

Thyroxine Analogs. XVIII.¹

3,5-Dialkyl-3'-halo-DL-thyronines and Their 3'-Methyl and 4'-Amino Analogs

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The synthesis of 3,5-diisopropyl- and 3,5-di-*sec*-butyl-DL-thyronines and their 4'-amino, 3'-bromo, and 3'-iodo analogs is reported. 3,5-Diisopropyl-3'-methyl-DL-thyronine was also prepared. All 3,5-diisopropyl- and 3,5-di-*sec*-butyl-DL-thyronines and their derivatives and analogs were inactive as thyromimetics in the rat antigoiter test. The 3,5-dialkyl-3'-iodo-DL-thyronines of this series were also inactive as thyroxine-like agents by the rat heart-rate and tadpole metamorphosis methods. All analogs tested as thyroxine antagonists by the antigoiter assay were inactive.

The replacement of some, but not all, of the I atoms of the thyroid hormones by alkyl groups has yielded compounds in which hormonal activity has been retained.² In particular, replacement of the 3'-I substituent of 3,5,3'-triiodothyronine (L-T₃) with a series of alkyl or aryl groups, including Me, Et, *i*-Pr, *t*-Bu, cyclohexyl, and Ph, produced compounds with thyromimetic activities. The 3'-*i*-Pr analog was the most active, exceeding L-T₃ in its potency.^{2e,g} By contrast, only Br³ or Me⁴ substitution for I in the 3,5-positions has produced active analogs in the limited series studied. In no case has a completely halogen-free derivative shown thyroid hormonal activity.

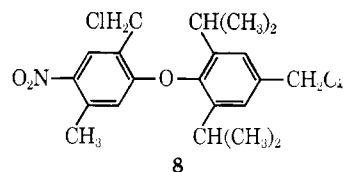
Since the *i*-Pr group is the most effective substituent in the 3' position of L-T₃, it was desirable to test the effectiveness of this group and that of the closely related *sec*-Bu group in replacing the 3,5-iodines of L-T₃. Such analogs would also test the applicability to the 3 and 5 positions of the correlation of lipophilic character and biological activity noted for 3'-substituents.^{1,5} As a potential halogen-free thyromimetic agent, a representative 3,5,3'-trialkylthyronine in this series was also desirable.

Previous attempts to prepare 3,5-diisopropylthyronines have been unsuccessful.⁶ However, using a method different from that employed in this investigation, the synthesis and lack of hormonal activity for

3,5-diisopropyl-3'-iodo-DL-thyronine have been reported⁷ since the completion of the present work.

Alterations of substituents of L-T₃ by other than alkyl substitution have produced thyroactive analogs. These include 4'-NH₂ in place of 4'-OH,⁸ and 3'-Br in place of 3'-I.⁹ Since the synthetic route used provided ready access to these derivatives, 3,5-diisopropyl- and 3,5-di-*sec*-butyl-DL-thyronines and their 3'-I, 3'-Br, and 4'-NH₂ analogs were prepared by the synthetic steps shown in Scheme I.

The 3'-Me analog of L-T₃ is about 75% as active as L-thyroxine (L-T₄), while the 3'-unsubstituted analog, 3,5-diiodo-L-thyronine, is only about 5% as active as L-T₄ in the rat antigoiter assay.^{2b} The Me group is therefore an activating substituent in the 3' position of 3,5-diiodothyronines and 3,5-diisopropyl-3'-methyl-DL-thyronine was prepared as a potentially active halogen-free 3,5,3'-trialkylthyronine derivative as shown in Scheme I using 5-chloro-2-nitrotoluene and 2,6-diisopropylphenol for the initial condensation reaction.¹⁰ However, the route was complicated at the chloromethylation stage due to the ready formation of a dichloromethyl derivative. The desired monochloromethyl compound **7** could only be isolated in reasonable yield if the reaction temperature was maintained below 25–30°. Above 30° the main product was the 4,2'-dichloromethyl derivative **8**. Similar attempts to



8

chloromethylate 2,6-di-*sec*-butylphenyl 3'-methyl-4'-nitrophenyl ether (**4**) resulted in the corresponding dichloromethyl di-*sec*-Bu derivative **9**, Table I. Chloromethylations carried out using chloromethyl methyl ether and SnCl₄ at 25° in the absence of CS₂ resulted in almost quantitative yields of **8** and **9**.

The nmr spectrum of **8** showed three singlets in the aromatic region, two of which integrated for one H (δ 8.32 and 6.31) and one for 2 H (δ 7.35), a pattern which would only be accounted for by chloromethyl

(1) Paper XVII: E. C. Jorgensen, R. O. Muhlhauser, and R. A. Wiley, *J. Med. Chem.*, **12**, 689 (1969). This research was supported by Research Grant AM-04223 from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service. Presented at the Seventh International Congress of Biochemistry, Tokyo, Japan, Aug 1967, Abstract G-172.

(2) (a) E. C. Jorgensen, N. Zenker, and C. Greenberg, *J. Biol. Chem.*, **235**, 1732 (1960); (b) E. C. Jorgensen, P. A. Lehman, C. Greenberg, and N. Zenker, *ibid.*, **237**, 3832 (1962); (c) E. C. Jorgensen and J. A. W. Reid, *J. Med. Chem.*, **8**, 533 (1965); (d) B. Blank, F. R. Pfeiffer, C. M. Greenberg, and J. F. Kerwin, *ibid.*, **6**, 554 (1963); (e) C. M. Greenberg, B. Blank, F. R. Pfeiffer, and J. F. Pauls, *Amer. J. Physiol.*, **205**, 821 (1963); (f) C. S. Pittman, H. Shida, and S. Barker, *Endocrinology*, **68**, 248 (1961); S. B. Barker, M. Shimada, and M. Makiuchi, *ibid.*, **76**, 115 (1965); (g) M. Wool, V. S. Fang, and H. A. Selenkow, *ibid.*, **78**, 29 (1966); (h) C. M. Buess, T. Giudici, N. Kharasch, W. King, D. D. Lawson, and N. N. Saha, *J. Med. Chem.*, **8**, 469 (1965).

(3) (a) E. C. Jorgensen and J. R. Nulu, *J. Pharm. Sci.*, **58**, 1139 (1969); (b) R. E. Taylor, Jr., T. Tu, S. B. Barker, and E. C. Jorgensen, *Endocrinology*, **80**, 1143 (1967).

(4) E. C. Jorgensen and R. A. Wiley, *J. Med. Pharm. Chem.*, **5**, 1307 (1962).

(5) (a) C. Hansch and T. Fujita, *J. Amer. Chem. Soc.*, **86**, 1616 (1964); (b) C. Hansch, A. R. Steward, J. Iwasa, and E. W. Deutsch, *Mol. Pharmacol.*, **1**, 205 (1965); (c) E. C. Jorgensen in "Medicinal Chemistry," A. Burger, Ed., 3rd ed. John Wiley & Sons, Inc., New York, N. Y., Chapter 31, in press.

(6) B. Blank and F. R. Pfeiffer, *J. Med. Chem.*, **10**, 653 (1967).

(7) T. Matsuura, T. Nagamachi, K. Matsuo, and A. Nishinaga, *ibid.*, **11**, 899 (1968).

(8) E. C. Jorgensen and P. Slade, *ibid.*, **5**, 729 (1962).

(9) M. V. Mussett and R. Pitt-Rivers, *Metab. Clin. Exp.*, **6**, 18 (1957).

(10) J. Wright and E. C. Jorgensen, *J. Org. Chem.*, **33**, 1245 (1968).

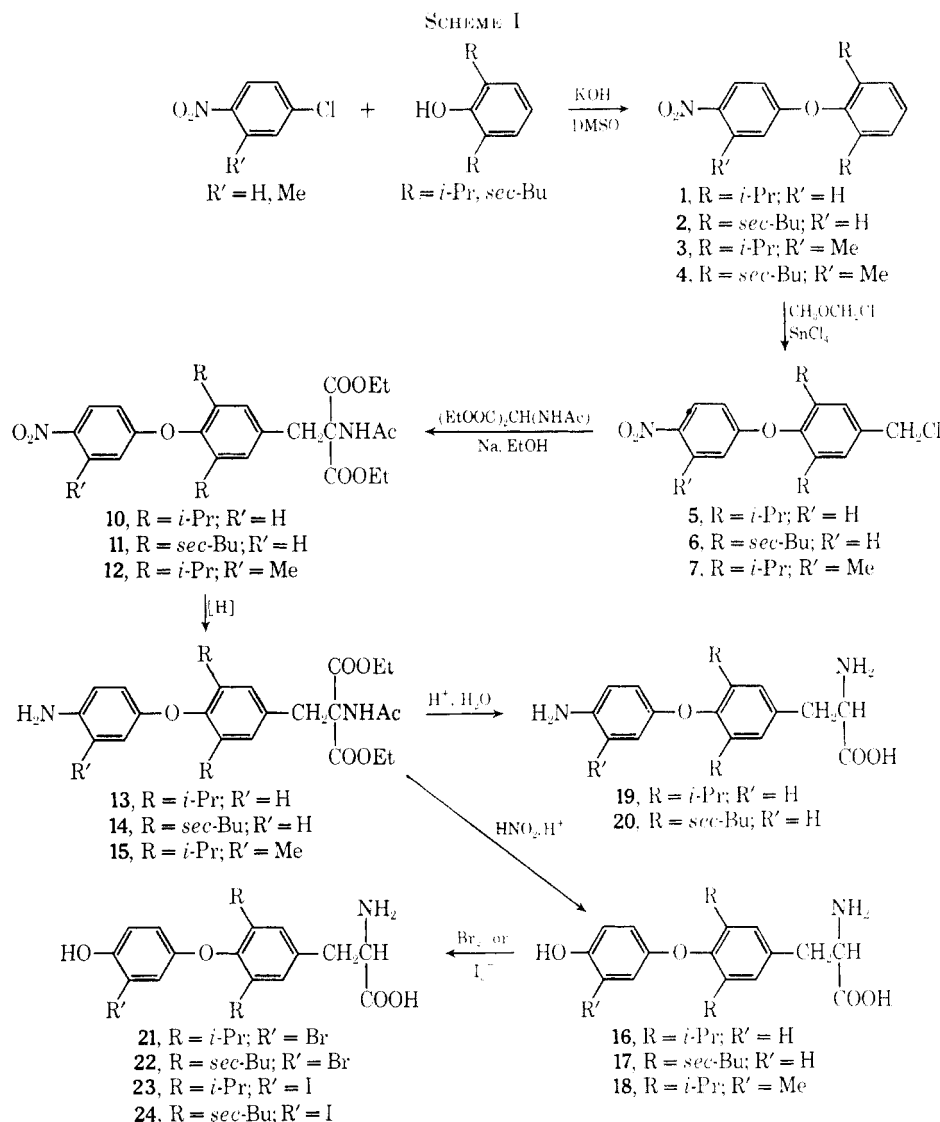


TABLE I
CHLOROMETHYLATED PRODUCTS FROM 2,6-DIALKYLPHENYL
4'-NITROPHENYL ETHERS

No.	R ₁	R ₂	R ₃	Mp, °C	Yield, %	Formula ^a
5	<i>i</i> -Pr	H	H	165-166	92	C ₁₉ H ₂₂ ClNO ₃
6	<i>sec</i> -Bu	H	H	89-90	88	C ₂₁ H ₂₆ ClNO ₃
7	<i>i</i> -Pr	Me	H	127-128	55	C ₂₀ H ₂₄ ClNO ₃
8	<i>i</i> -Pr	Me	CH ₂ Cl	84-86	95	C ₂₁ H ₂₅ Cl ₂ NO ₃
9	<i>sec</i> -Bu	Me	CH ₂ Cl	125	95	C ₂₃ H ₂₉ Cl ₂ NO ₃

^a All compounds were analyzed for C, H, Cl, N and the values obtained were within $\pm 0.4\%$ of the calculated figures.

substitution in the positions indicated in 8. The signal at abnormally high field (δ 6.31) was interpreted as being due to the 6'-H being held in the shielding zone of the adjacent ring, the positioning being caused by the orientating effect of the ClCH_2 in position 2' (cf. ref 11). It was also noted that whereas the nmr spectrum of the monochloromethyl compound 7 showed a sharp doublet

at δ 1.15 due to the CH_3 's of the *i*-Pr groups, the corresponding signal in the spectrum of 8 was two overlapping doublets at δ 1.18 and 1.09 indicating magnetic nonequivalence of the Me groups in this compound.

The difficulty encountered in attempts to monochloromethylate the diphenyl ethers 3 and 4 could be explained by the steric effect of Me *ortho* to NO_2 in the outer ring. This effect would impair the coplanarity of NO_2 and the aromatic ring, thus reducing the resonance interaction. Deactivation of the position *meta* to NO_2 would therefore be mainly due to the less powerful inductive effect, leaving this position potentially available for electrophilic attack. Evidence indicating the noncoplanarity of the ring and NO_2 was obtained from uv spectral data, the results being comparable with those of Brown and Reagan,¹² who investigated the steric effect of *o*-, *m*-, and *p*-alkyl substituents in PhNO_2 by uv spectroscopy.

Biological Results¹³ and Discussion.—The substituted thyronines 16–24 were tested for thyromimetic activity by the rat antiother assay.⁸ Compounds 16–20, each at a molar dose 100 times that of an effective dose of L-T_4 (2.8 mcg/100 g of body weight), and 21–24, each

(12) W. G. Brown and H. Reagan, *J. Amer. Chem. Soc.*, **69**, 1032 (1947).

(13) Detailed biological results have been submitted and are on file in the office of the American Chemical Society.

(11) P. A. Lehman and E. C. Jorgensen, *Tetrahedron*, **21**, 363 (1965).

at a molar dose 50 times that of L-T₄, were completely inactive as antagoitrogenic agents. Compounds **16–20** and **23** were inactive as thyroxine antagonists in thio-uracil-fed rats when administered concomitantly with L-T₄ (2.8 mcg/100 g of body weight) at a molar dose 100 times that of L-T₄.^{2b} No thyroxine-like actions on either rat heart-rate or on tadpole metamorphosis were detectable for **23** and **24** at doses (or concentrations) up to 200 times higher than effective doses of L-T₄.¹⁴

Since replacement of 3'-I of L-T₃ by *i*-Pr and related alkyl groups produces compounds of high thyromimetic activity, while replacement of the 3,5-I atoms with *i*-Pr or *sec*-Bu results in loss of activity, properties contributing to hormonal activity by substituents in the 3' position are different from those for substituents in the 3,5 positions. Among these, it is apparent that the correlation of lipophilic properties and biological activity noted for 3' substituents does not apply to inner ring alkyl substituents. The reported thyromimetic activity of 3,5-dimethyl-3'-iodo-DL-thyronine⁴ indicated that size or symmetry of inner ring substituents may be important for thyromimetic activity, in a molecule which contains, in addition, a halogen atom in the 3' position.

Experimental Section¹⁵

2,6-Dialkylphenyl 4'-Nitrophenyl Ethers (1–4).—The appropriate 2,6-dialkylphenol (0.12 mol) was condensed with *p*-ClC₆H₄NO₂ or 5-chloro-2-nitrotoluene (0.10 mol) in DMSO (150 ml) in the presence of KOH or NaOH (0.10 mol) as described by Wright and Jorgensen.¹⁰

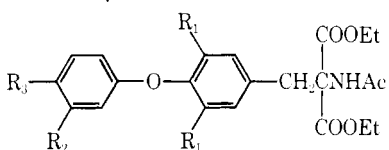
4-Chloromethyl-2,6-dialkylphenyl 4'-Nitrophenyl Ethers (Table I, 5–9).—To an ice-cooled, stirred solution of 2,6-dialkylphenyl 4'-nitrophenyl ether (0.1 mol) and chloromethyl methyl ether (16 ml, 0.2 mol) in CS₂ (60 ml) was added anhydrous SnCl₄ (9 g), dropwise, during 30 min.¹⁶ The temp was allowed to rise to 25°, and stirring was continued for 24 hr. A white crystalline ppt **5** or oil **6,7** sepd. The oil **6** was distd *in vacuo*, bp 190° (2 mm). The products were recrystd from EtOH. If the reaction temp for chloromethylation of **3** or **4** exceeded 30° for any appreciable time, the only products isolated were the dichloromethyl derivatives **8** and **9**.

Diethyl 4-(4-Nitroaryloxy)-3,5-dialkylbenzylacetamidomalonate (Table II, 10–12).—To 0.14 g-atom of Na in 300 ml of abs EtOH was added 0.14 mol of diethyl acetamidomalonate. After heating under reflux for 90 min, 0.13 mol of 4-chloromethylphenyl 4'-nitrophenyl ether (**5–7**) was added and heating was continued for a further 2 hr. The solution was coned to 150 ml by distillation, filtered while hot, and refrigerated overnight. The crystalline product sepd and was recrystd from EtOH.

Diethyl 4-(4-Aminoaryloxy)-3,5-dialkylbenzylacetamidomalonate (Table II, 13–15).—A solution of 0.1 mol of 4-(4-nitroaryloxy)-3,5-dialkylphenyl ester (**10–12**) in 50 ml of EtOH was hydrogenated at an initial pressure of 2.1 kg/cm² for 2 hr over 1.0 g of 10% Pd-C. The reaction vessel was heated to dissolve the pptd product, and the catalyst was removed by filtration of the hot solution. On cooling, the product sepd and was recrystd from EtOH.

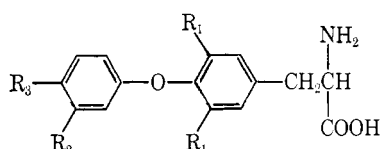
3,5-Dialkyl-DL-thyronines (Table III, 16–18).—Diethyl 4-(4-aminoaryloxy)-3,5-dialkylbenzylacetamidomalonate (**13–15**, 0.05 mol) was dissolved in a warm mixture of 20 ml of 20% H₂SO₄,

TABLE II
DIETHYL 4-ARYLOXY-3,5-DIALKYL-BENZYLACETAMIDOMALONATES

No.				Mp, °C	Yield, %	Formula ^a
	R ₁	R ₂	R ₃			
10	<i>i</i> -Pr	H	NO ₂	127–128	88	C ₂₈ H ₃₆ N ₂ O ₈
11	<i>sec</i> -Bu	H	NO ₂	116–117	75	C ₃₀ H ₄₀ N ₂ O ₈
12	<i>i</i> -Pr	Me	NO ₂	149–151	90	C ₂₉ H ₃₈ N ₂ O ₈
13	<i>i</i> -Pr	H	NH ₂	172–173	90	C ₂₈ H ₃₈ N ₂ O ₆
14	<i>sec</i> -Bu	H	NH ₂	213	88	C ₃₀ H ₄₂ N ₂ O ₆ ·HCl
15	<i>i</i> -Pr	Me	NH ₂	160–161	92	C ₂₉ H ₄₀ N ₂ O ₆

^a All compounds were analyzed for C, H, N and the values obtained were within ±0.4% of the calculated values.

TABLE III
3,5-DIALKYL-DL-THYRONINES
AND 4'-AMINO AND 3'-HALO ANALOGS

No.				Mp, °C dec	Yield, %	Formula ^a
	R ₁	R ₂	R ₃			
16	<i>i</i> -Pr	H	OH	225–230 ^b	92	C ₂₁ H ₂₇ NO ₄ ^c
17	<i>sec</i> -Bu	H	OH	215–220	90	C ₂₃ H ₃₁ NO ₄ ^d
18	<i>i</i> -Pr	Me	OH	205–210	40 ^e	C ₂₂ H ₂₉ NO ₄ ^f
19	<i>i</i> -Pr	H	NH ₂	210	75	C ₂₁ H ₂₈ N ₂ O ₃ ^g
20	<i>sec</i> -Bu	H	NH ₂	200	80	C ₂₃ H ₃₂ N ₂ O ₃ ^h
21	<i>i</i> -Pr	Br	OH	185–190	70	C ₂₁ H ₂₆ BrNO ₄ ^{i,j}
22	<i>sec</i> -Bu	Br	OH	180–185	65	C ₂₃ H ₃₀ BrNO ₄ ^{i,k}
23	<i>i</i> -Pr	I	OH	195–200 ^l	75	C ₂₁ H ₂₆ INO ₄ ^{i,m}
24	<i>sec</i> -Bu	I	OH	195–200	70	C ₂₃ H ₃₀ INO ₄ ^{i,n}

^a All compounds were analyzed for C, H, N. Except where noted, all results were within ±0.4% of the calculated values. ^b Literature mp 227°. See ref 7. ^c Equiv wt 371, hemihydrate. ^d *N,O*-diacetyl methyl ester, mp 116–117°. *Anal.* (C₂₈H₃₃NO₆) C, H, N. ^e Equiv wt 410, hemihydrate. ^f Diazotization in aqueous H₂SO₄. ^g Equiv wt 390, hemihydrate. C: calcd, 69.47; found, 69.01. H: calcd, 7.89; found, 7.46. ^h Sulfate, dihydrate. N: calcd, 5.93; found, 6.41. ⁱ Sulfate, monohydrate. N: calcd, 5.40; found 6.07. ^j Analyzed for halogen. Except where noted, all results were within ±0.4% of the calculated values. ^k C: calcd, 57.76; found, 57.21. N: calcd, 3.21; found, 3.67. ^l N: calcd, 3.02; found, 3.44. ^m Literature mp 185° dec. See ref 7. ⁿ Hydrate. ^o Hemihydrate. I: calcd, 24.42; found, 23.72.

40 ml of H₂O, and 40 ml of AcOH, then cooled below 10°. With continuous stirring a solution of 0.4 g of NaNO₂ in 4 ml of H₂O was added, followed by 0.25 g of urea. After refrigeration for 2 hr, the diazonium salt solution was added dropwise during 30 min to a vigorously stirred refluxing solution of 45 ml of H₂SO₄ and 90 ml of AcOH in 100 ml of H₂O. H₂O (30 ml) was added and heating under reflux was continued for a further 2 hr, after which the mixture was cooled to below 10°. The pH was adjusted to 5.0 by addition of coned NH₄OH to the ice-cooled, stirred solution. After refrigeration for 1 hr, the light brown ppt was removed by filtration. Purification was effected by several isoelectric pptns from AcOH, by adjusting the pH to 5.0 with 10% NaOH.

When AcOH was absent from the diazotization reaction, considerable tars were formed, and yield of purified product **18** was reduced.

To confirm the presence of the 4'-hydroxyl group, 3,5-diisopropyl-DL-thyronine was converted into its *N,O*-diacetyl methyl

(14) R. E. Taylor, Jr., and S. B. Barker, personal communication.

(15) Melting points (corrected) were determined with a Thomas-Hoover capillary melting point apparatus. Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley, Calif. Nmr spectra were obtained in CDCl₃ on a Varian A-60A (Me₄Si). Ultraviolet spectra were determined in 95% EtOH using a Beckman DB-G instrument. Equivalent weights were measured with a standardized solution of 0.02 N perchloric acid in glacial AcOH using a 1% crystal violet glacial AcOH solution as indicator. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values.

(16) R. C. Fuson and C. H. McKeever, *Org. React.*, **1**, 68 (1942).

ester, which crystallized from 50% EtOH as white needles, mp 116–117°.

3,5-Dialkyl-4-(4-aminophenoxy)phenyl-DL-alanines (Table III, 19–20).—Diethyl 4-(4-aminoaryloxy)-3,5-dialkylbenzylacetamidomalonate (**13**, **14**; 0.005 mol) was heated under reflux with 50 ml of 50% H₂SO₄ for 4 hr. On cooling, white plates of the hydrated sulfate salt pptd. The salt was recrystd from H₂O containing a few drops of H₂SO₄.

3,5-Dialkyl-3'-halo-DL-thyronines (Table III, 21–24).—To the 3,5-dialkyl-DL-thyronines (**16**, **17**; 0.4–0.8 mmol) dissolved in 10 ml of vigorously stirred 40% MeNH₂ maintained at 5–10° was quickly added 90–100% of the calcd amount of I₂ as a 1 *N* solution in aq KI.¹⁷ Stirring was continued for 10 min after the addition was complete. The solution was adjusted to pH 5 with concd HCl. The pptd 3'-I derivatives (**23**, **24**) were collected by filtration and purified by several isoelectric pptns from 10% NaOH solution by adjusting the pH to 5.0 with concd HCl.

The 3'-Br derivatives (**21**, **22**) were prepared by dropwise addi-

tion of Br₂ (176 mg, 1.10 mmol) in 5 ml of AcOH to a solution (maintained at 50–60°) of 3,5-dialkyl-DL-thyronine (**16**, **17**; 1.0 mmol) in 30 ml of AcOH containing a few drops of concd HCl.¹⁸ Fifteen minutes after addition was complete, the solution was decolorized with sodium metabisulfite, diluted with H₂O, and adjusted to pH 3.7 with 20% NaOAc. The ppt was washed with H₂O, dissolved in aq EtOH containing a few drops of concd HCl, and reprecipitated at pH 5.0 with 20% NaOAc.

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(17) E. C. Jorgensen and R. A. Wiley, *J. Pharm. Sci.*, **52**, 122 (1963).

(18) E. C. Jorgensen and P. A. Lehman, *J. Org. Chem.*, **26**, 897 (1961).

Synthetic Schistosomicides. XVI.

5-(Mono- and Dialkylamino)-2-nitrosophenols, 2-Amino-5-(dialkylamino)phenols, and Related Compounds¹

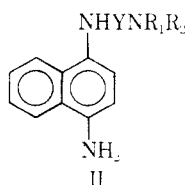
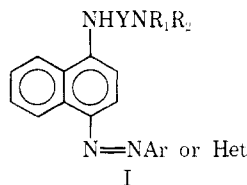
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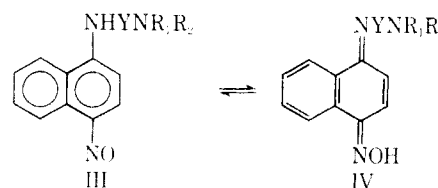
Various 5-(mono- and dialkylamino)-2-nitrosophenols VIII were prepared by nitrosation of the corresponding *m*-(mono- and dialkylamino)phenols. The latter intermediates were obtained by heating resorcinol with an excess of the appropriate amine at 200°, or by alkylation of *m*-aminophenol with an alkyl halide. 5-(Dimethylamino)-2-nitrosophenol (**6**), 5-(diethylamino)-2-nitrosophenol (**9**), 2-nitroso-5-(1-pyrrolidinyl)phenol (**7**), and 2-amino-5-(diethylamino)phenol (**17a**), a potential metabolite of **9**, displayed strong schistosomicidal activity and effected a 70–100% reduction of adult *Schistosoma mansoni* in mice at daily doses of 177–568 mg/kg for 14 days. Structure-activity relationships are summarized, and information concerning potential metabolites and the possible mode of action of the nitrosophenols is discussed.

The potent chemotherapeutic effects of various *N,N*-dialkyl-*N'*-(4-aryloxy- and 4-heterocyclic azo-1-naphthyl)alkylenediamines (I)^{2–9} and the corresponding *N*-(dialkylaminoalkyl)-1,4-naphthalenediamines (II)¹⁰

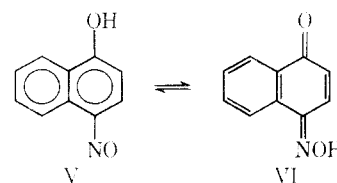


against infections of *Schistosoma mansoni* and *S. japonicum* in experimental animals stimulated the synthesis

of various *N,N*-dialkyl-*N'*-(4-nitroso-1-naphthyl)alkylenediamines (III) that also displayed strong anti-



schistosome properties.¹¹ The latter substances exist in a higher oxidation state than the naphthylamine derivatives II, and also have the potential to exist in the tautomeric quinoid structure IV, a form possibly necessary for biological activity within these series.^{10,12} Moreover, 4-nitroso-1-naphthol (V), which is tautomeric with 1,4-naphthoquinone monoxime (VI), has



(1) For paper XV, see E. F. Elslager, M. P. Hutt, and L. M. Werbel, *J. Med. Chem.*, **13**, 542 (1970).

(2) E. F. Elslager, D. B. Capps, L. M. Werbel, D. F. Worth, J. E. Meisenhelder, H. Najarian, and P. E. Thompson, *ibid.*, **6**, 217 (1963).

(3) E. F. Elslager, D. B. Capps, D. H. Kurtz, L. M. Werbel, and D. F. Worth, *ibid.*, **6**, 646 (1963).

(4) S. T. Ch'en, I. F. Ch'en, P. C. Kun, Y. C. Hu, J. H. Yao, and T. H. Chou, *Yao Hsueh Hsueh Pao*, **13**, 30 (1966).

(5) E. F. Elslager, D. B. Capps, D. H. Kurtz, F. W. Short, L. M. Werbel, and D. F. Worth, *J. Med. Chem.*, **9**, 378 (1966).

(6) A. Korolkovas, *Rev. Fac. Farm. Bioquim. Univ. Sao Paulo*, **5**, 5 (1967).

(7) E. F. Elslager, D. B. Capps, D. H. Kurtz, and D. F. Worth, *J. Med. Chem.*, **11**, 1201 (1968).

(8) A. Korolkovas, *Rev. Fac. Farm. Bioquim. Univ. Sao Paulo*, **6**, 115 (1968).

(9) E. F. Elslager and A. A. Phillips, *J. Med. Chem.*, **12**, 519 (1969).

(10) E. F. Elslager, D. B. Capps, L. M. Werbel, D. F. Worth, J. E. Meisenhelder, and P. E. Thompson, *ibid.*, **7**, 487 (1964).

(11) L. M. Werbel, E. F. Elslager, and D. F. Worth, *ibid.*, **11**, 950 (1968).

(12) E. F. Elslager, D. B. Capps, and L. M. Werbel, *ibid.*, **7**, 658 (1964).