New 2-Methyl-6-alkylamino-5,8-quinolinequinones and 1,2,3,4-Tetrahydro Derivatives (1,2)

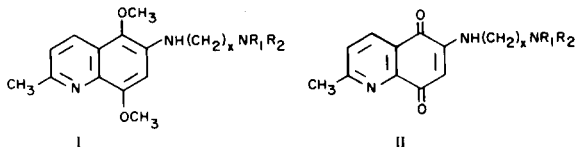
Yieh-Ping Wan, Thomas H. Porter, and Karl Folkers

Institute for Biomedical Research, The University of Texas at Austin, Austin, Texas 78712

Received September 17, 1973

The syntheses of six new 2-methyl-6-alkylamino-5,8-quinolinequinones, three 1,2,3,4-tetrahydro-5,8-quinolinequinones, and 7-(2′,6′,10′-trimethylundecyl)-6-hydroxy-5,8-quinolinequinone are described as potential antimetabolites of coenzyme Q and as potential antimalarial agents. The six 2-methyl-6-alkylamino-5,8-quinolinequinones were prepared by a six-step synthesis. 2-Methyl-6-methoxy-8-nitroquinoline was prepared from 2-nitro-4-methoxyaniline and crotonaldehyde by a Skraup reaction. Raney nickel reduction gave 2-methyl-6-methoxy-8-aminoquinoline, which upon diazotization followed by dithionite reduction yielded 2-methyl-6-methoxy-5,8-diaminoquinoline. Subsequent dichromate oxidation gave 2-methyl-6-methoxy-5,8-quinolinequinone, which yielded the corresponding 2-methyl-6-alkylamino-5,8-quinolinequinone in good yield when treated with the appropriate alkylamine. The tetrahydro-5,8-quinolinequinones were prepared by catalytic hydrogenation of the appropriate 5,8-quinolinequinones at elevated H_2 pressure followed by air oxidation of the reduction product. 7-(2′,6′,10′-Trimethylundecyl)-6-hydroxy-5,8-quinolinequinone was synthesized by radical alkylation of 6-hydroxy-5,8-quinolinequinone by thermal decomposition of di-3,7,11-trimethyldodecanoyl peroxide, which was prepared by a multistep procedure from farnesol. Of the five new 2-methyl-6-alkylamino-5,8-quinolinequinones tested against *P. berghei* in mice (blood schizonticidal test), only 2-methyl-6-cycloheptylamino-5,8-quinolinequinone was active (T-C = 6.1 at 320 mg./kg.). Both 7-(2′,6′,10′-trimethylundecyl)-6-hydroxy-5,8-quinolinequinone and the tetrahydro derivatives were inactive in this same test system.

In 1969, Elslager, *et al.*, (3) reported the syntheses and antimalarial activity of certain 6-[[(dialkylamino)alkyl]-amino]-5,8-dimethoxyquinaldines (I). These compounds were highly active in suppression of parasitemia when given continuously in the diet over a six-day period to mice infected with *Plasmodium berghei* and also showed some cures against *P. gallinaceum* in the chick. Elslager postulated that the antimalarial activity of these new 5,8-dimethoxyquinaldines (I) may be due to their conversion to the active quinone metabolites (II) in the host.



I II

The syntheses of six new 2-methyl-6-alkylamino-5,8-quinolinequinones, three new 1,2,3,4-tetrahydro-5,8-quinolinequinones, and 7-(2′,6′,10′-trimethylundecyl)-6-hydroxy-5,8-quinolinequinone are now described from our continuing program on new heterobicyclic quinone systems as potential antimetabolites of coenzyme Q and as potential antimalarial agents.

2-Methyl-6-methoxy-5,8-quinolinequinone (**3**) was prepared from 2-nitro-4-methoxyaniline by the multistep procedure depicted in Scheme I. Subsequent treatment of 2-methyl-6-methoxy-5,8-quinolinequinone (**3**) with the appropriate alkylamines yielded the corresponding 2-methyl-6-alkylamino-5,8-quinolinequinones (**4-9**) in good yield (Table I).

Scheme I

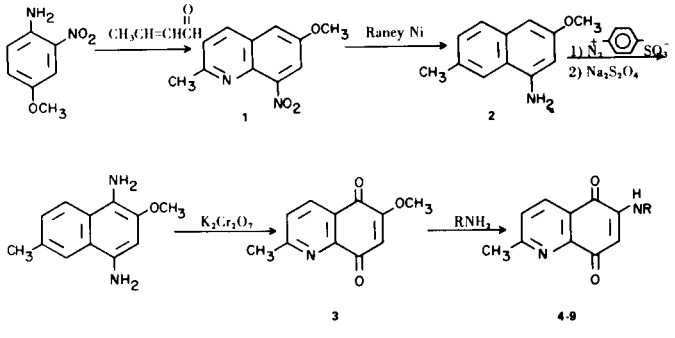
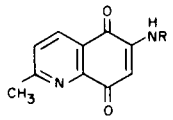


TABLE I

Chemical Data and Antimalarial Results of Certain 2-Methyl-6-alkylamino-5,8-quinolinequinones



No.	R	m.p. °C	% Yield (a)	T-C (e) mg/kg
4	$(CH_2)_{11}CH_3$ (b)	90-91	45.7	0.3 at 320
5	cyclo C_7H_{13} (b)	120-121	29.6	6.1 at 320 (f)
6	$(CH_2)_2C_6H_5$ (b)	150-151	54.2	0.3 at 320
7	$(CH_2)_3N(n\text{-}C_4H_9)_2$ (c)		56.8	0.1 at 320
8	$(CH_2)_4$-cycloC_6H_{11} (b)	124-125	62.5	untested
9	$(CH_2)_2N(CH_2CH_3)_2$ (d)	105-106	49.5	5.9 at 160 (g)

(a) Yields were based on starting quinone. (b) Work-up included silica gel chromatography (chloroform) and then recrystallization (ethyl acetate). (c) Work-up included silica gel chromatography (chloroform). (d) Work-up included silica gel chromatography (chloroform) and then recrystallization (ethyl acetate-hexanes). (e) Blood schizonticidal test; T-C = change in survival time, in days, of treated and nontreated mice. Control mice survive an average of ~ 6.2 days. (f) This compound was declared "active". (g) This compound showed 2/5 toxic deaths at 160 mg./kg. and 5/5 toxic deaths at 320 mg./kg.

TABLE II

Analytical Data for New Compounds

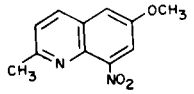
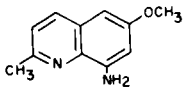
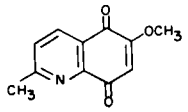
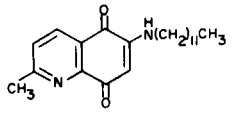
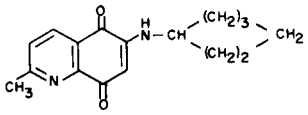
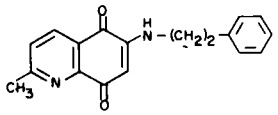
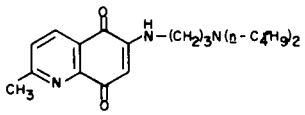
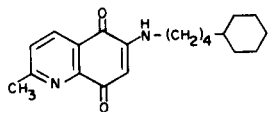
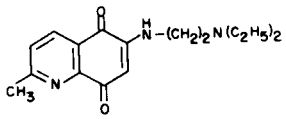
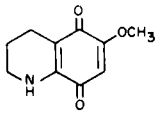
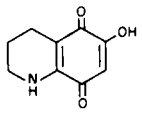
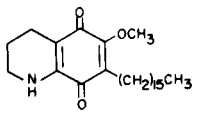
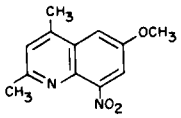
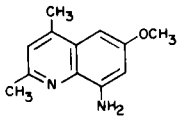
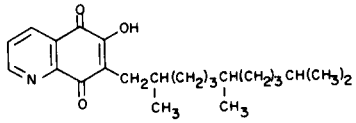
		Calculated Values			Found Values			
No.	Compound	C	H	N	C	H	N	Formula
1		60.54	4.54	12.84	60.79	4.56	13.02	$C_{11}H_{10}N_2O_3$
2		70.21	6.38	14.89	70.00	6.19	14.92	$C_{11}H_{12}N_2O$
3		65.02	4.46	6.89	64.72	4.65	6.83	$C_{11}H_9NO_3$
4		74.12	9.05	7.86	74.16	9.08	8.13	$C_{22}H_{32}N_2O_2$
5		71.81	7.09	9.85	71.82	7.23	9.78	$C_{17}H_{20}N_2O_2$
6		73.95	5.52	9.58	73.84	5.61	9.51	$C_{18}H_{16}N_2O_2$
7		70.55	8.74	11.75	70.18	8.80	11.62	$C_{21}H_{31}N_3O_3$

TABLE II (continued)

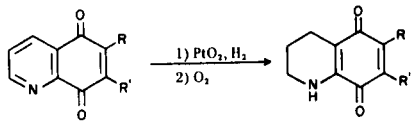
Analytical Data for New Compounds

No.	Compound	Calculated Values C	H	N	Found Values C	H	N	Formula
8		73.59	8.03	8.58	73.80	8.23	8.43	$C_{20}H_{26}N_2O_2$
9		66.88	7.36	14.62	66.93	7.57	14.42	$C_{16}H_{21}N_3O_2$
10		74.77	10.38	3.35	74.72	10.30	3.35	$C_{10}H_{11}NO_3$
11		60.33	5.06	7.82	60.06	5.10	7.42	$C_9H_9NO_3$
12		62.16	5.74	7.25	62.14	5.73	7.21	$C_{26}H_{43}NO_3$
13		62.07	5.17	12.07	62.23	5.14	12.04	$C_{12}H_{12}N_2O$
14		71.29	6.93	13.86	71.30	6.82	13.64	$C_{12}H_{14}N_2O$
15		74.36	8.95	3.77	74.57	8.88	3.70	$C_{23}H_{33}NO_3$

Of the five new 2-methyl-6-alkylamino-5,8-quinolinequinones tested against *P. berghei* in mice (blood schizonticidal test) (4), only 2-methyl-6-cycloheptylamino-5,8-quinolinequinone was active (T-C = 6.1 at 320 mg./kg.). The addition of the 2-methyl moiety to an alkylamino-5,8-quinolinequinone does not seem to significantly effect antimalarial activity in this assay, since the desmethyl analog, 6-cycloheptylamino-5,8-quinolinequinone, exhibited T-C = 6.5 at 320 mg./kg. in this same type of assay (5). 2-Methyl-6-[2′-diethylaminoethyl]amino-5,8-quinolinequinone showed T-C = 5.9 at 160 mg./kg. and 2/5 toxic deaths at 160 mg./kg. and 5/5 toxic deaths at 320 mg./kg.

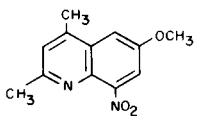
The synthesis of three new 1,2,3,4-tetrahydro-5,8-quinolinequinones (**10**, **11**, and **12**) were prepared (Scheme II) by catalytic hydrogenation of the appropriate 5,8-quinolinequinones in a manner similar to that described by Porter, *et al.* (6).

Scheme II

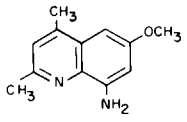


10, R = OCH_3, R′ = H
11, R = OH, R′ = H
12, R = OCH_3, R′ = $(CH_2)_{15}CH_3$

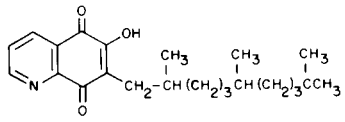
After hydrogenation, air oxidation occurred almost immediately to give high yields of dark purplish colored quinones.



13



14



15

7-(2′,6′,10′-Trimethylundecyl)-6-hydroxy-5,8-quinolinequinone (**15**) was synthesized by radical alkylation of 6-hydroxy-5,8-quinolinequinone by thermal decomposition of di-3,7,11-trimethyldodecanoyl peroxide, which was prepared by a multistep procedure from farnesol. The branched side chain of this 5,8-quinolinequinone simulates the isoprenoid character of coenzyme Q. This branched-chain 5,8-quinolinequinone was tested against *P. berghei* in the mouse (blood-induced) according to the methodology of Osdene, *et al.*, (4) and showed a (T-C) = 2.7 at 160 mg./kg., which was the highest level tested. A compound is arbitrarily declared "active" by the standard criterion of 100% increase or greater in survival time for antimalarial activity against *P. berghei* (T-C ≅ 6.2 days). Although this quinone was declared inactive at the dosage, a (T-C) of 2.7 could indicate low activity. A different dosage schedule might reveal definitive antimalarial activity. Compounds **10** and **11** and a very crude sample of compound **12** were also inactive against *P. berghei* in the mouse (blood-induced).

EXPERIMENTAL

Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analytic results are in Table II. Nmr data were obtained for compounds **1-9** and **13-15** (Varian A-60) and for compounds **10-11** (Varian A-100) and were consistent with proposed structures.

2-Methyl-6-methoxy-8-nitroquinoline (**1**).

This compound was prepared by a procedure similar to that described for the synthesis of 2-methyl-6-nitro-5,8-dimethoxyquinoline by Elslager, *et al.* (3). A mixture of 2-nitro-4-methoxyaniline (42 g., 250 mmoles), arsenic acid (71 g., 500 mmoles), and 85% phosphoric acid (250 ml.) in a three-neck 1-liter round bottom flask was heated to 90° on a steam bath with vigorous stirring. The external heat was removed, and crotonaldehyde (27 g., 470 mmoles) was added dropwise over a 30-minute period at a rate to maintain the reaction temperature between 92-95°. After the addition was complete, the mixture was heated at 97° for 30 minutes and poured into 2 l. of iced water. The resulting mixture was made alkaline with concentrated ammonium hydroxide (500 ml.). The crude product was removed by filtration, pressed, and dried overnight. The dried product was extracted with cyclohexane using a soxhlet extractor until no yellow color was evident in the effluent. The extract was chilled to give 14.5 g. of brown crystals, m.p. 174-181°. Recrystallization from 95% ethanol gave 10.4 g. of product; m.p. 183-184°, yield 20%.

2-Methyl-6-methoxy-8-aminoquinoline (**2**).

This compound was also prepared by a procedure similar to that described for the synthesis of 2-methyl-6-amino-5,8-dimethoxyquinoline by Elslager, *et al.* (3). 2-Methyl-6-methoxy-8-nitroquinoline (4.0 g., 18 mmoles) in 95% ethanol (≅ 50 ml.) was hydrogenated over Raney nickel (1 g.) at 25° at an initial hydrogen pressure of 40 psi. The catalyst was collected by filtration, and the filtrate was concentrated at room temperature. The product crystallized to give 3.1 g. of 2-methyl-6-methoxy-8-aminoquinoline, m.p. 97-99°. Recrystallization from 95% ethanol gave 2.8 g. of colorless crystalline product, m.p. 102-103°, yield 83%.

2-Methyl-6-methoxy-5,8-quinolinequinone (**3**).

A solution of sulfanilic acid (9.6 g., 50 mmoles) in 50% acetic acid (105 ml.) containing sodium acetate (9.6 g., 120 mmoles) was cooled in an ice bath, and then diazotization was with sodium nitrite (3.2 g., 47 mmoles). With stirring in an ice bath, a solution of 2-methyl-6-methoxy-8-aminoquinoline (8 g., 40 mmoles) in acetic acid (~ 30 ml.) was added in portions. The solution turned dark red immediately. The mixture was allowed to stand in ice for 15 minutes after the final addition of 2-methyl-6-methoxy-8-aminoquinoline. The product was collected, washed with water twice, and dissolved in 5% sodium hydroxide solution (105 ml.). The solution was filtered and treated with sodium dithionite (24 g., 110 mmoles). The diamino compound precipitated as orange crystals. This compound was collected and was treated with 12*N* sulfuric acid (15 ml.) and water (110 ml.) at 20° and then was treated with a mixture of 20 ml. of potassium dichromate solution (100 g. of potassium dichromate in one liter of water) and 12*N* sulfuric acid (13 ml.). After one minute the reaction mixture was treated again with potassium dichromate (56 ml.) and 12*N* sulfuric acid (7 ml.). Chloroform (150 ml.) was added. The oxidation mixture was extracted repeatedly with chloroform over a 3 hour period. The chloroform extracts were washed with water and dried over sodium sulfate (anhydrous). Evaporation of solvent gave 7.5 g. of brown solid. Recrystallization from methanol gave 6 g. of a yellow crystalline product; m.p. 202-204°, yield 74%.

2-Methyl-6-alkylamino-5,8-quinolinequinones (**4-9**).

Six new 2-methyl-6-alkylamino-5,8-quinolinequinones were prepared by treating 2-methyl-6-methoxy-5,8-quinolinequinone with the appropriate alkylamine at room temperature in a manner similar to that previously described (7,8,5). After stirring at room temperature, the reaction mixture was evaporated *in vacuo*. Work-up usually included silica gel chromatography and then recrystallization. Generally, dark brown or orange red crystalline products were isolated. A representative synthesis is given.

2-Methyl-6-cycloheptylamino-5,8-quinolinequinone (**5**).

A mixture of 2-methyl-6-methoxy-5,8-quinolinequinone (1 g., 5 mmoles), cycloheptylamine (0.8 g., 7 mmoles), and 95% ethyl alcohol (100 ml.) was stirred at room temperature for three hours. The reaction mixture was evaporated *in vacuo* to give

640 mg. of brown solid which was dissolved in chloroform, placed on a silica gel column, and then eluted with chloroform. Removal of the solvent and crystallization from ethyl acetate gave 420 mg. of red-brown crystalline product; m.p. 120-121°, yield 30%.

1,2,3,4-Tetrahydro-6-methoxy-5,8-quinolinequinone (**10**).

A mixture of 6-methoxy-5,8-quinolinequinone (7) (1.2 g., 6.3 mmoles), platinum oxide, and acetic acid-dioxane was hydrogenated in a Parr hydrogenator at an initial pressure of 45 psi overnight. During the hydrogenation, the reaction mixture color changed from yellow to colorless. After hydrogenation, the catalyst was removed by filtration to yield a filtrate which was air oxidized almost immediately to give a dark cherry red solution. Evaporation of solvents *in vacuo* gave a dark red residue which upon crystallization from chloroform-hexane yielded 900 mg. of maroon solid, m.p. 204-205°, yield 75%. An analytical sample was recrystallized from ether-ethanol-chloroform-hexane, m.p. 216-218°.

1,2,3,4-Tetrahydro-6-hydroxy-5,8-quinolinequinone (**11**).

A mixture of 6-hydroxy-5,8-quinolinequinone (7) (1.5 g., 8.6 mmoles), platinum oxide, and acetic acid-dioxane was hydrogenated for 6 hours at an initial hydrogen pressure of 45 psi. A stream of air was then passed through the reaction mixture for 2 hours. Catalyst was removed by filtration, and the filtrate was evaporated *in vacuo* to a residue which was crystallized from chloroform-ethanol to yield 1.4 g. of purple powder; m.p. 204-206°, yield ≅ 93%. An analytical sample was recrystallized from ether-ethanol-chloroform, m.p. 215-216° with decomposition from ≅ 200°.

1,2,3,4-Tetrahydro-7-*n*-hexadecyl-6-methoxy-5,8-quinolinequinone (**12**).

The diacyl peroxide was prepared from heptadecanoic acid (10 g., 37 mmoles), thionyl chloride (18 ml.), 30% hydrogen peroxide (5.5 ml.), and pyridine (6.5 ml.) by a procedure similar to that described for other alkanoyl peroxides by Silver and Swern (10), except 30% hydrogen peroxide was used. 6-Methoxy-5,8-quinolinequinone (7) (4.0 g., 21.1 mmoles) in acetic acid (150 ml.) was treated with crude di-*n*-heptadecanoyl peroxide in a manner similar to the syntheses of certain alkylated 5,8-quinolinequinones as described by Pratt and Drake (9). The reaction mixture was stirred at ≅ 70° for 5 hours. Acetic acid was removed *in vacuo*, and the oily residue after addition of water was extracted repeatedly with ether. The ether extract was dried over sodium sulfate (anhydrous) and treated with charcoal and corn starch. Solids were removed by filtration, and the filtrate was evaporated to a reddish oil which crystallized upon cooling and upon addition of hexane to yield 2.2 g. of yellow powder, m.p. 45-60°. The product was recrystallized from ether-hexane, m.p. 75-80°. Crude 7-*n*-hexadecyl-6-methoxy-5,8-quinolinequinone (1.2 g.) in ethanol was hydrogenated at an initial pressure of 44 psi for 5 hours using platinum oxide as catalyst. Catalyst was removed by filtration, and the filtrate, upon concentration and addition of hexane, yielded a dark solid, which was placed on a silica gel column; elution was with ether:hexane, 1:1. A purple banded fraction was collected which yielded 200 mg. of purple solid, m.p. 56-64°. A sample of this crude product from another reaction was repeatedly recrystallized from hexane to give an analytical sample, m.p. 73-74°.

2,4-Dimethyl-6-methoxy-8-nitroquinoline (**13**).

This compound was prepared by a procedure similar to that described for the synthesis of **1** except 3-pentene-2-one was used instead of crotonaldehyde, yield 14%, m.p. 193-194°.

2,4-Dimethyl-6-methoxy-8-aminoquinoline (**14**).

This compound was prepared by a procedure similar to that described for the synthesis of 2-methyl-6-methoxy-8-aminoquinoline (**2**). The yield of desired product was 1.8 g., m.p. 108-112°. Recrystallization from 95% ethanol gave 1.6 g. of colorless crystalline product, m.p. 114-115°, yield 93%.

7-(2′,6′,10′-Trimethylundecyl)-6-hydroxy-5,8-quinolinequinone (**15**).

Farnesol (10 g., ≅ 0.045 mole, 95% from Aldrich Chemical Co.) was hydrogenated (platinum oxide, palladium on charcoal) at an initial hydrogen pressure of 47 psi. Workup in the usual manner gave a light colored syrup, which was oxidized with potassium permanganate and sulfuric acid (11). The oxidation mixture was an oily syrup which appeared to be primarily one product by thin layer chromatography.

A mixture of 8 g. (33 mmoles) of this crude 3,7,11-trimethyldodecanoic acid, thionyl chloride (15 ml.), and dry benzene (150 ml.) was refluxed overnight. The reaction mixture was evaporated to a yellow syrup which was codistilled three times with dry benzene. The yellow syrup was distilled under reduced pressure to give 5 g. of liquid, b.p. 105-118° at ~1 mm Hg. The acid chloride (5 g., 19 mmoles) was dissolved in 150 ml. of dry ether, and the mixture was cooled in an ice-salt bath. Then 7.0 ml. of 30% hydrogen peroxide was added dropwise over a period of several minutes, and the reaction mixture was stirred for about 20 minutes before pyridine (8 ml.) was slowly added dropwise over a 15 minute period. The mixture turned cloudy at first; then it cleared with the addition of the rest of the pyridine. The resulting solution was allowed to stir at room temperature for another 30 minutes. The ether layer was separated and washed with water, 5% hydrochloric acid, water, 2% sodium hydroxide, and then water. The ether extract was dried over anhydrous sodium sulfate. The solvent from the filtrate, after removal of drying agent, was evaporated to yield 2.5 g. of colorless oil. This material was used for the next step without further purification.

6-Hydroxy-5,8-quinolinequinone (7) (2.0 g., 10 mmoles) was dissolved in 75 ml. of glacial acetic acid, and the mixture was heated to about 80° under nitrogen. Then a mixture of diacyl peroxide (2.5 g., 10 mmoles) in about 7 ml. of acetic acid was added dropwise over a 4 hour period. The reaction mixture was allowed to stir for another 9-10 hours at ~80°, and then evaporated to dryness; water was added. The mixture was extracted with ether, and the combined ether extracts were washed repeatedly with water until no starting material appeared on tlc plates. The ether layer was dried over anhydrous magnesium sulfate. After removal of drying agent and solvent, the residue (an oil) was dissolved in hexane. The mixture was cooled, and an oily yellow solid was collected by filtration with difficulty. Recrystallization of this substance gave 240 mg. of yellow powder, m.p. 86-87°, yield 6%; (deuteriochloroform): δ ppm, 0.81-0.97 (m, 12H); 1.15-1.50 (m, 15H), 2.52-2.80 (m, 2H), 7.57-7.80 (m, 1H); 8.38-8.58 (m, 1H); and 9.03-9.15 (m, 1H).

REFERENCES

(1) Coenzyme Q. 172. Antimetabolites of Coenzyme Q. 23.

(2) This work was supported by U. S. Army Medical Research and Development Command Contract No. DADA 17-69-C-9067. This is Contribution No. 1193 from the Army Research Program

on malaria. A grant from the Robert A. Welch Foundation provided certain equipment.

(3) E. F. Elslager, M. P. Hutt, and L. M. Werbel, *J. Heterocyclic Chem.*, 6, 99 (1969).

(4) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, 10, 431 (1967).

(5) T. H. Porter, F. S. Skelton, and K. Folkers, *ibid.*, 15, 34 (1972).

(6) T. H. Porter, F. S. Skelton, and K. Folkers, *ibid.*, 14, 1029 (1971).

(7) Y. T. Pratt and N. L. Drake, *J. Am. Chem. Soc.*, 77, 37 (1955).

(8) T. H. Porter, F. S. Skelton, C. M. Bowman, and K. Folkers, *J. Med. Chem.*, 15, 504 (1972).

(9) Y. T. Pratt and N. L. Drake, *J. Am. Chem. Soc.*, 77, 4664 (1955).

(10) L. S. Silbert and D. Swern, *ibid.*, 81, 2364 (1959).

(11) L. Crombie and S. H. Harper, *J. Chem. Soc.*, 2688 (1950).