Tests of Compounds for Molluscicidal Activity. VI. 4-(Substituted Phenoxy)-3,β-dinitrostyrenes[1]

HOWARD W. BOND, JOSEPH S. O'GRODNICK, AND BENJAMIN H. PRINGLE

Department of Pharmaceutical Chemistry, College of Pharmacy, University of Rhode Island, Kingston, Rhode Island 02881, and Northeastern Water Hygiene Laboratory, Public Health Service, Narragansett, Rhode Island 02879

Received July 3, 1969

β-Nitrostyrenes and other nitroolefins are known[1a,2] to be highly toxic to the snail, *Australorbis glabratus*, that serves as the intermediate host of *Schistosoma mansoni*, the human schistosomiasis of the Western Hemisphere. As part of a study of structure *vs.* molluscicidal activity of substituted β-nitrostyrenes, some 4-(substituted phenoxy)-3,β-dinitrostyrenes have been prepared and tested for their toxicity to *A. glabratus*. It was felt that inclusion of the highly molluscicidal phenolic moiety[3] might possibly impart increased activity to the β-nitrostyrene molecule. Such was not the case; all six of the new compounds are less active against *A. glabratus* than is β-nitrostyrene itself (Table I).

The 4-(substituted phenoxy)-3,β-dinitrostyrenes (IV) were prepared according to Scheme I.

Experimental Section[4]

The intermediate 4-(substituted phenoxy)-3-nitrobenzaldehydes (III) (Table II) were prepared by the method of Constantin and L'Écuyer,[5] which involves reaction of the appropriately substituted phenol (I) with 4-chloro-3-nitrobenzaldehyde (II) in the presence of NaOH plus pyridine.

The 4-(substituted phenoxy)-3,β-dinitrostyrenes (IV) (Table I) were prepared by modifications of known procedures for the synthesis of β-nitrostyrenes.

The biological testing procedure has been previously described.[1a,3]

4-(*p*-Acetamidophenoxy)-3-nitrobenzaldehyde (General Procedure for III).—To 7.55 g (0.05 mole) of *p*-hydroxyacetanilide dissolved in 15 ml of redistilled C_5H_5N were added 1.0 g of NaOH and 3.6 g (0.018 mole) of 4-chloro-3-nitrobenzaldehyde (II) with stirring. The solution was refluxed for 20 min, poured into ice-cold H_2O, and extracted ($CHCl_3$). The combined $CHCl_3$ extracts were washed (H_2O, dilute HCl, and H_2O) and dried ($MgSO_4$). The $CHCl_3$ solution was filtered and evaporated to an oil under reduced pressure, and 20 ml of EtOH was added. A precipitate formed which was recrystallized three times from EtOH to yield 3.5 g (65%) of the desired product, mp 164°. *Anal.* ($C_{15}H_{12}N_2O_5$) C, H, O; N: calcd, 9.33; found, 9.95.

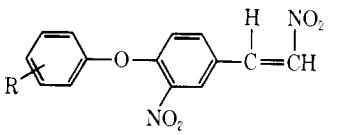
4-(Pentachlorophenoxy)-3,β-dinitrostyrene (Method A).—To 1.0 g (0.0028 mole) of 4-(pentachlorophenoxy)-3-nitrobenzaldehyde dissolved in 20 ml of CH_3NO_2, 5 drops of piperidine was added. The mixture was refluxed with stirring for 2.5 hr and the excess solvent was removed by evaporation. A small amount of Me_2CO was added, followed by H_2O dropwise until the solution turned cloudy. The precipitate which formed was recrystallized twice (EtOH–H_2O) to yield 0.15 g (8%) of the desired product, mp 153–156°. *Anal.* ($C_{14}H_5Cl_5N_2O_5$) N: calcd, 6.11; found, 6.56.

4-(*p*-Acetamidophenoxy)-3,β-dinitrostyrene (Method B).—To 1.0 g (0.0033 mole) of 4-(*p*-acetamidophenoxy)-3-nitrobenzaldehyde dissolved in 10 ml of MeOH and 15 ml of CH_3NO_2 was added dropwise 0.5 g of KOH dissolved in 5 ml of H_2O while the temperature was maintained at 0° by an ice–salt bath. The mixture was stirred for 25 min, diluted to twice its volume with H_2O, and slowly poured into 25 ml of 5 *M* HCl. A yellow precipitate formed which was recrystallized from EtOH to give 0.5 g (45%) of the product, mp 105–106°. The ir spectrum (KBr) included bands at 6.00 (amide carbonyl), 6.52, 6.95, 7.50, and 7.56 (two nitro's), 10.35 (*trans*-CH=CH–), and a broad peak at 3.0 μ (hydroxyl). *Anal.* ($C_{16}H_{13}N_3O_6 \cdot 2H_2O$) H; C: calcd, 50.66; found, 51.08; N: calcd, 11.08; found, 11.62.

4-(Pentabromophenoxy)-3,β-dinitrostyrene (Method C).—To 1.0 g (0.0016 mole) of 4-(pentabromophenoxy)-3-nitrobenzalde-

TABLE I

PROPERTIES AND MOLLUSCICIDAL ACTIVITY OF 4-(SUBSTITUTED PHENOXY)-3,β-DINITROSTYRENES

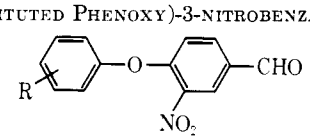


R	Yield, %	Mp, °C	Method	Formula	Analyses	EC_{90}, ppm
H	11	98–99	B	$C_{14}H_{10}N_2O_5$	C, H, N	8.5
p-OCH_3	30	126–128	B	$C_{15}H_{12}N_2O_5$	N	22
p-$NHCOCH_3$	45	105–106	B	$C_{16}H_{13}N_3O_6 \cdot 2H_2O$	H; C, N[a]	8.5
2,4-Cl_2	9	97–98	B	$C_{14}H_8Cl_2N_2O_5$	C, H, N	12
Cl_5	8	153–156	A	$C_{14}H_5Cl_5N_2O_5$	N[b]	37
Br_5	10	196–198	C	$C_{14}H_5Br_5N_2O_5$	C, N	25
β-Nitrostyrene						1.3

[a] C: calcd, 50.66; found, 51.08; N: calcd, 11.08; found, 11.62. [b] N: calcd, 6.11; found, 6.56.

TABLE II

4-(SUBSTITUTED PHENOXY)-3-NITROBENZALDEHYDES



R	Yield, %	Mp, °C	Formula	Analyses
p-NO_2	68	128	$C_{13}H_8N_2O_6$	C, H, N
p-$NHCOCH_3$	65	164	$C_{15}H_{12}N_2O_5$	C, H, O; N[a]
2,4-Cl_2	72	120	$C_{13}H_7Cl_2NO_4$	N
Cl_5	48	168	$C_{13}H_4Cl_5NO_4$	N
Br_5	16	198	$C_{13}H_4Br_5NO_4$	C, H, N

[a] N: calcd, 9.33; found, 9.95.

(1) (a) Paper V in this series: H. W. Bond, J. S. O'Grodnick, and B. H. Pringle, *Am. J. Trop. Med. Hyg.*, accepted for publication. (b) This work was supported in part by the Office of Water Resources Research, Department of Interior, under PL 88-379.

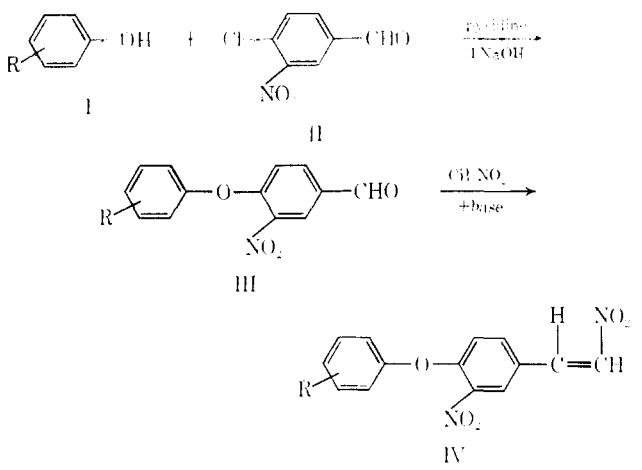
(2) T. von Brand, B. Mehlman, and M. O. Nolan, *J. Parasitol.*, **35**, 475 (1949).

(3) M. O. Nolan, H. W. Bond, and E. R. Mann, *Am. J. Trop. Med. Hyg.*, **2**, 716 (1953).

(4) Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

(5) R. Constantin and P. L'Écuyer, *Can. J. Chem.*, **36**, 1627 (1958).

SCHEME I



hyde dissolved in 10 ml of CH_3NO_2 and 10 ml of EtOH was added 1.5 g of NH_4OAc and 2 ml of glacial HOAc. The mixture was heated with stirring for 45 min. Cooling gave a precipitate, which was recrystallized twice (Me_2CO–H_2O) to yield 0.1 g (10%) of the desired product, mp 196–198°. *Anal.* ($C_{14}H_5Br_5N_2O_5$) C, N.

Acknowledgment.—We wish to extend our sincere appreciation to Mrs. Carolyn A. Rogers, of the Northeastern Water Hygiene Laboratory, for her work in the testing program.

Antimalarials. 3,3′-Dinitro(or amino)-4,4′-di(substituted amino)diphenyl Sulfones

HENRY BADER, JOHN F. HOOPS, JOHN H. BIEL, HARLEN H. KOELLING, ROBERT G. STEIN, AND TARA SINGH

Research Laboratories, Aldrich Chemical Company, Inc., Milwaukee, Wisconsin 53233

Received June 19, 1969

Making use of the activated fluorine atoms in 4,4′-difluorodiphenyl sulfone, we have already[1] prepared a number of substituted aminodiphenyl sulfones. Some of these compounds showed promising antimalarial activity.

The reactions of 4,4′-difluorodiphenyl sulfone with various amines showed a broad pattern of reactivity in the replacement of the F atoms. Weak amines, such as aniline, did not react while others like piperidine, morpholine, and hydrazine reacted easily to replace both F atoms. NH_3 replaced only one F atom, even at 140°.

With a view to enhance the activity of the F atoms, it was considered logical to introduce another electron-withdrawing group at 3,3′ positions. Thus 4,4′-difluoro-3,3′-dinitrodiphenyl sulfone was selected as starting material for the preparation of many compounds. It was found to be much more reactive than 4,4′-difluorodiphenyl sulfone and presented no problem in reacting with aniline and other weak amines. The compounds and their constants are detailed in Table I on the following page.

Pharmacology.—The compounds were tested for their antimalarial activity against *Plasmodium berghei* in mice by Dr. L. Rane, University of Miami, Miami, Fla., according to the screening procedure previously described.[2] None of the compounds were found to be significantly active. The maximum increase in mean survival time of the treated mice was 1.6 days for **1**, 1.4 days for **3**, 1.0 day for **20**, and 0.8 day for **13**. The last one showed two toxic deaths. All others were nontoxic.

Experimental Section

4,4′-Di(substituted amino)-3,3′-dinitrodiphenyl Sulfones (16, 18, 19).—The starting material for these compounds was 4,4′-difluoro-3,3′-dinitrodiphenyl sulfone and the desired amines. DMSO was used as a solvent and the mixture was heated at various temperatures and for various periods of time as shown in the table. Two variations of the general procedure were employed. In one, the reacting amine was used in 3–5 *M* excess and this excess took care of the liberated HF. Where only molar proportions of the reacting amines were available, Et_3N was added as an acid acceptor. Two typical procedures are given below.

4,4′-Dibenzylamino-3,3′-dinitrodiphenyl Sulfone (4).—A mixture of 4,4′-difluoro-3,3′-dinitrodiphenyl sulfone (25.0 g, 0.073 mol), benzylamine (32.0 g, 0.30 mol), and 100 ml of DMSO was heated at 95° for 2 hr. The mixture was cooled to room temperature and diluted with 1500 ml of H_2O. The precipitated solid was removed by filtration and crystallized from CH_2Cl_2 to give 34.3 g (90.0%) of the product, mp 233–234°.

4,4′-Diadamantylamino-3,3′-dinitrodiphenyl Sulfone (9).—A mixture of 4,4′-difluoro-3,3′-dinitrodiphenyl sulfone (5.3 g, 0.026 mol), adamantylamine hydrochloride (10.0 g, 0.0532 mol), Et_3N (20.2 g, 0.2 mol), and 50 ml of DMSO was refluxed for 3 hr. The reaction mixture was cooled to room temperature, diluted with about 1 l. of H_2O and the precipitated solid was removed by filtration. It was crystallized from toluene to give 12.6 g (88.0%) of the product, mp 298–301°.

4,4′-Di(substituted amino)-3,3′-diaminodiphenyl Sulfones (20, 22–25).—The reduction of the corresponding 3,3′-dinitro derivatives was carried out with Fe and HCl in EtOH. Compounds **20**, **23–25** were isolated as free bases while **22** was characterized as an HCl. The general procedure is exemplified by the following reduction experiment.

A mixture of 4,4′-dipiperidino-3,3′-dinitrodiphenyl sulfone (10.0 g, 0.021 mol), Fe powder (39.0 g, 0.7 g-atom), and 2 l. of EtOH was heated on the steam bath and concentrated HCl (80 ml) was added to it in small portions over a period of about 0.25 hr. Heating was continued for another 2 hr. The hot mixture was filtered to remove excess Fe, made basic with 50% NaOH, and filtered and the filtrate was evaporated to dryness. The residue was crystallized from MeOH to give 7.0 g (80.0%) of the product, mp 196–198°.

4,4′-Di(N-isopropylidenehydrazino)-3,3′-dinitrodiphenyl Sulfone (17).—To a refluxing solution of 4,4′-dihydrazino-3,3′-dinitrodiphenyl sulfone (3.5 g, 0.0095 mol) in 25 ml of 2 *N* HCl and 300 ml of MeOH was added 100 ml of Me_2CO. A yellow precipitate was immediately formed, which was removed by filtration and twice crystallized from Me_2CO to give 3.0 g (70.5%) of the product as yellow-orange needles, mp 250–252°.

4,4′-Di(4-methylpiperazino)-3,3′-diacetamidodiphenyl Sulfone (21).—A solution of 4,4′-di(4-methylpiperazino)-3,3′-diaminodiphenyl sulfone (3.5 g) in 50 ml of Ac_2O was refluxed for 1 hr. Excess Ac_2O was removed under vacuum, the residue was taken up in Me_2CO and made basic with a saturated solution of $NaHCO_3$, and the precipitate was filtered. It was crystallized from a C_6H_6–xylene mixture to give 1.3 g (31.6%) of the product, mp 228–231°.

Acknowledgment. This work was supported by the U. S. Army Medical Research and Development Command through Research Contract No. DA-49-193-MD-2869. This is Contribution No. 486 from the Army Research Program on Malaria.

(1) H. Bader, J. F. Hoops, J. H. Biel, H. H. Koelling, R. G. Stein, and T. Singh, *J. Med. Chem.*, **12**, 709 (1969).

(2) T. S. Osdene, P. B. Russell, and L. Rane, *ibid.*, **10**, 431 (1967).