Isoquinolines. 1. 3-Amino- and 3-Fluoroisoquinoline Derivatives as Potential Antimalarials[1a,b]

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The synthesis of new 3-aminoisoquinoline analogs and their antimalarial activity are presented. Isoquinoline analogs substituted at the 1 position with Cl, Br, I, or OMe; at the 3 position with NH_2 or F; at the 4 position with Br or Me; or at the 6 position with OMe have been synthesized. Several derivatives of 3-aminoisoquinoline, such as the acetamides, sulfonamides, and ureas, have been prepared and screened for antimalarial activity. 3-Amino-1-bromo-4-methylisoquinoline (**6**) was shown to be curative in the *Plasmodium gallinaceum* screen, yet was found to be inactive in the *P. berghei* rodent screen. All other substituted isoquinolines were generally inactive as antimalarial compounds.

The 4-aminoquinoline antimalarials are highly effective and rapid schizontocides; they have gametocytocidal action against *Plasmodium vivax, P. ovale,* and *P. malariae,* but not against *P. falciparum.* The 8-aminoquinolines are poor blood schizontocides but are highly active against primary exoerythrocytic forms of *P. falciparum* and *P. vivax* and secondary exoerythrocytic forms of *P. vivax.*[3] Because such quinolines have played such an important role in the chemotherapy of malaria, we believed that the class of 3-aminoisoquinolines, a novel class of isoquinolines in the antimalarial program, deserved a thorough investigation. It was our purpose to prepare a series of substituted aminoisoquinolines, containing substituents which could be expected to have antimalarial activity on the basis of their structural relationship to the aminoquinoline antimalarial drugs.

The compounds reported in part 1 of this study can be considered intermediates used for the preparation of the target compounds, the dialkylaminoalkylamino isoquinolines, whose preparation and biological activity will be reported in part 2[4] of this series.

In the evaluation of such an intermediate prepared for this program, 3-amino-1-bromo-4-methyliosquinoline (**6**) was shown to be curative in the standard inoculum of *P. gallinaceum.* Structure–activity relationships have thus been examined for a series of substituted 3-aminoisoquinolines (Table I), 1-bromo-3-fluoro- (**25**), and 1-bromo-3-fluoro-4-methylisoquinoline (**26**).

Chemistry.—The method of synthesis of the 3-aminoisoquinolines reported in Table I involve the preparation of the appropriate α-cyano-*o*-tolunitrile (III) which can be cyclized with HBr or HI in PhH–Et_2O to yield the corresponding 1-bromo- or 1-iodo-3-aminoisoquinoline by the methods described by Johnson and Nasutavicus.[5] This method permitted the preparation of a variety of 3-aminoisoquinolines directly from readily available starting materials and represents a useful and convenient route to the desired substituted isoquinolines. Previous methods used for the preparation of 3-aminoisoquinoline involved a tedious 6-step process.[6]

The syntheses of the dinitriles III (Scheme I) were carried out from 4-methoxy-2-methylaniline (Ib) or from *o*-cyanotoluene (IIa) *via* the benzyl bromides.

The isoquinoline derivatives further substituted in the 4 position can also be prepared readily *via* the dinitriles III by prior alkylation with an appropriate alkyl halide and NaOEt in EtOH by methods previously described.[5,7-9] The cyclization of III or IV with HBr or with HI afforded the desired 3-aminoisoquinolines V in excellent yields. It should be noted that this procedure could not be employed for the preparation of the 1-chloro substituted isoquinoline **7** (Table I) by treatment with anhydrous HCl under a variety of conditions. Electrophilic substitution of the labile Br atom at the 1 position of 3-amino-1-bromo-4-methylisoquinoline (**6**) was achieved by a 3-step reaction sequence which involved acetylation of the amino group **12**, halogen exchange with CuCl in α-picoline[10] (**13**), and subsequent removal of the protecting acetyl group on **13** to yield the desired 1-chloro compound **7**.

With a ready source of 1-bromo-3-aminoisoquinoline available a number of halogen-substituted isoquinolines which could serve as useful starting materials for the synthesis of other substituted isoquinolines were prepared (Scheme II). The novel 1-bromo-3-fluoroisoquinolines (**25** and **26**) were prepared by a modified Schiemann reaction[6,11] from the appropriate aminoisoquinoline. The fluoroborates, intermediates in the Schiemann reaction, were prepared from the amines, and were then treated with $NaNO_2$ to give the corresponding F compounds. Similarly prepared from VI was 3-fluoroisoquinoline, a compound previously reported.[6]

Biological Activity.—All the compounds reported in Table I and **25** and **26** were tested in mice for their antimalarial activity.[12] *N*-(3-Isoquinolyl)-4-nitrobenzenesulfonamide (**18**) showed a change in the mean survival time of 4.5 days at the 640 mg/kg dose level.

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(3) Chemotherapy of Malaria, *World Health Organ. Tech. Rep. Ser.*, **375**, 1967.

(4) J. L. Neumeyer and K. K. Weinhardt, *J. Med. Chem.*, **13**, in press.

(5) F. Johnson and W. A. Nasutavicus, *J. Org. Chem.*, **27**, 3953 (1962).

(6) C. E. Teague and A. Roe, *J. Amer. Chem. Soc.*, **73**, 688 (1951).

(7) S. Gabriel, *Ber.*, **20**, 2499 (1887).

(8) S. Gabriel and T. Posner, *ibid.*, **27**, 2492 (1894).

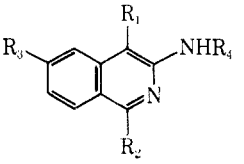
(9) G. Eichelbaum, *ibid.*, **21**, 2679 (1888).

(10) The procedure of W. B. Hardy and R. B. Fortenbaugh [*J. Amer. Chem. Soc.*, **80**, 2726 (1958)] for the replacement of Br with Cl in aromatic compounds was adopted for the synthesis of **13**.

(11) A. Roe, *Org. React.*, **5**, 193 (1949).

(12) Tests were carried out in 5 mice infected with *P. berghei* at 40, 160, and 640 mg/kg in the screening facility of Dr. L. Rane of the University of Miami [T. S. Osdene, P. B. Russel, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967)].

TABLE I
3-AMINOISOQUINOLINES AND DERIVATIVES



Compd	R_1	R_2	R_3	R_4	Mp, °C	Recrystn solvent	Formula	Analyses
1	H	H	H	H	177–178[a]	C_6H_6	$C_9H_8N_2$	
2	H	Br	H	H	152–153[b]	$C_6H_5CH_3$	$C_9H_7N_2Br$	
3	CH_3	H	H	H	116.5–118	Et_2O	$C_{10}H_{10}N_2$	C, H, N
4	H	H	OCH_3	H	220–221	EtOH	$C_{10}H_{10}N_2O$	C, H, N
5	Br	Br	H	H	191–192[c]	EtOH	$C_9H_6N_2Br_2$	
6	CH_3	Br	H	H	139–140.5[d]	Et_2O–EtOH	$C_{10}H_9N_2Br$	C, H, N
7	CH_3	Cl	H	H	119–120	Et_2O	$C_{10}H_9N_2Cl$	C, H, N
8	CH_3	I	H	H	114.5–146	Et_2O	$C_{10}H_9N_2I$	C, H, N
9	H	Br	OCH_3	H	176–178.5	C_6H_6	$C_{10}H_9N_2BrO$	C, H, N, Br
10	CH_3	OCH_3	H	H	163 dec	MeCN–EtOH	$C_{11}H_{12}N_2O \cdot HCl$	C, H, N, Cl
11	CH_3	Br	OCH_3	H	168–171	EtOH	$C_{11}H_{11}N_2BrO$	C, H, N, Br
12	CH_3	Br	H	$COCH_3$	223–224	Me_2CO–EtOH	$C_{12}H_{11}N_2BrO$	C, H, N
13	CH_3	Cl	H	$COCH_3$	209–210	EtOH	$C_{12}H_{11}N_2ClO$	C, H, N, Cl
14	H	H	H	$COCH{=}CH_2$	152[e]	Hexane–EtOH	$C_{12}H_{10}N_2O$	C, H, N
15	H	H	H	$COCH{=}CHCH_3$	151–152	Hexane–EtOH	$C_{13}H_{12}N_2O$	H, N; C[f]
16	H	H	H	COC_6H_5	176–178	C_6H_6	$C_{16}H_{12}N_2O$	C, H, N
17	H	H	H	COC_6H_4-*m*-NO_2	180–181	Dioxane–hexane	$C_{16}H_{11}N_3O_3$	C, H, N
18	H	H	H	$SO_2C_6H_4$-*p*-NO_2	249–251	Dioxane	$C_{15}H_{11}N_3O_4S$	C, H, N
19	H	H	H	$SO_2C_6H_4$-*p*-NH_2	242–243 dec	Me_2CO	$C_{15}H_{13}N_3O_2S$	C, H, N, S
20	H	H	H	$SO_2C_6H_4$-*p*-NHAc	247–248.5	Diglyme–Py	$C_{17}H_{15}N_3O_3S$	C, H, N, S
21	H	Br	H	$SO_2C_6H_4$-*p*-NO_2	178–179	C_6H_6	$C_{15}H_{10}N_3BrO_4S$	C, H, N
22	H	Br	H	$CONHCH_3$	261[g]	DMF	$C_{11}H_{10}N_3BrO$	C, H, N, Br
23	CH_3	Br	H	$CONHC_6H_4$-*m*-Cl	257–258	DMF	$C_{17}H_{13}N_3BrClO$	C, H, N, Br, Cl
24	H	Br	H	$CSNHCH_3$	185 dec	DMF	$C_{11}H_{10}N_3BrS$	C, H, N, Br, S

[a] Lit.[5] mp 178–179°. [b] Lit.[5] mp 153–154°. [c] Lit.[5] mp 193–194° from EtOAc. [d] Lit.[5] mp 143–145°. [e] Mp 152° when immersed at 150°, with resolidification. [f] C: calcd 73.56; found 72.85. [g] Determined on a Dupont thermoanalyzer, Model 900.

No other compounds tested caused any increase in the mean survival time of more than 1.5 days in the mouse screen. All the compounds tested were nonlethal. Only compound **3** (3-amino-4-methylisoquinoline) was toxic at the 640 mg/kg dose level. No toxic symptoms in mice were recorded for any of the other compounds.

In the bird screen[13] 3-amino-1-bromo-4-methylisoquinoline (**6**) was rated "active" at 60 mg/kg (the increase in mean survival time at that dose was 5.2 days) and "curative" at 120 mg/kg. As in the mouse screen, this compound was nontoxic at 30, 60, and 120 mg/kg dose levels. The close analogs of **6** (**5**, **7**, 8, **10**, **11**, **12**, **13**, and **26**) (Table I) were unfortunately not tested in the bird screen. Compounds **3** and **18** were inactive in the bird screen, however.

Experimental Section[14]

2-Methyl-*p*-anisonitrile (IIb).—For the preparation of this compound a Sandmeyer-type reaction was employed, using the procedure of Hodgson and Heyworth[15] for the preparation of 2- and 4-methoxybenzonitrile. Freshly distilled [bp 138–139° (20 mm)] 2-methyl-*p*-anisidine (Ib) (10 g, 0.07 mol) was dissolved in a mixture of 30 ml of concd H_2SO_4 and 50 ml of H_2O. Ice (100 g) was added and a solution of 7.5 g (0.108 mol) of $NaNO_2$ in 135 ml of H_2O was added slowly, maintaining the reaction temperature at 0–5°. The diazonium salt solution was neutralized by pouring it carefully over a mixture of 50 g of $CaCO_3$ and 50 g of ice. The insoluble Ca salts were removed on a Büchner funnel. The cold filtrate (pH 6–7) was run slowly into a 65–75° hot solution of 25 g of CuCN and 50 g of KCN in 125 ml of H_2O. The reaction mixture was heated for a short time to ~80° and then cooled to room temperature. The product was extracted into two 150-ml aliquots of C_6H_6 and the combined extracts were washed (H_2O) and the solvent was removed. The residue was distilled [bp 77–80.5° (0.15 mm)] to yield 4.2 ml (4.45 g, 41%) of product IIb (yellow oil); $n^{25}D$ 1.5445. *Anal.* (C_9H_9NO) C, H, N.

2-Bromomethyl-*p*-anisonitrile.—A mixture of 17 g (0.115 mol) of 2-methyl-*p*-anisonitrile (IIb), 21 g (0.118 mol) of powdered NBS, and *ca.* 0.3 g of benzoyl peroxide in 100 ml of CCl_4 was stirred and refluxed for 20 hr. The mixture was cooled (ice bath) and filtered. The filtrate was concentrated and the waxy residue was dissolved in 75 ml of warm Et_2O, treated with charcoal, and filtered. The filtrate was treated cautiously with 50 ml of petr ether under constant scratching with a glass rod. After crystallization had set in the mixture was allowed to stand at room temperature for several hours and was then stored in a refrigerator overnight. The crystals were collected; 12.6 g (48%); mp 65–68°. An analytical sample (mp 71–72°) was prepared (petr ether–5% Et_2O). *Anal.* (C_9H_8BrNO) C, H, N, Br.

The benzyl bromide is a powerful skin irritant and should be handled with care.

2-Cyanomethyl-*p*-anisonitrile (IIIb).—A sample of 31 g (0.137 mol) of 2-bromomethyl-*p*-anisonitrile in *ca.* 0.9 l. of AcCN was stirred with 30 g (0.61 mol) of NaCN for 3 days. The inorganic

[13] Tests were conducted by Dr. L. Rane, University of Miami. Chicks were infected with *P. gallinaceum* fatal to 100% of untreated controls within 3–4 days. An increase of at least 100% survival time of treated animals was considered an active dose. Chicks that survived for 30 days were recorded as cured.

[14] All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. The microanalyses were performed by Galbraith Laboratories, Inc. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Nmr spectra were obtained on a Varian Model A-60 spectrophotometer. Peak positions are reported in terms of parts per million from Me_4Si. Uv absorption spectra were determined on a Beckman DK-1A recording spectrophotometer. Ir spectra were recorded on a Perkin-Elmer 237 spectrometer.

[15] H. H. Hodgson and F. Heyworth, *J. Chem. Soc.*, 1131 (1949).

material was removed by filtration and the filtrate was concentrated to dryness. The residue was recrystallized from 60 ml of C_6H_6 to give 14.2 g (IIIb), mp 100–105°. Repeated recrystallization (Et_2O–petr ether) raised the melting point to 108–111°. A satisfactory analysis could not be obtained.

3-Amino-1-bromo-6-methoxyisoquinoline (9).—The recrystallized 2-cyanomethyl-*p*-anisonitrile (IIIb) (3.7 g, mp 108–111°) was dissolved in 130 ml of C_6H_6. The solution was diluted with 100 ml of Et_2O and cyclization was accomplished with HBr gas. The precipitated product was collected on a Büchner funnel, treated with $KHCO_3$, washed (H_2O), and vacuum dried, yielding 4.9 g (90%), mp 176–178°. An analytical sample was prepared from C_6H_6, mp 176–178.5° (Table I).

3-Amino-1-bromo-4-methyl-6-methoxyisoquinoline (11).—A sample of 2 g of 2-cyanomethyl-*p*-anisonitrile (IIIb) was methylated by the procedure of Gabriel.[7] The crude product was an oily mixture of at least 5 compounds (tlc). No attempts at purification was made and the mixture was dissolved in Et_2O and treated with HBr gas. The precipitated solid was collected, neutralized ($KHCO_3$), washed (H_2O), and dried, yielding 2 g, mp 155–165°. A product of analytical purity was obtained by one recrystallization from AcCN and one from EtOH; 0.85 g (27%) overall yield, mp 168–171° (Table I).

3-Amino-4-methylisoquinoline (3).—3-Amino-1-bromo-4-methylisoquinoline[5] (**6**) (4.0 g, 0.017 mol) and 2.0 g of KOH were dissolved in 200 ml of EtOH and hydrogenated on a Parr apparatus, using 200 mg of 10% Pd–C. The mixture was then filtered and the filtrate was concentrated to dryness. The yellow solid residue was treated with H_2O and extracted into two 100-ml aliquots of Et_2O. The combined Et_2O extracts were stirred with $MgSO_4$ and charcoal. Stepwise concentration of the filtrate yielded 1.75 g of analytically pure yellow crystals, mp 116.5–118°, and 0.6 g of a product of lesser purity, mp 113–115°. The total yield of **3** was 2.35 g (88%) (Table I).

3-Acetamido-1-bromo-4-methylisoquinoline (12).—A solution of 5.15 g (0.0217 mol) of 3-amino-1-bromo-4-methylisoquinoline (**3**) was dissolved in 40 ml of pyridine. Ac_2O (80 ml) was added and the solution was stirred for 3 hr. A crystalline precipitate had formed and the mixture was poured into 0.8 l. of H_2O. The precipitate was collected, washed (H_2O), and dried at 100°, to give 5.78 g (95%) of **12**; mp 222–223°; white crystals from EtOH–Me_2CO, mp 223–224 (Table I).

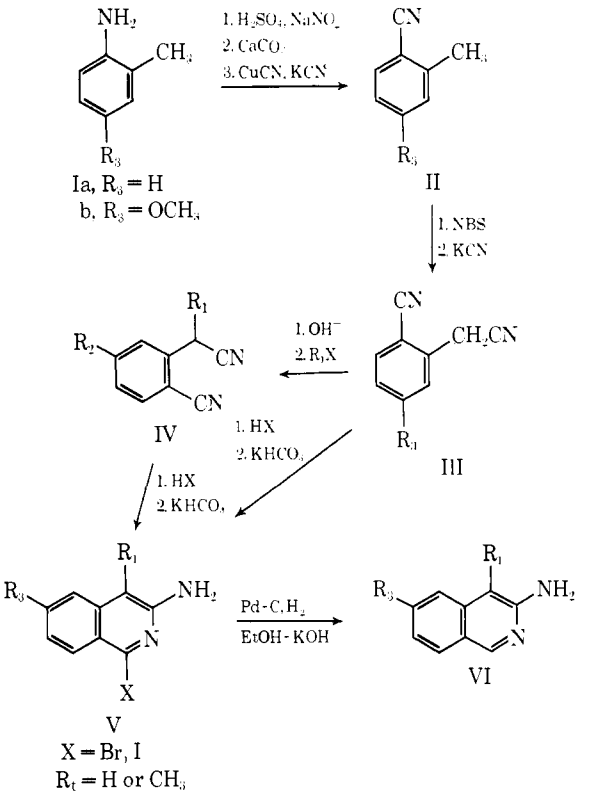
3-Acetamido-1-chloro-4-methylisoquinoline (13).—A mixture of 10 g (0.0358 mol) of 3-acetamido-1-bromo-4-methylisoquinoline, 4.5 g (0.043 mol) of CuCl, and 0.2 g of $CuCl_2 \cdot H_2O$ in 350 ml of freshly distilled α-picoline was refluxed for 4 hr. The black mixture was poured into 2 l. of ice–water and the pH was adjusted to *ca.* 4 (300 ml of concd HCl). Treatment with charcoal and filtration (Celite filtering aid) resulted in a yellow solution. After 2 weeks 2.86 g (dried at 100°, mp 208–210°) of **13** was obtained. An additional 2.5 g (mp 207–209°) was obtained when the Celite filtering aid was extracted with MeOH. The total yield was 5.36 g (64%). The analytical sample was recrystallized from EtOH, mp 209–210° (Table I).

3-Amino-1-chloro-4-methylisoquinoline (7).—The acetamide **13** (1.86 g, 0.0097 mol) was hydrolyzed for 2 hr in a refluxing mixture of 35 ml of EtOH and 8 ml of concd HCl. The yellow solution was poured into an excess of aq $KHCO_3$ solution. The precipitate was collected on a Büchner funnel, washed (H_2O), and dried under vacuum: 1.4 g (92%); mp 116–118°; recrystallized Et_2O, mp 119–120° (Table I).

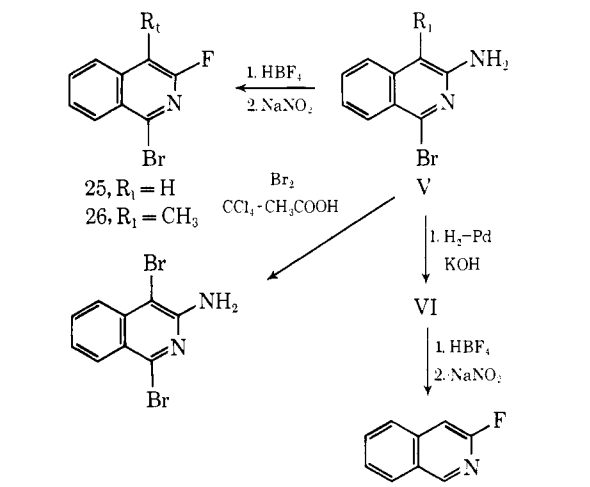
3-Amino-1-methoxy-4-methylisoquinoline·HCl (10).—A sample of 4.1 g (0.0169 mol) of 3-amino-1-bromo-4-methylisoquinoline (**6**) was added to a solution of 0.58 g (0.025 g-atom) of Na in 40 ml of anhydrous MeOH. A catalytic amount (0.2 g) of CuCN was added and the mixture was heated in a sealed tube to 100° (2 hr). The cooled mixture was treated with 10 ml of H_2O, filtered, and concentrated to near dryness. The residue was taken up with H_2O and the product was extracted (Et_2O). The extract was washed (H_2O, brine) and was stirred with $MgSO_4$ and charcoal. The filtrate was concentrated to near dryness and dissolved in 10 ml of EtOH. The HCl salt was precipitated by addition of 10 ml of ethanolic HCl to give 2.3 g (59%) of **10**, mp 163° dec. It was recrystallized (MeCN–EtOH), without a change in the melting point.

A small amount of the free base **3-amino-1-chloro-4-methylisoquinoline** was liberated from the purified HCl salt and extracted into Et_2O. Removal of the solvent and storage of the residue at −5° for several weeks caused solidification, to give a crystalline product, mp 45–47°.

SCHEME I



SCHEME II



3-Amino-1-iodo-4-methylisoquinoline (8).—A solution of 2.37 g (0.0156 mol) of α-methylhomo-*o*-phthalonitrile[7] in 100 ml of Et_2O was treated at 5° with HI gas. A yellow precipitate had formed after *ca.* 1 hr. Et_2O was decanted and the remaining yellow semisolid was caused to solidify by repeated treatment with fresh portions of ether. The solid was removed by filtration, treated with aq $KHCO_3$, and collected on a Büchner funnel, dried, and recrystallized from MeCN to yield 3.0 g (70%) of **8**, mp 141–145° (recrystallization from Et_2O, mp 114.5–146°) (Table I).

1-Bromo-3-fluoroisoquinoline (25) and 1-Bromo-3-fluoro-4-methylisoquinoline (26).—The procedure of Teague and Roe[6] for the synthesis of 3-fluoroisoquinoline was adopted for both compounds. The BF_4^- salt of 3-amino-1-bromoisoquinoline (**2**) was isolated and dried at room temperature *in vacuo*. It was then treated as a slurry with powdered $NaNO_2$ in dry C_6H_6. The product could ge purified by sublimation and recrystallization from hexane, to give 30–35% yield of **25**, mp 82°. *Anal.* (C_9H_5NBF) C, H, N.

The preparation and purification of 1-bromo-3-fluoro-4-methylisoquinoline (**26**) was carried out under identical condi-

tions, except that the sublimtation of the crude product required a longer time (2 days, 60° oil bath) and the sublimate was recrystallized from Et_2O–low boiling petr ether; 25% yield; mp 87.5–89°. *Anal.* ($C_{16}H_7NBrF$) C, H, N.

General Procedure for Preparation of Urea and Thiourea Derivatives of 3-Aminoisoquinolines 22, 23, 24.—The urea derivatives were prepared by condensation of the 3-aminoisoquinolines with the corresponding isocyanates and isothiocyanates in warm C_6H_6 solutions (several days). The yields (purified) were 85% for **22**, 61% for **23**, and 30% for **24**. Recrystallization solvents and elements analyzed are given in Table I.

General Procedure for Preparation of Sulfonamides of 3-Aminoisoquinolines.—The sulfonamides **18**, **20**, and **21** were obtained by heating at *ca.* 90° the aminoisoquinolines with the corresponding sulfonyl chlorides in pyridine. The yields of purified materials were 59% for **18**, 90% for **20**, and 55% for **21**. The acetamide **20** was deacetylated in a refluxing (30 min) mixture of EtOH-concd HCl (5:1) for 30 min and the sulfanilamide **19** was isolated in *ca.* 60% yield as the free base.

***N*-(3-Isoquinolyl)crotonamide (15).**—In an attempt to aminate *N*-(3-isoquinolyl)-3-chlorobutyramide[4] with excess of *N*,*N*-dimethyl-*N'*-ethylethylenediamine in refluxing $CHCl_3$ only the elimination product *N*-(3-isoquinolyl)crotonamide was isolated (48%), mp 150–152° (Table I).

***N*-(3-Isoquinolyl)acrylamide (14).**—This compound was isolated as the elimination product of *N*-(3-isoquinolyl)-3-chloropropionamide[4] with PhNHMe in refluxing $CHCl_3$ in the presence of Na_2CO_3 (Table I).

3-Benzamidoisoquinolines.—*N*-(3-Isoquinolyl)benzamide (**16**) and *N*-(3-isoquinolyl)-3-nitrobenzamide (**17**) were obtained in fair yields by the reactions of 3-aminoquinoline with the appropriate benzoyl chlorides in refluxing C_6H_6 (Table I).

Lincomycin. XI. Synthesis and Structure of Clindamycin.[1] a Potent Antibacterial Agent[2]

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Several processes for preparing clindamycin·HCl (**4a**) are described and evidence is presented indicating that the chloro substituent is in the 7(*S*) configuration. This compound and its 7-Br and 7-I analogs (**4c**, **4d**) are potent antibacterial agents.

The structure of the antibiotic lincomycin·HCl (**1a**) and the spectrum of its antibacterial activity were described in previous communications from this laboratory.[3,4] As part of a continuing program on the chemical modification of lincomycin directed toward the examination of structure–activity relationships,[5] the preparation of a halogen-containing analog was initiated.

Treatment of lincomycin·HCl (**1a**) with $SOCl_2$ in CCl_4 at room temperature afforded a product which was assigned the 3,4-cyclic sulfite structure (**2a**) on the basis of its elemental and spectral analyses and its facile regeneration of lincomycin on alcoholysis. Both the *in vitro* and *in vivo* assays of antibacterial activity of **2a** were equivalent to those of **1a**. Formation of the cyclic sulfite is not unexpected in view of the *cis* relationship of the C-3 and C-4 OH groups and the ease of formation of other similar cyclic derivatives such as the isopropylidene ketal **2b** and the cyclic carbonate **2c**.[6]

Further treatment of **2a** with $SOCl_2$ in boiling CCl_4 yielded chlorinated products **3** and **5**. Structure assignments were made on the basis of elemental and spectral analyses and quantitative conversion by alcoholysis to clindamycin (**4a**).[1] Evidence for the structure **4a** was provided by its elemental and spectral analyses, the ir spectrum clearly showing the presence of amide I and amide II absorptions similar to those observed in lincomycin.[3] The position of the Cl atom is **4a** was inferred from the downfield shift in the 60-MHz nmr spectrum of the doublet attributable to the hydrogens of the terminal Me (C-8). In lincomycin (**1a**) these C-8 hydrogens are recognizable by the doublet they produce at 66 and 73 Hz. In the chlorinated product **4a** these absorptions are shifted downfield to 84 and 91 Hz, as expected if the C-7 OH group were replaced by Cl.[7] When a Br or I atom was substituted for OH, the downfield shift of the C-8 Me doublet was greater, appearing at 94 and 101 Hz for **4c** and 108–115 Hz for **4d**. With the exception of the C-8 Me shift, the nmr spectra of the monohalolincomycins were essentially the same as that of lincomycin.

The configuration of the OH at C-7 in lincomycin was previously established as 7(*R*) and the sugar side chain (C-6 and C-7) as D-*erythro*.[3] When epilincomycin·HCl (**1b**) (OH at C-7 in the S configuration, side chain D-*threo*)[8] was treated with $SOCl_2$ under the conditions cited, a new monochlorolincomycin was formed. This compound was less mobile on tlc than **4a** and exhibited about 0.5 the antibacterial activity of **4a**. Since the elemental and spectral data were essentially the same as that obtained for clindamycin·HCl (**4a**), we

(1) Clindamycin is the generic name for 7(*S*)chloro-7-deoxylincomycin.

(2) A preliminary announcement of a portion of this work was presented earlier: R. D. Birkenmeyer, B. J. Magerlein, and F. Kagan, Fifth Interscience Conference on Antimicrobial Agents and Chemotherapy and Fourth International Congress of Chemotherapy, Oct 17–21, 1965, Washington, D. C.

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(5) (a) B. J. Magerlein, R. D. Birkenmeyer, and F. Kagan, *J. Med. Chem.*, **10**, 355 (1967); (b) B. J. Magerlein, *ibid.*, **10**, 1161; (c) B. J. Magerlein and F. Kagan, *ibid.*, **12**, 780 (1969).

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(8) H. Hoeksema, Abstracts of Papers, 149th National Meeting of the American Chemical Society, Detroit, Mich., 1965, p 9c.