tion cooled to 10° of 0.01 mol of α-keto aldehyde in 50 ml of dioxane. The mixture was stirred at 10° for 4 hr and the separated crystals were collected and crystallized (see Table IV).

Pharmacological Methods.—For all tests NMRI albino mice (18–20 g) and Wistar albino rats (200–250 g) were used.

Acute Toxicity.—LD_{50} values were determined in mice intraperitoneally, and the mortality over 48 hr was recorded. The animals were also observed for behavior and objective symptoms according to the Irwin scheme.[15]

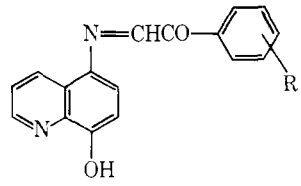
Other Tests.—All compounds were screened also for their antispasmodic activity *in vitro* following the methods described by Setnikar and Tirone,[16] and for their coronary vasodilatator activity on the isolated rabbit heart following the method of Setnikar, *et al.*[17]

Antimicrobial and antifungal activity *in vitro*, peritonitis with *E. coli* 100 in mice, antiviral activity, anticonvulsant activity, and antiinflammatory activity were determined according to the methods previously described [18]

Infection with *M. tuberculosis*.—A group of 25 female mice (16–18 g) was challenged intravenously with 0.2 ml of a suspension of *M. tuberculosis murium* SG 851 Vole strain, in buffered saline solution at pH 7.2 containing 10 LD_{95} (lethal dose 95 calculated at day 40) The infected mice and control groups of 10 mice were treated subcutaneously 1 day after infection and daily for 40 days with a suspension 10% arabic gum of 0.4 mmol/kg per 10 ml of the compound. The increase in weight and mortality of the animals was recorded.

TABLE IV

5-ARYLGLYOXYLIDENAMINO-8-HYDROXYQUINOLINES



No.	R	Recrystn solvent[a]	Mp, °C	Yield, %	Formula[b]
21	H	A	158	47	$C_{17}H_{12}N_2O_2$
22	*p*-NO_2	D	234	56	$C_{17}H_{11}N_3O_4$
23	*p*-Cl	A	188	71	$C_{17}H_{11}ClN_2O_2$
24	*m*-Cl		175	87	$C_{17}H_{11}ClN_2O_2$
25	*p*-CH_3	A	160	49	$C_{18}H_{14}N_2O_2$
26	*p*-OCH_3	A	159	79	$C_{18}H_{14}N_2O_3$
27	*p*-OC_6H_5	A	142	55	$C_{23}H_{16}N_2O_3$
28	*p*-SC_6H_5	A	161	65	$C_{23}H_{16}N_2O_2S$
29	*p*-C_6H_5	A	178	58	$C_{23}H_{16}N_2O_2$

[a] A = EtOAc, D = dioxane. [b] All compounds were analyzed for C, H, N.

(15) This scheme was discussed informally by S. Irwin at a Gordon Research Conference, New London, N. H., 1959.

(16) I. Setnikar and P. Tirone, *Arzneimittel-Forsch.*, **16**, 1146 (1966).

(17) I. Setnikar, W. Murmann, and M. T. Ravasi, *Arch. Intern. Pharmacodyn.*, **131**, 187 (1961).

(18) E. Massarani, D. Nardi, L. Degen, and M. J. Magistretti, *J. Med. Chem.*, **9**, 617 (1966).

Potential Antimalarials. IV.[1,2] Quinoline-α,α-dialkylmethanols

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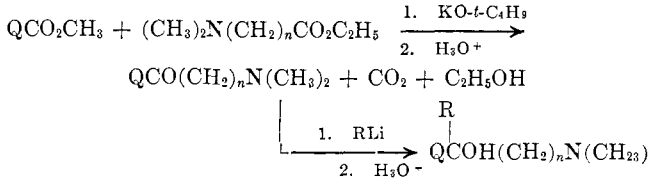
Quinoline-α,α-dialkylmethanols, tertiary alcohols, $QC(R)(OH)(CH_2)_nNR'_2$, have been made to compare their antimalarial activity with the corresponding secondary α-alkylmethanols, $QCHOH(CH_2)_nNR'_2$. Feasible routes for their synthesis are described: a mixed Claisen route for compounds where n is 3 or greater and an epoxidation route for compounds where $n = 1$. All quinoline-α,α-dialkylmethanols synthesized herein have greatly reduced antimalarial activity compared with the corresponding secondary alcohols and, in the 2-aryl-4-quinoline-α,α-dialkylmethanol family, retain their high phototoxicity.

Very few quinoline-α,α-dialkylmethanols have been made[5,6] and none has been compared rigorously with the highly active secondary quinoline-α-alkylmethanols. Model compounds were synthesized first to explore Grignard routes to quinoline-α,α-dialkylmethanols (see Table I and Experimental Section). They were not expected to have, nor did they have, antimalarial activity. More suitable quinoline-α,α-dialkylmethanols were then synthesized by the mixed Claisen route (see below) which served well to make the intermediate ketones (see Table II) as long as n was 3 or greater for reasons that the amino ketones with smaller chains ($n = 1$ or 2) were less stable under conditions of condensation.



Grignard reagents would not add to these ketones, but alkyllithiums did (see Table III and Experimental Section). The antimalarial activity of compounds in Table III was quite low, the best having an increased survival time of only 1.8 days at 640 mg/kg. With the exception of methylquinine and dihydroquinine, a true comparison with the best of the highly active quinoline-*sec*-methanols had not been made (C side chains were too long, $n \geq 3$). Another route had to be devised to obtain shorter side chains ($n = 1$), a necessity which resulted in the development of the epoxidation route:

(1) Paper I: D. E. Pearson and J. C. Craig, *J. Med. Chem.*, **10**, 737 (1967). Paper II: J. C. Craig and D. E. Pearson, *J. Heterocycl. Chem.*, **5**, 631 (1968). Paper III: J. B. Wommack, T. G. Barbee, Jr., D. J. Thoennes, M. A. McDonald, and D. E. Pearson, *J. Heterocycl. Chem.*, **6**, 243 (1969).

(2) Contribution No. 712 to the Army Research Program on Malaria. We are indebted to the U.S. Army Medical Research and Development Command for Grant DA-49-193-MD-2752 in support of this program.

(3) Taken from the Ph.D. thesis of J. B. W., Vanderbilt University, 1968, "The Synthesis of Quinoline Tertiary Alcohols of Antimalarial Potential," University Microfilms Order No. 68-18003, Ann Arbor, Mich.

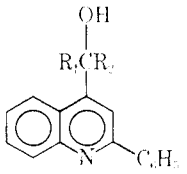
(4) To whom correspondence should be addressed.

(5) K. Feist, W. Awe, and M. Kuklinski, *Arch Pharm.*, **276**, 420 (1938).

(6) R. B. Woodward, N. L. Wendler, and F. J. Brutschy *J. Amer. Chem. Soc.*, **67**, 1425 (1945).

TABLE I

MODEL α,α-DIALKYL- (OR ARYL)-2-PHENYLQUINOLINE-4-METHANOLS



R_1	R_2	% yield	Mp, °C
CH_3	C_6H_5	44	129–130[a]
m-$CH_3C_6H_4$	*m*-$CH_3C_6H_4$	34	195–196
C_6H_5	C_6H_5	55	207–208
p-$(CH_3)_3CC_6H_4$	*p*-$(CH_3)_3CC_6H_4$	15	204.5–205.5
CH_3	*p*-$(CH_3)_3CC_6H_4$	15	194.5–196
p-$C_6H_5C_6H_4$	*p*-$C_6H_5C_6H_4$	55	248–249
CH_3	CH_3	84	126–128[b]
2-(4-Chlorophenyl)-6,8-α,α-tetramethyl-4-quinolinemethanol		95	154–156

[a] Picrate mp 194–195°. [b] Literature[6] mp 129°.

Experimental Section

Melting points were determined with an Arthur H. Thomas Uni-Melt apparatus. Analyses on all new compounds were determined by Galbraith Laboratories and are recorded in the thesis of J. B. W.,[3] as well as on deposit with the Editor, *J. Med. Chem.* Nmr spectra were taken with an A-60 Varian spectrometer,[7] and the original recordings are available from this laboratory. If deviation from theoretical was considerable, analyses are recorded in this section.

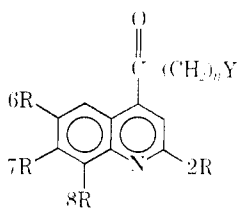
Model 2-Phenylquinoline-4-methanols.—The compounds listed in Table I were prepared by the addition of methyl 2-phenyl-4-quinolinecarboxylate, mp 56–57°,[8] to 3 equiv of the appropriate Grignard reagent when R_1 and R_2 were the same. When R_1 and R_2 were different, the compounds were made from 4-acetyl-2-phenylquinoline, mp 74–75°,[9] and the appropriate excess Grignard reagent. The products were recrystallized from aqueous Me_2CO or from EtOH.

1,6-Bis-(2-quinolyl)-1,6-hexanediol.—2-Quinolinecarboxaldehyde (0.2 mol) in Et_2O was added to the Grignard reagent from 0.15 mol of $ClCH_2(_4)Cl$ and 0.25 g-atom of Mg turnings in Et_2O. The product was a pale yellow solid, mp 136–138° from *i*-PrOH–H_2O, yield 10%. C analysis was low by 0.5%.

Mixed Claisen Route (for More Than Two-Carbon Chains). Ethyl ϵ-Dimethylaminocaproate. Hydrolysis of Caprolactam.—Caprolactam (4 mol), 160 ml of H_2O, and 110 ml of cond HC

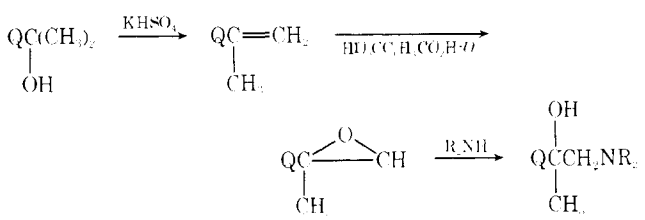
TABLE II

QUINOLYL KETONES



Y	2R	6R	7R	8R	*n*	% yield	Derivative
$(CH_3)_2N$	C_6H_5	H	H	H	3	50	$(HCl\cdot H_2O)_2$ salt, mp 118–120°
$(CH_3)_2N$	H[c]	CH_3O	H	H	3	57	Bp 170° (0.06 mm),[c] picrate, mp 183–185°
$(CH_3)_2N$	*p*-C_6H_4Cl	H	Cl	CH_3	3	55	Picrate, mp 188–190°
$(CH_3)_2N$	$(CH_2)_5N$[b]	H	H	H	3	47	Dipicrate,[f] mp 161–163°
$(CH_3)_2N$	C_6H_5	H	H	H	5	60	Picrate, mp 173–173.5°
H_2N	C_6H_5[e]	H	H	H	5	33	HBr salt, mp 230–232°[g]
CH_3SO	C_6H_5[d]	H	H	H	1	64	Mp 153–154°

[a] From ethyl 6-methoxyquinoline-4-carboxylate (K. N. Campbell, *et al.*, *J. Org. Chem.*, 11, 803 (1946)). [b] From ethyl 2-piperidinoquinoline-4-carboxylate (S. Winstein, *et al.*, *J. Amer. Chem. Soc.*, **68**, 2714 (1946)). [c] Made from ethyl ϵ-benzamidocaproate by the method of Sargent [H. Sargent, *ibid.*, **68**, 2688 (1946)]. [d] Made inadvertently using DMSO as solvent. Product converted into 2-phenyl-4-quinolylglyoxal hemimethyl thioacetal, mp 142–143°, by Pummerer reaction (H.-D. Becker, *et al.*, *ibid.*, **85**, 3410 (1963)). [e] C anal. was low by 0.85%. [f] N anal. was low by 0.6%. [g] Lit. mp 227° (J. B. Koepfli, *et al.*, *ibid.*, **68**, 2697 (1946)).



The route is smooth but restricted in the first step to dehydration of tertiary alcohols (secondary alcohols gave side-products including the *sym*-ether). The quinoline-α,α-dialkylmethanols are shown in Table IV and, in comparison with a known, highly active quinoline-*sec*-methanol, have greatly reduced antimalarial activity (*ca.* 0.04 times the activity of the corresponding quinoline-*sec*-methanol). A comparable loss of activity is found in the quinine series where methylquinine and methyldihydroquinine are compared with quinine and dihydroquinine, respectively (see Table III).

were refluxed 4 hr and concentrated under water vacuum.—The residue was dissolved in H_2O and neutralized with Na_2CO_3 solution. Eschweiler–Clarke methylation: the above solution, 175 ml of 35% formalin, and 110 g of 90% HCO_2H were refluxed until CO_2 evolution nearly ceased; formalin (20 ml) and 10 ml of HCO_2H were then added 3 times at spaced intervals. The mixture was concentrated under water vacuum, the residue dissolved in *i*-PrOH and filtered, and the filtrate reconcentrated.

Esterification.—The viscous residue, 280 ml of absolute EtOH, and 40 ml of concentrated H_2SO_4 were refluxed 6 hr, EtOH was removed, and the residue poured into H_2O, neutralized, and extracted: product: bp 89–94° (5 mm) (foaming during distillation); $n^{25}D$ 1.4297; 94 g; 52%; glpc pure; lit.[10]

Ethyl γ-dimethylaminobutyrate was obtained as above from 1-methyl-2-pyrrolidone; γ-methylaminobutyric acid·HCl was a

(7) We are indebted to the National Science Foundation for funds to purchase this instrument (NSF-1683).

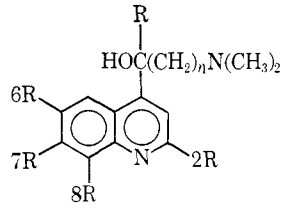
(8) W. Pfitzinger, *J. Prakt. Chem.*, **56**, 283 (1897).

(9) K. Miescher, U. S. Patent 1,434,306 (1922); *Chem. Abstr.*, **17**, 402 (1923).

(10) R. Fusco, G. Palazzo, S. Chiavarelli, and D. Bovet, *Gazz. Chim. Ital.*, **79**, 836 (1949).

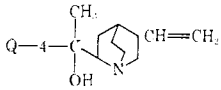
TABLE III

QUINOLINE-4-α,α-DIALKYLMETHANOLS



R	2R	6R	7R	8R	n	% yield	Mp, °C	Derivative (mp, °C)	Relative activity[a]
CH_3	C_6H_5	H	H	H	3	71	127–129		0.1
CH_3	CH_3[b]	CH_3O	H	H	3	31	Oil	HCl (240–242)	0.5
CH_3	p-C_6H_4Cl	H	Cl	CH_3	3	52	146–148		0.8
CH_2=CH	C_6H_5	H	H	H	3	64	110–111		0.5[c]
CH_3	C_6H_5	H	H	H	5	9	113.5–115	Dipicrate (163.5–165)	0.2
H[d]	C_6H_5	H	H	H	3	88	Oil	Di(HCl·H_2O) (222–224)	0.2
Methylquinine hydrate[e]						20	102–112 dec[f]		0.0[g]
Methyldihydroquinine dihydrate						61	106–116 dec		0.0

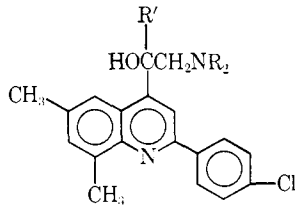
[a] *P. berghei* relative activity: the 4th compound in Table IV was arbitrarily given a relative activity rating = 100. It showed ΔMST (mean survival time in days increased over that of controls) of 11.5 days at 10 mg/kg dose). Other relative activities were calculated from the formula 100 × ΔMST/11.5 × 10/dose on the assumption that relative activity is linearly related to ΔMST and linearly inversely related to dose, an estimate that is better at the lower dose levels. [b] MeLi added to the 2 position as well as to the C=O group. [c] Toxic at 160 mg/kg. [d] A *sec*-quinolinemethanol made from ketone by reduction with $NaBH_4$ in EtOH–dioxane.

[e] Methylquinine:  Q = 6-methoxy-4-quinolyl; methyldihydroquinine has an Et rather than a vinyl group.

[f] Lit.[6] mp 105–112° dec; ΔMST = 0.1 day. [g] Quinine relative activity = 1, that of dihydroquinine = 5.

TABLE IV

2-(4-CHLOROPHENYL-α-(DIALKYLAMINOMETHYL)-6,8,α-TRIMETHYL-4-QUINOLINEMETHANOLS AND STANDARD



R′	R_2	% yield	Mp, °C	Dose (mg/kg)	ΔMST[a]	Relative activity
CH_3	C_4H_9	42	Oil[b,c]	160	1.8	4
				640	6.0	2
CH_3	CH_3	68	151–152	640	0.4	0
CH_3	$(CH_2)_5$	64	119–120.5[d]	640	0.8	0
H	C_4H_9	(gift, used as a standard)	c	10	11.5	100

[a] Mean survival time in days of mice in *P. berghei* test [T. S. Osdene, P. B. Russel, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967)]: MST of control mice (6 days). [b] Dihydrochloride mp 167–169°. [c] Phototoxic at 30 mg/kg. [d] Highly phototoxic at 300 mg/kg.

solid, mp 120–121°:[11] product: bp 78–79° (25 mm); $n^{25}D$ 1.4213; 40%; lit.[12]

Typical Mixed Claisen Reaction. 7-Chloro-2-(4-chlorophenyl)-4-(γ-dimethylaminobutyryl)-8-methylquinoline.—Methyl 7-chloro-2-(4-chlorophenyl)-8-methyl-4-quinolinecarboxylate (0.028 mol) and 0.056 mol of commercial KO-*t*-Bu in 200 ml of C_6H_6 were stirred under anhydrous conditions at 80° 0.028 mol of ethyl γ-dimethylaminobutyrate in 50 ml of C_6H_6 was added in 6 hr from a Kontes constant dropping funnel, the mixture refluxed an additional 25 hr and cooled, and 115 ml of concentrated HCl and 20 ml of H_2O were added. C_6H_6 was removed by distillation, 50 ml of dioxane was added, and mixture was refluxed for 21 hr. It was made basic, extracted with $CHCl_3$, dried, and concentrated. The product is described in Table II together with other ketones but the nmr spectrum which is typical is given here: δ 8.2–7.5 (m, 8, aromatic H), 3.1 (t, 2, $COCH_2$), 2.85 (s, 3, aromatic CH_3), 1.5–2.2 [m, 8, $(CH_3)_2NCH_2$].

Conversion of Ketones into Quinoline-α,α-dialkylmethanols.—One typical example is described and all are listed in Table III.

α-(γ-Dimethylaminopropyl)-α-methyl-2-phenyl-4-quinolinemethanol.—MeLi (50 ml, 2.76 *M*) in Et_2O was stirred under N_2 while 0.0126 mol of 4-(γ-dimethylaminobutyryl)-2-phenylquinoline in 50 ml of C_6H_6 was added in 45 min and the mixture refluxed 6 hr. It was poured on to cracked ice and NH_4Cl, Et_2O extracted, and the ether evaporated: product: from hexane, fine needles; 3 g; 71%; mp 127–129°.

Methylquinine and Methyldihydroquinine.—Quinine and dihydroquinine were oxidized to quininone and dihydroquininone, respectively, by a modified procedure of Warnhoff.[13] Quinine (0.046 mol), 0.25 mol of fluorenone, and 0.15 mol of KO-*t*-Bu in 300 ml of C_6H_6 under N_2 were held at 25° for 4 days, at which time an additional 0.12 mol of fluorenone was added, and the mixture was allowed to stand 2 days more. It then

(11) S. M. McElvain and J. F. Vozza, *J. Amer. Chem. Soc.*, **71**, 896 (1949).
(12) M. Olomucki, *Ann. Chim.* (Paris), **5**, 845 (1960).
(13) E. W. Warnhoff and P. Reynolds-Warnhoff, *J. Org. Chem.*, **28**, 1431 (1963).

was poured on to cracked ice and extracted into 2 N HCl and the acid extract poured slowly on to cracked ice–NH_3 solution; product: yellow crystals; 85%; mp 93.5–95.5°. Dihydroquininone was prepared similarly in 80% yield, mp 94–96° from C_4H_9Cl. The tertiary alcohols from these ketones by addition of MeLi are described in Table III.

Epoxidation Route (for Two-Carbon Side Chains). 2-Phenyl-4-(2-propenyl)quinoline.—Freshly fused $KHSO_4$ (0.28 mol) pulverized with 0.057 mol of α,α-dimethyl-2-phenyl-4-quinolinemethanol (see Table I) was held in an oil bath at 170° for 4 hr with occasional stirring of the mixture. The mixture was cooled, made strongly alkaline, and extracted (Et_2O); the residue [bp 167° (0.13 mm), 14 g, 86%] was a viscous, pale yellow oil; nmr ($CDCl_3$) δ 7.2–8.3 (10, m, aromatic H), 5.1 and 5.4 (2, m, vinyl H), 2.2 (3, d, CH_3); HCl salt, mp 180–182°, needles from i-PrOH.

2-(4-Chlorophenyl)-6,8-dimethyl-4-(2-propenyl)quinoline was prepared as above from 0.14 mol of 2-(4-chlorophenyl)-6,8-α,α-tetramethyl-4-quinolinemethanol except that the reaction mixture was held at 180° for 6 hr: product: 40 g; 93%; mp 110–112°; golden crystals from MeOH (and Norit), mp 114–115°; nmr ($CDCl_3$) δ 7.4–8.3 (m, 7, aromatic H), 5.15 and 5.5 (m, 2, vinyl H), 2.87 and 2.48 (s, 3, aromatic CH_3) 2.25 (d, 3, vinyl CH_3).

2-(4-Chlorophenyl)-6,8-dimethyl-4-(2-epoxypropyl)quinoline.—The alkene (0.016 mol) above and 0.0735 mol of freshly prepared monoperoxyphthalic acid solution[14] in 115 ml of Et_2O were held at 25° for 6 days. The phthalic acid was filtered, and the filtrate was washed with four 70-ml portions of 5% aqueous $NaHCO_3$; product: 4.8 g; 91%; mp 135–140°; from MeOH fine, yellow crystals, mp 143–144°; nmr ($CDCl_3$); δ 7.45–8.4 (m, 7, aromatic H), 2.85 and 2.5 (s, 3, aromatic CH_3), 3.1 (q, 2, CH_2), 1.85 (s, 3, CH_3).

Similar treatment of 2-phenyl-4-(2-propenyl)quinoline gave 67% (crude) of 4-(2-epoxypropyl)-2-phenylquinoline 1-oxide, yellow crystals from C_8H_8–C_8H_{14}, mp 140.5–141.5°.

2-(4-Chlorophenyl)-α-(dialkylaminomethyl)-6,8-α-trimethyl-4-quinolinemethanols.—The corresponding epoxide (0.025 mol) and 0.4 mol of dialkylamine were stirred magnetically under N_2 in a simple Parr pressure vessel at 140° for 72 hr (with Me_2NH, 50 ml of DMF was used as the solvent). The mixture was steam distilled to remove excess secondary amine, and the residue extracted into 10% aq HCl which was then basified. If the precipitate was a solid, it was filtered, washed, and recrystallized (MeOH). If an oil, it was dissolved in Et_2O and precipitated as the dihydrochloride with HCl. Results are shown in Table IV.

(14) G. B. Payne, *J. Org. Chem.*, **24**, 1354 (1959).

Chemical Conversion of Desacetylcephalothin Lactone into Desacetylcephalothin. The Final Link in a Total Synthesis of Cephalosporanic Acid Derivatives

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Desacetylcephalothin lactone was rapidly hydrolyzed to desacetylcephalothin in 10–20% yield in phosphate and borate buffers (pH 6–9, 100°), in borate and carbonate buffers (pH 9–10.8, 25°), and in 0.01 N KOH (25°). In addition, other uncharacterized products were formed. The desacetylcephalothin formed was isolated as its cephalothin Me ester after esterification and acetylation. These findings establish the final link in the total synthesis of cephalosporins by the lactone route.

The total synthesis of compounds related to the antibiotic cephalosporin C (Ib) has been a concern of several laboratories.[1]

Two possible routes to these compounds have been described employing intermediate lactone derivatives with the general structure II in which R is one of several different amino, amido, or imido groups.[1a,d] Compounds of this type have been synthesized from cephalosporanic acid derivatives[2] and are now available by totally synthetic means.[1a,d] However, no chemical method for opening the lactone ring without simultaneous destruction of the β-lactam ring has been available for the conversion of II into III.[3] In addition, the possibility of microbial hydrolysis has been deemed unlikely.[4]

We report, in this paper, a simple chemical procedure for performing this transformation in yields of 10–20% (estimated biologically).

Studies were performed with pure desacetylcephalothin lactone (IIa) prepared from cephalothin[5] (Ia) by a modification of the procedure of Chauvette and Flynn.[6] Hydrolysis of the lactone was accomplished by adding IIa in DMSO to a buffer of appropriate pH at 25–100°, or to dilute KOH at 25° for 10 min or less. The reaction mixture was chromatographed in parallel with standard IIIa,[6] then bioautographed on *Staphylococcus aureus* 209P.[7] Both residual IIa and product IIIa were thus visualized, and yield estimates could be made.

Conversion of IIa into IIIa occurred in phosphate, borate, and carbonate buffer of pH 6–11 maintained at 25–100° for 2–10 min. Except in pH 11.5 KOH solution where 2 min was optimal, at least 10-min incubations were required to obtain product at temperatures below 50°. Buffers prepared from strong nucleophiles such as imidazole, glycine, and mercaptoethanol caused destruction of IIa, with no detectable IIIa formed, under a variety of conditions of temperature and pH. It should be emphasized that at pH 6–8, heating was required to bring about the conversion of IIa into IIIa,

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