ether to furnish 4 as a colorless crystalline material, yield 233 mg (80%), which on tlc with (n-BuOH-H_2O 86:14) gave a single spot. To eliminate the possible presence of even traces of 5-fluorouracil which would interfere with the biological assay of the compound, further purification was carried out on prewashed 3-mm paper using the same solvent: mp 155–157°; λ_{max} (MeOH) 268 nm (ϵ 7699); mass spectrum m/e 130, 131 (b + H, RI 100, b + 2 H, RI 7.4), 154 (M − 107, RI 4.5). *Anal.* ($C_9H_{12}FN_3O_5 \cdot 0.5H_2O$) C, H, N, F.

Biological Procedures. The techniques used for assaying the growth inhibitory activity of the analogs in the bacterial and leukemia L-1210 systems and the procedures employed for isolating the fluoropyrimidine resistant strains have been published previously.[7-9]

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Antimalarials. 2.[1] α-Di-n-butylaminomethyl-2-(*p*-chlorophenyl)-5-quinazolinemethanol

Philip A. Cruickshank* and William E. Hymans

Chemical Research and Development Center, FMC Corporation, Princeton, New Jersey 08540. *Received November 5, 1973*

The characterization of quinine as a quinolylcarbinolamine led to the synthesis of related compounds, many of which were potent antimalarial agents.[2] The greatest activity was encountered with compounds containing 2-aryl substituents as a deterrent to metabolic inactivation.[3] However, toxic effects due to prolonged photosensitization have, until recently,[4] precluded use of these materials in chemotherapy.[5]

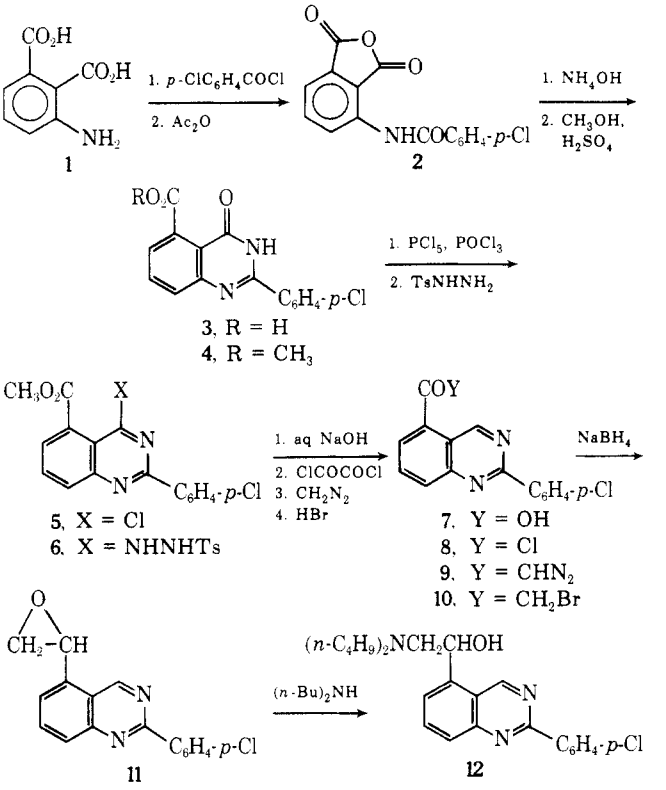
Several quinazoline derivatives are known to possess antimalarial properties.[6] Activity of the natural material Ch'ang Shan, obtained from the roots of *Dichroa febrifuga*, is associated with the alkaloid febrifugine.[7] Synthetic materials include 4-dialkylaminoalkylaminoquinazolines,[8] 2-arylamino-4-dialkylaminoalkylaminoquinazolines,[9] and 2,4-diamino-6-benzylaminoquinazolines.[10]

This report describes the synthesis of a quinazolylcarbinolamine derivative, α-dibutylamino-2-(*p*-chlorophenyl)-5-quinazolinemethanol (**12**). Although it was recognized that incorporation of the 2-aryl substituent could result in toxic photosensitizing effects, the group was included in order to maximize any antimalarial activity.

Chemistry. A modification of a procedure described by Bogert and Jouard[11] for the synthesis of 3,4-dihydro-2-methyl-4-oxo-5-quinazolinecarboxylic acid was used for the preparation 2-(*p*-chlorophenyl)-3,4-dihydro-4-oxo-5-quinazolinecarboxylic acid (**3**). Treatment of 3-aminophthalic acid (**1**) with *p*-chlorobenzoyl chloride gave 3-(*p*-chlorobenzamido)phthalic acid, which was converted to the corresponding anhydride **2** with acetic anhydride. Upon heating with ammonium hydroxide under pressure, **2** was converted directly to **3**. The acid could not be purified but afforded the corresponding methyl ester **4** by acid-catalyzed esterification.

Conversion of the quinazolone **4** to 2-(*p*-chlorophenyl)-5-quinazolinecarboxylic acid (**7**) was effected by the method of Armarego[12] *via* methyl 4-chloro-2-(*p*-chlorophenyl)-5-quinazolinecarboxylate (**5**) and the corresponding 4-(*p*-toluenesulfonylhydrazino) derivative **6**. Elaboration of the carbinolamine side chain closely paralleled methods described for preparation of 2-aryl-4-quinolinemethanol.[13] The acid **7** was converted to the bromomethyl ketone **10** *via* the acid chloride **8** and the diazomethyl ketone **9**. Sodium borohydride reduction afforded 2-(*p*-chlorophenyl)-5-epoxyethylquinazoline (**11**), which upon treatment with di-n-butylamine gave the target compound **12** (Scheme I).

Scheme I



Biology. Compound **12** was tested for antimalarial activity against *Plasmodium berghei* in mice[14] and against *P. gallinaceum* in chicks; results are summarized in Table I. Although similar in activity to the 4-quinolinemethanols [*e.g.*, α-(di-n-butylaminomethyl)-7-chloro-2-(*p*-chlorophenyl)-4-quinolinemethanol was found to be curative against *P. berghei* in mice at 480 mg/kg], **16** was of no further interest because it also produced the severe photosensitivity observed with the 2-arylquinolinemethanols. Intermediates **4**–**7** were screened and found to be inactive.

Experimental Section

Melting points were determined on a Thomas-Hoover Uni-Melt capillary melting point apparatus and are not corrected. Elemental analyses for those elements indicated by symbols were within ±0.4%. The ir and nmr spectra of all compounds were consistent with the assigned structures.

3-(*p*-Chlorobenzamido)phthalic Acid. A mixture of 3-aminophthalic acid hydrochloride (**1**, 2.18 g, 10 mmol) and $NaHCO_3$ (3.80 g, 45 mmol) in 25 ml of water was treated with *p*-chloro-

Table I. Antimalarial Test Data for Compound **12**

Test species	Dose, mg/kg	MST increase[a]	Cures	Remarks[b]
P. berghei	20	1.2	0	
(mice)	80	6.9	0	Active
	160	9.3	0	Active
	320	11.6	0	Active
	640	19.8	3	Curative
P. gallinaceum	80	2.5	0	
(chicks)	160	8.1	0	Active
	320	9.1	0	Active

[a]Increase in mean survival time of the treated animals over the control group. [b]A compound is active in mice if the increased MST exceeds 6.1 days and is curative if at least one mouse survives for 60 days or more after infection. A compound is active in chicks if the MST of the control group is twice that of the treated group. Five animals were used in each test.

benzoyl chloride (1.92 g, 11 mmol) in five portions with vigorous stirring. The mixture was acidified to Congo Red affording 3.10 g (97%) of product, mp 196–198° (C_6H_6-Me_2CO). *Anal.* ($C_{15}H_{10}ClNO_5$) C, H, N.

3-(*p*-Chlorobenzamido)phthalic Anhydride (2). A solution of 3-(*p*-chlorobenzamido)phthalic acid (1.60 g, 5 mmol) in Ac_2O (25 ml) was heated under reflux for 1 hr. The mixture was concentrated under reduced pressure and the residue triturated with petroleum ether to give 1.37 g (80%) of **2**, mp 198–200°. *Anal.* ($C_{15}H_8ClNO_4$) C, H, N.

Methyl 2-(*p*-Chlorophenyl)-3,4-dihydro-4-oxo-5-quinazolinecarboxylate (4). A solution of **2** (7.5 g, 25 mmol) in concentrated NH_4OH (100 ml) was heated in a steel bomb at 150° for 6 hr. The cooled mixture was added to water and boiled with 10% KOH (150 ml) for 1 hr. Neutralization afforded 6.85 g (92%) of 2-(*p*-chlorophenyl)-3,4-dihydro-4-oxo-5-quinazolinecarboxylic acid (**3**), mp >280°.

A mixture of crude **3** (3.00 g, 10 mmol), MeOH (10 ml), ethylene dichloride (30 ml), and concentrated H_2SO_4 (1.5 ml) was heated under reflux for 24 hr. A precipitate which formed upon cooling was recovered and dissolved in water, and the solution was neutralized with 10% NaOH to give 1.56 g (50%) of **4**, mp 281–282° (DMF-MeCN). *Anal.* ($C_{16}H_{11}ClN_2O_3$) C, H, N.

Methyl 4-Chloro-2-(*p*-chlorophenyl)-5-quinazolinecarboxylate (5). A mixture of **4** (1.90 g, 6 mmol), PCl_5 (1.27 g, 6.1 mmol), and $POCl_3$ (30 ml) was heated under reflux for 30 min beyond the time required for complete solution. After evaporating the mixture under reduced pressure, the residue was dried over KOH pellets, dissolved in $CHCl_3$, washed with saturated Na_2CO_3 and saturated NaCl, and dried ($MgSO_4$). Evaporation of solvent gave 1.83 g (90%) of **5**, mp 145–147° (C_6H_6-heptane). *Anal.* ($C_{16}H_{10}Cl_2N_2O_2$) C, H, N.

Methyl 2-(*p*-Chlorophenyl)-4-[2-(*p*-toluenesulfonylhydrazino)]-5-quinazolinecarboxylate Hydrochloride (6). A solution of **5** (1.16 g, 5 mmol) and *p*-toluenesulfonylhydrazine (0.93 g, 5 mmol) in a minimum amount of $CHCl_3$ was left at room temperature overnight. The solvent was removed under reduced pressure, and the residue triturated with ether to give 2.35 g (86%) of **6**, mp 243–250° (EtOH-MeOH). *Anal.* ($C_{23}H_{20}Cl_2N_4O_4S$) C, H, N.

2-(*p*-Chlorophenyl)-5-quinazolinecarbonyl Chloride (8). A suspension of **6** (24.1 g, 46 mmol) in 0.9 *N* NaOH (900 ml) was heated with stirring on a steam bath until all solids had dissolved (*ca.* 3 hr). Upon cooling, crystals of 2-(*p*-chlorophenyl)-5-quinazolinecarboxylic acid (**7**) separated (concentration of the mother liquor gave a second crop): total recovery of **7** was 9.9 g (75%); mp 335–338°; mass spectrum (70 eV) *m/e* (rel intensity) 286 (33), 284 (100). Extensive recrystallization failed to give samples with consistent elemental analyses.

A solution of **7** (1.42 g, 5 mmol) in C_6H_6 (50 ml) was boiled under a Dean-Stark trap to remove traces of water. After cooling to 0°, a solution of oxalyl chloride (3.17 g, 25 mmol) in C_6H_6 (10 ml) was slowly added. After warming to room temperature, the solution was heated under reflux for 18 hr. The residue remaining after evaporation of solvent was triturated with heptane to give 1.55 g (92%) of **8**, mp 160–161.5°. *Anal.* ($C_{15}H_{18}Cl_2N_2O$) C, H, N.

2-(*p*-Chlorophenyl)-5-epoxyethylquinazoline (11). A suspension of **8** (849 mg, 2.8 mmol) in an ethereal solution of diazomethane was left at room temperature for 18 hr. Filtration afforded 786 mg (97%) of crude 2-(*p*-chlorophenyl)-5-quinazolinyl diazomethyl ketone (**9**), mp 185–186° dec.

The crude **9** (500 mg, 1.55 mmol) was suspended in saturated ethereal HBr (100 ml) and left at room temperature overnight. Recrystallization (EtOH) of the solid product gave 406 mg (60%) of bromomethyl 2-(*p*-chlorophenyl)-5-quinazolinyl ketone hydrobromide (**10**), mp 152–159° dec.

Sodium borohydride (150 mg) was added in portions to a suspension of **10** (440 mg, 1.0 mmol) in MeOH (25 ml) at 0°. The mixture was heated under reflux for 1 hr and evaporated to dryness. The residue was partitioned between water and $CHCl_3$, and the organic phase was washed with saturated NaCl and dried ($MgSO_4$). Recrystallization (C_6H_6-heptane) of the residue following evaporation of solvent gave 140 mg (50%) of **11**, mp 181–182.5° ($CHCl_3$). *Anal.* ($C_{16}H_{11}N_2O$) C, H, N.

α-(Di-*n*-butylaminomethyl)-2-(*p*-chlorophenyl)-5-quinazolinemethanol (12). A mixture of **11** (432 mg, 1.5 mol) and di-*n*-butylamine (15 ml) was heated at 100° for 15 hr. Excess dibutylamine was removed by steam distillation. The product was extracted with $CHCl_3$, washed with saturated NaCl, and dried ($MgSO_4$). After evaporation of the solvent, the residue was triturated with petroleum ether, affording 260 mg (42%) of **12**, mp 71–72° (pentane). *Anal.* ($C_{24}H_{30}ClN_3O$) C, H, N.

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