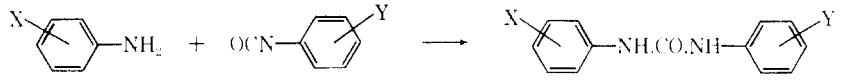
TABLE I
CARBANILIDES



Carbanilide	X	Y	Yield, %	Mp, °C	Formula	Calcd, % C	H	Cl	N	Found, % C	H	Cl	N
1	2-(*p*-ClC$_6$H$_4$O)	H	78	200	$C_{18}H_{13}ClN_2O_2$	67.3	4.4	10.7	8.5	67.4	4.5	10.5	8.3
2	2-(*p*-ClC$_6$H$_4$O)-5-Cl	4-Cl	45	184–185	$C_{18}H_{12}Cl_3N_2O_2$	56.0	3.2	26.1	6.9	55.9	3.0	25.8	6.6
3	2-(*p*-ClC$_6$H$_4$O)	4-Cl	16.5	284–285	$C_{18}H_{14}Cl_2N_2O_2$	61.1	3.8	19.0	7.5	60.5	3.6	19.2	7.7
4	2-(*p*-ClC$_6$H$_4$O)-4,5-Cl$_2$	3,4-Cl$_2$	69	229–230	$C_{19}H_{11}Cl_5N_2O_2$	47.9	2.3	37.2	5.9	47.8	2.2	37.1	6.1
5	3-Cl-4-(*p*-ClC$_6$H$_4$O)	4-Cl	60	208–209	$C_{19}H_{13}Cl_3N_2O_2$	56.0	3.2	26.1	6.9	56.2	2.8	25.4	6.8
6	3-Cl-4-(*p*-ClC$_6$H$_4$O)	3,4-Cl$_2$	68.5	208–211	$C_{19}H_{12}Cl_4N_2O_2$	51.6	2.7	32.1	6.35	50.8	2.45	31.2	6.2
7	2-(*p*-ClC$_6$H$_4$O)-5-Cl	3-Cl	81.5	188–189	$C_{18}H_{12}Cl_3N_2O_2$	56.0	3.2	26.1	6.9	56.0	3.0	25.8	6.7

TABLE II
BACTERIOSTATIC PROPERTIES AND HYDROLYSIS RATE CONSTANTS

Compd	MIC, ppm	$k \times 10^5$, sec^{-1}
1	100	4.7
2	0.02	
3	0.2	
4	0.15	4.5
5	10	0.84
6	0.25	0.76
7	0.5	6.0
Carbanilide	>200	3.2
3,4,4′-Trichlorocarbanilide	0.2	1.0

anhydrous ether or benzene was added dropwise with stirring to a solution of the aminodiphenyl ether (0.005 mole) in anhydrous Et_2O or C_6H_6. The resulting solution was boiled under reflux with stirring for 1 hr. A precipitate formed which was filtered, washed with Et_2O, and dried. The product was further purified if necessary by recrystallization from EtOH. All the carbanilides had characteristic "amide bands I–III" at 1600–1700, 1540–1560, and 1260–1320 cm^{-1}.

Isocyanates.—The method of Allen and Bell[7] was followed. A solution of the acyl chloride in Me_2CO was added dropwise with vigorous stirring to an excess of NaN_3 in H_2O at 10–15°. The mixture was then stirred for 1 hr, the aqueous layer was removed, and the organic layer (acyl azide) was added to a solution of C_6H_6 at 60°, or toluene at 100°, during which a vigorous evolution of N_2 occurred. The mixture was kept at 60° (100° for toluene) for 1 hr and was then dried ($MgSO_4$). The solvent was removed *in vacuo*, and, after the residue had been checked for absence of residual azide,[8] it was distilled. Yields of isocyanates by this method were 70–90%. The compounds had physical constants in agreement with the literature values and had a pronounced peak at 2280 cm^{-1} (N=C=O) in their infrared spectra.

Nitrodiphenyl Ethers.—The following compounds were prepared by the Ullmann synthesis, and had physical constants in agreement with the literature values: 2-nitro-4-chlorodiphenyl ether,[9] 2-nitro-4,4′-dichlorodiphenyl ether,[10] and 4-nitro-2,4′-dichlorodiphenyl ether.[10]

2-Nitro-4,5,4′-trichlorodiphenyl Ether.—2,4,5-Trichloronitrobenzene[11] (22.6 g), K_2CO_3 (39 g), *p*-chlorophenol (19.2 g), pyridine (1 ml), and Cu bronze (1 g) were heated at 200° for 2 hr (air condenser). The mixture was allowed to cool below 100°, then extracted with hot H_2O. The aqueous solution was extracted with four 200-ml portions of $CHCl_3$, and the $CHCl_3$ extracts were washed successively with H_2O, 2 *N* KOH, 4 *N* HCl, and H_2O. The solution was dried ($MgSO_4$) and distilled; yield 10.4 g (33%), bp 170–180° (1 mm).

Aminodiphenyl Ethers.—The nitro compounds were reduced by Zn dust in boiling, aqueous ethanolic $CaCl_2$.[12] The resulting amino compounds were isolated in $CHCl_3$ and recrystallized from Et_2O-C_6H_6.

Rates of Hydrolysis.—The hydrolyses were carried out in 2 *N* KOH in DMSO-H_2O (1:1 v/v) by heating in a thermostatic bath maintained at 95.2 ± 0.1°. The carbanilide was added quickly to the KOH solution at the reaction temperature, when, in all cases, it readily and completedly dissolved. Aliquots (5 ml) were removed from the reaction flasks at 1-hr intervals, H_2O was added to precipitate unreacted carbanilide, and the mixture was then extracted thoroughly with Et_2O to remove the carbanilide and anilines. The anilines were removed from this solution by extraction with 4 *N* HCl. The acid solution was titrated at 5° with standard $NaNO_2$ solution to form the diazonium salt, the end point being detected by the blue color imparted to starch-iodide paper.

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Synthesis and Antimalarial Evaluation of Some 1,7-Naphthyridines and 2,9-Diazaanthracenes[1]

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Chloroquine, quinacrine, and other 4-aminoquinolines and 9-aminoacridines, which have been of great clinical value in the treatment of malaria, have all encountered the problem of parasite resistance.[2] This suggests that further synthetic designs involving the attachment of

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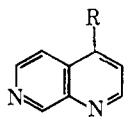
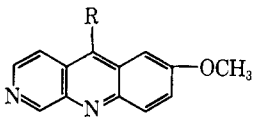
different alkylamino side chains to the same ring systems may not be practical. Proper modification of the ring nucleus, on the other hand, might provide valuable antimalarial agents with less probability of cross resistance.

The cinnoline analogs of chloroquine[3] and quinine[4] were studied in 1946. Magidson,[5] Endicott,[6] Price,[7] and Curd,[8] and their co-workers have synthesized a number of 4-dialkylaminoalkylamino derivatives in the quinazoline series. The corresponding phthalazine analog of chloroquine was prepared by Drake and Peck.[9] Certain 1,5- and 1,8-naphthyridine derivatives with a 4-diethylamino-1-methylbutylamino moiety were reported by Adams, *et al.*,[10] and by Goldberg, *et al.*[11] 2-Butoxy-8-(4-diethylamino-1-methylbutylamino)-1,5-naphthyridine was found to be more active than quinacrine against *Plasmodium gallinaceum* in chicks, and equiactive against *Plasmodium berghei* in mice.[11] In the quinacrine series, the isoalloxazine[12] and the phenazine[13] analogs have been synthesized. Many of these analogs have shown antimalarial activity.[14] In particular, 2-methoxy-6-chloro-9-(4-diethylamino-1-methylbutylamino)-1,10-diazaanthracene (Azacrin) is highly active against *P. gallinaceum* in chicks, *P. berghei* in mice, and *Plasmodium vivax* and *Plasmodium falciparum* in man.[15]

Since a chlorine atom attached to a phenyl ring is known for its electron-withdrawing effect, introduction of a nitrogen in the ring in place of the C–Cl linkage in the chloroquine and quinacrine structure would also be expected to produce systems having a similar inductive effect. The same type of activity would probably be retained in these aza analogs. The synthesis of some 4-(substituted amino)-1,7-naphthyridines (Ia–c) and 10-(substituted amino)-2,9-diazaanthracenes (IIa, b) has therefore been studied in our laboratory.



Ia, R = $NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$
b, R = $NH(CH_2)_3N(C_2H_5)_2$
c, R = $NH\text{-}3\text{-}CH_2N(C_2H_5)_2\text{-}4\text{-}OHC_6H_3$
d, R = OH
e, R = Cl



IIa, R = $NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$
b, R = $NH\text{-}3\text{-}CH_2N(C_2H_5)_2\text{-}4\text{-}OHC_6H_3$
c, R = OH
d, R = Cl
e, R = H

4-Chloro-1,7-naphthyridine (Ie), the key intermediate for the synthesis of Ia–c, was prepared *via* Id according to the method of Murray and Hauser[16] and others,[17,18] with the exception that the starting material, 3-aminopyridine 1-oxide, was obtained by a different method. In the present work, the peracetic acid oxidation of 3-acetamidopyridine followed by hydrolysis[19–21] was found to be more efficient than the method involving the hydrogen peroxide oxidation and amination of 3-bromopyridine.

For the preparation of the chloroquine analog Ia, 1-diethylamino-4-aminopentane was condensed with Ie at elevated temperature. The solid product was obtained by distillation of the crude syrupy residue through a short-path column under reduced pressure followed by induced crystallization. A related compound, 4-(3-diethylaminopropylamino)-1,7-naphthyridine (Ib), was prepared in a similar fashion. Although this compound was smoothly distilled and correctly analyzed, it remained as a viscous oil even after long standing and many crystallization efforts. On the other hand, the corresponding amodiaquine analog Ic was readily obtained as a crystalline product by the treatment of compound Ie with 3-(diethylaminomethyl)-4-hydroxyaniline.

Bachman and Barker[22] reported failure in preparing 6-methoxy-10-chloro-2,9-diazaanthracene (IId) by the attempted chlorination–cyclization reaction of 3-(*p*-anisidino)isonicotinic acid with phosphorus oxychloride. When 3-(*p*-anisidino)isonicotinic acid was heated in polyphosphoric acid in the presence of a small amount of phosphorus oxychloride, according to the reaction conditions for the synthesis of a similar compound,[23] cyclization was readily achieved to yield 6-methoxy-10-hydroxy-2,9-diazaanthracene (IIc or 6-methoxypyrido-[3,4-*b*]quinolin-5(10H)-one). Chlorination of IIc with phosphorus oxychloride gave compound IId in good yield.

Heating a mixture of 3-diethylaminomethyl-4-hydroxyaniline and IId readily yielded 6-methoxy-10-(3-diethylaminomethyl-4-hydroxyanilino)-2,9-diazaanthracene (IIb) as an orange-red crystalline compound. An analogous preparation of the corresponding quinacrine analog IIa failed to yield a solid derivative. Attempted distillation of the crude reaction product, as for the purification of Ia, gave a yellow solid. Elemental analysis and nmr study revealed that the compound was 6-methoxy-2,9-diazaanthracene (IIe). The same product was obtained when the crude reaction product was first heated at a relatively high temperature *in vacuo* (for the removal of solvent) and purified by silica gel chromatography. Albert[24] reported that acridine could readily be obtained from 9-chloroacridine through treatment of the latter with a substituted sulfonylhydrazide or hydrazine. Studies of the mechanism of this reaction and its possible relationship to that of Albert's will be conducted in the future.

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TABLE I

TEST RESULTS OF 1,7-NAPHTHYRIDINE AND 2,9-DIAZAANTHRACENE DERIVATIVES AGAINST *Plasmodium berghei* IN MICE[a,b]

Compd	Dose, mg/kg	Mean survival time, days: Treated	Control	Toxic deaths	Mean survival time of toxic deaths, days
Ia	40	6.8	6.1	0	
	160	7.4	6.1	0	
	640	10.2	6.1	0	
IIb	20	6.6	6.1	0	
	80	6.6	6.1	0	
	320	6.8	6.1	0	
Ic	40	7.2	6.5	0	
	160	9.2	6.5	0	
	640	11.2	6.5	0	
Id	40	9.6	7.7	0	
	160	10.2	7.7	0	
	640	0	7.7	5	3
Ie	40	7.4	7.7	0	
	160	7.6	7.7	0	
	640	7.6	7.7	0	
IIb	20	6.4	6.2	0	
	40	6.4	6.2	0	
	80	7.6	6.2	0	
	160	9.4	6.2	0	
	320	11.0	6.2	0	
	640	12.2	6.2	0	
IIc	40	6.2	6.1	0	
	160	6.4	6.1	0	
	640	6.4	6.1	0	
IId	40	6.2	6.1	0	
	160	6.4	6.1	0	
	640	6.4	6.1	0	
Chloroquine phosphate	20	13.5	6.9	0	
	40	14.3	6.9	0	
	80	14.9	6.9	0	
	160	15.4	6.9	0	
	320	0	6.9	5	3
Quinacrine dihydrochloride	5	9.6	7.0	0	
	10	10.8	7.0	0	
	20	11.6	7.0	0	
	40	12.6	7.0	0	
	80	15.2	7.0	0	
	160	16.4	7.0	0	
	320	30.4	7.0	0	
	640	0	7.0	5	4

[a] Test results were obtained by Dr. Leo Rane, University of Miami School of Medicine (Contract DA-49-193-MD-2218), and provided by the Division of Medicinal Chemistry, Walter Reed Army Institute of Research. [b] Mice were infected with a lethal dose of *P. berghei* 3 days prior to administration of the chemical (subcutaneously in oil) at each dose level; five mice in each test group.

Many of the new compounds have been tested against *Plasmodium berghei* (see Table I; for comparison, test results of chloroquine and quinacrine are also included). The mean survival time of infected control mice is 7.0 ± 0.7 days and extension in survival time of treated mice is interpreted as evidence of antimalarial activity.[25]

Among the compounds tested, 4-hydroxy-1,7-naphthyridine (Id) was found to provide a 2.5-day extension of survival time at a dose of 160 mg/kg. However, this compound is toxic at 640 mg/kg. Both the aza analogs of chloroquine and amodiaquine (Ia and Ic, respectively) were found to provide 4–5-day extension of survival time at 640 mg/kg. No toxicity is indicated at this dose level. The chloroquine and amodiaquine side chains seem to be of importance in the present study; the related analog, 4-(3-diethylaminopropylamino)-1,7-naphthyridine (Ib), gives no extension of survival time in the treated animals. In the 2,9-diazaanthracene series, derivative IIb provides a 6-day extension of survival time at 640 mg/kg in both female and male mice. Again, no toxicity is observed at this dose level.

Experimental Section[26]

4-(4-Diethylamino-1-methylbutylamino)-1,7-naphthyridine (Ia).—4-Chloro-1,4-naphthyridine[19] (Ie, 5.27 g, 0.032 mole) and 15.8 g (0.1 mole) of 1-diethylamino-4-aminopentane were heated at 158–160° for 6 hr. The reaction mixture was then poured into 100 ml of H_2O, made basic with NH_4OH, and extracted with four 50-ml portions of $CHCl_3$. The combined extracts were washed (H_2O), dried ($MgSO_4$), and evaporated. In order to remove as much of the unreacted dialkylaminoalkylamine as possible, the residue was first evaporated at 130–140° (H_2O aspirator), then at 0.1–0.2 mm. To the residue was added 15 ml of diphenyl ether, and the mixture was distilled *in vacuo* until *ca.* 10 ml of diphenyl ether was collected. The residue was taken up in dilute HCl and extracted with petroleum ether (bp 35–60°). The aqueous phase was made basic with 10% NaOH solution and extracted again with three 50-ml portions of $CHCl_3$. The residue obtained on evaporation of the $CHCl_3$ was subjected to short-path distillation under a vacuum to afford 6.70 g (73%) of Ia as a yellow, viscous oil, bp 180–182° (0.25 mm). It solidified very slowly to pale yellow crystals, mp 67–69°. When the fresh distillate was seeded with previously obtained crystals, solidification proceeded without difficulty. However, attempts at recrystallization of the solid from various solvents were unsuccessful. Its monohydrochloride or phosphate salt also could not be induced to solidify. The infrared spectrum of Ia has absorption at 2.9, 3.1, 6.3, 6.4, 6.6, 11.2, and 12.3 μ; $\lambda_{max}^{95\%\ EtOH}$ 230, 330 mμ (ϵ 19,000, 12,000).

Anal. Calcd for $C_{17}H_{26}N_4$: C, 71.28; H, 9.15; N, 19.56. Found: C, 71.00; H, 9.10; N, 19.40.

4-(3-Diethylaminopropylamino)-1,7-naphthyridine (Ib).—A mixture of 4.95 g (0.03 mole) of 4-chloro-1,7-naphthyridine and 26 g (0.2 mole) of 3-diethylaminopropylamine was heated under reflux for 18 hr. The reaction mixture was worked up as for Ia to furnish 5.45 g (70%) of IIb as a yellow, viscous oil, bp 193–195° (0.3 mm), λ_{max}^{EtOH} same as Ia.

Anal. Calcd for $C_{15}H_{22}N_4$: C, 69.73; H, 8.58; N, 21.72. Found: C, 69.40; H, 8.65; N, 21.99.

4-(3-Diethylaminomethyl-4-hydroxyanilino)-1,7-naphthyridine (Ic).—2-(Diethylaminomethyl)-4-acetamidophenol (2.36 g, 0.01 mole) was boiled with 20 ml of 15% HCl for 2 hr. The solution was allowed to cool, and its pH was adjusted to 6 with 10% NaOH. To the solution was added 1.65 g (0.01 mole) of 4-chloro-1,7-naphthyridine. The mixture was heated on a steam bath for 6 hr, made basic with concentrated NH_4OH, and extracted with five 40-ml portions of $CHCl_3$. The combined extracts were washed with H_2O, dried ($MgSO_4$), and evaporated on a steam bath. The residue was crystallized from ethyl acetate to give 1.90 g (59%) of Ic as yellow crystals, mp 173.5–175.5°; analytical sample, mp 174.5–176.5°.

(25) Printout interpretation for rodent antimalarial test results, Walter Reed Army Institute of Research.

(26) Unless otherwise stated, all melting points were corrected and were taken on a Thomas-Hoover melting point apparatus. Uv spectra were determined with a Beckman DK-2 spectrophotometer, ir spectra were taken with a Perkin-Elmer Infracord, and the nmr with a Varian A-60 spectrometer.

Anal. Calcd for $C_{19}H_{22}N_4O$: C, 70.78; H, 6.88; N, 17.38. Found: C, 70.60; H, 6.80; N, 17.30.

The **monohydrochloride** of Ic, prepared by addition of 1 equiv of dilute HCl to an ethanolic solution of Ic followed by evaporation to dryness under reduced pressure, was recrystallized from MeOH–EtOAc; pale yellow crystals: mp 232–234°; $\lambda_{max}^{EtOH-H_2O}$ 249, 345 mμ (ε 20,300, 11,800).

Anal. Calcd for $C_{19}H_{22}N_4O \cdot HCl$: C, 63.59; H, 6.46; N, 15.61; Cl^-, 9.88. Found: C, 63.80; H, 6.30; N, 15.30; Cl^-, 9.70.

6-Methoxy-10-hydroxy-2,9-diazaanthracene (IIc, 6-Methoxypyrido[3,4-*b*]quinolin-5(10H)-one).—A mixture of 2.5 g (0.01 mole) of 3-(*p*-anisidino)isonicotinic acid, 40 g of polyphosphoric acid, and 2 ml of $POCl_3$ was heated on a steam bath, with manual stirring, for 7 hr until the evolution of HCl could no longer be detected. The syrup was added to 200 ml of ice–H_2O and the resulting solution was made basic with NH_4OH. The yellow solid was collected, washed with H_2O, and dried in air. On recrystallization from MeOH, 2.0 g (87%) of IIc was obtained as golden yellow leaflets: mp 333–335° dec (uncor); λ_{max}^{EtOH} 242, 279, 309, 322, 408, 425 mμ (ε 28,000, 40,000, 3600, 2500, 8800, 8100); $\lambda_{max}^{pH\ 1}$ 294, 458 mμ (ε 32,000, 6800).

Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.29; H, 4.46; N, 12.50.

6-Methoxy-10-chloro-2,9-diazaanthracene (IId).—A mixture of 2.5 g (0.01 mole) of IIc and 60 ml of $POCl_3$ was heated under reflux for 15 hr. After removal of the excess $POCl_3$ (reduced pressure), the mixture was poured onto 200 g of crushed ice and made basic with NH_4OH. The resulting solid product was collected, washed (H_2O), and dried in air. It was recrystallized (Me_2CO) to furnish 2.25 g (83%) of IId as yellow needles: mp 187–188°; λ_{max}^{EtOH} 229, 237, 258, 362 mμ (ε 33,000, 32,000, 74,000, 11,000).

Anal. Calcd for $C_{13}H_9ClN_2O$: C, 63.81; H, 3.71; N, 11.45. Found: C, 63.64; H, 3.61; N, 11.48.

6-Methoxy-10-(3-diethylaminomethyl-4-hydroxyanilino)-2,9-diazaanthracene (IIb).—2-Diethylaminomethyl-4-acetamidophenol (3.07 g, 0.013 mole) was boiled with 20 ml of 20% HCl for 3 hr. The solution was allowed to cool and was neutralized with 10% NaOH to pH 6. Compound IId (3.18 g, 0.013 mole) was then introduced. The mixture was heated on a steam bath for 6 hr, cooled, diluted with 50 ml of H_2O, and made basic with NH_4OH. The precipitate was collected, washed (H_2O), and allowed to dry in air. On recrystallization (EtOAc) there was obtained 3.80 g (73%) of IIb as orange-red crystals, mp 189–193°. Further recrystallization raised the melting point to 191–193°; λ_{max}^{EtOH} 252, 290, 445 mμ (ε 41,000, 24,000, 10,000).

Anal. Calcd for $C_{24}H_{26}N_4O_2$: C, 71.62; H, 6.51; N, 13.92. Found: C, 71.53; H, 6.47; N, 14.02.

Attempted Preparation of IIa. Isolation of 6-Methoxy-2,9-diazaanthracene (IIe).—A mixture of 4.90 g (0.02 mole) of IId and 17 ml of 1-diethylamino-4-aminopentane was heated at 145–150° for 5 hr (N_2 atmosphere). The mixture was diluted with 100 ml of H_2O, made basic with NH_4OH, and filtered to remove the precipitated IIc (0.55 g). The filtrate was extracted repeatedly with $CHCl_3$ (total, 250 ml), and the combined extracts were washed (H_2O), dried ($MgSO_4$), and evaporated at atmospheric pressure. After excess dialkylaminoalkylamine was removed (rotary evaporator, steam bath), the tarry substance, which did not solidify on standing, was collected and subjected to short-path distillation (burner, heat source). There was obtained at 220–230° (1 mm) 0.85 g of a yellow solid, mp 136–138°. Recrystallization from EtOAc gave light yellow crystals, mp 139.5–140.5°. Its spectrum ($CDCl_3$) showed aromatic proton signals at τ 3.46 (1 H, doublet), 2.83 (2 H, 2 doublets), 2.27 (1 H, doublet), 2.18 (1 H, singlet), 1.84 (1 H, doublet), and 0.72 (1 H, singlet) and the methoxy singlet at 6.3 (3 H); infrared, 6.13, 6.21, 6.34, 6.68, 7.16, 7.9, 8.5, 8.9, 9.8, 11.0, 12.0, and 12.4 μ; λ_{max}^{EtOH} 226–233, 256, 358 mμ (ε 24,000, 53,000, 14,000).

Anal. Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.17; H, 4.73; N, 13.53.

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1-Substitution in 2-Methyl-4(5)-nitroimidazole. I. Synthesis of Compounds with Potential Antitrichomonal Activity

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In view of the known antitrichomonal activity of some 1-substituted 2-methyl-4(5)-nitroimidazoles, a series of 4-nitro and 5-nitro isomers was synthesized and evaluated for their activity against *Trichomonas vaginalis*. Earlier authors[2–4] have prepared some other series of such compounds and determined[3,5] some structure–activity relationships.

The methods employed and characteristic data for the compounds synthesized are shown in Tables I and II. The starting material for all preparations was 2-methyl-4(5)-nitroimidazole (III).[6] A number of 1-substituted 2-methyl-5-nitroimidazoles was obtained by a general method which consisted of the use of one of the lower carboxylic acids with high polarity, which activates nucleophilic agents and allows the formation of 5-nitro isomers only.[7] The influence of the carboxylic acids is not yet clearly explained,[8] but a greater ratio of these reagents, empirically established, is always necessary to give rise to only 5-nitro isomers (see procedure A). 4-Nitro isomers were obtained when a molar excess of alkylating agents was used without addition of carboxylic acid, or when the solution of the sodium salt of III was employed according to an earlier described procedure.[9] Another synthetic peculiarity is found in procedure E where a supersaturated solution of potassium iodide in methyl isobutyl ketone is found to give significantly better results than the classical Finkelstein method.[10]

In preparing picrates of the compounds listed in Tables I and II, we were able to confirm the observation[11] that only 5-nitro isomers form stable hydrochlorides and picrates (see Table I). This fact could serve to distinguish 5-nitro and 4-nitro isomers if carboxyl functions are absent. Another possibility for such distinction is offered by the nmr spectra of these isomers if there is at least one proton on the α-carbon of the substituting side chain attached to ring nitrogen.

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