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).

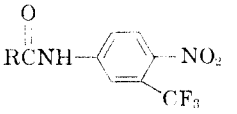
(2) (a) W. Frick and W. Stammbach, Swiss Patent 359,841 (March 15, 1962); *Chem. Abstr.*, **58**, 416 (1963); (b) P. P. Hoffman, R. K. Madison, and W. B. Hardy, *J. Med. Chem.*, **7**, 665 (1964).

(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).

TABLE I

NITROTRIFLUOROMETHYLANILIDES

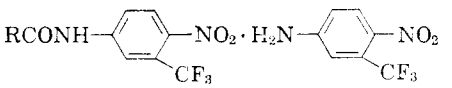


No.[a]	R	Method	Yield, %	Mp, °C[b]	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found	Concn for inhib of *S. aureus*[c]
1	C_6H_5	A	93	121–122[d]	$C_9H_7F_3N_2O_3$	43.5	43.5	2.84	2.69			T
2	CH_3CH_2	A	97	165–166	$C_{10}H_9F_3N_2O_3$	45.8	45.7	3.46	3.70	10.7	10.6	+
3	$CH_3(CH_2)_2$	B	85	131–132	$C_{11}H_{11}F_3N_2O_3$	47.8	47.8	4.01	4.20	10.1	10.1	+
4	$(CH_3)_2CH$	B	77	110–111	$C_{11}H_{11}F_3N_2O_3$	47.8	47.8	4.01	4.23	10.1	10.4	+
5	$CH_3(CH_2)_3$	B	91	94–95	$C_{12}H_{13}F_3N_2O_3$	49.7	4 .7	4.51	4.84	9.65	9.49	100T
6	$(CH_3)_2CHCH_2$	B	82	103–104	$C_{12}H_{13}F_3N_2O_3$	49.7	49.9	4.51	4.75	9.65	9.49	100T
7	$CH_3CH_2CH(CH_3)$	B	65	111–112	$C_{12}H_{13}F_3N_2O_3$	49.7	49.7	4.51	4.33	9.65	9.64	100T
8	$(CH_3)_3C$	B	70	135–136	$C_{12}H_{13}F_3N_2O_3$	49.7	49.3	4.51	4.70	9.65	9.60	+
9	$CH_3(CH_2)_4$	B	63	73–74	$C_{13}H_{15}F_3N_2O_3$	51.3	51.6	4.97	5.17	9.21	.14	M
10	$(CH_3)_2CH(CH_2)_2$	B	68	85–87	$C_{13}H_{15}F_3N_2O_3$	51.3	51.4	4.97	5.13	9.21	8.91	M
11	$CH_3(CH_2)_5$	C	35	64–65	$C_{14}H_{17}F_3N_2O_3$	52.8	52.7	5.38	5.18	8.80	8.69	M
12	$CH_3(CH_2)_2C(CH_3)_2$	B	77	110–112	$C_{14}H_{17}F_3N_2O_3$	52.8	52.9	5.38	5.73	8.80	8.95	1×0T
13	$CH_3(CH_2)_6$	C	40	72–73	$C_{15}H_{19}F_3N_2O_3$	54.2	54.1	5.76	5.90	8.43	8.19	M
14	$CH_3(CH_2)_7$	C	45	69–70	$C_{16}H_{21}F_3N_2O_3$	50.0	50.0	4.74	4.85	10.1	10.1	M
15[e]	$CH_3(CH_2)_7$	F	71	1.5049[f]	$C_{17}H_{23}F_3N_2O_2$					7.78	7.69	–
16	$CH_3(CH_2)_8$	B	85	77–78	$C_{17}H_{23}F_3N_2O_3$	56.7	56.8	6.43	6.75	7.78	7.64	M
17	$CH_3(CH_2)_9$	B	91	82–83	$C_{18}H_{25}F_3N_2O_3$	57.7	57.5	6.23	6.60	7.48	7.29	M
18	$CH_3(CH_2)_{10}$	C	77	78–79	$C_{19}H_{27}F_3N_2O_3$	58.7	58.6	7.01	6.85	7.21	7.11	M
19	$CH_3(CH_2)_{11}$	B	81	88–90	$C_{20}H_{29}F_3N_2O_3$	59.7	59.8	7.26	7.43	6.96	6.90	+
20	$CH_3(CH_2)_{12}$	B	97	88–89	$C_{21}H_{31}F_3N_2O_3$	60.6	60.6	7.50	7.52	6.73	6.45	+
21	$CH_3(CH_2)_{14}$	B	84	92–93	$C_{23}H_{35}F_3N_2O_3$	64.5	64.6	8.24	8.58	6.54	6.65	+
22	$CH_3(CH_2)_6CHCl$	B	33	55–56	$C_{16}H_{20}ClF_3N_2O_3$	50.4	50.5	5.27	5.44	7.36	7.53	M
23	$CH_3(CH_2)_6CHBr$	B	38	102–103	$C_{16}H_{20}BrF_3N_2O_3$	18.6[g]	18.8			6.59	6.60	M
24	$CH_3(CH_2)_5CHBrCHBr$	D	34	107–108	$C_{16}H_{19}Br_2F_3N_2O_3$					5.57	5.62	M
25	$CH_2{=}CH(CH_2)_8$	C	91	77–78	$C_{18}H_{23}F_3N_2O_3$					7.52	7.18	M
26	$CH_3(CH_2)_5CH{=}CH$	B	67	59–60	$C_{16}H_{19}F_3N_2O_3$	54.8	54.9	5.45	5.45	8.14	7.88	M
27	$CH_3(CH_2)_2C(C_2H_5){=}CH$	B	80	90–91	$C_{15}H_{17}F_3N_2O_3$	54.5	54.5	5.18	5.37	8.48	8.30	M
28	$CH_3CH{=}CHCH{=}CH$	B	53	123–124	$C_{13}H_{11}F_3N_2O_3$	52.	52.1	3.69	3.71	9.33	9.55	M
29	$CH_3(CH_2)_5CH{=}CBr$	E	72	Oil	$C_{16}H_{18}BrF_3N_2O_3$	18.8[g]	18.6					M
30	Cyclobutyl	B	83	110–111	$C_{12}H_{11}F_3N_2O_3$	50.0	50.0	3.85	3.98	9.72	9.49	10T
31	Cyclopentyl	B	85	143–144	$C_{13}H_{13}F_3N_2O_3$	53.9	54.2	4.51	4.85	9.65	9.41	100T
32	Cyclohexyl	B	84	135–136	$C_{14}H_{15}F_3N_2O_3$	53.2	53.2	4.78	5.27	8.86	9.15	M
33	$C_6H_5CH_2$	B	89	163–164	$C_{15}H_{11}F_3N_2O_3$	55.6	55.5	3.42	3.66	8.64	8.53	+
34	$C_6H_5CH_2CH_2$	B	48	90–92	$C_{16}H_{13}F_3N_2O_3$	56.8	56.6	3.87	4.11	8.28	7.95	100T
35	$2,4\text{-}Cl_2C_6H_3OCH_2$	B	71	159–161	$C_{15}H_9Cl_2F_3N_2O_4$	17.3[h]	17.4			6.85	6.73	+
36	$2,4,5\text{-}Cl_3C_6H_2OCH_2$	B	70	194–196	$C_{15}H_8Cl_3F_3N_2O_4$	24.0[h]	24.0			6.31	6.03	–
37[i]	$CH_3(CH_2)_7$	B	75	79–80	$C_{16}H_{21}F_3N_2O_3$	55.5	55.4	6.11	6.35	8.09	7.99	–
38[j]	$CH_3(CH_2)_7$	B	65	72–73	$C_{16}H_{21}F_3N_2O_3$	55.5	55.5	6.11	6.28	8.09	8.10	–

[a] Compounds **1–3, 8, 9, 11–13, 18, 19, 26, 28, 30, 35,** and **36** were recrystallized from toluene; **5, 17, 20–22,** and **37** from methylcyclohexane; **6, 7, 10, 16, 23, 25, 27,** and **31–33** from methylcyclohexane–toluene; **14, 34,** and **38** from hexane, and **24** from heptane–toluene. [b] All melting points, taken on a Fisher-Johns melting point apparatus, are corrected. [c] ATCC No. 6538; + represents growth at a concentration of 1×10^3; T, 10T, 100T, and M represent no growth at a concentration of 1×10^3, 1×10^4, 1×10^5, and 1×10^6, respectively. [d] H. Rouche [*Bull. Sci. Acad. Roy. Belg.*, **13,** 346 (1927)] reports mp 123.5°. [e] Methyl group substituted on N. [f] Refractive index ($n^{25}D$). [g] Bromine analysis. [h] Chlorine analysis. [i] Substituents on phenyl ring are $2\text{-}CF_3\text{-}4\text{-}NO_2$. [j] Substituents on phenyl ring are $2\text{-}NO_2\text{-}4\text{-}CF_3$.

TABLE II

ANILIDE–ANILINE COMPLEXES



No.[a]	R	Method	Yield, %	Mp, °C	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found
39	$CH_3(CH_2)_3$	G	82	96–97	$C_{19}H_{18}F_6N_4O_5$	45.9	45.9	3.65	3.70	11.3	10.9
40	$(CH_3)_2CHCH_2$	G	98	103–104	$C_{19}H_{18}F_6N_4O_5$	45.9	46.1	3.65	3.74	11.3	11.3
		C	17	103–104							
41	$CH_3(CH_2)_4$	G	83	106–107	$C_{20}H_{20}F_6N_4O_5$	47.1	47.2	3.95	4.05	11.0	10.7
42	$(CH_3)_2CHCH_2CH_2$	G	88	97–98	$C_{20}H_{20}F_6N_4O_5$	47.1	47.1	3.95	4.01	11.0	11.0
43	$CH_3(CH_2)_5$	C	98	94–95	$C_{21}H_{22}F_6N_4O_5$	48.1	48.2	4.23	4.40	10.7	10.4
44	$CH_3(CH_2)_6$	C	90	90–91	$C_{22}H_{24}F_6N_4O_5$	49.1	49.1	4.49	4.75	10.4	10.5
45	$CH_3(CH_2)_7$	C	65	84–85	$C_{23}H_{26}F_6N_4O_5$	50.0	50.1	4.75	4.85	10.1	10.1
		G	92	85–86							

[a] Compounds **39–42** and **45** were recrystallized from methylcyclohexane–toluene, **43** and **44** from toluene.

α-bromononanoyl chloride,[5] α-chlorononanoyl chloride,[3] sorbyl chloride,[6] 2-nonenoyl chloride,[7] 2,4-dichlorophenoxyacetyl chloride,[8] and 2,4,5-trichlorophenoxyacetyl chloride[8] which were prepared in a manner similar to those reported in the literature.

3-Ethyl-2-hexenoyl chloride was prepared from the corresponding acid and $SOCl_2$ by a procedure employed for the preparation of similar acid chlorides;[7] bp 72–74° (12 mm), yield 84%. This material was characterized by conversion to **27**.

Anilides and Complexes. Method A.—A solution of the substituted aniline (0.05 mole) and a drop of H_2SO_4 in 15–18 ml of the acid anhydride was refluxed for 2–3 hr, cooled, and poured into water. The anilide was collected, washed with water, and recrystallized.

Method B.—The acid chloride (0.055 mole) was added slowly to a stirred and refluxed solution of the aniline (0.050 mole) in 150–200 ml of toluene, methylcyclohexane, or a mixture of these solvents. Reflux was continued until HCl evolution ceased. The solution was cooled to allow crystallization or, in some cases, the solvent was evaporated and the anilide was recrystallized.

Method C.—The acid chloride (0.05 mole) was added dropwise to a stirred solution of the aniline and triethylamine (0.05 mole of each) in 200–300 ml of ether. The mixture was refluxed for 2–4 hr, cooled, and filtered to remove triethylamine hydrochloride. The solvent was evaporated and the anilide was recrystallized using activated carbon. In those instances [**6** (**40**), **11** (**43**), **13** (**44**), and **14** (**45**)] in which a complex formed between the 4-nitro-3-trifluoromethylaniline and the corresponding anilide, the complexes were broken up by dissolving the complex in ether and adding an excess of ethereal HCl. The precipitated aniline hydrochloride was separated and the filtrate was evaporated to yield the anilide. The aniline hydrochloride readily lost HCl and reverted to the aniline. No reaction occurred between the complexes and dilute HCl.

Method D.—Bromine (0.014 mole) in 25 ml of CCl_4 was added dropwise at 0° to a stirred mixture of 0.014 mole of the unsaturated anilide (**26**) in 100 ml of CCl_4 and stirred at 0–5° for 6 hr and at reflux for 0.5 hr. The solvent was evaporated and the residue was recrystallized.

Method E.—A solution of 0.003 mole of **24** and 0.006 mole of potassium acetate in 50 ml of ethanol was refluxed for 2 hr. The mixture was cooled and filtered, and the filtrate was evaporated. An ether solution of the oily residue was washed with water, dried, and evaporated.

Method F.—The salt of the anilide was prepared by refluxing for 2 hr equimolar quantities (0.014 mole) of the anilide (**14**) and sodium in 50 ml of dry toluene. Dimethyl sulfate (0.007 mole) was added. The solution was refluxed for 2 hr, washed with water, dried, treated with activated carbon, and evaporated.

Method G.—Equimolar quantities (0.003 mole) of 4-nitro-3-trifluoromethylaniline and the 4-nitro-3-trifluoromethylanilide were dissolved in 35 ml of a 1:1 mixture of methylcyclohexane and toluene. Upon cooling, the complex precipitated and was purified by recrystallization.

Infrared Spectra.—The infrared spectra of the solid anilides and complexes were taken as Nujol mulls using a Beckman IR-5 spectrophotometer. The liquid samples were measured as thin layers between salt plates.

Bacteriostatic Test Procedure.—The standard procedure used in screening the compounds against *S. aureus* (ATCC No. 6538) was as follows. Stock solutions were prepared by dissolving 100 mg of the test compound in 10 ml of acetone, alcohol, or other solvent. The stock solutions were diluted serially by pipetting 2 ml of the stock solutions into 18 ml of sterile nutrient agar to obtain a 1×10^3 dilution and continuing in the same manner for dilutions up to 1×10^6. The agar was poured into Petri dishes, allowed to harden, and spot inoculated with one drop of a cell suspension of *S. aureus* which was prepared by suspending the growth from a 24-hr nutrient agar slant culture in 10 ml of distilled water. The plates were incubated at 37° for 48 hr and examined for the presence or absence of growth. The results reported are the minimum concentration of the test compound which will completely inhibit the growth of the bacteria.

(5) A. Hopwood and C. Weizmann, *J. Chem. Soc.*, 1577 (1911).
(6) H. Staudinger and H. Schneider, *Ber.*, **56**, 699 (1923).
(7) E. Ott and K. Zimmermann, *Ann.*, **425**, 314 (1921).
(8) J. W. Wood and T. D. Fontaine, *J. Org. Chem.*, **17**, 891 (1952).

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The Mitomycin Antibiotics. Synthetic Studies. XIX.[1] Synthesis of Indoloquinone Analogs with Certain C-3 Variants

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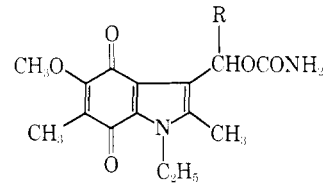
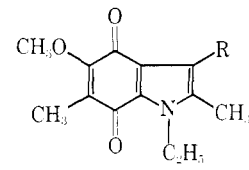
As part of our program for the preparation of analogs of indoloquinones (*e.g.*, Ia)[2] related to the mitomycin antibiotics, it was of interest to ascertain those structural features at C-3 consistent with biological activity. In this paper we report the preparation of analogs of Ia wherein the 3-carbamoyloxymethyl group is substituted with an α-methyl group or is replaced by hydrogen, methyl, or certain substituted methyl functions.

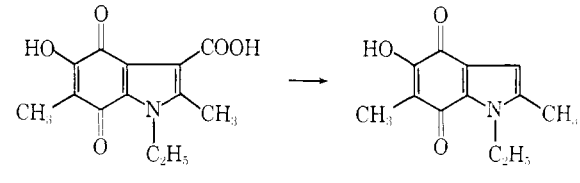


Ia, R = H
Ib, R = CH_3



IIa, R = H
IIb, R = CH_3

The 3-hydrogen analog IIa was obtained by acid-catalyzed decarboxylation of the known quinone acid III.[2b] Methylation of the resulting IV to the desired methoxyquinone IIa was effected with methyl sulfate and potassium carbonate in acetone. A similar methylation of 1-ethyl-5-hydroxy-2,3,6-trimethylindole-4,7-dione[2b] gave the 3-methyl analog IIb.



III IV

For the preparation of the α-methyl homolog Ib, 1-ethyl-2,6-dimethyl-5-methoxyindole (V)[2] was converted to the 3-acetyl derivative VI with acetic anhydride and sodium acetate.[3] This ketone was then converted into Ib using the procedures previously described for the transformation of the corresponding 3-formyl derivative VII into Ia.[2b] With respect to the homolog

(1) Paper XVIII: G. R. Allen, Jr., and M. J. Weiss, *J. Med. Chem.*, **10**, 23 (1967).
(2) (a) G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Am. Chem Soc.*, **86**, 3878 (1964); (b) G. R. Allen, Jr., and M. J. Weiss, *J. Med. Chem.* **10**, 1 (1967).
(3) A. N. Grinev, V. I. Shvedov, and A. P. Terent'ev, *Zh. Obshch. Khim.*, **26**, 1449 (1956); *Chem. Abstr.*, **50**, 14710i (1956).