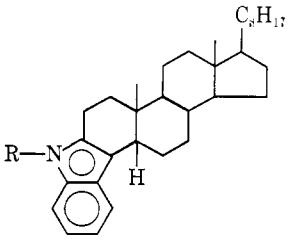
TABLE II



Compd	R	Method[a]	Yield, %	Recrystn solvent	Mp, °C[c]	$[\alpha]^{25}D$, deg[d]	Formula	Analyses[e]
VIII	CH_3	A	90	C_6H_6–MeOH	147–149	+137.4	$C_{34}H_{51}N$	C, H, N
IX	NO	B	71	EtOEt	146–148 dec	+132.2	$C_{33}H_{48}N_2O$	C, H, N
X	NH_2	C	89	*b*	164–165	+156.0	$C_{33}H_{50}N_2$	C, N; H[f]
XI	$NHCOCH_3$	D	79	MeOH	85–89	+118.8	$C_{35}H_{52}N_2O$	C, H, N

[a] Prepared as follows: A, treatment of 5β-cholestan-3-one with N-methyl-N-phenylhydrazine in HOAc at 95°; B, treatment of indolo[3,4-*b*]-5β-cholest-3-ene[6a] in HOAc–dioxane at 10° with a concentrated H_2O solution of KNO_2 in 10 *M* excess; C, treatment of IX with $LiAlH_4$; D, treatment of X with Ac_2O. [b] Purified by trituration with MeOH. [c] Melting points were taken on a Fisher-Johns apparatus and are corrected. [d] *c* 0.5, $CHCl_3$. [e] See footnote *d*, Table I. [f] H: calcd, 10.62; found, 10.15.

positive bacteria (*Staphylococcus aureus, Sarcina lutea,* and *Streptococcus pyogenes*), yeasts (*Candida albicans* and *Saccharomyces cerevisae*), and molds (*Sporotrichum schenckii* and *Trichophyton mentagrophytes*). A gradient plate technique[10] was used. None of these steroids exhibited activity.

Neither VI nor VII exhibited anabolic, androgenic, antianabolic, or antiandrogenic activity upon subcutaneous administration to castrate male rats as determined by its effect alone and in combination with testosterone upon seminal vesicles and levator ani muscle. II–VII were inactive upon subcutaneous administration to castrate male rats in a general endocrine screen.

(10) R. F. Smith, D. E. Shay, and N. J. Doorenbos, *J. Bacteriol.*, **85**, 1295 (1963).

Penicillins from 3- and 5-Phenylisothiazole-4-carboxylic Acids and Alkoxy Derivatives

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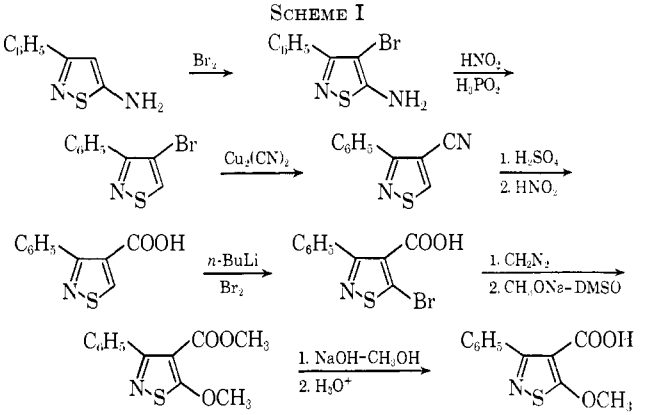
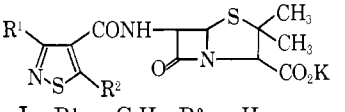
A study of penicillins derived from sterically hindered carboxylic acids[1,2] has shown that such penicillins show a high degree of resistance to the action of the enzyme penicillinase. This study has resulted in clinically useful penicillins such as 2,6-dimethoxyphenylpenicillin (methicillin), 3-phenyl-5-methyl-4-isoxazolylpenicillin (oxacillin), 3-*o*-chlorophenyl-5-methyl-4-isoxazolylpenicillin (cloxacillin), and 2-biphenylylpenicillin (diphenicillin). The analogy between the isoxazole and isothiazole[3] ring suggested that penicillins derived from hindered isothiazolecarboxylic acids should also show resistance to the action of penicillinase. Some penicillins of this type were recently reported by Grant, Pain, and Slack.[4] The present paper reports the synthesis and antibacterial activity of some phenyl- and alkoxy-substituted 4-isothiazolylpenicillins.

Chemistry.—3-Phenylisothiazole-4-carboxylic acid and 5-methoxy-3-phenylisothiazole-4-carboxylic acid were synthesized from 5-amino-3-phenylisothiazole[5] by the sequence of reactions illustrated in Scheme I.

SCHEME I



5-Phenylisothiazole-4-carboxylic acid was prepared from 3-amino-4-bromo-5-phenylisothiazole[6] by reductive deamination, followed by cyanation and hydrolysis. 3-Alkoxy-4-bromo-5-phenylisothiazoles[6] were converted to 3-alkoxy-5-phenylisothiazole-4-carboxylic acids in the same manner *via* the cyanides. The carboxylic acids were converted to the corresponding acid chlorides, which upon reaction with 6-aminopenicillanic acid and subsequent treatment with potassium 2-ethylhexonate provided the penicillins Ia–e.



Ia, $R^1 = C_6H_5$; $R^2 = H$
b, $R^1 = C_6H_5$; $R^2 = OCH_3$
c, $R^1 = H$; $R^2 = C_6H_5$
d, $R^1 = OCH_3$; $R^2 = C_6H_5$
e, $R^1 = OC_2H_5$; $R^2 = C_6H_5$

(1) J. C. Hanson, J. H. C. Nayler, T. Taylor, and P. H. Gore, *J. Chem. Soc.*, 5984 (1965), and preceding publications.

(2) A. W. Chow, N. M. Hall, J. R. E. Hoover, M. M. Dolan, and R. J. Ferlunto, *J. Med. Chem.*, **9**, 551 (1966), and preceding publications.

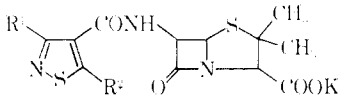
(3) R. Slack and K. R. H. Wooldridge, *Advan. Heterocyclic Chem.*, **4**, 107 (1965).

(4) M. S. Grant, D. L. Pain, and R. Slack, *J. Chem. Soc.*, 3842 (1965).

(5) J. Goerdeler and H. W. Pohland, *Chem. Ber.*, **94**, 2950 (1961).

(6) J. G. Goerdeler and W. Mittler, *ibid.*, **96**, 944 (1963).

TABLE I
MINIMUM INHIBITORY CONCENTRATIONS (μg/ml) OF POTASSIUM 6-(4-ISOTHIAZOLYLCARBOXAMIDO)PENICILLANATES



			Gram-positive microorganisms			Penicillin G resistant	
No.	R^1	R^2	*D. pneumoniae*	*S. pyogenes*	*S. aureus* Smith	*S. aureus* BX1633-2	*S. aureus* 32-75
Ia	C_6H_5	H	0.031	0.031	0.031	1.6	3.1
Ib	C_6H_5	OCH_3	0.25	0.125	0.25	1.6	1.6
Ic	H	C_6H_5	0.016	0.031	0.031	3.1	12.5
Id	OCH_3	C_6H_5	0.125	0.031	0.125	0.8	0.8
Ie	OC_2H_5	C_6H_5	0.5	0.031	0.25	1.6	1.6
Oxacillin			0.031	0.031	0.062	0.4	0.4

Antibacterial Activity.—The compounds were tested for antibacterial activity by Dr. A. Gourevitch and his associates in the Microbiology Department of Bristol Laboratories, Syracuse, N. Y., using published techniques.[7]

In Table I the MIC values of the penicillins Ia–e against some gram-positive microorganisms and against two penicillinase-producing *Staphylococcus aureus* strains are compared with the values for oxacillin, obtained under the same conditions. Although all the compounds exhibit activity against the resistant *S. aureus* strains, only Id shows an activity comparable to that of oxacillin. When administered by the intramuscular route, the median curative dose in mice against *S. aureus* BX1633-2 was found to be 45 mg/kg for both Id and oxacillin.

Experimental Section[8]

5-Phenylisothiazole-4-carboxylic acid was obtained from 3-amino-4-bromo-5-phenylisothiazole[6] using procedures already described in the patent literature.[9] 4-Bromo-5-phenylisothiazole, mp 30–32°, obtained in 27% yield by the reductive deamination of 3-amino-4-bromo-5-phenylisothiazole,[6] when heated with cuprous cyanide in dimethylformamide, gave 4-cyano-5-phenylisothiazole, mp 103–107°, in 80% yield. The 4-cyano-5-phenylisothiazole on acid hydrolysis gave 5-phenylisothiazole-4-carboxylic acid, mp 174–176° (70%). *Anal.* ($C_{10}H_7NO_2S$) C, H, N, S; neut equiv, found 203.

5-Phenylisothiazole-4-carbonyl chloride, mp 72–75° (95%), was obtained by heating 5-phenylisothiazole-4-carboxylic acid with excess $SOCl_2$ under reflux for 1 hr.

3-Ethoxy-5-phenylisothiazole-4-carbonyl chloride, bp 138–140° (0.7 mm) (79%), was obtained from 3-ethoxy-5-phenylisothiazole[6] using identical procedures as described for 3-methoxy-5-phenylisothiazole-4-carbonyl chloride.[9] The intermediate compounds prepared were 4-bromo-3-ethoxy-5-phenylisothiazole, bp 128–131° (0.5 mm) (90%); 4-cyano-3-ethoxy-5-phenylisothiazole, mp 72–78° (93%); 3-ethoxy-5-phenylisothiazole-4-carboxamide, mp 165–180° (98%); 3-ethoxy-5-phenylisothiazole-4-carboxylic acid, mp 124–127° (90%). *Anal.* ($C_{12}H_{11}NO_3S$) C, H, N, S; neut equiv, found 247.

Acknowledgments.—The authors thank Professor R. U. Lemieux for guidance and advice in the conduct of this research and Messrs. R. A. Fortier and P. K. Wolfert for their capable technical assistance.

(7) A. Gourevitch, G. A. Hunt, J. R. Luttinger, C. C. Carmack, and J. Lein, *Proc. Soc. Exptl. Biol. Med.*, **107**, 455 (1961).

(8) As most of the experimental procedures have already been described in a recent patent,[9] only new compounds are reported here. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(9) R. U. Lemieux and R. G. Micetich, U. S. Patent 3,311,611 (1967).

Quinolone Antibacterial Agents. Oxolinic Acid and Related Compounds

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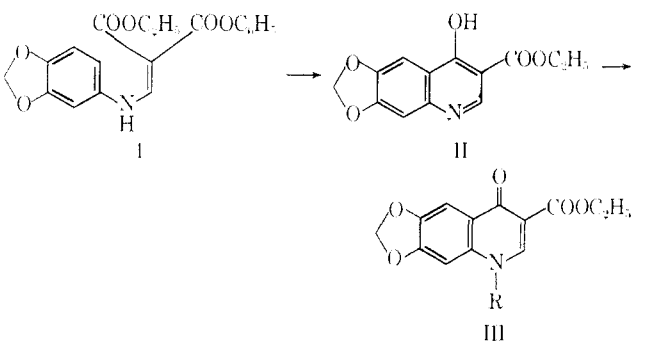
Extension of our efforts[1] at preparing more efficient agents *vs.* gram-negative organisms led to the discovery of oxolinic acid (IVb).[2] In order to investigate a possible structure–activity relationship, we prepared a number of analogs and derivatives. Condensation of 3,4-methylenedioxyaniline with diethyl ethoxymethylenemalonate gave the unsaturated ester I, and thermal cyclization in refluxing Dowtherm A[3] resulted in 70–95% yields of II. The quinolone ethyl esters (III) (see Table I) were prepared by alkylation of II, with the appropriate alkyl or substituted-alkyl halide. The free acids were obtained by basic and/or acid hydrolysis of the esters. No evidence of hydrolysis of the methylenedioxy group was noted during 1–6 hr (reflux) with 2–10% aqueous caustic or with 5–10% hydrochloric acid. In the case of III (R = ethyl), hydrolysis gave



I II III

IVb, which, upon treatment with thionyl chloride, gave the acid chloride V. Treatment of this acid chloride with an appropriate alcohol gave the desired ester of IV. In a similar manner the esters of other N-

(1) D. Kaminsky and R. I. Meltzer, U. S. Patent 3,172,811 (March 9, 1965).

(2) Generic name for 5-ethyl-5,8-dihydro-8-oxo-1,3-dioxolo[4,5-*g*]quinoline-7-carboxylic acid.

(3) A eutectic mixture containing 26.5% diphenyl and 73.5% diphenyl ether.