2H_5		B	43	80-82	col	$C_{22}H_{22}N_2O$	C, H, N	30	NSE
13		NO_2	CH_3		B	38.5	158-160	C_2H_5OH	$C_{21}H_{19}N_3O_3$	C, H, N	NSE	16
14		OCH_3	CH_3		B	46		col	$C_{22}H_{22}N_2O_2$	C, H, N	20	22
15		Cl	C_3H_7		B	64.5	70-72	C_2H_5OH	$C_{23}H_{23}ClN_2O$	C, H, Cl, N	33	NSE
16		OH	CH_3		B	49		col	$C_{21}H_{20}N_2O_2$	C, H, N	17	NSE
17		OH	C_2H_5		B	67.5	144-146	C_2H_5OH	$C_{22}H_{22}N_2O_2$	C, H, N	45*	NSE
18		OH	H		C		42-45	CH_3OH	$C_{20}H_{18}N_2O_2$	C, H, N	37*	NSE
acetylsalicylic acid											40*	32
phenylbutazone											42*	66*

[a] The letters A-C refer to general preparative procedures exemplified under Experimental Section. [b] Compounds whose melting points are not specified are oils directly recovered from the chromatographic column. The eluent is generally made up with a solvent mixture. [c] 200 mg/kg po (5 rats/group); acetylsalicylic acid 200 mg/kg; phenylbutazone 50 mg/kg. [d] 50 mg/kg/die po for 14 days (4 rats/groups); acetylsalicylic acid 200 mg/kg; phenylbutazone 50 mg/kg. [e] * = statistically different from control groups, $p < 0.01$; ** = statistically different from control groups, $p < 0.05$; NSE, no significant effect (percent inhibition ≤ 15).

Table II. Compound 4 LD_{50} and Antiinflammatory and Analgesic Activities

		antiinflammatory act.[b]							analgesic act.[b] (phenylquinone writhing test)	
		carrageenan edema		carrageenan pleurisy, 6 h exudate			adjuvant arthritis			
compd	oral LD_{50} in mice, mg/kg	po dose, mg/kg	% inhibn	po dose, mg/kg	vol % reduction	leucocytes, % reduction	po dose, mg/kg	% inhibn	po dose, mg/kg	% inhibn
4	1129 (747-1895)[a]	200	54*	200	48*	35*	50	33**	200	34*
phenylbutazone	650 (535-806)[a]	50	42*	100	43*	35*	50	66*	100	45*

[a] *Fiducial limits*, $p < 0.05$. [b] * = statistically different from control group, $p < 0.01$; ** = statistically different from control group, $p < 0.05$.

temperature for 3–5 h. The structures of all compounds were proved through IR and NMR spectra and elemental analyses.

Experimental Section

All melting points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 377 spectrometer. NMR spectra were determined in a Hitachi Perkin-Elmer R-24 Model spectrometer. Elemental analyses were performed by "Istituto di chimica Farmaceutica dell'Università di Padova".

2-Amino-2′-[*N*-[(diethylamino)propyl]amino]biphenyl (Method A). Into a 500-mL round-bottomed flask were placed 14.7 g (0.080 mol) of 2,2′-diaminobiphenyl, 12.5 g (0.084 mol) of 3-(diethylamino)propyl chloride, and 130 mL of methanol. The mixture was refluxed for 20 h and, after cooling, was evaporated under reduced pressure. The oily residue was treated with slightly (HCl) acidic water and extracted twice with 50-mL portions of ether. The aqueous phase was basified with 80 mL of 1 N NaOH and extracted with two 50-mL portions of ether. The collected ethereal extract was dried overnight over KOH pellets and evaporated under reduced pressure to give 24 g of yellow-brown oil. This residue was found to be a 3:1 mixture of mono- and dialkylated 2,2′-diaminobiphenyl derivatives, besides some starting 2,2′-diaminobiphenyl. Using MeOH as the eluent, 15 g (0.050 mol, 63%) of the title compound was separated by column chromatography on silica gel.

2-[*N*-[(*p*-Nitrophenyl)acetyl]amino]-2′-[*N*-[(diethylamino)ethyl]amino]biphenyl (Method B, Compound 4). In a two-necked round-bottomed flask 3.24 g (0.02 mol) of *p*-nitrophenylacetonitrile, 60 mL of anhydrous chloroform, and 1.1 mL of absolute ethanol were mixed under dried N_2 flow. The solution was saturated with dry hydrogen chloride at 0 °C and allowed to stand overnight. The solvent was removed under vacuum at a temperature between 20 and 25 °C, and the residue was treated with 150 mL of acetic acid and 5.66 g (0.02 mol) of 2-amino-2′-[*N*-[(diethylamino)ethyl]amino]biphenyl. The mixture was heated at 60 °C for 16–20 h and then most of the acetic acid was evaporated under reduced pressure. The residue was treated with a 10% solution of hydrochloric acid and extracted with ether. The aqueous phase was basified with 1 N NaOH solution and again extracted with ether. The combined ethereal extract was dried over KOH pellets, and the solvent was removed to give an oily residue which crystallized within few hours at room temperature. By recrystallization from ethanol, 4.75 g of the yellow title compound was obtained.

2-[*N*-[(*p*-Hydroxyphenyl)acetyl]amino]-2′-aminobiphenyl (Method C, Compound 18). As previously described in method B, 6.5 g (0.05 mol) of *p*-hydroxyphenylacetonitrile, 2.5 mL of absolute ethanol, and 70 mL of anhydrous chloroform were mixed and treated with dry hydrogen chloride.

After ether was removed, the residue was combined with 150 mL of acetic acid and 6.42 g (0.03 mol) of 2-amino-2′-nitrobiphenyl.[2] The mixture was heated at 90 °C for about 16 h and, after cooling to about 30 °C, the solvent was removed under reduced pressure.

The residue was treated with 1 N hydrochloric acid and extracted twice with chloroform. The combined organic extract was washed with 5% sodium bicarbonate solution and then with water. Evaporation of the solvent gave an oil, which was chromatographed on a silica gel column using 1:1 cyclohexane–ethyl acetate as eluent; 5.76 g (yield 33%) of 2-[*N*-[(*p*-hydroxyphenyl)-acetyl]amino]-2′-nitrobiphenyl was obtained.

Using 0.5 g of 5% Pd/C as catalyst in 70 mL of a 4:1 THF–EtOH solvent mixture, 2.06 g of the latter nitro compound was reduced at room temperature with H_2 at 3 atm of pressure. Removing the solvent under reduced pressure and drying the residue at 60 °C in a vacuum oven gave 1.35 g of the title compound.

Pharmacology. Materials and Methods. CD-COBS albino rats and CD1 mice of both sexes purchased from Charles River (Italy) were used. Compounds were suspended in 1% acacia gum and orally administered in a volume of 10 mL/kg in the rat and 20 mL/kg in the mouse. The Dunnet's test was used for statistical evaluations. The LD_{50} was calculated with the method of probits.

The carrageenan foot edema test was performed following the method described by Winter et al.[3] (N = 5 rats per group).

Carrageenan-induced pleurisy was performed following the method described by Di Rosa et al.;[4] drugs were administered 48, 24, and 1 h before and the activity was assessed 6 h after the intrapleural injection of the irritant (N = 8 rats per group).

Adjuvant-induced polyarthritis was produced, in female rats (140–160 g), by intradermal injection into the tail of 0.1 mL of a fine suspension of *Mycobacterium butiricum* in mineral oil (6 mL/mL).[5] After 14 days, animals were chosen on the basis of their arthritic score and treated daily (oral route) for 14 days with the test compound. Activity was assessed by scoring the animals at the end of the treatment (N = 4 rats per group).

The analgesic activity was studied in female mice injected intraperitoneally with 0.2 mL of 0.2% phenylquinone;[6] drugs were administered 1 h prior to the injection of the irritant, and the animals, individually caged, were observed for abdominal contractions for a period of 20 min after the injection (N = 4 mice per group).

The LD_{50} was determined in female mice and calculated on the basis of the 7-day mortality (N = 4 mice per group).

(3) Winter, C. A.; Risley, E. A.; Nuss, G. W. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544.
(4) Di Rosa, M.; Giroud, J. P.; Willoughby, D. A. *J. Pathol.* **1971**, *104*, 15.
(5) Pearson, C. M. *Proc. Soc. Exp. Biol. Med.* **1956**, *91*, 95.
(6) Siegmuns, E. H.; Cadmus, R.; Lu, G. *Proc. Soc. Exp. Biol. Med.* **1957**, *95*, 729.

erythro-5-[1-Hydroxy-2-(isopropylamino)butyl]-7-hydroxycarbostyril, a Terbutaline-Type Derivative of the Bronchodilator Procaterol

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erythro-5-[1-Hydroxy-2-(isopropylamino)butyl]-7-hydroxycarbostyril (**4**), which is a terbutaline-type derivative of the bronchodilator procaterol, was synthesized by transfer of the 8-hydroxyl group of procaterol to the 7 position. Compound 4 showed less potent β-adrenoceptor stimulant activities than procaterol or terbutaline in an in vitro test using guinea pig tracheal muscle and right atrium. In an in vivo assay on anesthetized dogs, compound 4 showed 42 times less bronchodilator activity and 87 times less effect on the heart rate than *l*-isoproterenol.

The new β-adrenoceptor stimulant procaterol, *erythro*-5-[1-hydroxy-2-(isopropylamino)butyl]-8-hydroxycarbostyril (**1**),[1,2] was shown to have very potent bronchodilator activity and weak side effects in double blind tests on

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