contractions were complete; for IX a 5-min incubation was employed and a dose ratio plot using four antagonist concentrations constructed.

Calcium free experiments were conducted on rat vas deferens equilibrated in Ca^{2+} free Tyrode's solution for 1 hr. Norepinephrine (10^{-4} M) was then without affect on the tissue and in its presence Ca^{2+} dose-response curves could be determined.

For the study of catecholamine-depleted systems rats were injected with 3 mg/kg of reserpine (Serpasil) ip 20 hr prior to use.

The Student's t test was used to test the null hypothesis that both the drug-treated and control responses were from the same population or represented identical responses. The standard error of the mean was determined for all points in each dose-response curve representing 4-8 experiments.

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1-Alkylamino-3-(2-thiazolyloxy)-2-propanols. A Novel Class of Mixed Myocardial β-Stimulants/β-Blockers†

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The synthesis of a series of 1-alkylamino-3-(2-thiazolyloxy)-2-propanols is described. Several compounds in this series, *e.g.*, (±)-1-isopropylamino-3-(2-thiazolyloxy)-2-propanol, are selective myocardial β-stimulants with a prolonged duration of action. The structure-activity relationships of these compounds are described.

Extensive investigations by the Imperial Chemical Industries (ICI) group have demonstrated that 1-amino-3-naphthoxy-2-propanols and 1-amino-3-(substituted phenoxy)-2-propanols possess potent β-adrenergic blocking properties.[2,3] Synthesis and evaluation of other compounds based on the ICI lead by various laboratories have indicated that the ability of 1-amino-3-aryloxy-2-propanols to antagonize the action of isoproterenol hydrochloride (a general β-stimulant) is a general pharmacological property of this class of compounds.[4-8]

The present communication describes the synthesis and pharmacology of a series of 1-alkylamino-3-(2-thiazolyloxy)-2-propanols which were prepared at Syntex Research in connection with a general program aimed at the development of agents useful in treating cardiovascular disease. In contrast to the known 1-amino-3-aryloxy-2-propanols[2-8] which exhibit β-blocking properties, a number of the title compounds are selective myocardial β-stimulants with β-blocking properties as well.‡ They have a prolonged duration of action [in some cases, *e.g.*, **15a** (Table I), greater than 6 hr]. These compounds increase the contractile force of the heart and heart rate but produce minimal or no effects on blood pressure. They are largely or completely devoid of vascular β-receptor stimulant properties. Because of their prolonged and selective action on the heart and their lack of effect on blood pressure, compounds of the thiazolyl-2-oxy series may be useful in the treatment of heart failure and myocardial depression.

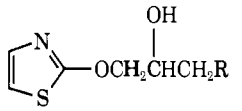
Chemistry. The synthesis of the title compounds, starting from readily available 2-bromothiazole (1),[9] is outlined in Scheme I. Treatment of 1 with the Na alkoxide of (±)-glycerol 1,2-acetonide in DME yielded the ether **2** which was hydrolyzed to the diol **3a** with dilute HCl. Reaction of **3a** with 1 equiv of CH_3SO_2Cl in C_5H_5N gave a mixture containing predominantly the requisite monomesylate **3b**. This mixture was then allowed to react with an excess of NaOMe to yield the liquid epoxide **4**. Exposure of the resulting epoxide **4** to the appropriate amine furnished the corresponding 1-amino, 1-alkylamino, or 1-dialkylamino-3-(2-thiazolyloxy)-2-propanol (see Table I).

This procedure appeared to afford an efficient route to the optically active forms of 1-alkylamino-3-(2-thiazolyloxy)-2-propanols by starting with (+)- or (−)-glycerol

† For a preliminary account of this work, see ref 1.

‡ Studies in dogs pretreated with β-blockers (propranolol or practolol) and in reserpinized dogs indicate that the compounds act *via* a direct β-adrenergic receptor mechanism. These studies will be published elsewhere by Dr. A. Strosberg and colleagues.

Table I



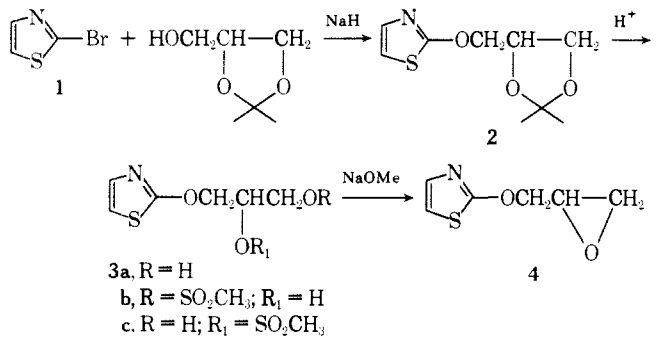
Compd	R	Form	Mp, °C	Crystn solvent	Formula	Analyses	% yield[a]	Method[b]	Biol evaluation[c]
5	NH_2	Base	Oil		$C_6H_{10}N_2O_2S$	MS[d]	80	A	1.6×10^4
6	$NHCH_3$	Base	Oil		$C_7H_{12}N_2O_2S$	MS[d]	68	A	2×10^5
7	$NHCH_2CH_3$	Base	Oil		$C_8H_{14}N_2O_2S$	MS[d]	70	A	6×10^3
8	$NHCH_2CH{=}CH_2$	Maleate	112–113	EtOH–ether	$C_{13}H_{16}N_2O_6S$	C, H, N	45	B	5×10^{12}
9	$NHCH_2CH_2OH$	Base	Oil		$C_6H_{14}N_2O_3S$	MS[d]	53	B	6×10^3
10	$NHCH_2CH_2OCH_3$	Maleate	125	EtOH–ether	$C_{13}H_{20}N_2O_7S$	C, H, N	52	B	1.5×10^4
11	$NH(CH_2)_3$-C_6H_5	Base	Oil		$C_{15}H_{20}N_2O_2S$	MS[d]	52	B	1.4×10^3
12	$NH(CH_2)_3N(CH_3)_2$	Bis-maleate	117–119	EtOH–ether	$C_{19}H_{29}N_3O_{10}S$	C, H, N	15	B	6.4×10^4
13	$NH(CH_2)_3$-c-NC_5H_{10}	Base	Oil		$C_{14}H_{25}N_3O_2S$	MS[d]	60	B	Questionable activity[e]
14	$NH(CH_2)_2$-C_6H_3-3,4-OCH_3	Base	101–103	Acetone–hexane	$C_{16}H_{22}N_2O_4S$	C, H, N	15	B	5×10^2
15a	$NHCH(CH_3)_2$	HCl	163–164	MeOH–acetone	$C_9H_{17}ClN_2O_2S$	C, H, N	50	C	7×10^2
15b	$NHCH(CH_3)_2$ [*R*-(+)]	HCl	112–113	MeOH–acetone	$C_9H_{17}ClN_2O_2S$	C, H, N		F	1.3×10^2
15c	NH-$CH(CH_3)_2$ [*S*-(−)]	HCl	112–113	MeOH	$C_9H_{17}ClN_2O_2S$	C, H, N		G	3×10^2
16	$NHCH(CH_3)CH_2CH_3$[f]	Base	Oil		$C_{10}H_{18}N_2O_2S$	MS[d]	40	B	5×10^2
17	$NHCH(CH_3)CH_2OH$[f]	Maleate	108–110	EtOH–ether	$C_{13}H_{20}N_2O_7S$	C, H, N	42	B	8×10^3
18a	$NHCH(CH_3)CH_2$-C_6H_5[g]	Maleate	158–159	EtOH–ether	$C_{19}H_{24}N_2O_6S$	C, H, N	25	B	1.4×10^3
18b	$NHCH(CH_3)CH_2C_6H_5$[h]	Maleate	158–159	EtOH–ether	$C_{19}H_{24}N_2O_6S$	C, H, N	25	B	1.6×10^3
19	$NHCH(CH_3)CH_2$-C_6H_4-4-OCH_3[f]	Maleate	113–114	EtOH–ether	$C_{20}H_{26}N_2O_7S$	C, H, N	15	B	1.1×10^3
20a	$NHCH(CH_3)$-C_6H_5[f]	Maleate	149–152	EtOH–ether	$C_{18}H_{22}N_2O_6S$	C, H, N	64	B	3.1×10^3
20b	$NHCH(CH_3)$-C_6H_5[g]	Maleate	132–134	EtOH–ether	$C_{18}H_{22}N_2O_6S$	C, H, N	70	B	7×10^2
20c	$NHCH(CH_3)$-C_6H_5[h]	Maleate	133–134	EtOH–ether	$C_{18}H_{22}N_2O_6S$	C, H, N	50	B	8.6×10^4
21	NH-c-C_3H_5	Maleate	142–143	*n*-PrOH–ether	$C_{13}H_{18}N_2O_6S$	C, H, N	37	B	7×10^2
22	NH-c-C_5H_9	Maleate	184–186	EtOH–ether	$C_{15}H_{22}N_2O_6S$	C, H, N	33	B	5×10^2
23	NH-2-adamantyl	Maleate	144–146	EtOH–ether	$C_{20}H_{28}N_2O_6S$	C, H, N	10	B	Questionable activity[e]
24	$NHC(CH_3)_3$	Maleate	193–195	MeOH–ethyl acetate	$C_{14}H_{22}N_2O_6S$	C, H, N	50	B	Low potency[i]
25	$N(CH_3)_2$	Base	Oil		$C_{10}H_{14}N_2O_2S$	MS[d]	12	D	2.4×10^5
26	$N(CH_2CH_2OH)_2$	Base	Oil		$C_{10}H_{18}N_2O_4S$	MS[d]	57	B	Questionable activity[e]
27	c-$N(CH_2CH_2)_2O$	Base	Oil		$C_{10}H_{16}N_2O_3S$	MS[d]	80	E	4×10^6
28	c-$N(CH_2CH_2)_2$-NCH_2CH_2OH	Bis-maleate	150–151	EtOH	$C_{20}H_{29}N_3O_{11}S$	C, H, N	35	B	Questionable activity[e]

[a] Isolated yields calculated from epoxide IV. [b] Method A. (±)-**4** treated with a saturated solution of NH_3 or free amine in EtOH. Method B. (±)-**4** treated with 1–5 equiv of amine in EtOH at room temperature. Method C. (±)-**4** and excess amine heated in a Parr screw cap bomb for 1 hr at 80°. Method D. Solution of (±)-**4**, excess amine HCl, and KOH in MeOH heated in a Parr screw cap bomb for 2 hr at 90°. Method E. Solution of (±)-**4** and amine in C_6H_6 heated at reflux for 18 hr. Method F. Resolution of (±)-**15a** with (−)-malic acid. Method G. Resolution of (±)-**15a** with (+)-malic acid. [c] Relative dose required to produce an increase in myocardial contractile force equivalent to that produced by isoproterenol (where isoproterenol = 1). [d] Mass spectrum showed correct molecular ion and fragmentation pattern. [e] No response observed at 0.1 mg/kg. [f] (±)-Amine used; compound is racemic mixture. [g] (+)-Amine used; compound is mixture of diastereomers. [h] (−)-Amine used; compound is mixture of diastereomers. [i] This compound is considered to have a low stimulant potential because it showed no stimulant activity in two of four studies.

1,2-acetonide. Thus, reaction of (+)-glycerol 1,2-acetonide[10] with 2-bromothiazole, followed by acid hydrolysis, epoxide formation, and treatment with isopropylamine, furnished (+)-1-isopropylamino-3-(2-thiazolyloxy)-2-propanol hydrochloride, $[\alpha]_D$ +9°, whereas use of (−)-glycerol 1,2-acetonide[11,12] in the same reaction sequence produced the (−) enantiomer, $[\alpha]_D$ −9°.

In order to establish the optical purity of the synthetic enantiomers, a chemical resolution of racemic **15a** was carried out. This was achieved using (+)-malic acid,

Scheme I

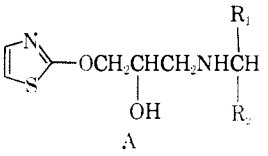


which formed a well-crystallized salt from *i*-PrOH. Multiple crystallizations of this salt to constant melting point and specific rotation followed by liberation of the free base (NH_4OH) and treatment with HCl gas furnished (−)-**15c**, $[\alpha]_D$ −15.2°. Similarly, use of (−)-malic acid gave (+)-**15b**, $[\alpha]_D$ +15.9°. The marked differences in rotation between the enantiomers prepared by total synthesis and by resolution with malic acid indicate that partial racemization has occurred at some stage in the former reaction sequence. Presumably the mesylation reaction is not specific for the primary alcohol and the product of this reaction is contaminated with the secondary monomesylate **3c**. Conversion of the latter product to the epoxide **4** by methoxide treatment proceeds with inversion at the C_2 center and leads to partially racemized amino alcohol. Danilewicz and Kemp have employed the same sequence of reactions for the synthesis of (*R*)-(+)-practolol, starting with (*R*)-(−)-α-(4-toluenesulfonyl)acetone glycerol.[13] In the latter synthesis the epoxide forming reaction was carried out on the primary monotosylate intermediate with no evidence of racemization. Thus, $CH_3C_6H_4SO_2Cl$ appears to be a more selective reagent than CH_3SO_2Cl for the conversion of 3-aryloxypropane-1,2-diols to the primary sulfonate.

Attempts to determine the optical purities of resolved **15b,c** using Mosher's reagent were unsuccessful, since these amino alcohols failed to react with the acid chloride derived from (−)-α-methoxy-α-trifluoromethylphenylacetic acid under a variety of conditions.[14]

Correlation of the absolute configuration of (+)-glycerol acetonide with (+)-**15b** leads to the 2*R* assignment for this amino alcohol; (−)-**15c** has the 2*S* configuration.

Structure–Activity Relationships. The myocardial β-stimulant potencies of 24 1-amino-3-(2-thiazolyloxy)-2-propanols are listed in Table I. These data indicate that there are two prerequisites for high biological activity in this series of compounds: (1) the presence of a secondary amine in the side chain; (2) the carbon atom to which the nitrogen atom is attached in the *N*-alkyl substituent must bear a methine H. Thus, primary and tertiary amino compounds (*e.g.*, **5**, **25–28**) and compounds in which R_1 = a methyl or a lower alkyl group (with or without a terminal amino substituent) and R_2 = H (see general structure A) were *weak stimulants* (*e.g.*, **6–10**, **12**, **13**). The 3,4-dimethoxyphenylethylamino compound **14** and the adamantylamino compound **23** were exceptions in this series, since **14** was an active stimulant, whereas the latter amine **23** was virtually inactive at comparable dose levels. The *tert*-butylamino compound **24** was also weakly active and illustrates the importance of a methine H in the N-substituent. The highest myocardial β-stimulant activity was observed in compounds where R_1, R_2 = methyl or ethyl (*e.g.*, **15a,c**, **16**) or where the R_1R_2 substituents comprised a cyclopropane or cyclopentane ring (*e.g.*, **21**, **22**). Attachment of a polar oxygen or nitrogen substituent to the terminus of the R_1 or R_2 alkyl groups reduced β-stimulant activity (*e.g.*, **12**, **13**, **17**).



In addition to myocardial β-stimulant activity, most of the 1-amino-3-(2-thiazolyloxy)-2-propanols were found to possess β-blocking activity. The latter effect appeared to be cardioselective in all compounds except **18a,b** and **19**, which exhibited general β-blocking activity (*i.e.*, they blocked other β-receptor sites in addition to those of the myocardium). In general, the most active myocardial β-stimulants (*e.g.*, **11**, **14**, **15a,c**, **16**, **21**, **22**) possessed the greatest amount of β-blocking activity. This β-blocking activity appeared to be considerably less than that of propranolol. Compounds which were weak myocardial stimulants (*e.g.*, **5–10**, **12**, **20a,c**, **27**) exhibited minimal β-blocking activity. The exceptions were **17** and **24**, which exhibited weak myocardial β-stimulation but possessed a similar degree of β-blocking activity to that of the most active myocardial β-stimulants listed in Table I. Compounds **5** and **25** did not possess β-blocking activity.

The myocardial β-stimulant activity of (2*S*)-(−)-1-isopropylamino-3-(2-thiazolyloxy)-2-propanol (**15c**) was approximately two times and its myocardial β-blocking activity approximately 1.2 times that of the racemic mixture **15a**. In contrast, the (2*R*)-(+)-1-isopropylamino-3-(2-thiazolyloxy)-2-propanol (**15b**) antipode exhibited minimal myocardial β-stimulant (*ca.* 0.2 × **15c**) and blocking (less than 0.3 × **15c**) activities. These data indicate that the biological activity is found mainly in the levorotatory antipode and is, thus, consistent with the biological profiles exhibited by (−)-propranolol and the levorotatory arylethanolamines.[15]

Experimental Section§

(±)-3-(2-Thiazolyloxy)-1,2-propanediol Acetonide (2). A suspension of NaH (18.0 g) (50% dispersion in mineral oil), prewashed with hexane, in dry DME (100 ml) was stirred with (±)-glycerol 1,2-acetonide (44.5 g) in a N_2 atmosphere until the evolution of H_2 ceased. 2-Bromothiazole (**1**, 55 g) was added and after 15 min the reaction mixture was heated under reflux for 1 hr. The solvents were evaporated under reduced pressure, H_2O was added, and the product was isolated by extraction with Et_2O. The resulting oil was distilled to give (±)-**2** (32 g): bp 95–100° (0.3 mm); $n^{25}D$ 1.4966; λ max 235 nm (log ε 3.73). *Anal.* ($C_9H_{13}NO_3S$) C, H, N.

(±)-3-(2-Thiazolyloxy)-1,2-propanediol (3a). A mixture of **2** (300 g) in H_2O (2000 ml) containing concentrated HCl (2 ml) was heated on the steam bath for 2 hr. Evaporation of the solvents under reduced pressure furnished (±)-**3a** as a liquid (250 g): $n^{25}D$ 1.5470; λ max 336 nm (log ε 3.71). *Anal.* ($C_6H_9NO_3S$) C, H, N.

(2*R*)- and (2*S*)-2 and 3a. Repetition of the foregoing reactions with (2*R*)-glycerol 1,2-acetonide, $[\alpha]_D$ +15°, furnished (+)-3-(2-thiazolyloxy)-1,2-propanediol acetonide (**2**), $[\alpha]_D$ +9.5° (neat), and (+)-3-(2-thiazolyloxy)-1,2-propanediol (**3a**), $[\alpha]_D$ +9.6°. Treatment of (2*S*)-glycerol 1,2-acetonide, $[\alpha]_D$ −15.2°, furnished (−)-**2**, $[\alpha]_D$ −10° (neat), and (−)-**3a**, $[\alpha]_D$ −2°.

(±)-3-(2-Thiazolyloxy)-1,2-epoxypropane (4). Freshly distilled CH_3SO_2Cl (22.5 ml) was added to a solution of **3a** (50 g) in dry C_5H_5N (100 ml) at 15–20°. After 10 min, the solution was diluted with Et_2O (1000 ml) and solid NaOMe (10 g) was added. After 1 hr at 20°, the mixture was poured onto crushed ice and the organic phase was separated, washed with H_2O, 20% AcOH, and 5%

§ All melting points were determined in a Thomas-Hoover apparatus in capillary tubes and are uncorrected. Elemental analyses, indicated by symbols of the elements, were within ±0.4% of the theoretical values. Noncrystalline compounds were analyzed by mass spectroscopy and showed the correct molecular ions and fragmentation patterns for the proposed structures. Ir and nmr spectra of all new compounds were consistent with the proposed structures. We thank Dr. L. Throop and staff of Syntex Research for these determinations.

$NaHCO_3$, dried (Na_2SO_4), and evaporated. The resulting oil was distilled to give (±)-4 (32 g): bp 75–80° (0.05 mm); $n^{25}D$ 1.5254; λ max 235 nm (log ε 3.71). *Anal.* ($C_6H_7NO_2S$) C, H, N.

(+)- and (−)-1-Isopropylamino-3-(2-thiazolyloxy)-2-propanol Hydrochlorides by Synthesis. Freshly distilled CH_3SO_2Cl (1.7 ml) was added to a solution of (+)-**3a** (4.0 g) in dry C_5H_5N (15 ml) at 0°. After 10 min, the mixture was diluted with Et_2O (100 ml) and treated with solid NaOMe (15 g) for 10 min. H_2O was added and the crude epoxide was isolated by extraction with Et_2O. The residue was dissolved in C_6H_6 and this solution was washed with H_2O, 20% HOAc, saturated NaCl, saturated $NaHCO_3$, and H_2O and evaporated to dryness. A solution of the residue in isopropylamine (20 ml) was heated in a Parr screw cap bomb for 2 hr at 90°. The excess isopropylamine was evaporated under reduced pressure to yield a gum which was dissolved in 2 *N* HCl (100 ml). This solution was washed twice with CH_2Cl_2, then made alkaline with KOH, and extracted with Et_2O. The Et_2O solution was washed with H_2O, dried (Na_2SO_4), and treated with dry HCl. The precipitate was collected and recrystallized from MeOH–acetone to yield 0.6 g of (+)-hydrochloride; $[\alpha]D$ +9° (MeOH).

Treatment of (−)-**3a** in the same manner provided the (−)-hydrochloride; $[\alpha]D$ −9° (MeOH).

(2*R*)-(+)- and (2*S*)-(−)-1-Isopropylamino-3-(2-thiazolyloxy)-2-propanol Hydrochlorides (15b,c) by Chemical Resolution. (±)-**15a** (2 g) was treated with 1.3 equiv of (+)-malic acid in *i*-PrOH and allowed to crystallize. The resulting white crystalline salt was recrystallized 14 times to constant mp 132–132.5° and $[\alpha]D$ −13.8°. *Anal.* ($C_{13}H_{22}O_7N_2S$) C, H, N. Treatment of the pure salt with NH_4OH followed by extraction with CH_2Cl_2 provided the free base which upon exposure to dry HCl gave (2*S*)-(−)-**15c**: mp 112–113°; $[\alpha]D$ −15.2°.

Treatment of (±)-**15a** in the same manner with (−)-malic acid gave the malic acid salt [mp 132–132.5°; $[\alpha]D$ +15.6°. *Anal.* ($C_{13}H_{22}O_7N_2S$) C, H, N] and the hydrochloride (2*R*)-(+)-**15b** [mp 112–113°; $[\alpha]D$ +15.9°].

Pharmacological Method. The myocardial stimulant activities (*i.e.*, the myocardial contractile force and heart rate increasing effects) of 1-alkylamino-3-(2-thiazolyloxy)-2-propanols were studied in bilaterally vagotomized open chest mongrel dogs of both sexes (weight 5–20 kg), which were anesthetized intravenously with 30 mg/kg of sodium pentobarbital supplemented by 5 mg/kg/hr. Myocardial contractile force was recorded by a Walton-Brodie strain gage,[16] sutured to the right ventricle, heart rate from a cardiotachograph, and systemic blood pressure from a femoral artery.

One to six dose levels of the general β-stimulant (±)-isoproterenol hydrochloride (0.0158–1.58 μg/kg) were administered at 10-min intervals before and after each dose of test compound. Three doses of test compound (0.1–3.16 mg/kg) were usually administered. The doses of test compounds required to produce an increase in myocardial contractile force equivalent to that produced by isoproterenol (where isoproterenol = 1) appear in Table I. These were calculated by use of Finney's parallel line assay, which was modified to accept *one observation* per dose[17] and in which dose levels of isoproterenol and test compounds and the responses induced were converted to common logarithms. Compound potencies were not estimated from heart rate increases because of the variability of these increases.

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Furazanobenzofuroxan, Furazanobenzothiadiazole, and Their *N*-Oxides. A New Class of Vasodilator Drugs

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Furazanobenzofuroxan, furazanobenzothiadiazole, and their *N*-oxides have been found to be potent *in vivo* and *in vitro* vasodilators. Structure–activity relationships within this series and structural comparisons with glyceryl trinitrate (GTN) are described.

Nitrites, nitrous esters, and organic nitrates are widely used in the treatment of peripheral vascular disorders. Previous studies[1-4] of the benzoheterocyclic system benzo-2,1,3-oxadiazole, commonly known as benzofurazan (**1**), and its *N*-oxide benzofuroxan (**2**) indicated that in some instances this ring system could be considered as a cyclized form of a nitro group. With this in mind we examined a series of benzofurazans and their tricyclic derivatives **3** (X = S), **4** (X = S or O) and **5** for potential vasodilatory and hypotensive activity in the spinal cat and isolated rabbit ear artery preparations.

Chemistry. Benzofuroxan,[5] benzofurazan,[6] and 4-nitro-