or silyl heparin (0.1%) in water was applied and electrophoresis was run at 550 V, 18 mA, for 70 min. The spots were developed with Toluidine Blue indicator. Identical spots were obtained at about 3 cm from the points of application on the slide.

**WBCT of Rat Blood.** Cyclopal was given intravenously (iv) to anesthesia. An abdominal incision was made, the inferior vena cava was exposed, and 0.5 ml of blood was drawn with a 1-ml Stylex (Pharmaseal Labs., Glendale, Calif.) syringe and 26 G × 0.5 in. needle. At 20 sec from venipuncture 0.3 ml of blood was placed in a Fibrocup and the clotting time determined with a Fibrometer (B.B.L., Baltimore 18, Md).

**WBCT of Rabbit Blood.** Cyclopal was given iv to anesthesia and an abdominal incision made to expose the inferior vena cava. Blood samples (1.1 ml) were drawn with a 1-ml syringe and 26 G × 0.5 in. needle. Aliquots (0.5 ml) of blood were placed in disposable 12 × 75 mm culture tubes approximately 20 sec from venipuncture. The tubes were placed in a water bath (37°) and tilted every 30 sec to see if the blood was fluid. WBCT was recorded when blood was no longer fluid and would not flow up the side of the tube.

**Anticoagulant Activity** *in Vitro.* Heparin was dissolved in and serially diluted with saline. Aliquots (0.05 ml) were placed in disposable 10 × 75 mm culture tubes containing 0.1 ml of 0.25 *M* $CaCl_2$ in saline. Blood (9 ml) was drawn from rats into syringes containing 3.8% citrate (1 ml) and mixed. Aliquots of blood (0.9 ml) were placed in culture tubes containing the heparin and $CaCl_2$ solutions and placed on a Lab-Tek mixer (Ames Lab-Tek, Westmont, Ill.) and the time to clotting was recorded as recalcification time. Comparisons between sodium heparin and silylized heparin were made by their ability to prolong the recalcification time. Comparisons between sodium heparin and silylized heparin were made by their ability to prolong the recalcification time.

**Heparin Administration.** Compounds were given ig to fasted (>16 hr) animals or id by injecting through the stomach wall through the pyloric sphincter into the duodenum using a syringe and 19 G × 1 in. needle.

**Suspension or Solution of Compounds.** Heparin preparations were suspended in Carbowax, Tween 80, or mineral oil by sonication (<10 sec) to give a homogeneous suspension or dissolved in saline prior to mixing with a vehicle. Carbowax 1000 was warmed to approximately 40° in order to suspend the heparin.

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# Chemotherapeutic Nitroheterocycles. 18.† 2-(5-Nitro-2-imidazolylmethylene)-1-indanones, -1-tetralones, and -acetophenones Substituted by Aminoalkoxy Groups


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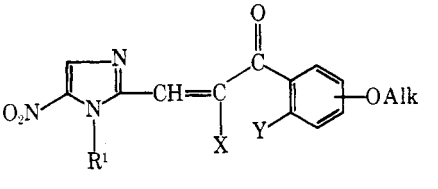
2-(5-Nitro-2-imidazolylmethylene)-1-indanones, -1-tetralones, and -acetophenones substituted by aminoalkoxy groups and related compounds (**41–69,** Table II) were synthesized and their antimicrobial activities were evaluated (Table III). Some of these compounds (*e.g.,* **47, 52,** and **59**) surprisingly exhibited a broad antibacterial spectrum including *Proteus* species and *Pseudomonas aeruginosa.* Extraordinary antitrichomonal activities could also be observed *in vitro* (MIC of compound **59,** 0.0004 μg/ml) and six of the title compounds (**48, 49, 52, 58, 64, 66**) displayed *in vivo* activity in mice against *Trichomonas vaginalis* comparable to that of metronidazole (**70**).


In two previous papers of this series[2,3] 5-nitro-2-imidazolylmethylene derivatives of alkoxy-1-indanones (**1**), alkoxy-1-tetralones (**2**), and alkoxyacetophenones (**3**) were shown to possess considerable activity against *Trichomonas vaginalis* (*T. vaginalis*) *in vitro;* however, in general their *in vivo* efficacy in mice (subcutaneous) was disappointing. The rather poor solubility of the compounds in inorganic and organic solvents may lead to an extremely low absorption rate from the gastrointestinal tract which would explain the discrepancy between *in vitro* and *in vivo* activity.

In order to enhance the solubility we intended to introduce substituted amino groups into the alkoxy residue (OAlk in formulas **1–3**) of the compounds as similar modifications within the series of 5-alkoxy-2-(5-nitro-2-furfurylidene)-1-indanones led to low MIC values against *T. vaginalis.*[4]

This communication is concerned with the synthesis and the results of the microbiological screening of 2-(5-nitro-2-imidazolylmethylene)-1-indanones, -1-tetralones, and -acetophenones substituted by aminoalkoxy groups and some related structures (physical and chemical data are given in Table II; Table III shows the microbiological results).



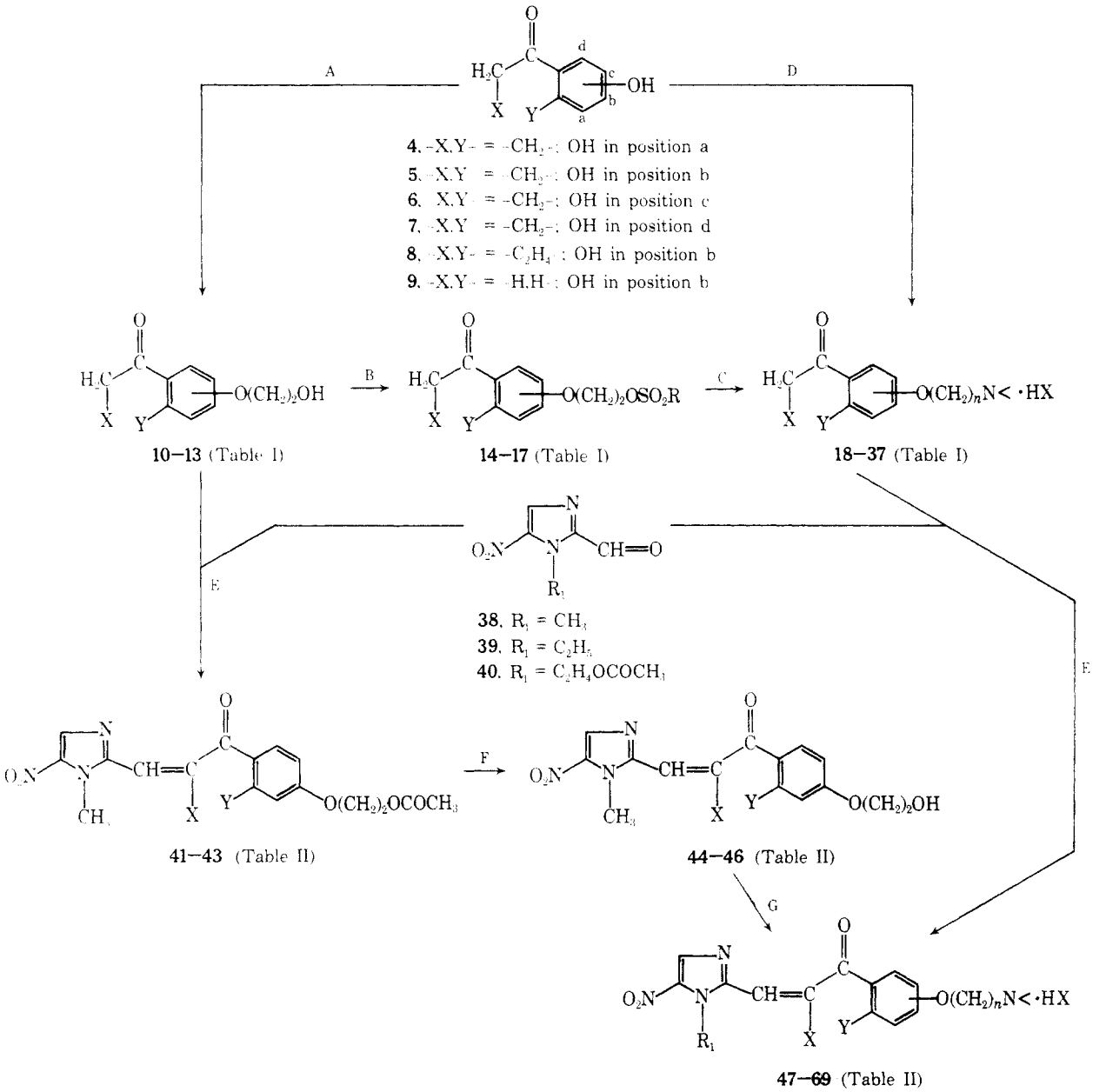

**1,** –X, Y– = $-CH_2-$
**2,** –X, Y– = $-C_2H_4-$
**3,** –X, Y– = –H, H–

**Chemistry.** The methods used for the synthesis of the compounds listed in Table II are given in Scheme I.

The starting materials, 4-, 5-, 6-, and 7-hydroxy-1-indanone, 6-hydroxy-1-tetralone, and 4′-hydroxyacetophenone (compounds **4–9**), were purchasable or known from the literature. Alkylation with 2-bromoethanol led to the 2-hydroxyethoxy derivatives (method A, **10–13**) which could be

† For part 17 of this series, see ref 1.

**Scheme I**




transformed *via* tosylation‡ (method B, 14–17) followed by displacement with amines into the corresponding aminoalkoxy derivatives (method C, **20–22, 24–28, 32, 34, 35,** and **37**). The remaining aminoalkoxyindanones, -tetralones, and -acetophenones (**18, 19, 23, 29–31, 33,** and **36**) were prepared by direct alkylation of the hydroxyindanones, -tetralones, and -acetophenones with the corresponding aminoalkyl chlorides (method D) (see Table I).

Most of the desired 5-nitro-2-imidazolylmethylene derivatives compiled in Table II were synthesized by condensation of the above-mentioned key intermediates (**10–13** and **18–37**) with the corresponding 5-nitroimidazole-2-carbaldehydes[5] (**38–40**) (method E). The reaction conditions (acetic acid at 100° with catalytic amounts of $H_2SO_4$) caused a simultaneous acetylation of free hydroxy groups; compounds **44–46** were prepared by hydrolysis of the corresponding acetoxy derivatives **41–43** (method F). Finally, 2-(1-methyl-5-nitro-2-imidazolylmethylene)-4′-(2-morpholinoethoxy)acetophenone **69** was prepared by tosylation of compound **46**, followed by displacement with morpholine (method G).

**Biological Activity.**§ The substituted alkoxy-2-(5-nitro-2-imidazolylmethylene)-1-indanones, -1-tetralones, and -acetophenones **41–69** shown in Table II were screened *in vitro* against gram-positive and gram-negative bacteria, fungi, and protozoa (tube dilution assay). Fungicidal activity could not be observed in any case. The minimum inhibitory concentrations (MIC values) against selected bacteria and protozoa are given in Table III.

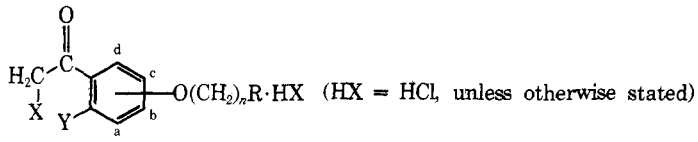
Follow-up studies against subcutaneous *T. vaginalis* infections in mice ($ED_{50}$ determinations) were done with those compounds which were active at orally given dosages of 12.5 or 50 mg/kg, respectively. Systemic (ip) infections of mice with *Staphylococcus aureus* and *Escherichia coli* were used to evaluate the antibacterial efficacy of selected compounds *in vivo* (oral treatment with 200 mg/kg).

The indanone derivatives **41** and **44** substituted by a 2-

‡ Compound **11** [7-(2-hydroxyethoxy)-1-indanone] did not react with tosyl chloride and therefore the mesyloxy derivative **15** was prepared. The reaction of 7-hydroxy-1-indanone (**7**) with 2-dimethylaminoethyl chloride (method C in Scheme I) did not proceed.

§ For experimental details of the biological evaluation, see ref 2 and 4.

**Table I.** Substituted Alkoxy-1-indanones, -1-tetralones, and -acetophenones (10-37)




(HX = HCl, unless otherwise stated)

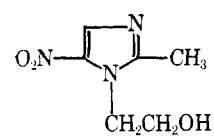
| Compd | Position -X,Y- of subst | | n | R | Method | Starting compd | Yield, % | Mp, °C | Recrystn solvent | Formula (analyses) |
|---|---|---|---|---|---|---|---|---|---|---|
| 10[a,m] | $-CH_2-$ | b | 2 | OH | $A_1$ | 5 | 78 | 130 | EtOAc | $C_{11}H_{12}O_3$ |
| 11[a,m] | $-CH_2-$ | d | 2 | OH | $A_2$ | 7 | 40 | 69 | MeOH–$H_2O$ | $C_{11}H_{12}O_3$[l] |
| 12[a,m] | $-C_2H_4-$ | b | 2 | OH | $A_1$[j] | 8 | 78 | 92 | $C_6H_6$ | $C_{12}H_{14}O$ |
| 13[a,o] | -H,H- | b | 2 | OH | $A_1$[i] | 9 | 96 | 66 | $Me_2CO$–*i*-$Pr_2O$ | $C_{10}H_{12}O_3$ |
| 14[a,m] | $-CH_2-$ | b | 2 | OTs | $B_1$ | 10 | 73 | 99 | EtOH | $C_{18}H_{18}O_5S$ |
| 15[a] | $-CH_2-$ | d | 2 | OMs | $B_2$ | 11 | 44 | 131 | *i*-PrOH | $C_{12}H_{14}O_5S$ (C, H) |
| 16[a] | $-C_2H_4-$ | b | 2 | OTs | $B_1$ | 12 | 82 | 111 | *i*-PrOH | $C_{19}H_{20}O_5S$ (S) |
| 17[a] | -H,H- | b | 2 | OTs | $B_1$ | 13 | 72 | 85 | *i*-PrOH | $C_{17}H_{18}O_5S$ (S) |
| 18[a,n] | $-CH_2-$ | b | 2 | $N(CH_3)_2$ | D | 5 | 80 | 198 | EtOEt[d] | $C_{13}H_{18}ClNO_2$ |
| 19[m] | $-CH_2-$ | b | 2 | $N(C_2H_5)_2$ | D | 5 | 61 | 177 | *i*-PrOH | $C_{15}H_{22}ClNO_2$ |
| 20 | $-CH_2-$ | b | 2 | $N(i\text{-}C_3H_7)_2$ | $C_1$ | 14 | 57 | | | $C_{17}H_{26}ClNO_2$[c] |
| 21 | $-CH_2-$ | b | 2 | $N(CH_2CH{=}CH_2)_2$ | $C_2$ | 14 | 46 | 136 | $Et_2O$[d] | $C_{17}H_{22}ClNO_2$ (Cl, N) |
| 22 | $-CH_2-$ | b | 2 | $NHC_3H_7$ | $C_2$[e] | 14 | 42 | 213 | EtOH | $C_{14}H_{20}ClNO_2$ (Cl, N) |
| 23[m] | $-CH_2-$ | b | 2 | c-$NC_4H_8$ | D[f] | 5 | 26 | 188 | $Et_2O$[d] | $C_{15}H_{20}ClNO_2$ |
| 24 | $-CH_2-$ | b | 2 | c-$NC_5H_{10}$ | $C_2$ | 14 | 81 | 190 | MeOH–$Et_2O$ | $C_{16}H_{22}ClNO_2$ (Cl, N) |
| 25 | $-CH_2-$ | b | 2 | c-$NC_6H_{12}$ | $C_2$ | 14 | 54 | 179 | MeOH–$Et_2O$ | $C_{17}H_{24}ClNO_2$ (Cl, N) |
| 26 | $-CH_2-$ | b | 2 |  | $C_2$[g] | 14 | 59 | 110 | MeOH[d] | $C_{19}H_{26}ClNO_2$ (Cl, N) |
| 27 | $-CH_2-$ | b | 2 | c-$N(CH_2CH_2)_2O$ | $C_2$ | 14 | 85 | 220 | EtOH | $C_{15}H_{20}ClNO_3$ (Cl, N) |
| 28[b] | $-CH_2-$ | b | 2 | c-$N(CH_2CH_2)_2NCH_3$ | $C_2$ | 14 | 75 | 238 | MeOH–*i*-PrOH | $C_{16}H_{24}Cl_2N_2O_2$[k] |
| 29 | $-CH_2-$ | b | 3 | $N(CH_3)_2$ | D[h] | 5 | 72 | 201 | $Et_2O$[d] | $C_{14}H_{20}ClNO_2$ (Cl, N) |
| 30 | $-CH_2-$ | a | 2 | $N(CH_3)_2$ | D | 4 | 51 | 184 | $Et_2O$[d] | $C_{13}H_{18}ClNO_2$ (Cl, N) |
| 31[n] | $-CH_2-$ | c | 2 | $N(CH_3)_2$ | D | 6 | 42 | 210 | *i*-PrOH | $C_{13}H_{18}ClNO_2$ |
| 32 | $-CH_2-$ | d | 2 | $N(CH_3)_2$ | $C_2$ | 15 | 30 | 209 | $Et_2O$ | $C_{13}H_{18}ClNO_2$ (Cl, N) |
| 33[m] | $-C_2H_4-$ | b | 2 | $N(CH_3)_2$ | D | 8 | 62 | 182 | $Et_2O$[d] | $C_{14}H_{20}ClNO_2$ |
| 34 | $-C_2H_4-$ | b | 2 | c-$NC_4H_8$ | $C_2$ | 16 | 77 | 203 | $Et_2O$[d] | $C_{16}H_{22}ClNO_2$ (Cl, N) |
| 35 | $-C_2H_4-$ | b | 2 | c-$N(CH_2CH_2)_2O$ | $C_2$ | 16 | 56 | 198 | $Et_2O$[d] | $C_{16}H_{22}ClNO_3$ (Cl, N) |
| 36 | -H,H- | b | 2 | $N(CH_3)_2$ | D | 9 | 32 | 163 | EtOAc | $C_{12}H_{18}ClNO_2$ (Cl, N) |
| 37 | -H,H- | b | 2 | c-$NC_4H_8$ | $C_2$ | 17 | 49 | 130 | $Et_2O$[d] | $C_{14}H_{20}ClNO_2$ (Cl, N) |

[a]The substance does not contain HCl. [b]Compound 28 was isolated as the dihydrochloride. [c]Structure was confirmed by nmr. [d]The compound was insoluble even when refluxed in the solvent. [e]Six equivalents of propylamine were used. [f]Reaction time, 5 hr. [g]When 1 *N* NaOH was added to the residue after removal of the solvent, crystals precipitated which were isolated and dissolved in *i*-PrOH–EtOAc. Addition of methanolic HCl yielded **26**. [h]3-Dimethylaminopropyl chloride (3 equiv) in EtOAc (not benzene) was used. Reaction time, 36 hr. [i]The product did not crystallize even if triturated with water and therefore was extracted into EtOAc. [j]Reaction time, 48 hr. [k]Cl: calcd, 20.42; found, 19.53. N: calcd, 8.07; found, 7.56. [l]C: calcd, 68.74; found, 66.30. H: calcd, 6.29; found, 6.75. [m]R. Albrecht and E. Schröder, *Justus Liebigs Ann. Chem.*, **736**, 110 (1970). [n]J. Sam and J. N. Plampin, *J. Amer. Chem. Soc.*, **82**, 5205 (1960). [o]Eastman Kodak, U.S. Patent 2,816,091 (1957); *Chem. Abstr.*, **52**, 4369 (1958).

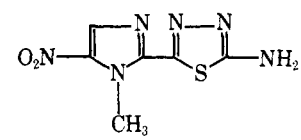
acetoxyethoxy and a 2-hydroxyethoxy group, respectively, inhibit the growth of *T. vaginalis in vitro* at 0.003 μg/ml but are inactive *in vivo*. The corresponding tetralone (**42**, **45**) and acetophenone (**43**, **46**) derivatives are considerably less active against *T. vaginalis in vitro;* however, *in vivo* the 6-(2-acetoxyethoxy)-1-tetralone derivative **42** proves to be effective ($ED_{50}$ = 58.6 mg/kg). None of the mentioned substances (**41**–**46**) display remarkable antibacterial activity *in vitro*.

Unexpectedly, the introduction of a 2-dimethylaminoethoxy side chain into the 5 position of the indanone moiety (compound **47**) gives rise to a broad spectrum antibacterial efficacy (Table III). Additionally, the MIC value against *T. vaginalis* is extraordinary low (0.0015 μg/ml).

In general, the antiparasitic nitroimidazole derivatives, *e.g.*, metronidazole[6] (**70**), inhibit specifically the growth of anaerobic bacteria, *e.g., clostridia,*[7] and do not affect those aerobic species which we use in our screening program. 2-Amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-




**70**




**71**

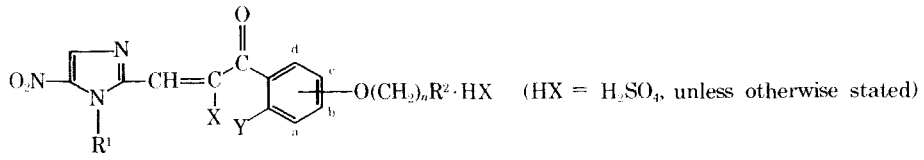
thiadiazole (**71**) is a well-known exception[8] and its antibacterial spectrum is shown for comparison at the bottom of Table III.

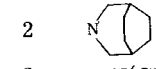
Compound **47** displays an appreciable *in vivo* activity ($ED_{50}$ 25.2 mg/kg) against sc *Trichomonas* infection in mice, but no activity could be observed in mice infected with *Staph. aureus* and *E. coli*. This holds true for all other compounds of this series tested in the above-mentioned systemic bacterial infections of mice.

Chemical modification of compound **47** leads to the following structure–activity relationships.

1. Substitution of the dimethylamino group by a diethyl (**48**) or by a diisopropylamino group (**49**) results in a

**Table II.** Substituted Alkoxy-2-(5-nitro-2-imidazolylmethylene)-1-indanones, -1-tetralones, and -acetophenones (41–69)




| Compd | –X,Y– | $R^1$ | Position of subst | $n$ | $R^2$ | Method | Starting compds | Yield, % | Mp, °C | Recrystn solvent | Formula (analyses) | S: calcd (found) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **41**[a] | $-CH_2-$ | $CH_3$ | b | 2 | $OCOCH_3$ | $E_1$[b] | **10** + **38** | 15 | 216 | DMF | $C_{18}H_{17}N_3O_6$ (N) | |
| **42**[a] | $-C_2H_4-$ | $CH_3$ | b | 2 | $OCOCH_3$ | $E_1$[b] | **12** + **38** | 19 | 169 | DMF | $C_{19}H_{19}N_3O_6$(N) | |
| **43**[a] | –H,H– | $CH_3$ | b | 2 | $OCOCH_3$ | $E_1$[b] | **13** + **38** | 38 | 163 | EtOH | $C_{17}H_{17}N_3O_6$ (N) | |
| **44**[a] | $-CH_2-$ | $CH_3$ | b | 2 | OH | F | **41** | 77 | 260 | DMF | $C_{16}H_{15}N_3O_5$ (N) | |
| **45**[a] | $-C_2H_4-$ | $CH_3$ | b | 2 | OH | F[c] | **42** | 59 | 232 | EtOH[e] | $C_{17}H_{17}N_3O_5$ (N) | |
| **46**[d] | –H,H– | $CH_3$ | b | 2 | OH | F | **43** | 93 | 210 | EtOH[e] | $C_{15}H_{16}ClN_3O_5$ (Cl, N) | |
| **47** | $-CH_2-$ | $CH_3$ | b | 2 | $N(CH_3)_2$ | $E_1$ | **18** + **38** | 29 | 210 | DMF–EtOH | $C_{18}H_{22}N_4O_8S$ (N) | 7.06 (6.50) |
| **48** | $-CH_2-$ | $CH_3$ | b | 2 | $N(C_2H_5)_2$ | $E_2$ | **19** + **38** | 31 | 196 | $H_2O$–*i*-PrOH | $C_{20}H_{26}N_4O_8S$ (N) | 6.55 (5.66) |
| **49** | $-CH_2-$ | $CH_3$ | b | 2 | $N(i\text{-}C_3H_7)_2$ | $E_2$ | **20** + **38** | 26 | 200 | MeOH–*i*-PrOH[e] | $C_{22}H_{30}N_4O_8S$ (N) | 6.29 (5.68) |
| **50** | $-CH_2-$ | $CH_3$ | b | 2 | $N(CH_2CH{=}CH_2)_2$ | $E_1$ | **21** + **38** | 30 | 172 | $H_2O$–*i*-PrOH | $C_{22}H_{26}N_4O_8S$ (N) | 6.33 (7.00) |
| **51** | $-CH_2-$ | $CH_3$ | b | 2 | $NHC_3H_7$ | $E_2$ | **22** + **38** | 9 | 244 | *f* | $C_{19}H_{24}N_4O_8S$ (N) | 6.85 (6.61) |
| **52** | $-CH_2-$ | $CH_3$ | b | 2 | c-$NC_4H_8$ | $E_1$ | **23** + **38** | 30 | 228 | MeOH–*i*-PrOH[e] | $C_{20}H_{24}N_4O_8S$ (N) | 6.68 (5.39) |
| **53** | $-CH_2-$ | $CH_3$ | b | 2 | c-$NC_5H_{10}$ | $E_2$ | **24** + **38** | 36 | 239 | *f* | $C_{21}H_{26}N_4O_8S$ (N) | 6.49 (5.75) |
| **54** | $-CH_2-$ | $CH_3$ | b | 2 | c-$NC_6H_{12}$ | $E_2$ | **25** + **38** | 27 | 226 | MeOH[g] | $C_{22}H_{28}N_4O_8S$ (N) | 6.31 (7.12) |
| **55** | $-CH_2-$ | $CH_3$ | b | 2 |  | $E_1$ | **26** + **38** | 30 | 248 | *f* | $C_{24}H_{30}N_4O_8S$[c] | 6.00 (6.14) |
| **56** | $-CH_2-$ | $CH_3$ | b | 2 | c-$N(CH_2CH_2)_2O$ | $E_1$ | **27** + **38** | 35 | 247 | $H_2O$–EtOH | $C_{20}H_{24}N_4O_9S$ (N) | 6.46 (5.13) |
| **57** | $-CH_2-$ | $CH_3$ | b | 2 | c-$N(CH_2CH_2)_2NCH_3$ | $E_2$ | **28** + **38** | 66 | 218 | $H_2O$–*i*-PrOH | $C_{21}H_{27}N_5O_8S$[g] | 6.30 (6.18) |
| **58** | $-CH_2-$ | $CH_3$ | b | 3 | $N(CH_3)_2$ | $E_1$ | **29** + **38** | 34 | 220 | *f* | $C_{19}H_{24}N_4O_8S$ (N) | 6.85 (5.92) |
| **59** | $-CH_2-$ | $CH_3$ | a | 2 | $N(CH_3)_2$ | $E_1$ | **30** + **38** | 65 | 226 | *f* | $C_{18}H_{22}N_4O_8S$ (N) | 7.06 (7.33) |
| **60** | $-CH_2-$ | $CH_3$ | c | 2 | $N(CH_3)_2$ | $E_1$ | **31** + **38** | 39 | 223 | *f* | $C_{18}H_{22}N_4O_8S$ (N) | 7.06 (6.12) |
| **61** | $-CH_2-$ | $CH_3$ | d | 2 | $N(CH_3)_2$ | $E_2$ | **32** + **38** | 26 | 260 | *f* | $C_{18}H_{22}N_4O_8S$ (N) | 7.06 (6.12) |
| **62** | $-CH_2-$ | $C_2H_5$ | b | 2 | $N(CH_3)_2$ | $E_1$ | **18** + **39** | 48 | 222 | *f* | $C_{19}H_{24}N_4O_8S$ (N) | 6.85 (6.55) |
| **63** | $-CH_2-$ | $C_2H_4OCOCH_3$ | b | 2 | $N(CH_3)_2$ | $E_2$ | **18** + **40** | 6 | 195 | *f* | $C_{21}H_{26}N_4O_{10}S$ (N) | 6.08 (5.81) |
| **64** | $-C_2H_4-$ | $CH_3$ | b | 2 | $N(CH_3)_2$ | $E_2$ | **33** + **38** | 40 | 206 | MeOH–$Et_2O$ | $C_{19}H_{24}N_4O_8S$ (N) | 6.85 (7.05) |
| **65** | $-C_2H_4-$ | $CH_3$ | b | 2 | c-$NC_4H_8$ | $E_2$ | **34** + **38** | 19 | 204 | $H_2O$–*i*-PrOH | $C_{21}H_{26}N_4O_8S$ (N) | 6.49 (6.34) |
| **66** | $-C_2H_4-$ | $CH_3$ | b | 2 | c-$N(CH_2CH_2)_2O$ | $E_1$ | **35** + **38** | 52 | 225 | MeOH[g] | $C_{21}H_{26}N_4O_9S$ (N) | 6.29 (6.31) |
| **67** | –H,H– | $CH_3$ | b | 2 | $N(CH_3)_2$ | $E_1$ | **36** + **38** | 51 | 185 | *f* | $C_{17}H_{22}N_4O_8S$ (N) | 7.25 (7.37) |
| **68** | –H,H– | $CH_3$ | b | 2 | c-$NC_4H_8$ | $E_2$ | **37** + **38** | 58 | 184 | *i*-PrOH[e] | $C_{19}H_{24}N_4O_8S$ (N) | 6.85 (7.44) |
| **69**[d] | –H,H– | $CH_3$ | b | 2 | c-$N(CH_2CH_2)_2O$ | G | **46** | 84 | 212 | MeOH | $C_{19}H_{23}ClN_4O_5$ (N)[h] | |

[a] The substance does not contain $H_2SO_4$. [b] Only 4 mmol of $H_2SO_4$ was used. [c] N: calcd, 10.48; found, 9.91. [d] The substance was isolated as the hydrochloride. [e] The compound was insoluble even when heated in the refluxing solvent. [f] The compound was heated in refluxing EtOH with a few drops of $H_2SO_4$, and water was added until the solution became clear. After cooling the precipitate was isolated. [g] N: calcd, 13.74; found, 12.96. [h] Cl: calcd, 8.39; found, 10.23.

**Table III.** Antimicrobial Activity of Compounds 41–69 (Table II)[a]

| | MIC (serial dilution assay), μg/ml | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Compd | *Staph. aureus* 30–8[b] | *Strep. faecalis* 32–2 | *E. coli* 1–19 | *Prot. mirabilis* 2–3 | *Prot. vulgaris* 2–2 | *K. pneumoniae* 4–4 | *Pseud. aeruginosa* 3–2 | *E. histolytica* 105–2 | *T. vaginalis* 100–1 | $ED_{50}$ value, mg/kg (oral treatment of mice sc infected with *T. vaginalis*) |
| **41** | – | n.t. | >3.1 | – | – | – | – | >3.1 | 0.003 | ϕ |
| **42** | – | – | – | – | – | – | – | >6.3 | 0.05 | 58.6 (35.2–103)[c] |
| **43** | >12.5 | n.t. | – | – | – | – | – | >12.5 | 0.1 | ϕ |
| **44** | >25 | n.t. | >25 | – | >25 | >25 | – | >25 | 0.003 | ϕ |
| **45** | – | – | – | – | – | – | – | >25 | 0.024 | ϕ |
| **46** | 6.25 | n.t. | >25 | – | >25 | – | – | >25 | 0.1 | ϕ |
| **47** | 6.3 | 3.1 | 1.6 | – | 1.6 | 6.3 | 6.3 | 100 | 0.0015 | 25.2 (19.8–33.2) |
| **48** | 12.5 | 6.3 | 6.3 | – | 3.1 | 25 | 25 | >100 | 0.003 | 3.46 (1.99–5.36) |
| **49** | 50 | 50 | 12.5 | – | 100 | >100 | – | 25 | 0.0015 | 4.67 (0.844–7.16) |
| **50** | – | – | – | – | – | – | – | 50 | 0.012 | 15.8 (10.2–26.8) |
| **51** | >6.3 | >6.3 | 1.6 | – | 3.1 | >6.3 | >6.3 | >6.3 | 0.006 | n.t. |
| **52** | 6.3 | 3.1 | 1.6 | – | 3.1 | 12.5 | 25 | 100 | 0.006 | 2.90(0.954–5.30) |
| **53** | 25 | 12.5 | 6.3 | – | 25 | – | – | 50 | 0.0015 | 10.9 (6.96–15.0) |
| **54** | >100 | 12.5 | 6.3 | – | 12.5 | – | – | 50 | 0.0008 | ϕ |
| **55** | – | – | – | – | – | – | – | >100 | 0.0008 | ϕ |
| **56** | >50 | >50 | >50 | – | >50 | >50 | >50 | 50 | 0.012 | 25.7 (17.6–34.2) |
| **57** | 6.3 | 3.1 | 6.3 | >100 | 3.1 | 50 | 25 | 50 | 0.012 | n.t.[d] |
| **58** | 12.5 | 1.6 | 3.1 | – | 1.6 | 25 | 12.5 | >100 | 0.0008 | 2.57 (0.67–3.55) |
| **59** | 3.1 | 3.1 | 0.8 | 50 | 1.6 | 25 | 12.5 | 25 | 0.0004 | 19.1 (13.9–25.9) |
| **60** | 6.3 | 6.3 | 1.6 | – | 12.5 | 25 | 25 | >100 | 0.012 | ϕ |
| **61** | >3.1 | >3.1 | >3.1 | – | >3.1 | >3.1 | >3.1 | >3.1 | 0.012 | n.t. |
| **62** | 25 | 6.3 | 12.5 | – | 25 | – | – | 100 | 0.003 | 11.2 (7.56–16.6) |
| **63** | 50 | 25 | 25 | – | >50 | 50 | – | >50 | 0.2 | n.t. |
| **64** | 100 | 100 | 50 | – | 6.3 | 100 | 50 | >100 | 0.05 | 5.18 (1.81–9.72) |
| **65** | 100 | 50 | 100 | – | 100 | >100 | – | 50 | 0.025 | n.t.[e] |
| **66** | >100 | – | – | – | – | – | – | 100 | 0.05 | 3.19 (1.67–5.05) |
| **67** | 25 | 50 | 50 | – | 12.5 | 100 | – | >100 | 0.05 | ϕ |
| **68** | 25 | 25 | 50 | – | 50 | – | – | >100 | 0.1 | n.t.[f] |
| **69** | 12.5 | 25 | – | – | 12.5 | – | – | >100 | 0.2 | 33.5 (24.8–44.2) |
| **70**[g] | – | n.t. | – | – | – | – | – | 100 | 1.6 | 3.86 (3.19–4.84) |
| **71**[h] | 25 | n.t. | 12.5 | 50 | 0.2 | 1.6 | – | >50 | 0.05 | 5.94 (3.61–14.61) |

[a] Symbols and abbreviations: –, a preliminary paper disk assay revealed no activity at a level of 200 μg/disk; n.t., not tested; >6.3, >25, etc, the compound was insoluble at higher concentrations (in μg/ml) and no activity could be observed below or at this point (concentrations >100 μg/ml were not investigated); ϕ, a preliminary *in vivo* test at a dose level of 12.5 mg/kg (compounds **41**, **43**, **45**, and **46**, 50 mg/kg) did not show a significant effect. [b] Strain no., collection of Department of Chemotherapy, Schering AG. [c] Range of confidence at the 95% level in parentheses. [d] Compound **57** was active at the 12.5 mg/kg dose level. However, oral toxicity in mice was relatively high ($LD_{50}$ *ca.* 0.5–1 g/kg) and therefore $ED_{50}$ was not determined. [e] Toxic at the 12.5 mg/kg dose level. [f] Active at the 12.5 mg/kg dose level, but toxic with 200 mg/kg. [g] Metronidazole, see ref 6. [h] 2-Amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole, see ref 8.

decrease of antibacterial activity *in vitro*, whereas the MIC against *T. vaginalis* is hardly influenced. The antitrichomonal $ED_{50}$ values of compound **48** (3.46 mg/kg) and **49** (4.67 mg/kg) are in the range of metronidazole (**70**, 3.86 mg/kg).

The diallylamino group (compound **50**) abolishes antibacterial and diminishes antitrichomonal activity, whereas the monopropylamino derivative **51** is obviously more effective against bacteria and parasites. Its rather low solubility made it impossible to test the compound in concentrations higher than 6.3 μg/ml.

Within a small set of compounds (**52–55**) the amino group nitrogen is part of a heterocycle. The pyrrolidine derivative **52** gives rise to the lowest antibacterial MIC values compared to compounds containing larger ring systems. The MIC's against *T. vaginalis* are nearly constant in this series, but the remarkable *in vivo* activity of compound **52** ($ED_{50}$ 2.9 mg/kg) is decreased by ring enlargement.

The morpholino (**56**) and the 4-methylpiperazino derivatives (**57**) are less trichomonicidal; the latter possesses similar antibacterial potency compared to compound **52**.

2. Lengthening of the side chain of compound **47** leads to compound **58** and causes a slight decrease in antibacterial activity, whereas the MIC against *T. vaginalis* is not changed. The *in vivo* activity against *T. vaginalis* is remarkable ($ED_{50}$ 2.57 mg/kg).

Extremely low MIC values against bacteria and *T. vaginalis* are observed if the basically substituted side chain is fixed to position 4 of the 1-indanone moiety (position a in the general formula at the top of Table II); *e.g.*, 4-(2-dimethylaminoethoxy)-2-(1-methyl-5-nitro-2-imidazolylmethylene)-1-indanone (**59**) inhibits the growth of all our test bacteria within a concentration range of 0.8–50 μg/ml including *Proteus mirabilis* and *Pseudomonas aeruginosa*. Against *T. vaginalis* the MIC value is 0.0004 μg/ml for **59**, but the $ED_{50}$ value (19.1 mg/kg) against *T. vaginalis* in mice is rather disappointing.

Derivatives bearing the 2-dimethylaminoethoxy group in position 6 (**60**) and 7 (**61**) of the 1-indanone ring system are less active (positions c and d in the general formula at the top of Table II).

3. The residue $R^1$ at the imidazole N atom of all derivatives mentioned so far was represented by a methyl group. Replacement of the methyl group in compound **47** by an ethyl group lowers the antibacterial activity. The antitrichomonal effect is similar to that of **47** *in vitro* and *in vivo*. The introduction of a 2-acetoxyethyl side chain as residue $R^1$ results in a marked decrease in antimicrobial activity (compound **63**).

4. In another series the indanone moiety was replaced by the tetralone or acetophenone systems. Generally these modifications diminish the antitrichomonal activity *in vitro* and nearly eliminate the antibacterial activity as can be seen by comparison of compounds **47, 52,** and **56** with compounds **64–66** and **67–69.** This is in marked contrast to the low antitrichomonal $ED_{50}$ values of the tetralone derivatives **64** (5.18 mg/kg, compared with 25.2 mg/kg of **47**) and **66** (3.19 mg/kg, compared with 25.7 mg/kg of **56**). These findings correspond to previous observations in the series of 2-(5-nitro-2-imidazolylmethylene)-1-indanones and -tetralones[3,9] which show some tetralone derivatives superior *in vivo,* whereas the corresponding indanone derivatives display much better *in vitro* activity.

## Experimental Section

**General.** Where analytical results are indicated only by symbols of the elements, values for those elements were within ±0.4% of the calculated values. The salts **47–68** compiled in Table II do not always contain accurately stoichiometric amounts of $H_2SO_4$; therefore the S values for all these compounds are given in the table. Melting points are uncorrected and taken on a Tottoli melting point apparatus (W. Büchi, Switzerland).

**Substituted Alkoxy-1-indanones, -1-tetralones, and -acetophenones (10–37, Table I). Method $A_1$.** 5-Hydroxy-1-indanone (**5,** 0.1 mol) was dissolved in a solution of sodium (0.1 mol) in 130 ml of ethanol. 2-Bromoethanol (0.2 mol) and KI (1 g) were added, and the mixture was refluxed for 72 hr. After removal of EtOH *in vacuo,* the residue was triturated with $H_2O$ (2.2 l.) and the product (**10**) was collected.

**Method $A_2$.** A mixture of 7-hydroxy-1-indanone (**7,** 0.1 mol), $K_2CO_3$ (38 g), and 2-bromoethanol (0.2 mol) was stirred at 100° for 4 hr under a nitrogen atmosphere. After removal of excess 2-bromoethanol a saturated NaCl solution was added and the product was extracted with EtOAc. The organic layer was concentrated *in vacuo* and the residue was dissolved in $CHCl_3$. For separation of starting material, this solution was stirred for 3 hr with 10 *N* NaOH. The organic layer again was concentrated *in vacuo* and the residue was recrystallized from MeOH–$H_2O$ (1:1) to yield **11.**

**Method $B_1$.** A pyridine (200 ml) solution of 5-(2-hydroxyethoxy)-1-indanone (**10,** 0.1 mol) and tosyl chloride (0.11 mol) was stirred at room temperature for 3 hr. The solution was poured onto ice–$H_2O$ and the solid (**14**) collected.

**Method $B_2$.** A pyridine (300 ml) solution of 7-(2-hydroxyethoxy)-1-indanone (**11,** 0.1 mol) and mesyl chloride (0.13 mol) was stirred at room temperature for 20 hr. After pouring onto ice–$H_2O$ the mixture was acidified with 5 *N* HCl and the solid (**15**) was collected.

**Method $C_1$.** A mixture of 5-(2-tosyloxyethoxy)-1-indanone (**14,** 10 mol) and diisopropylamine (80 mmol) was refluxed for 4 days. After removal of excess amine *in vacuo,* the residue was partitioned between 0.5 *N* NaOH (150 ml) and EtOAc and the organic layer was extracted with 5 *N* HCl. The acidic aqueous solution was made alkaline with 5 *N* NaOH and the product was again extracted into EtOAc. After removal of the organic solvent, methanolic HCl was added to the residue and the mixture concentrated to dryness. The crude product (**20**) was used for the next step.

**Method $C_2$.** A solution of 5-(2-tosyloxyethoxy)-1-indanone (**14,** 10 mmol) and diallylamine (40 mmol) in EtOH (100 ml) was refluxed under a nitrogen atmosphere for 5 hr. After removal of the solvent the residue was partitioned between 1 *N* NaOH (100 ml) and EtOAc. The organic layer was concentrated to dryness and the residue was dissolved in ether. Addition of ethereal HCl yielded the product (**21**).

**Method D.** A benzene (90 ml) solution of 2-dimethylaminoethyl chloride (0.14 mol, freshly prepared from its hydrochloride in the usual manner) was added to a solution of 5-hydroxy-1-indanone (**5,** 0.1 mol), NaOEt (0.1 mol), and KI (0.1 g) in 100 ml of EtOH. The mixture was refluxed for 20 hr. After removal of the solvent *in vacuo* and addition of brine, the product was extracted into EtOAc. Concentration of the organic layer *in vacuo* to dryness and addition of ethereal HCl yielded the hydrochloride **18.**

**Substituted Alkoxy-2-(5-nitro-2-imidazolylmethylene)-1-indanones, -1-tetralones, and -acetophenones (41–69, Table II). Method $E_1$.** A mixture of 1-methyl-5-nitroimidazole-2-carbaldehyde (**38,** 10 mmol), 5-(2-dimethylaminoethoxy)-1-indanone hydrochloride (**18,** 10 mmol), $H_2SO_4$ (11 mmol), and 10 ml of AcOH was stirred at 100° for 6 hr. After cooling to room temperature the precipitate (**47**) was filtered off and washed with MeOH.

**Method $E_2$.** 1-Methyl-5-nitroimidazole-2-carbaldehyde (**38,** 10 mmol) and 6-(2-dimethylaminoethoxy)-1-tetralone hydrochloride (**33,** 10 mmol) were treated as described in method $E_1$. The reaction mixture was concentrated *in vacuo* and the residue was triturated with MeOH–*i*-PrOH. Filtration and washing with MeOH yielded the product (**64**).

**Method F.** A suspension of 5-(2-acetoxyethoxy)-2-(5-nitro-1-methyl-2-imidazolylmethylene)-1-indanone (**41**) in EtOH (80 ml) and concentrated HCl (40 ml) was refluxed for 2 hr. After cooling the precipitate (**44**) was isolated by filtration.

**Method G.** 4′-(2-Hydroxyethoxy)-2-(1-methyl-5-nitro-2-imidazolylmethylene)acetophenone hydrochloride (**46,** 10 mmol) was triturated with a 20% solution of $NaHCO_3$ in $H_2O$ and the product was filtered off and dried. It was suspended in pyridine (40 ml) and 20 mmol of tosyl chloride was added. The mixture was stirred at room temperature for 4 hr and subsequently poured onto ice–$H_2O$ (400 ml) to yield 4 g (85%) of 2-(1-methyl-5-nitro-2-imidazolylmethylene)-4′-(2-tosyloxyethoxy)acetophenone, mp 146° (*i*-PrOH). *Anal.* ($C_{22}H_{21}N_3O_7S$) N, S.

A solution of this compound (10 mmol) and 40 mmol of morpholine in EtOH (35 ml) was refluxed for 4 hr. After concentration *in vacuo* 100 ml of $H_2O$ and 16 ml of 2 *N* NaOH were added and the mixture was extracted with EtOAc. Removal of the solvent and trituration with methanolic HCl yielded compound **69.**

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