# Antimalarials. 1. Aminoalkylamino Derivatives of 2,3-Dihydrofuroquinolines

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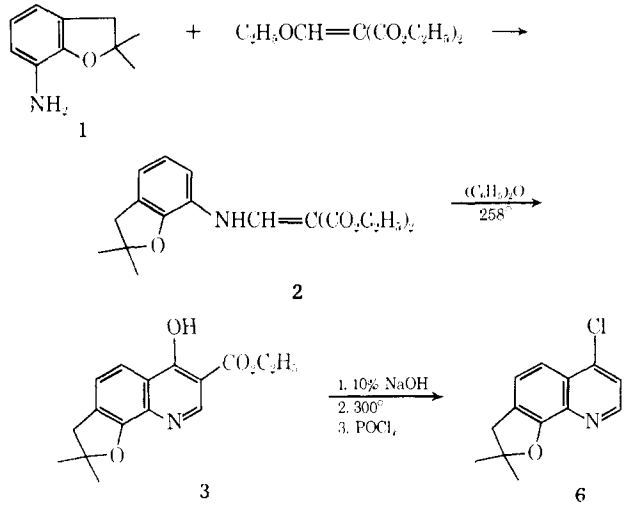
Derivatives of 5-amino-2,3-dihydro-2,2-dimethylfuro[3,2-*g*]quinoline, 6-amino-2,3-dihydro-2,2-dimethylfuro[3,2-*h*]quinoline, 7-amino-2,3-dihydro-2,2-dimethylfuro[2,3-*h*]quinoline, and 8-amino-2,3-dihydro-2,2-dimethylfuro[2,3-*g*]quinoline were prepared *via* the ethyl α-carbethoxy-β-aminoacrylates derived from 4-, 5-, 6-, and 7-amino-2,3-dihydro-2,2-dimethylbenzofurans. The compounds were tested for activity against *Plasmodium berghei* in mice; some antimalarial effects were observed, but only at toxic doses.

For many years 7-chloro-4-(1-diethylamino-4-pentylamino)quinoline (chloroquine) has been one of the most effective antimalarial drugs.[1] However, strains of malaria recently have appeared which are resistant to this drug. As part of a program to investigate new antimalarial compounds, a series of 4-aminoquinolines was prepared with a fused oxygen heterocyclic ring in an effort to enhance potency and overcome resistance.

The 2,3-dihydro-2,2-dimethylbenzofuran ring system has been found to be an effective carrier for toxophoric groups leading to potent insecticides and fungicides.[2] We now report the preparation of furoquinoline derivatives containing this moiety, as well as some aminoalkylamino derivatives of amino-2,3-dihydro-2,2-dimethylbenzofurans.

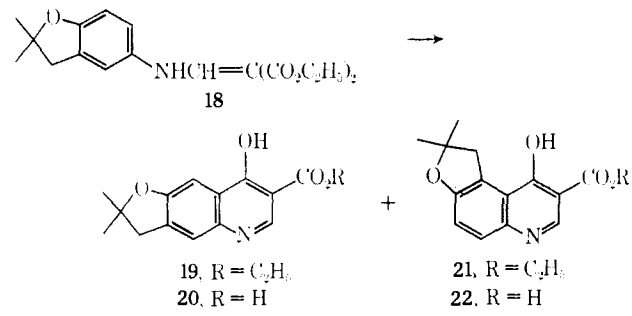
**Chemistry.**—The quinoline synthesis of Price and Roberts[3] was used to prepare the furoquinolines. Scheme I illustrates the reaction steps leading from

SCHEME I

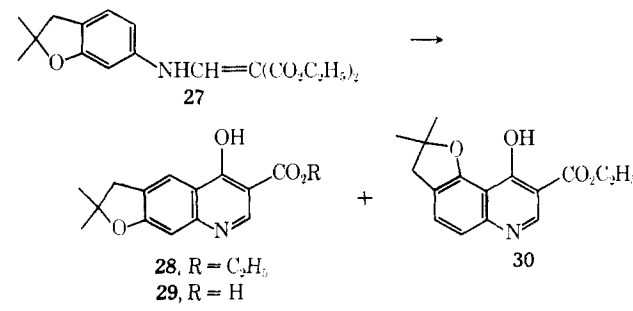



7-amino-2,3-dihydro-2,2-dimethylbenzofuran (**1**) to 6-chloro-2,3-dihydro-2,2-dimethylfuro[3,2-*h*]quinoline (**6**); upon treatment of **6** with appropriate diamines the aminoalkylamino derivatives **7–9** (Table I) were obtained.

In the series illustrated, cyclization of the aminoacrylate **2** can give only the furoquinoline **3**. Cyclization of the aminoacrylate **53** from 4-amino-2,3-dihydro-2,2-dimethylbenzofuran (**43**) also will afford only one isomeric series, the furo[2,3-*h*]quinolines (Table II). However, the aminoacrylate **18** obtained from 5-amino-2,2-dimethyl-2,3-dihydrobenzofuran (**44**) cyclized to give a mixture of ethyl 2,3-dihydro-2,2-dimethyl-8-hydroxyfuro[2,3-*g*]quinoline-7-carboxylate (**19**) and ethyl 2,3-dihydro-2,2-dimethyl-4-hydroxyfuro[3,2-*f*]quinoline-5-carboxylate (**21**) in a 10:1 ratio. Pure **19** was isolated by crystallization of the mixture from EtOH; the [3,2-*f*] isomer could not be obtained in pure form. A separation of 8-chloro-2,3-dihydro-2,2-dimethylfuro[2,3-*g*]quinoline (**24**) and 4-chloro-2,3-dihydro-2,2-dimethylfuro[3,2-*f*]quinoline could be effected by glpc, but no effort was made to utilize this technique on a preparative scale. Compounds in the [2,3-*g*]isomer series are listed in Table III.




Cyclization of the aminoacrylate **27** from 6-amino-2,3-dihydro-2,2-dimethylbenzofuran (**45**) gave only ethyl 2,3-dihydro-2,2-dimethyl-5-hydroxyfuro[3,2-*g*]-quinoline (**28**); no ethyl 2,3-dihydro-2,2-dimethyl-2-hydroxyfuro[2,3-*f*]quinoline (**30**) could be detected. Table IV lists the compounds prepared in the [3,2-*g*] isomer series.




* To whom correspondence should be addressed.

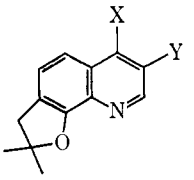
(1) J. R. DiPalma, "Drill's Pharmacology in Medicine," 3rd ed, McGraw-Hill, New York, N. Y., 1965, p 1376.

(2) (a) W. G. Scharpf, U.S. Patent 3,474,170 (1969), or Netherlands Application 6,500,340(1965); *Chem. Abstr.*, **64**, 3484*e* (1966). (b) FMC Corporation, Japanese Patent 12263/67 (1967).

(3) C. C. Price and R. M. Roberts, *J. Amer. Chem. Soc.*, **68**, 1204 (1946).

TABLE I

2,3-DIHYDRO-2,2-DIMETHYLFURO[3,2-*h*]QUINOLINES

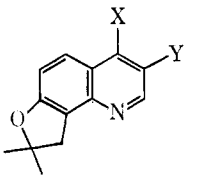


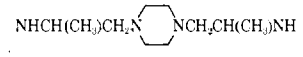
| Compd | X | Y | Yield, % | Mp, °C | Formula[a] |
|---|---|---|---|---|---|
| 3 | OH | $CO_2C_2H_5$ | 97 | 254–255 | $C_{16}H_{17}NO_4$ |
| 4 | OH | $CO_2H$ | 84 | 272 dec | $C_{14}H_{13}NO_4$ |
| 5 | OH | H | 70 | 242–243 | $C_{13}H_{13}NO_2$[b] |
| 6 | Cl | H | 83 | 130–131 | $C_{13}H_{12}ClNO$ |
| 7 | $NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$ | H | 26 | 152–153 | $C_{22}H_{33}N_3O$ |
| 8 | $NH(CH_2)_3N(n\text{-}C_4H_9)_2$ | H | 31 | 130.5–131.5 | $C_{24}H_{37}N_3O$ |
| 9 | $NH(CH_2)_3N(C_2H_5)_2$ | H | 25 | 139–140.5 | $C_{20}H_{29}N_3O$ |

[a] All compds were analyzed for C, H, N. [b] C: Calcd, 72.5; found, 73.5.

TABLE II

2,3-DIHYDRO-2,2-DIMETHYLFURO[2,3-*h*]QUINOLINES

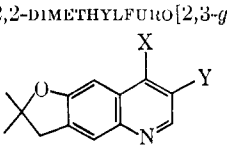


| Compd | R | Y | Yield, % | Mp, °C | Formula[a] |
|---|---|---|---|---|---|
| 10 | OH | $CO_2C_2H_5$ | 79 | 266.5–267 | $C_{16}H_{17}NO_4$ |
| 11 | OH | $CO_2H$ | 76 | 268–270 dec | $C_{14}H_{13}NO_4$ |
| 12 | Cl | H | 57 | 87.5–88 | $C_{13}H_{12}ClNO$ |
| 13 | $NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$ | H | 65 | 149.5–150 | $C_{22}H_{33}N_3O$ |
| 14 | $NH(CH_2)_3N(n\text{-}C_4H_9)_2$ | H | 9 | 85–86 | $C_{24}H_{37}N_3O$ |
| 15 | $NH(CH_2)_3N(C_2H_5)_2$ | H | 30 | 122–123 | $C_{20}H_{29}N_3O$ |
| 16 | $NHCH_2CHOHCH_2N(C_2H_5)_2$ | H | 60 | 193–202 | $C_{20}H_{32}ClN_3O_3$[b,c] |
| 17 |  | H | 14 | 250–260 dec | $C_{36}H_{46}N_6O_2$[d] |

[a] All compds were analyzed for C, H, N. [b] Hydrochloride hydrate. [c] C: calcd, 60.4; found, 59.6. [d] C: calcd, 72.7; found, 71.2.

TABLE III

2,3-DIHYDRO-2,2-DIMETHYLFURO[2,3-*g*]QUINOLINES



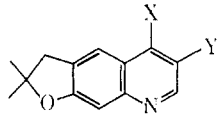
| Compd | X | Y | Yield, % | Mp, °C | Formula[a] |
|---|---|---|---|---|---|
| 19 | OH | $CO_2C_2H_5$ | 75 | 254–256 | $C_{16}H_{17}NO_4$ |
| 20 | OH | $CO_2H$ | | 265 dec | $C_{14}H_{13}NO_4$[b] |
| 23 | OH | H | 51 | 220 | $C_{14}H_{14}Cl_3NO_2$[c] |
| 24 | Cl | H | 74 | 63–66 | $C_{13}H_{12}ClNO$ |
| 25 | $NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$ | H | 16 | 95–96.5 | $C_{22}H_{33}N_3O$[d] |
| 26 | $NH(CH_2)_3N(n\text{-}C_4H_9)_2$ | H | 22 | | $C_{24}H_{41}Cl_2N_3O_2$[e] |

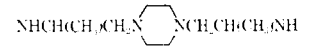
[a] All compds were analyzed for C, H, N. [b] No satisfactory elemental analysis was obtained. [c] $CHCl_3$ solvate: calcd for Cl, 31.8 found, 31.9. [d] C: calcd, 74.3; found, 75.0. [e] Dihydrochloride hydrate. The product was extremely hygroscopic; no characteristic melting point was obtained.

Structural assignments for the isomeric furoquinolines were confirmed by nmr spectrometry of the 2,3-dihydro-2,2-dimethylhydroxyfuroquinolinecarboxylic acids (Table V). Compounds **4** and **11** show the expected ortho protons on the benzenoid ring. The major product from cyclization of **18** exhibits a para relationship between the carbocyclic protons, confirming **20** as the structure of the acid; the minor component was shown to be **22** by the ortho relationship of the protons. The only product obtained upon cyclization of **27** showed a para relationship for the benzenoid protons, confirming **29** as the structure.

Key intermediates for the synthesis of the dihydrofuroquinolines were the isomeric amino-2,3-dihydro-

TABLE IV
2,3-DIHYDRO-2,2-DIMETHYLFURO[3,2-*g*]QUINOLINES



| Compd | X | Y | Yield, % | Mp, °C | Formula[a] |
|---|---|---|---|---|---|
| 28 | OH | $CO_2C_2H_5$ | 87 | 269–269.5 | $C_{16}H_{17}NO_4$ |
| 29 | OH | $CO_2H$ | | 299 dec | $C_{14}H_{13}NO_4$[b] |
| 31 | OH | H | 51 | 244–246 | $C_{13}H_{13}NO_2$ |
| 32 | Cl | H | 54 | 94–95 | $C_{13}H_{12}ClNO$ |
| 33 | $NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$ | H | 21 | 145–145.5 | $C_{22}H_{33}N_3O$[c] |
| 34 | $NH(CH_2)_3N(n\text{-}C_4H_9)_2$ | H | 37 | 87–88 | $C_{24}H_{37}N_3O$ |
| 35 | $NH(CH_2)_3N(C_2H_5)_2$ | H | 50 | 90–92 | $C_{20}H_{29}N_3O$ |
| 36 |  | H | 30 | 230–234 | $C_{36}H_{46}N_6O_2$ |

[a] All compds were analyzed for C, H, N. [b] No satisfactory elemental analysis was obtained. [c] H: calcd, 9.36; found, 9.97.

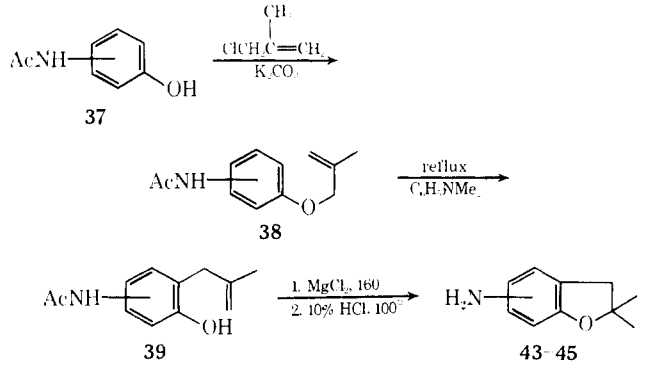
TABLE V
NMR DATA FOR AROMATIC PROTONS OF 2,3-DIHYDRO-2,2-DIMETHYLHYDROXYFUROQUINOLINECARBOXYLIC ACIDS

| Compd | Isomer | Relationship | Benzoid protons, ppm | *J* (Hz) | Heterocyclic protons, ppm |
|---|---|---|---|---|---|
| 4[a] | [3,2-*h*] | ortho | 7.41 (d), 7.77 (d) | 8.0 | 8.50 |
| 11[a] | [2,3-*h*] | ortho | 6.80 (d), 8.05 (d) | 8.5 | 8.51 |
| 20[b] | [2,3-*g*] | para | 7.55 (s), 7.62 (s) | | 8.53 |
| 22[b,c] | [3,2-*f*] | ortho | 7.14 (d), ca. 7.63 (?)[d] | 9.0 | 8.50 |
| 29[b] | [3,2-*g*] | para | 6.84 (s), 7.98 (s) | | 8.45 |

[a] DMSO solution. [b] With NaOD in $D_2O$ solution. [c] Mixture containing *ca.* 20% **22** and 80% **20**. [d] Signal largely masked by absorption of **20**.

2,2-dimethylbenzofurans. A synthesis of the 7-amino isomer has been described.[4] Syntheses of the 4-, 5-, and 6-amino isomers (**43–45**) were carried out by a modification of this procedure utilizing *m*- and *p*-acetamidophenols **37** as starting materials. The reaction steps involve formation of the methallyl ethers **38**, Claisen rearrangement to the methallylphenols **39**,[5] cyclization to the dihydrobenzofurans **40–42**, and hydrolysis of the acetamido group (Scheme II).

SCHEME II




Rearrangement of *p*-acetamidophenyl methallyl ether can give only one isomer, 4-acetamido-2-methallylphenol. The *m*-acetamidophenyl methallyl ether gives a mixture of 3-acetamido- and 5-acetamido-2-methallylphenols in a 1:1 ratio, together with some 3-acetamido-2-(2-methyl-1-propenyl)phenol. The isomers were separated by fractional precipitation from alkaline solution, a technique used by Budeshinski and Rochkova[6] to separate isomers obtained from the rearrangement of *m*-acetamidophenyl allyl ether. The isomeric compounds are readily distinguished by nmr spectrometry. A 1,2,4-trisubstituted benzene ring is apparent from the ABX pattern of the aromatic protons in 5-acetamido-2-methallylphenol and the observation that one proton has both ortho and meta coupling, while the two remaining protons are not coupled to each other. An ABC pattern characteristic of 1,2,3-trisubstituted benzenes is observed for the aromatic protons of 3-acetamido-2-methallylphenol and 3-acetamido-2-(2-methyl-1-propenyl)phenol; each proton is coupled to the two other protons. The methallyl and 2-methyl-1-propenyl groups are readily distinguished by the number of olefinic and Me protons, and the presence and absence, respectively, of $CH_2$.

The isomeric amino-2,3-dihydro-2,2-dimethylbenzofurans were converted into 1-diethylamino-4-pentylamino derivatives (**45–49**) by the method of Toptchiev and Braude;[7] the aminobenzofurans were converted into Schiff's bases by treatment with 4,4-diethoxy-1-diethylaminopentane, and these bases were hydrogenated over Pt to give the desired diamines. Derivatives containing the 1-amino-4-pentylamino side chains (**50–52**) were prepared by the method of Elderfield and coworkers[8] utilizing 4-bromo-1-phthalimidopentane followed by hydrazinolysis of the phthaloyl group. The 2,3-dihydro-2,2-dimethylbenzofuran derivatives are listed in Table VI.

**Biological Data.**—All compounds were tested for antimalarial activity against *Plasmodium berghei* in mice.[9] None of the intermediates and only a few of the target compounds (Table VII) increased the

(4) W. G. Scharpf, U.S. Patent 3,412,110 (1968), or Netherlands Application 6,602,601 (1966); *Chem. Abstr.*, **66**, 46319b (1967).

(5) D. S. Tarbell, *Org. React.*, **2**, 1 (1944).

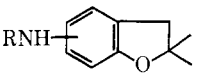
(6) Z. Budeshinski and E. Rochkova, *Coll. Czech. Chem. Commun.*, **19**, 966 (1954).

(7) K. S. Toptchiev and M. B. Braude, *Dokl. Akad. Nauk. SSSR*, **52**, 593 (1946).

(8) R. C. Elderfield, E. Claflin, H. Mertel, O. McCurdy, R. T. Mitch, C. Ver Nooy, B. H. Wark, and I. M. Wempen, *J. Amer. Chem. Soc.*, **77**, 4819 (1955).

(9) The screening tests were carried out at the University of Miami, Miami, Florida, under the direction of Dr. L. Rane. Details of the mouse screen with *P. berghei* have been published [T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967)].

TABLE VI
AMINO-2,3-DIHYDRO-2,2-DIMETHYLBENZOFURANS



| Compd | Isomer | R | Yield, % | Bp, °C (mm) | $n^{25}D$ | Mp, °C | Formula[a] |
|---|---|---|---|---|---|---|---|
| 40 | 4 | $COCH_3$ | 66 | | | 149.5–151 | $C_{12}H_{15}NO_2$ |
| 41 | 5 | $COCH_3$ | 23 | | | 114–116 | $C_{12}H_{15}NO_2$ |
| 42 | 6 | $COCH_3$ | 50 | | | 114.5–116 | $C_{12}H_{15}NO_2$ |
| 43 | 4 | H | 79 | 103–107 (3) | | 34–35 | $C_{10}H_{13}NO$ |
| 44 | 5 | H | 83 | 113 (2) | | 64–66 | $C_{10}H_{13}NO$ |
| 45 | 6 | H | 91 | 98–103 (3) | | 34.5–35.5 | $C_{10}H_{13}NO$ |
| 46 | 4 | $CH(CH_3)(CH_2)_3N(C_2H_5)_2$ | 36 | 175–176 (3) | 1.5200 | | $C_{19}H_{32}N_2O$ |
| 47 | 5 | $CH(CH_3)(CH_2)_3N(C_2H_5)_2$ | 8 | 176–178 (3) | 1.5130 | | $C_{19}H_{32}N_2O$ |
| 48 | 6 | $CH(CH_3)(CH_2)_3N(C_2H_5)_2$ | 38 | 145–146 (1.5) | 1.5220 | | $C_{19}H_{32}N_2O$ |
| 49 | 7 | $CH(CH_3)(CH_2)_3N(C_2H_5)_2$ | 7 | 171 (3) | 1.5160 | | $C_{19}H_{32}N_2O$ |
| 50 | 4 | $CH(CH_3)(CH_2)_3NH_2$ | 13 | 135–140 (1.5) | | 151–152 | $C_{19}H_{28}N_2O_5$[b] |
| 51 | 5 | $CH(CH_3)(CH_2)_3NH_2$ | 7 | [c] | | 158–160 | $C_{19}H_{28}N_2O_5$[b,d] |
| 52 | 6 | $CH(CH_3)(CH_2)_3NH_2$ | 18 | 170–171 (3) | | 149.5–150.5 | $C_{19}H_{28}N_2O_5$[b] |
| 53 | 7 | $CH(CH_3)(CH_2)_3NH_2$ | 17 | 168–169 (4) | | 157–158 | $C_{18}H_{28}N_2O_5$[b] |
| 54 | 4 | $CH{=}C(CO_2C_2H_5)_2$ | 89 | | | 69.5–70 | $C_{18}H_{23}NO_5$ |
| 2 | 7 | $CH{=}C(CO_2C_2H_5)_2$ | 79 | | | 62–65.5 | $C_{18}H_{23}NO_5$ |

[a] All compds were analyzed for C, H, N. [b] Fumarate salt. [c] Not distilled; crude product converted directly into fumarate. [d] C: calcd 62.5, found, 61.8.

TABLE VII
ANTIMALARIAL ACTIVITY OF
AMINOALKYLAMINO-2,3-DIHYDRO-2,2-DIMETHYLFUROQUINOLINES

| Compd | Dose level, mg/kg | Increase in mean survival time, days | Toxic deaths |
|---|---|---|---|
| 17 | 640 | 2.5 | 0 |
| 25 | 160 | 4.4 | 1 |
| | 320 | | 5 |
| 26 | 40 | 1.4 | 3 |
| 33 | 640 | 6.9 | 3 |
| 34 | 80 | 3.5 | 0 |
| | 160 | | 5 |
| 35 | 640 | 7.9 | 2 |

survival time of infected mice. Two compounds were considered active,[10] but only at dose levels which resulted in some toxic deaths. Only the "linear" furo[2,3-*g*]quinoline and furo[3,2-*g*]quinoline systems gave increased survival times greater than one day with the exception of the piperazine derivative **17**. The [2,3-*g*] ring system gave compounds of significantly greater toxicity than any of the other ring systems.

## Experimental Section

Melting points (taken on a Thomas-Hoover Uni-Melt capillary melting point apparatus) and boiling points are uncorrected. The ir and nmr spectra were as expected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Intermediates were not characterized in all cases. The diamines utilized in this work were furnished by the U.S. Army Research and Development Command.

**3-Acetamidophenyl Methallyl Ether.**—A mixture of 3-acetamidophenol (150 g, 1. 1 mole), $K_2CO_3$ (140 g, 1.6 moles), and $Me_2CO$ (700 ml) was heated under reflux, with stirring, while methallyl chloride (140 g, 1.5 moles) was added slowly. After 10 hr, $H_2O$ (200 ml) and 5% NaOH (200 ml) were added. The product was extracted into $Et_2O$, washed (5% NaOH), and dried ($K_2CO_3$). Partial evaporation of solvent under reduced pressure gave a cryst solid, mp 67–69°, yield 100 g (53%). *Anal.* ($C_{12}H_{12}NO_2$) C, H, N.

(10) To be considered active, the survival time of treated mice must be at least twice that of untreated controls. The average survival time of untreated mice is 6.5 ± 0.5 days.

**4-Acetamidophenyl methallyl ether** was prepared in a similar manner from 4-acetamidophenol (400 g, 2.64 moles), $K_2CO_3$ (530 g, 3.84 moles), methallyl chloride (325 g, 3.60 moles), and $Me_2CO$ (1600 ml). The product was extracted with $CHCl_3$, and was recovered as white plates, mp 85–86°, yield 540 g (100%). *Anal.* ($C_{12}H_{15}NO_2$)C, H, N.

**4-Acetamido-2-methallylphenol.**—A soln of 4-acetamidophenyl methallyl ether (53 g, 0.28 mole) in $PhNMe_2$ (140 g) was heated under reflux for 6 hr under $N_2$. After cooling petr ether was added until two phases sepd. The upper phase was decanted, and the residue was triturated with petr ether until the oil solidified. The product was filtered, washed (petr ether), and dried to give 53 g (100%) of white powder, mp 94.5–95.5°. Recrystallization from $CHCl_3$–petr ether gave mp 99–100°. *Anal.* ($C_{12}H_{14}NO_2$) C, H, N.

**Claisen Rearrangement of 3-Acetamidophenyl Methallyl Ether.**—The rearrangement was carried out with 80 g (0.42 mole) of the ether in dimethylaniline (200 ml) as described for the 4 isomer. Glpc analysis of the crude product (23% GESE-30, 60–80 mesh Gas Chrom Z, 1.3-m column) indicated a 1:1 mixture of two components. These were sepd by stepwise acidification (0.55 *N* $H_2SO_4$) of a soln of the crude product (10 g) in 10% NaOH with recovery of the ppt between each addition. The initial fraction comprised 3.8 g of pure 5-acetamido-2-methallylphenol: mp 160–162°; nmr ($CD_3COCD_3$) $\delta$ 7.75 (d, 1, $J_{meta}$ = 2 Hz), 7.03 (d, 1, $J_{ortho}$ = 8 Hz) and 6.72 ppm (q, 1, $J_{meta}$ = 2 Hz, $J_{ortho}$ = 8 Hz). After an impure intermediate fraction, 2.8 g of pure **3-acetamido-2-methallylphenol** was recovered: mp 152–154.5°; nmr ($CD_3COCD_3$) $\delta$ 7.33 (q, 1, $J_{ortho}$ = 8 Hz, $J_{meta}$ = 2 Hz), 7.03 (t, 1, $J_{ortho}$ = 8 Hz), and 6.72 (q, 1, $J_{ortho}$ = 8 Hz, $J_{meta}$ = 2 Hz), 4.73 (m, 2, C=$CH_2$), 3.49 (s, 2, C$H_2$) and 1.71 ppm (s, 3, C=$CCH_3$). Trituration of the crude products with cold $CHCl_3$ also gave pure 5-acetamido-2-methallylphenol as the less soluble component. Another compd crystallized from the oily phase recovered upon evaporation of the $CHCl_3$ and was identified as **3-acetamido-2-(2-methyl-1-propenyl)phenol:** mp 126–127°; nmr ($CD_3COCD_3$) $\delta$ 7.25 (q, 1, $J_{ortho}$ = 8 Hz, $J_{meta}$ = 2 Hz), 7.02 (t, 1, $J_{ortho}$ = 8 Hz), 6.63 (q, 1, $J_{ortho}$ = 8 Hz, $J_{meta}$ = 2 Hz), 5.92 (m, 1, CH=C), 1.88 (d, 3, $J$ = 1.3 Hz, C=$CCH_3$) and 1.43 ppm (d, 3, $J$ = 1.0 Hz, C=CC$H_3$). *Anal.* (all three compds have molecular formula $C_{12}H_{15}NO_2$) C, H, N.

**Acetamido-2,3-dihydro-2,2-dimethylbenzofurans (40–42).**—The appropriate acetamidomethallylphenol (50 g, 0.26 mole) and anhyd $MgCl_2$ (0.50 g) were heated at 155–180° under $N_2$ for 5 hr. The mixture then was cooled to *ca.* 60°, and 10% NaOH and $Et_2O$ were added cautiously. Products were recovered by evaporation of the $Et_2O$ phase and sublimation of the residue.

**Amino-2,3-dihydro-2,2-dimethylbenzofurans (43–45).**—A suspension of acetamido-2,3-dihydro-2,2-dimethylbenzofuran (18.5 g, 0.09 mole) in excess 5% HCl (200 ml) was heated under reflux until a homogeneous soln was obtained (*ca.* 1.5 hr). After cool-

ing, the soln was made basic with 40% NaOH and the product was extracted with $Et_2O$. The extracts were dried ($MgSO_4$) and concd, and the residue distd (short path) *in vacuo*; the distillate solidified on standing.

**(1-Diethylamino-4-pentylamino)-2,3-dihydro-2,2-dimethylbenzofurans (46–49).**—A mixture of amino-2,3-dihydro-2,2-dimethylbenzofuran (8.1 g, 0.05 mole) and 4,4-diethoxy-1-diethylaminopentane[7] (11.5 g, 0.05 mole) was heated slowly to 190–200°. Heating was stopped when EtOH no longer was evolved (*ca.* 2.5 hr). The resultant oil was dissolved in EtOH (50 ml) and hydrogenated over $PtO_2$ at 65° and 3.87 kg/cm². After filtering and evaporation of solvent, the product was distd *in vacuo*.

**(1-Amino-4-pentylamino)-2,3-dihydro-2,2-dimethylbenzofurans (50–53).**—A soln of amino-2,3-dihydro-2,2-dimethylbenzofuran (32.4 g, 0.2 mole) and 4-bromo-1-phthalimidopentane[8] (29.6 g, 0.1 mole) in EtOH (100 ml) was heated under reflux for 72 hr. Solvent then was removed under reduced pressure, and the residue triturated with $Et_2O$ to separate product from amine·HBr. The $Et_2O$ was evapd and the residue was dissolved in EtOH (200 ml) containing hydrazine hydrate (7.00 g). After heating under reflux for 24 hr, the mixture was filtered and the filter cake triturated with $Et_2O$. The combined filtrates were concd and the residues distd *in vacuo*. Fumarate salts were prepared by allowing the amino product to react with a calcd amount of fumaric acid in THF. The fumarates were recrystd from MEK.

**Ethyl α-Carbethoxy-β-(2,3-dihydro-2,2-dimethylbenzofuranylamino)acrylates.**—A mixture of amino-2,3-dihydro-2,2-dimethylbenzofuran (100 g, 0.62 mole) and diethyl ethoxymethylenemalonate (143 g, 0.66 mole) was heated in an open beaker until EtOH evolution ceased (*ca.* 30 min). Products from the 4-amino and 7-amino isomers solidified upon cooling, and were crystallized from 1:1 $Et_2O$–petr ether (**54** and **2**). Products from the 5-amino (**18**) and 6-amino (**27**) isomers could not be purified.

**Ethyl Hydroxy-2,3-dihydro-2,2-dimethylfuroquinolinecarboxylate (3, 10, 19, 28).**—The amino acrylates (50 g, 0.15 mole) were added in one portion to boiling $Ph_2O$ (350 g). The soln was heated under reflux for 30 min and then cooled and petr ether added to ppt the product. The ppt was washed thoroughly with petr ether to remove $Ph_2O$. Additional product could be obtained by recycling the filtrate.

**Hydroxy-2,3-dihydro-2,2-dimethylfuroquinolinecarboxylic Acids (4, 11, 20, 29).**—A suspension of the furoquinolinecarboxylate ester (31.8 g, 0.11 mole) in 10% NaOH (250 ml) was heated under reflux for 2 hr. The clear soln was acidified with concd HCl, and the resultant slurry was boiled for 40 min to insure complete conversion of Na salt into free acid. After filtering and drying, the product was purified by trituration with hot EtOH.

**Hydroxy-2,3-dihydro-2,2-dimethylfuroquinolines (5, 23, 31).**—The furoquinolinecarboxylic acids (45 g, 0.17 mole) were decarboxylated by heating to 290–300° in a beaker until effervescence ceased (*ca.* 15 min). The product solidified upon cooling.

**Chloro-2,3-dihydro-2,2-dimethylfuroquinolines (6, 12, 24, 32).**—A mixture of hydroxyfuroquinoline (15.7 g, 0.073 mole) and $POCl_3$ (53 ml) was heated under reflux for 1 hr. After cooling the mixture was carefully poured over crushed ice (200 g), and the resultant soln made basic with 40% NaOH. The chloroquinolines were recovered as fine needles; **12** ppted as an HCl salt which was converted into the free base by crystallization from $H_2O$.

**Aminoalkylamino-2,3-dihydro-2,2-dimethylfuroquinolines (7–9, 13–17, 25–26, 32–36).**—In most cases the chloroquinolines (4.0 g, 0.017 mole) and dialkylaminoalkylamine (0.038 mole) were heated until solid appeared or under reflux for 5 hr. With 3-diethylaminopropylamine the reaction was carried out in a sealed tube at 160° for 15 hr. With 1,4-bis(2-aminopropyl)-piperazine 1 equiv of $K_2CO_3$ was ground together with the reactants, and the paste was heated in a sealed tube at 160° for 15 hr. The reaction mixtures were partitioned between 20% AcOH and $CHCl_3$; the AcOH solns were made alkaline with 40% NaOH and extracted with $CHCl_3$. The extracts were dried ($MgSO_4$) and concd. Solid products were recrystd; oils were converted to HCl salts.

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# Chemistry of Cephalosporin Antibiotics. XX. Synthesis and Biological Properties of 3-Acyloxymethyl-7-[2-(thienyl)acetamido]-3-cephem-4-carboxylic Acid and Related Derivatives[1]

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The title compounds (VII) have been synthesized and evaluated as antimicrobial agents. These new cephalosporins have shown a broad-spectrum antibiotic activity.

Cephalothin (I),[2] a broad-spectrum antibiotic, is hydrolyzed after administration to experimental animals and to man to the less active deacetylcephalothin (II).[3]

It was of interest to determine whether replacement of the acetate by a sterically hindered ester group would render a compound more resistant to hydrolysis. Therefore, the synthesis of these compounds with more bulky ester groups in the 3 position was undertaken.

Several attempts to acylate the 3-hydroxymethyl group in $\Delta^3$-cephalosporins have been reported,[4] but these were not too successful because the molecule is prone to rearrange to the $\Delta^2$ compound or to form the lactone. Since $\Delta^2$ cephalosporins do not lactonize as easily and are more stable to alkaline conditions, $\Delta^2$-deacetyl cephalothin (III), prepared by alkaline hydrolysis of $\Delta^2$-cephalothin (IV),[5] was used as starting material.

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