(2) R. E. McMahon, *J. Pharm. Sci.*, **55**, 457 (1966).
(3) C. Elison, H. W. Elliot, M. Look, and H. Rapoport, *J. Med. Chem.*, **6**, 237 (1963).
(4) E. Kutter, A. Herz, H. Teschemacher, and R. Hess, *J. Med. Chem.*, **13**, 801 (1970).
(5) C. Mitoma, D. M. Yasuda, J. Tagg, and M. Tanabe, *Biochem. Biophys. Acta*, **136**, 566 (1967).
(6) E. H. Woudruff, J. P. Lamboog, and W. E. Burt, *J. Amer. Chem. Soc.*, **62**, 922 (1940).
(7) F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).

Notes

Antiparasitic Nitroimidazoles. 9. Synthesis of Some 2-(4-Dialkylaminomethylstyryl)- and 2-(4-Amidinostyryl)-5-nitro-1-vinylimidazoles

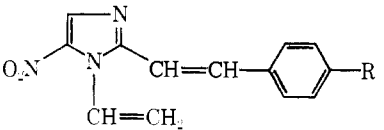
William J. Ross* and William B. Jamieson

Lilly Research Centre, Ltd., Erl Wood Manor, Windlesham, Surrey, England. *Received July 1, 1974*

A series of 2-styryl-5-nitro-1-vinylimidazoles carrying alkylaminomethyl or amidino functions in the 4 position of the styryl ring was prepared and evaluated for antitrypanosomal activity in mice infected with *Trypanosoma rhodesiense*. The alkylaminomethyl compounds were found inactive against *Trypanosoma cruzi* infections in mice. One compound, 2-(4-methylamidinostyryl)-5-nitro-1-vinylimidazole hydrochloride, showed antitrypanosomal activity comparable to the standard drugs suramin, pentamidine, diminazene, and melarsoprol when tested ip against *T. rhodesiense* infected mice and also showed some activity when tested ip against *T. cruzi* infected mice.

In paper 3[1] we described the antitrypanosomal activity of 1**a** and various amides derived from it. These amides can be regarded as intermediates, the further elaboration of which may yield compounds with enhanced biological activity. Firstly, reduction of the amides would give rise to 4-aminoalkylmethylstyrylnitroimidazoles **1b** in which the polar carboxyl group of 1**a** has been replaced by a strongly basic group, thus changing the character of the compounds. Secondly, the conversion of the amides to amidines **1c** would give tautomeric compounds which might be regarded as basic analogs of the acidic carboxyl group in **1a**.

The preparation of the amidines has the added attraction that the compounds may be considered as nitroimidazole analogs of 4,4′-diamidinostilbene (stilbamidine), a compound found to be active against a number of protozoal infections.[2] Although simple monoamidines are generally inactive,[3] Sexton[4] has pointed out that in the diamidine series it is possible to replace one amidine residue with another type of polar function and retain antiprotozoal activity. In our case, we would regard the nitro group as the second polar function.

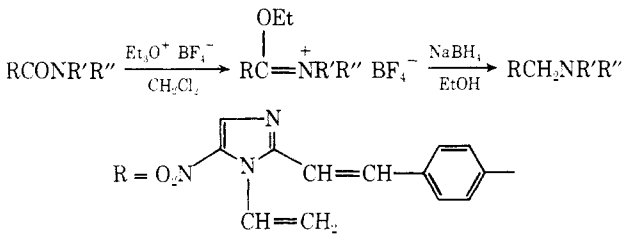


1a, R = COOH
b, R = $-CH_2NR_2'$
c, R = $-C(=NH)-NR'R''$
d, R = $-CONH_2$
e, R = $-CN$

Chemistry. The presence of a nitro group and an olefinic function in our starting compounds prevented the use of conventional reducing agents such as lithium aluminium hydride or diborane for the preparation of the alkylaminomethyl compounds.

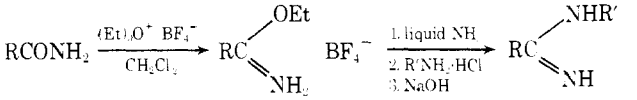
However, Borch[5] has recently described a procedure for the reduction of amides, *via* the imino ethers, using sodium borohydride (Scheme I) and we applied this method successfully to a number of tertiary amides. We were able to prepare only one example of a secondary amine **2** (Table I) because the intermediate imino ethers were either too unstable to isolate or did not form readily.

Scheme I



The amidines (Table II) were prepared *via* the imino ether derived from the primary amide[1] **1d** using modifications of the methods described by Barber and Slack[6] or Dox.[7] (Scheme II). The amidoxime **15** was prepared from the nitrile 1e.[1]

Scheme II

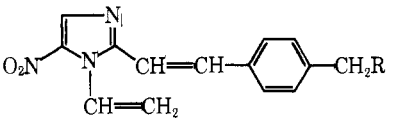


R as in Scheme I

Biological Results. All the compounds in Table III were tested ip or po against infections of *Trypanosoma rhodesiense* and *Trypanosoma cruzi* in mice according to procedures described by Hawking.[8] Apart from the secondary amine **2** none of the compounds approached the activity of **1a** against *T. rhodesiense* and all were inactive against *T. cruzi* at doses of up to 200 mg/kg × 5 ip. It thus appears that replacement of the carboxyl group of **1a** by a basic function reduces antitrypanosomal activity.

Compounds **10–15** (Table IV) were tested sc and po

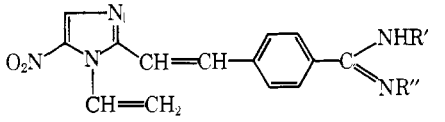
Table I



Compd	R	Yield, %	Crystn solvent	Mp, °C	Formula[a]
2	NHEt	6	EtOH–HCl	258–260 dec	$C_{18}H_{18}N_4O_2 \cdot HCl$
3	$N(Et)_2$	48	EtOH	89–90	$C_{18}H_{22}N_4O_2$
4	$N(Et)_2$	50	EtOH–HCl	227–228 dec	$C_{18}H_{22}N_4O_2 \cdot HCl$
5	$N(i\text{-}Pr)_2$	58	EtOH	128–129	$C_{20}H_{26}N_4O_2$
6	$N(n\text{-}Bu)_2$	45	EtOH	63–64	$C_{22}H_{30}N_4O_2$
7	$c\text{-}N(CH_2CH_2)_2O$	12	EtOH	133–134	$C_{18}H_{20}N_4O_3$
8	$c\text{-}N(CH_2)_4$	20	EtOH	99–100	$C_{18}H_{20}N_4O_2$
9	$c\text{-}N(CH_2)_4$	21	EtOH–HCl	225–227 dec	$C_{18}H_{20}N_4O_2 \cdot HCl$

[a]All compounds were analyzed for C, H, and N.

Table II



Compd	R′	R″	Yield, %	Crystn solvent	Mp, °C	Formula[a]
10	H	H	50	EtOH	188–190 dec	$C_{14}H_{13}N_5O_2$
11	Me	H	11	EtOH–HCl	279–280 dec	$C_{15}H_{15}N_5O_2 \cdot HCl \cdot 0.5H_2O$
12	Et	H	69	EtOH	190–191 dec	$C_{16}H_{17}N_5O_2$
13	$c\text{-}(CH_2)_3$	H	70	EtOH	199–200 dec	$C_{17}H_{17}N_5O_2$
14	n-Bu	H	40	$CHCl_3$	143–144 dec	$C_{18}H_{21}N_5O_2$
15	H	OH	66	DMF	249–250 dec	$C_{14}H_{13}N_5O_3$

[a]All compounds were analyzed for C, H, and N.

Table III. Minimum Dose Level in mg/kg 100% Effective against Trypanosomal Infections in Mice

	T. rhodesiense[a]			*T. rhodesiense*[a]	
Compd	ip	po	Compd	ip	po
2	30	30	9	>50	>50
3	200	200	1a	25	25
4	>50	>50	Suramin	1	Inact
5	200	>200	Pentamidine	1.25	Inact
6	200	200	Diminazene	1	Inact
7	100	200	Melarsoprol	0.75	0.5
8	100	>50			

[a]Mice were dosed for four consecutive days, commencing on the day of infection. 100% efficacy is equivalent to 30-day post-infection survival with negative parasitemia.

Table IV. Minimum Dose Level in mg/kg 100% Effective against Trypanosomal Infections in Mice

	T. rhodesiense[a]	
Compd	sc	po
10	1	10
11	2	12
12	3	>10
13	>>3	Inact at 10
14	3	>10
15	2	10
1a Na salt	15	50

[a]Mice were dosed for four consecutive days, commencing on the day of infection. 100% efficacy is equivalent to 30-day post-infection survival with negative parasitemia.

against *T. rhodesiense* infections in mice. The most active compound sc was **10** followed by 11. Lengthening of the alkyl chain to give the ethyl **12** and butyl 14 analogs of 11 reduced biological activity while introduction of a cyclopropyl group resulted in a barely active compound **13** at comparable dose levels.

The amidines, with the exception of **13**, and the amidoxime **15** were much more active sc than the sodium salt of **1a**. Compounds 11 and **15** exhibited good oral activity against *T. rhodesiense* 10 mg/kg × 4 but none of the other amidines cured mice of the infection at this dose level. Nevertheless, compounds **10**, **11**, **14**, and **15** compare favorably with **1a** (Table IV). Only one compound, 11, was tested ip against *T. rhodesiense* in mice giving a parasitological cure at 1 mg/kg × 4, a dose level comparable to the standard drugs suramin, pentamidine, diminazene, and melarsoprol (Table III). In addition, compound 11 was tested against *T. cruzi* infections in mice and gave an 80% cure rate at 50 mg/kg × 5 ip. None of the other amidines were tested against this organism.

In conclusion, we can say that replacement of the carboxyl group of **1a** by a basic dialkyl aminomethyl function is deleterious to the antitrypanosomal activity of this class of compound whereas introduction of an amidino residue appears to enhance activity, particularly against *T. rhodesiense*.

Experimental Section

Melting points were taken on a Gallenkamp apparatus (Registered Design No. 889339) using capillaries and are uncorrected. All compounds were characterized by ir, uv, nmr, and elemental analyses (C, H, N) which were within ±0.4% of the theoretical values.

Triethyloxonium fluoborate was prepared by the method of Meerwein[9] and successfully stored under anhydrous Et_2O for periods up to 6 months.

2-(4-*N,N*-Di-*n*-butylaminomethylstyryl)-5-nitro-1-vinylimidazole (6). 2-(4-*N,N*-Di-*n*-butylcarbamoylstyryl)-5-nitro-1-vinylimidazole, 18.2 g (0.046 mol), was stirred in CH_2Cl_2 (100 ml) at room temperature. A solution of triethyloxonium fluoborate, 9.8 g (0.051 mol), in CH_2Cl_2 (20 ml) was added rapidly and the clear orange yellow solution stirred for 20 hr. CH_2Cl_2 was removed *in vacuo* (rotary), the resultant viscous oil was stirred with EtOH (100 ml) and cooled to 0°, and $NaBH_4$ (4.5 g) added in small portions over 1 hr. After stirring at room temperature overnight, the hazy solution was poured into H_2O (300 ml) and the resultant yellow oily solid was separated, taken up in EtOH (50 ml), treated with EtOH–HCl, and evaporated to dryness twice in the presence of 2-propanol. The crystalline solid was treated with hot H_2O (100 ml) (small precipitate removed here by filtration), the clear filtrate made alkaline with Na_2CO_3 and extracted with $CHCl_3$, and the $CHCl_3$ removed *in vacuo* (rotary) to give a brownish yellow oil which was crystallized from EtOH: yield 7.8 g (45%); mp 63–64°.

Compounds **2**, **3**, **5**, **7**, and **8** were prepared in a similar manner. Compound **2** was very soluble in EtOH and was isolated as the hydrochloride salt.

2-(4-*N*-*n*-Butylamidinostyryl)-5-nitro-1-vinylimidazole (14). The primary amide **1d**, 28.4 g (0.1 mol), was suspended in dry CH_2Cl_2 (300 ml) and stirred with a solution of $Et_3O^+BF_4^-$, 20 g (0.11 mol), in CH_2Cl_2 (30 ml) for 20 hr at room temperature. The mixture was evaporated (rotary) to low volume and the solid stirred with anhydrous Et_2O, filtered, washed with further Et_2O, and dried *in vacuo*.

This product, 25 g (0.062 mol), was added with stirring to liquid ammonia (100 ml) and the excess ammonia allowed to evaporate overnight. The greenish yellow solid was extracted with hot $CHCl_3$ and the $CHCl_3$ evaporated (rotary) to give the free imino ether: yield 8.0 g (27%). Recrystallization from 2-propanol gave a highly crystalline solid: mp 178–179°.

The recrystallized imino ether, 3 g (*ca.* 0.01 mol), was refluxed in MeOH (150 ml) with *n*-butylamine hydrochloride, 1.5 g (0.014 mol), for 4 hr. The clear solution was cooled and the MeOH evaporated (rotary). The resultant solid was extracted with hot H_2O (2 × 200 ml) (some insoluble removed here) and the filtrate was made alkaline (4 *N* NaOH). After extraction into $CHCl_3$ and concentration, the product was obtained as yellow crystals: yield 1.4 g (40%); mp 143–144°. Compounds **10**, **12**, and **13** were similarly prepared.

2-(4-*N*-Methylamidinostyryl)-5-nitro-1-vinylimidazole Hydrochloride. The imino ether tetrafluoborate, 25 g (0.062 mol), prepared as above, was stirred in EtOH (200 ml) and treated with methylamine in EtOH (12 ml, 33% w/w solution). After stirring for 3 days at room temperature (closed flask), the resultant solid was filtered off, dissolved in warm water, and made alkaline (4 *N* NaOH). The yellow solid which formed was purified twice *via* the sequence: treatment with hot dilute HCl solution, filtration, and reprecipitation with 4 *N* NaOH and finally by crystallization from EtOH–HCl to give the desired compound as the hydrochloride: yield 2.2 g (11%); mp 279–280° dec.

2-(4-Hydroxyamidinostyryl)-5-nitro-1-vinylimidazole (15). A mixture of hydroxylamine hydrochloride, 2.45 g (0.035 mol), MeOH (35 ml), and 5 *N* NaOH solution (7 ml) was added to the cyano compound **1e**, 9.3 g (0.035 mol), in EtOH (500 ml) and refluxed for 24 hr. The mixture, containing a lighter yellow solid than at the start, was filtered hot and the resulting solid washed with H_2O (to remove NaCl), then extracted with boiling $CHCl_3$ (to remove unreacted cyano compound), and finally crystallized from DMF: yield 6.9 g (66%); mp 249–250° dec.

Acknowledgments. We thank Dr. M. D. Pittam and Miss J. A. O'Brien for the biological results and Mr. G. Maciak of the Lilly Research Laboratories, Indianapolis, Ind., for the microanalytical data on the compounds described in this paper.

References

(1) W. J. Ross, W. B. Jamieson, and M. C. McCowen, *J. Med. Chem.*, **16**, 347 (1973).
(2) E. M. Lourie and W. Yorke, *Ann. Trop. Med.*, **33**, 280 (1939).
(3) H. King, E. M. Lourie, and W. Yorke, *Lancet*, **2**, 1360 (1937).
(4) W. A. Sexton "Chemical Constitution and Biological Activity," 3rd ed, E & F. N. Spon, London, 1963, p 391.
(5) R. F. Borch, *Tetrahedron Lett.*, 61 (1968).
(6) H. J. Barber and R. Slack, *J. Amer. Chem. Soc.*, **66**, 1607 (1944).
(7) A. W. Dox, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N.Y., 1941, p 5.
(8) F. Hawking, *Exp. Chemother.*, **1**, 129 (1963).
(9) H. Meerwein, *Org. Syn.*, **46**, 113 (1966).

Cycloalkanones. 6. Separation of Hypocholesterolemic and Antifertility Activities in Derivatives of 2,8-Dibenzylcyclooctanone

G. L. Carlson,*,† I. H. Hall, and C. Piantadosi

Department of Medicinal Chemistry, School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27514.
Received October 3, 1974

Fluoro and hydroxy derivatives of 2,8-dibenzylcyclooctanone were prepared. Separation of antifertility activity from hypolipidemic and uterotropic effects was achieved with 2,8-bis(4-acetoxybenzyl)cyclooctanone. Some enhancement of the hypolipidemic effect in relation to the uterotropic and antifertility activities was seen in 2,8-bis(4-fluorobenzyl)cyclooctanone. Synthetic methods for the hydroxy compounds are presented.

The hypocholesterolemic uterotropic, and antifertility activities of compounds related to the parent 2,8-dibenzylcyclooctanone (**1**) have been reported (Figure 1).[1,2] An earlier study has shown that a causal relationship between uterotropic and hypolipidemic activities is unlikely;[3] however, the problem of separating the three activities remained. The changes in the effects of some derivatives [2,8-bis(4-methylbenzyl)cyclooctanone (**2**) and 2,8-bis(2-methylbenzyl)cyclooctanone (**3**)] led to the speculation that further modification of the aromatic nucleus could result in a separation of the antifertility activity from the hypolipidemic activity.

Experimental Section

2,8-Bis(4-fluorobenzyl)cyclooctanone, 2,8-bis(4-methoxybenzyl)cyclooctanone, and 2,8-bis(4-methoxybenzyl)cyclooctanone were prepared from the appropriate aldehydes using methods previously described.[3]

2,8-Bis(4-hydroxybenzyl)cyclooctanone (5). General Method for Aryl Methyl Ether Cleavage.[4] NaH (4 g, 50%) in mineral oil was added to 75 ml of freshly distilled DMF at 5°. Excess ethanethiol (7.5 ml) was added at a rate sufficiently slow to prevent foaming over the top of the flask. 2,8-Bis(4-methoxybenzyl)cy-

†This investigation was supported in part by a R. J. Reynolds Fellowship to Gerald L. Carlson. We wish to express our appreciation to Dr. Claude E. Teague, Jr., for his interest and encouragement.