was removed by distillation. To the cooled mixture was added dropwise 44 g (0.36 mole) of 1-dimethylamino-2-propyl chloride (prepared by treatment of a slurry of the hydrochloride in ether containing 1% of water with powdered NaOH, decantation, extraction by three portions of ether, drying, and distillation, bp 118–120°). The mixture was refluxed with stirring for 15 hr, cooled, and treated with 100 ml of water. The organic phase was washed with water and then added to dilute HCl. The aqueous phase was treated with dilute NaOH, and the mixture was extracted with ether. After drying (Na_2SO_4), the ether was evaporated and the residue was distilled under reduced pressure [47.4 g, bp 160–170° (0.1 mm)]. This material was dissolved in 250 ml of ether and treated with an equivalent quantity of HCl in ethanol. The solvent was evaporated to give 46.5 g of colorless solid, mp 168° (mixture of **33** and **32**, 80:20 by vpc analysis). The solid was dissolved in 100 ml of hot acetonitrile and cooled to give 32 g of pure **33**. An ethereal extract of the corresponding base was chromatographed (injection port at 450°) on a 2-m alkaline Carbowax 20M column at 120°; a single peak was observed whose retention time was identical with 2-dimethylamino-1-allyloxypropane; on a 2-m SE 30 gum silicone column at 200° a peak, developed as anthracene, was observed.

11-(2-Dimethylamino-1-methylethoxymethyl)-9,10-dihydro-9,10-ethanoanthracene Hydrochloride (32). Method G.—A mixture of 21.5 g (0.15 mole) of 1-dimethylamino-2-allyloxypropane, 26.7 g (0.15 mole) of anthracene, and 0.4 g of hydroquinone in 50 ml of toluene was stored in a pressure bottle at 210° for 15 hr. After cooling and extraction with dilute HCl, the aqueous acid layer was made basic with NaOH solution and extracted with ether. The ether extract was dried (Na_2SO_4) and evaporated *in vacuo*. The residual oil was converted to the **hydrochloride** by dissolving in dry ether and treating with HCl. Recrystallization from acetonitrile–ether gave 17.2 g of analytically pure **32**. An ethereal extract of the corresponding base was chromatographed as above to give on Carbowax 20M a single peak the retention time of which was identical with 1-dimethylamino-2-allyloxypropane and, on SE 30 gum silicone, a peak of anthracene.

9-[2-Methyl-3-(4-methyl-1-piperazinyl)propoxy]-9,10-dihydro-9,10-ethanoanthracene Dihydrochloride (64). Method H.—A solution of 22.2 g (0.1 mole) of 9,10-dihydro-9,10-ethano-9-anthrol in 250 ml of anhydrous toluene was treated with 5.3 g (0.11 mole) of a 50% dispersion of NaH in mineral oil. The mixture was refluxed with stirring under an atmosphere of dry nitrogen until the evolution of hydrogen ceased and the sodium salt precipitated (*ca.* 3 hr). To this suspension was then added 20.4 g (0.11 mole) of 1-chloro-2-methyl-3-(4-methyl-1-piperazinyl)propyl chloride[15] and the resulting mixture was stirred and refluxed under nitrogen for 24 hr. The mixture was filtered and the filtrate was evaporated to yield an oily residue. A solution of this material in 50 ml of ether was treated with an equivalent quantity of HCl in 100 ml of ethanol to give 21 g of white crystals: $\lambda_{max}^{95\%\ C_2H_5OH}$ 264 mμ (ε 1145), 271 mμ (ε 1410).

9-(2-Methylaminoethoxy)-9,10-dihydro-9,10-ethanoanthracene (38). Method I.—A solution of 10.85 g (0.1 mole) of ethyl chloroformate in 50 ml of benzene was added dropwise to a solution of 14.65 g (0.05 mole) of **40** in 50 ml of benzene, and the mixture was refluxed for 6 hr. After cooling, the solution was treated with 200 ml of 2 *N* HCl and with water. The solvent was removed under reduced pressure. The residual oily liquid (15.6 g, 86.5%) of crude 9-(N-carbethoxy-N-methyl-2-aminoethoxy)-9,10-dihydro-9,10-ethanoanthracene was added to a stirred solution of KOH (14 g) in 100 ml of diethylene glycol. The mixture was then refluxed for 8 hr and added to 200 ml of water. The solution was extracted with ether. Evaporation of the ether solution gave 10.5 g of product. For analysis the latter was crystallized from 200 ml of pentane to give 6 g of colorless solid.

Acknowledgment.—We are indebted to Dr. J. Hirtz and his staff for the analytical data. We wish to thank Mr. C. Demosthene for technical assistance.

(15) J. P. Bourquin, G. Schwarb, G. Gamboni, R. Fischer, L. Ruesch, S. Guldimann, V. Theus, E. Schenker, and J. Renz, *Helv. Chim. Acta*, **41**, 1072 (1958).

Notes

Nitrofuryl Heterocycles. V.[1] 4-Acyl-5,5-dialkyl-2-(5-nitro-2-furyl)-Δ^2-1,3,4-oxadiazolines

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A continuing search for nitrofuryl heterocyclic chemotherapeutic agents led to an investigation of 2-(5-nitro-2-furyl)-1,3,4-oxadiazole analogs (III). It was reported by Sherman[2] that 2-(5-nitro-2-furyl)-Δ^2-1,3,4-oxadiazolin-5-one possessed excellent antibacterial properties both *in vitro* and *in vivo*. Furthermore, antifungal and trichomonacidal activities have been reported recently for a series of 2-(5-nitro-2-furyl)-5-alkyl-1,3,4-oxadiazoles.[3] Thus, further work in this area appeared promising.

A survey of the literature revealed that very few analogs of 4-acyl-5,5-disubstituted Δ^2-1,3,4-oxadiazoline had been reported. Such compounds have been synthesized by four methods. Stolle[4] and later Fahr, *et al.*,[5] treated the silver salt of an acylhydrazone with an acid chloride. Yale, *et al.*,[6] and Sagitullin and Kost[7] improved this method by treating an acylhydrazone with an acid anhydride. A novel rearrangement of 5-benzyltetrazole to 2-benzylidene-3-aroyl-5-aryl-Δ^2-1,3,4-oxadiazoline on treatment with an aroyl chloride in pyridine was reported by Huisgen, *et al.*[8] Finally, Breslow[9] obtained 4-acyl-Δ^2-1,3,4-oxadiazolines from the reaction of azodicarbonyl compounds with aliphatic diazo compounds.

The method of Yale, *et al.*[6] (Scheme I), was chosen for this project because of the availability of starting

(1) For the previous paper in this series see H. A. Burch, *J. Med. Chem.*, **9**, 408 (1966).

(2) W. R. Sherman, *J. Org. Chem.*, **26**, 88 (1961).

(3) Y. Haraoka, A. Sugihara, and M. Ito, Japanese Patents 19,451 (1964) and 20,164 (1964); *Chem. Abstr.*, **62**, 10444*e*, 11821*d* (1965).

(4) R. Stolle, *J. Prakt. Chem.*, [2] **68**, 413, 418, 421 (1903); **70**, 412, 419 (1904); R. Stolle and G. Muench, *ibid.*, **70**, 408, 410 (1904).

(5) E. Fahr, K. Doeppert, and F. Scheckenbach, *Angew. Chem.*, **75**, 670 (1963).

(6) H. L. Yale, K. Losee, J. Martins, M. Holsing, F. M. Perry, and J. Bernstein, *J. Am. Chem. Soc.*, **75**, 1933 (1953).

(7) R. S. Sagitullin and A. N. Kost, *Vestn. Mosk. Univ., Ser. Mat., Mekhan., Astron., Fiz. i Khim.*, **14** (4), 187 (1959); *Chem. Abstr.*, **54**, 17383*h* (1960).

(8) R. Huisgen, J. Sauer, H. J. Sturm, and J. H. Markgraf, *Chem. Ber.*, **93**, 2111 (1960).

(9) R. Breslow, *Chem. Ind.* (London), 1961, (1961).

TABLE I

ACYLHYDRAZONES (II)

II	R	R¹	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
a	CH_3	CH_3	195–196	64	$C_5H_9N_3O_2$	45.50	4.30	19.90	45.42	4.39	19.93
b	CH_3	C_2H_5	140.5–142	67	$C_6H_{11}N_3O_2$	48.00	4.92	18.66	47.97	4.94	18.83
c	CH_3	$(CH_3)_2CHCH_2$	107–108	61	$C_8H_{15}N_3O_2$	52.17	5.97	16.59	52.19	5.90	16.72
d	CH_3	$C_6H_5CH_2$	160–161	88	$C_{12}H_{13}N_3O_2$	58.53	4.56	14.63	58.51	4.54	14.64
e		$-(CH_2)_5-$	155.5–157	79.8	$C_{11}H_{17}N_3O_2$	52.58	5.22	16.73	52.66	5.43	16.74
f		$-(CH_2)_4-$	172–173.5	68.5	$C_{10}H_{15}N_3O_2$	50.63	4.67	17.72	50.58	4.71	17.75
g	H	C_6H_5	210–211.5	76.4	$C_{12}H_{11}N_3O_2$	55.60	3.50	16.21	55.49	3.48	16.20
h	H	$(C_2H_5)_2CH$	136–137	65.6	$C_{11}H_{21}N_3O_2$	52.17	5.97	16.59	52.12	5.88	16.61
i	H	CH_3	225–227	70.6	$C_3H_7N_3O_2$	42.64	3.58	21.32	42.63	3.69	21.21
j	H	p-$O_2NC_6H_4$	243.5–244.5	69.5	$C_9H_6N_4O_4$	47.37	2.65	18.42	47.35	2.65	18.61

TABLE II

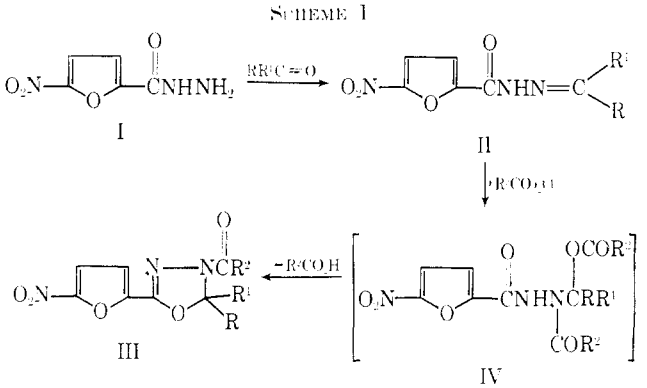
Δ^2-1,3,4-OXADIAZOLINES (III)

III	R	R¹	R²	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
a	CH_3	CH_3	CH_3	127.5–128.5	60.5	$C_6H_7N_3O_2$	47.43	4.38	16.16	47.09	4.23	16.49
b	CH_3	C_2H_5	CH_3	103–104	55.8	$C_7H_9N_3O_2$	49.43	4.90	15.73	49.19	4.92	15.69
c	CH_3	$C_6H_5CH_2$	CH_3	131–132.5	67	$C_{12}H_{13}N_3O_2$	58.35	4.59	12.76	58.21	4.66	12.72
d		$-(CH_2)_5-$	CH_3	156.5–158	43	$C_{11}H_{15}N_3O_2$	53.24	5.16	14.33	53.19	5.14	14.19
e	CH_3	CH_3	C_2H_5	145–146.5	56	$C_7H_9N_3O_2$	49.43	4.90	15.73	49.41	4.82	15.77
f	CH_3	CH_3	$(CH_3)_2CH$	135.5–137	56.5	$C_8H_{13}N_3O_2$	51.24	5.38	14.94	51.13	5.40	14.92
g	CH_3	CH_3	CH_2Cl	134.5–135.5	71.4	$C_6H_6ClN_3O_2$[a]	41.75	3.50	14.61	41.77	3.46	14.69
h		$-(CH_2)_5-$	C_2H_5	117.5–118	47.1	$C_{11}H_{17}N_3O_2$	54.72	5.58	13.68	54.63	5.68	13.69
i		$-(CH_2)_4-$	$CH_3(CH_2)_6$	82–82.5	57.2	$C_{16}H_{29}N_3O_2$	57.30	6.31	12.53	57.11	6.16	12.55
j		$-(CH_2)_5-$	CH_2Cl	155–156.5	66	$C_{11}H_{14}ClN_3O_2$[a]	47.64	4.31	12.82	47.71	4.35	12.85

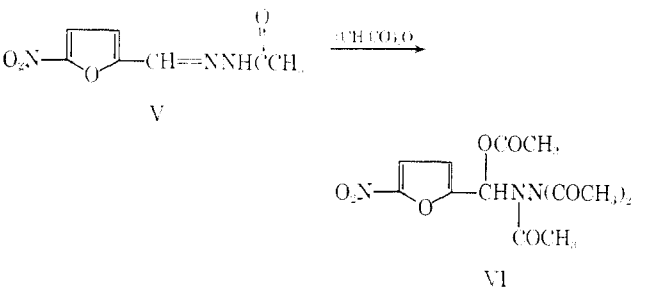
[a] Showed a correct analysis for Cl.

materials. Accordingly, 5-nitro-2-furoic acid hydrazide[6] (I) was condensed with several carbonyl compounds to give the acylhydrazones (II). Most of the ketone hydrazones could be cyclized to 4-acyl-Δ^2-1,3,4-oxadiazolines (III) in refluxing aliphatic acid anhydride solutions. None of the aldehyde hydrazones (IIIg–j, Table II) would cyclize in refluxing acetic anhydride, however.

SCHEME I



Yale[6] pictured the cyclization of II to III as going through intermediate IV. He offered as evidence the addition of acetic anhydride to benzal anil[10] yielding $C_6H_5CH(OCOCH_3)N(COCH_3)C_6H_5$. More recent work by Walker and Moore[11] on the addition of acetic anhydride to anils further supports intermediate IV. An example of the addition of an acid anhydride to a hydrazone linkage was obtained when 5-nitro-2-furaldehyde acetylhydrazone (V)[12] was refluxed in acetic anhydride to yield 1-(α-acetoxy-5-nitro-2-furfuryl)-1,2,2-triacetylhydrazine (VI). Compound VI could not be cyclized to an acyloxadiazoline by treatment with cold concentrated sulfuric acid or by heating in acetic acid or in the absence of any solvent. Decomposition occurred in each instance.



The compounds in Tables I and II were screened for antibacterial activity by methods reported previously.[13] Most of them were slightly active *in vitro* against both gram-positive and gram-negative organisms. No activity was observed at a dose of 100 mg/kg orally when the compounds were tested against *Staphylococcus aureus* and *Salmonella typhosa* infections in mice. Compound IIIa was found to be active against a vaginal infection of *Trichomonas foetus* in mice following an oral dose of 15 mg/kg.

Experimental Section

All melting points were determined on a hot stage (Fisher-Johns) melting point apparatus and are uncorrected.

5-Nitro-2-furoic Acid Isopropylidenehydrazide (IIa).—A mixture of 5-nitro-2-furoic acid hydrazide[6] (75.0 g, 0.44 mole) in 1 l.

(10) J. B. Ekely, M. C. Swisher, and C. C. Johnson, *Gazz. Chim. Ital.*, **62**, 81 (1932).

(11) G. N. Walker and M. A. Moore, *J. Org. Chem.*, **26**, 437 (1961).

(12) W. B. Stillman and A. B. Scott, U. S. Patent 2,416,234 (Feb 18, 1947); *Chem. Abstr.*, **41**, 3488i (1947).

(13) F. F. Eberino, W. F. Carey, and B. F. Stevenson, *J. Med. Chem.*, **6**, 633 (1963).

of acetone was refluxed with stirring overnight, concentrated under reduced pressure to about 300 ml, and chilled. The crude product was filtered and air dried to yield 88.4 g. Forty-four grams was recrystallized twice from nitromethane (charcoal) to yield 29.5 g of pure product as pale yellow needles. The other analogs of **II** in Table I were prepared from the appropriate carbonyl compound using ethanol as a solvent.

4-Acetyl-5,5-dimethyl-2-(5-nitro-2-furyl)-Δ^2-1,3,4-oxadiazoline (IIIa).—A solution of IIa (42.9 g, 0.20 mole) in 150 ml of acetic anhydride was refluxed for 1 hr, cooled, and poured into 500 ml of ice and water. Solid Na_2CO_3 was added in small portions with vigorous stirring until the mixture was neutral. The gummy product was washed with cold water by decantation until crystallization occurred. The solids were filtered and recrystallized twice from 95% ethanol (charcoal) to yield 31.1 g of product as short, yellow needles. The other analogs of III in Table II were prepared from the appropriate acid anhydride and II.

1-(α-Acetoxy-5-nitrofurfuryl)-1,2,2-triacetylhydrazine (VI).—A solution of 5-nitro-2-furaldehyde acetylhydrazone[12] (100 g, 0.51 mole) in 450 ml of acetic anhydride was refluxed for 1 hr. The product was obtained in the same manner as was IIIa. Four recrystallizations from 95% ethanol (charcoal) gave the product as pale yellow needles melting at 157–158.5°; yield 24.4 g (14.1%).

Anal. Calcd for $C_{13}H_{15}N_3O_8$: C, 45.75; H, 4.43; N, 12.31. Found: C, 45.94; H, 4.35; N, 12.12.

Carbonyl stretching bands were observed at 1695, 1710, and 1745 cm^{-1} in the infrared spectrum of a sample prepared as a Nujol mull using a Perkin-Elmer Model 21 spectrophotometer.

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Synthesis and Bacteriostatic Activity of Some Nitrotrifluoromethylanilides

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It has been reported for bacteriostatic halosalicylanilides[1] and halocarbanilides[2] that certain of the halo groups can be replaced with trifluoromethyl groups without lowering activity. In some instances enhanced activity is claimed. As an extension of our work on the bacteriostatic activity of a series of anilides[3] possessing both halo and nitro groups in the N-phenyl ring, we have prepared and evaluated a number of analogous anilides in which the halo groups are replaced with a trifluoromethyl group (Table I).

The anilides were prepared either by the acid-catalyzed reaction of an anhydride with a substituted aniline or by the condensation of an acid chloride with the aniline alone or in the presence of triethylamine as the hydrogen chloride acceptor. The reaction mixture was refluxed for several hours to expel hydrogen chloride when no acceptor was present. Compound **15**, an N-methylanilide, was obtained by the action of dimethyl sulfate on the sodium salt of **14**.

When C_{5-9} acid chlorides free of α substituents were allowed to react with 4-nitro-3-trifluoromethylaniline in the presence of triethylamine, a 1:1 molar complex of the anilide and aniline was obtained. The complexes were quite stable and were readily purified by recrystallization to give a sharp melting point which was depressed when admixed with the anilide. The complexes could be broken up by the addition of ethereal HCl to an ether solution of the complex and removing the 4-nitro-3-trifluoromethylaniline hydrochloride. The complexes were stable to dilute hydrochloride acid. They were also prepared by dissolving equimolar quantities of the anilide and the aniline in a mixture of methylcyclohexane and toluene and allowing the complex to precipitate on cooling. No complexes were formed when isomeric anilines were used.

The infrared spectra of the anilides were examined and displayed the characteristic[4] NH stretching band at 3250–3390 cm^{-1} and the amide I band at 1675–1725 cm^{-1}. Nitro stretching absorptions obscured the amide II band. The N-methylanilide **15** exhibited no characteristic NH stretching band. A comparison of these spectra with the corresponding complexes revealed marked differences. For example, anilide **14** showed a strong NH stretching band at 3320 cm^{-1}, a strong amide I band at 1725 cm^{-1}, and a very weak band at 1650 cm^{-1}. In the spectrum of the complex (**45**) the 3320-cm^{-1} band remained unchanged, the amide I band, reduced in intensity, shifted only slightly to 1700 cm^{-1}, and two new medium bands appeared at 3250 and 3450 cm^{-1}. The very weak 1650-cm^{-1} band found in the anilide appeared much stronger in the complex suggesting a higher degree of enolization to give the C=N group in the anilide portion of the complex.

The *in vitro Staphylococcus aureus* activity of the nitrotrifluoromethylanilides was obtained. Active structures included those which were substituted in the *meta* and *para* positions of the N-phenyl ring with a nitro and trifluoromethyl group and in which the acid-derived moiety incorporates alkyl, haloalkyl, cycloalkyl, alkenyl, haloalkenyl, alkyldienyl, and phenethyl groups and contains 5–12 carbon atoms. The benzyl and phenoxymethyl derivatives were inactive. N,N-Disubstituted and *ortho*-substituted derivatives were also inactive. Those anilides disubstituted in the α position possessed a lower order of activity. All of the complexes (Table II) were derivatives of active anilides and exhibited the same order of activity on a weight basis as the anilides themselves.

In general, the scope of activity of this series parallels that obtained for the previously studied halonitroanilide series.[3] Exceptions were **34**, the phenethyl derivative, which was active in this series, and **19**, the tridecanoic acid derivative, which was inactive. No direct comparisons were made for the haloalkenyl, alkyldienyl, and the phenyl derivatives between the two series.

Experimental Section

Chemical Procedures.—All of the anhydrides, acid chlorides, and substituted anilines were obtained commercially except

(1) (a) J. Bindler and E. Model, U. S. Patent 2,703,332 (March 1, 1955); (b) H. C. Stecker, U. S. Patent 3,041,236 (June 26, 1962).

(2) (a) W. Frick and W. Stammbach, Swiss Patent 359,841 (March 15, 1962); *Chem. Abstr.*, **58**, 416 (1963); (b) P. P. Hoffman, R. K. Madison, and W. B. Hardy, *J. Med. Chem.*, **7**, 665 (1964).

(3) J. W. Baker, I. Schumacher, G. L. Bachman, D. P. Roman, and A. L. Tharp, *ibid.*, **9**, 428 (1966).

(4) E. J. Forbes, K. J. Morgan, and J. Newton, *J. Chem. Soc.*, 835 (1963).