it to the hydroxycinnamic acid. Then 2 cc. (0.021 mole) of dimethyl sulfate was added dropwise and the mixture refluxed for forty minutes. An excess of 6 *N* sodium hydroxide was added and the resulting solution was refluxed for two hours. It was cooled and added to excess sulfuric acid in ice. The white precipitate that formed was taken up in ether and extracted with 2% sodium hydroxide. Acidification of the alkaline extract gave a colorless oil which was extracted with ether. The ether was dried with calcium chloride and evaporated, releasing 0.35 g. (76% yield) of well-formed white prisms of m. p. 73–76°. Two recrystallizations of the acid from petroleum ether (b. p. 60–70°) raised the m. p. to 77–77.8°.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.56; H, 8.79.

Summary

The ring closure of two dialkyltetrahydroxenylcarbinols under the influence of mixed acetic and hydrochloric acids has been studied. 1,2-Dimethyl-4-(*o*-methoxyphenyl)-5-(α-hydroxyisopropyl)-cyclohexene forms a liquid product believed to be 2,3,9,9-tetramethyl-5-methoxy-1,1a,-4,4a-tetrahydrofluorene. The corresponding compound, 1,2-dimethyl-4-(*o*-hydroxyphenyl)-5-(α-hydroxyisopropyl)-cyclohexene, affords a mixture of two products, 2,3,9,9-tetramethyl-5-hydroxy-1,1a,4,4a-tetrahydrofluorene and 6,6,8,9-tetramethyl-6-dibenzopyran, the latter being the result of simultaneous dehydrogenation.

The diene synthesis of 8,9-dimethyl-6a,7,10,-10a-tetrahydrodibenzopyrone from dimethylbutadiene and ethyl *o*-hydroxycinnamate, and of 4,5-dimethyl-2-(*o*-methoxy-*p*-tolyl)-4-cyclohexenecarboxylic acid from dimethylbutadiene and 2-methoxy-4-methylcinnamic acid are described.

The preparation of 2-methoxy-4-hexylcinnamic acid from *m*-hydroxybenzaldehyde is reported.

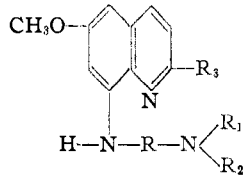
ROCHESTER, NEW YORK RECEIVED MAY 12, 1944

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Derivatives of 6-Methoxy-8-aminoquinoline and 2-Methyl-6-methoxy-8-aminoquinoline. I

BY EWALD ROHRMANN AND H. A. SHONLE

While a very considerable number of 6-methoxy quinolines substituted in the 8 position by dialkylaminoalkylamino groups have been reported,[1,2,3] most of these have been of the type in which R_1 and R_2 were the same and limited to methyl, ethyl or isoamyl



In view of the reputed gametocidal action of some of the 6-methoxy-8-substituted aminoquinolines, it was thought desirable to investigate compounds in which R_1 and R_2 were different. One of the objects of the present program was to determine what effect variations in R_1 and R_2 (in regard to both weight and configuration) have upon the activity and toxicity of the products. Some 2-methyl-6-methoxy-8-substituted aminoquinolines are also reported in the present work.[4,5]

In the examples of substituted 8-aminoquinolines reported at this time R is either $-CH_2CH_2-$, $-CH(CH_3)CH_2-$ or $-CH_2CH_2CH_2-$; R_1 and R_2 are alkyl, cycloalkyl, aryl or alkaryl, and R_3 is H or CH_3.

The intermediate aminoalkanols were prepared from the appropriate secondary amines by reaction with ethylene oxide, propylene oxide or propylene chlorohydrin or the corresponding halohydrins, respectively.

The resulting disubstituted aminoalkanols were converted to the disubstituted aminoalkyl chloride hydrochlorides by treatment with thionyl chloride in chloroform or benzene solution.[6] In those cases in which a crystalline disubstituted aminoalkyl chloride hydrochloride was not obtained, the crude reaction product was treated with an excess of alkali and the liberated disubstituted aminoalkyl chloride purified by distillation. The disubstituted aminoalkylamino chlorides and their hydrochlorides were not analyzed. The details of the preparation and properties of the unsymmetrical secondary amines will be published at a later date in THIS JOURNAL.

Condensation to the substituted quinoline was carried out by refluxing in ethanol solution, either the disubstituted aminoalkyl chloride hydrochloride or the free disubstituted aminoalkyl chlorides, with 6-methoxy-8-aminoquinoline or 2-methyl-6-methoxy-8-aminoquinoline. The use of an alkaline condensing agent appears to be unnecessary.

The compounds prepared are listed in the accompanying tables. These compounds have been tested for antimalarial action against *Plasmodium lophurae* in ducklings by Mr. C. L. Rose of these laboratories. Complete details of their pharmacological properties will be published elsewhere.

(1) Magidson and Strukov, *Arch. Pharm.*, **271**, 569 (1933).

(2) Magidson, Madajerva and Rubzon, *ibid.*, **273**, 320 (1935).

(3) Fourneau, *et al.*, *Ann. Inst. Pasteur*, **46**, 514 (1931).

(4) Brahmachari and Bhattacharjee, *J. Indian Chem. Soc.*, **8**, 571 (1931).

(5) Brahmachari and Das-Gupta, *ibid.*, **9**, 37, 207 (1932).

(6) Magidson, *et al.*, *Arch. Pharm.*, **272**, 78 (1934).

TABLE I

6-METHOXY-8-(β-R_1R_2-AMINOETHYLAMINO)-QUINOLINES

Compounds 1, 2, 3, 5, 10, 12, 13, 14, 15, 16. 17, 18. 19, 20, 21 and 23 were prepared from the disubstituted aminoalkyl chloride hydrochlorides.

	R_1	R_2	M. p., °C.	Formula	N analyses, % Calcd.	Found
1	Methyl	*n*-Propyl	210–213	$C_{16}H_{23}N_3O\cdot 2HCl$	12.13	12.04
2	Ethyl	Isopropyl	194–196	$C_{17}H_{25}N_3O\cdot 2HCl$	11.67	11.5
3	Ethyl	*n*-Propyl	160	$C_{17}H_{25}N_3O\cdot 2HCl$	11.67	12.0
4	Ethyl	*s*-Butyl	185–187	$C_{18}H_{27}N_3O\cdot 2HCl$	11.23	11.0
5	Ethyl	Isobutyl	139–141	$C_{18}H_{27}N_3O\cdot 2HCl$	11.23	11.18
6	Ethyl	1-Methylhexyl	165	$C_{21}H_{33}N_3O\cdot 2HCl$	10.1	10.1
7	Ethyl	1,3-Dimethylbutyl	178–180	$C_{20}H_{31}N_3O\cdot 2HCl$	10.44	10.43
8	Ethyl	1-Ethylpropyl	185–187	$C_{19}H_{29}N_3O\cdot 2HCl$	10.81	10.9
9	Ethyl	Cyclohexyl	191–193	$C_{20}H_{29}N_3O\cdot 2HCl$	10.49	10.34
10	Methyl	Phenylisopropyl	135–138	$C_{22}H_{27}N_3O\cdot 2HCl$	9.95	10.08
11	Ethyl	Phenyl	209–211	$C_{20}H_{23}N_3O\cdot 2HCl$	10.66	10.87
12	Ethyl	Benzyl	229–232	$C_{21}H_{25}N_3O\cdot 2HCl$	10.20	10.14
13	Ethyl	Phenylethyl	146–149	$C_{22}H_{27}N_3O\cdot 2HCl$	9.86	9.5
14	*n*-Propyl	*n*-Propyl	185–187	$C_{18}H_{27}N_3O\cdot 2HCl$	11.23	11.1
15	*n*-Propyl	Isopropyl	197–199	$C_{18}H_{27}N_3O\cdot 2HCl$	11.22	11.2
16	Isopropyl	Isopropyl	194–197	$C_{18}H_{27}N_3O\cdot 2HCl$	11.22	11.1
17	Isopropyl	*n*-Butyl	138–140	$C_{19}H_{29}N_3O\cdot 2HCl$	10.81	10.65
18	*n*-Propyl	*s*-Butyl	176–178	$C_{19}H_{29}N_3O\cdot 2HCl$	10.81	10.95
19	*n*-Propyl	Isobutyl	124–126	$C_{19}H_{29}N_3O\cdot 2HCl$	10.81	10.6
20	Isopropyl	Isobutyl	145	$C_{19}H_{29}N_3O\cdot 2HCl$	10.81	10.7
21	Isopropyl	*n*-Amyl	154–157	$C_{20}H_{31}N_3O\cdot 2HCl$	10.44	10.45
22	Isopropyl	Isoamyl	185	$C_{20}H_{31}N_3O\cdot 2HCl$	10.44	10.5
23	*n*-Butyl	*s*-Butyl	163–165	$C_{20}H_{31}N_3O\cdot 2HCl$	10.44	10.6
24	*n*-Butyl	Isobutyl	144–146	$C_{20}H_{31}N_3O\cdot 2HCl$	10.44	10.6
25	Isobutyl	*s*-Butyl	145–148	$C_{20}H_{31}N_3O\cdot 2HCl$	10.44	10.4
26	*s*-Butyl	*s*-Butyl	154–156	$C_{20}H_{31}N_3O\cdot 2HCl$	10.44	10.4
27	*n*-Butyl	*s*-Amyl	148–150	$C_{21}H_{33}N_3O\cdot 2HCl$	10.1	9.7
28	*s*-Butyl	*n*-Amyl	163–165	$C_{21}H_{33}N_3O\cdot 2HCl$	10.1	10.0
29	*s*-Butyl	Isoamyl	176–179	$C_{21}H_{33}N_3O\cdot 2HCl$	10.1	10.26
30	Isobutyl	*s*-Amyl	169–172	$C_{21}H_{33}N_3O\cdot 2HCl$	10.1	10.14
31	Isobutyl	1-Ethylpropyl	156–158	$C_{21}H_{33}N_3O\cdot 2HCl$	10.1	9.95
32	Isobutyl	2-Ethylbutyl	203–205	$C_{21}H_{33}N_3O\cdot 2HCl$	9.77	9.83
33	Isobutyl	1-Methylamyl	160–162	$C_{22}H_{35}N_3O\cdot 2HCl$	9.77	9.87
34	*n*-Butyl	Cyclopentyl	165–167	$C_{21}H_{31}N_3O\cdot 2HCl$	10.13	10.3
35	Isobutyl	Cyclopentyl	181–183	$C_{21}H_{31}N_3O\cdot 2HCl$	10.13	10.12
36	Isobutyl	Cyclohexyl	216–218	$C_{22}H_{33}N_3O\cdot 2HCl$	9.8	9.9
37	*n*-Amyl	*n*-Amyl	155–157	$C_{22}H_{35}N_3O\cdot 2HCl$	9.77	9.76
38	*n*-Amyl	1-Methylbutyl	124–126	$C_{22}H_{35}N_3O\cdot 2HCl$	9.77	9.73

We wish to thank Miss Shirley Crandall and the late Mr. J. T. Bryant of these laboratories for the microanalyses reported herein. We also wish to thank Mr. R. D. Stayner for his assistance in the preparation of the nuclear quinoline bases.

Experimental[7]

6-Methoxy-8-aminoquinoline.—This was prepared by the conventional Skraup method from nitro-acetoanisidide[8] and subsequent reduction with iron and hydrochloric acid.[9] The crude product was purified by distillation *in vacuo* to form a tan-colored solid.

2-Methyl-6-methoxy-8-aminoquinoline.—This product was prepared essentially by the method of Mathur and Robinson.[10] The nitro compound was reduced with iron and hydrochloric acid.[9] The reduction was carried out with iron and hydrochloric acid and the product purified by distillation *in vacuo*.

Disubstituted Aminoalkanols.—(a) **β-Disubstituted Aminoethanols.**—To a solution of 0.25 mole of the secondary amine in 40 cc. of methanol at about 0° was added 0.3 mole of cold ethylene oxide. The resulting solution was allowed to warm to room temperature and after standing at about 25° for two hours the unreacted ethylene oxide was removed *in vacuo* without heat. The residual liquid was subjected to distillation through a twelve-inch Vigreux column either at atmospheric pressure or in a vacuum. The yields were from 60 to 90% of the theoretical based on the amine. Those disubstituted amino alcohols derived from propylene oxide were prepared in an identical manner.

(b) **γ-Disubstituted Aminopropanols.**—A mixture of 2 mols of amine and 1 mol of trimethylene chlorohydrin or bromohydrin was heated at 95–100° for about two or three days. The mixture was then decomposed with aqueous 10% sodium hydroxide and the water insoluble layer separated and dried with anhydrous magnesium sulfate or potassium carbonate. The mixtures were then distilled

(7) All melting points are uncorrected.

(8) Magidson and Strukov, *Arch. Pharm.*, **271**, 359 (1933).

(9) West, *J. Chem. Soc.*, **127**, 494 (1925).

(10) Mathur and Robinson, *ibid.*, 1520 (1934).

TABLE II

6-METHOXY-8-(β-R_1R_2-AMINOISOPROPYLAMINO)-QUINOLINES

All of these compounds were prepared from the free disubstituted aminoalkyl chlorides.

	R_1	R_2	M. p., °C.	Formula	N analyses, % Calcd.	Found
1	Ethyl	Isopropyl	185–188	$C_{18}H_{27}N_3O\cdot 2HCl$	11.22	11.25
2	*n*-Propyl	*n*-Propyl	164–166	$C_{19}H_{29}N_3O\cdot 2HCl$	10.82	11.0
3	*n*-Propyl	Isopropyl	173–176	$C_{19}H_{29}N_3O\cdot 2HCl$	10.82	10.66
4	Isopropyl	Isobutyl	185	$C_{20}H_{31}N_3O\cdot 2HCl$	10.44	10.5
5	Isobutyl	Isobutyl	167–169	$C_{21}H_{33}N_3O\cdot 2HCl$	10.1	10.1
6	Isobutyl	*s*-Butyl	170–173	$C_{21}H_{33}N_3O\cdot 2HCl$	10.1	9.95

TABLE III

6-METHOXY-8-(γ-R_1R_2-AMINOPROPYLAMINO)-QUINOLINES

Compounds 1, 3, 4 and 7 were prepared from the disubstituted aminoalkyl chloride hydrochlorides.

	R_1	R_2	M. p., °C.	Formula	N analyses, % Calcd.	Found
1	Methyl	*n*-Propyl	186–189	$C_{17}H_{25}N_3O\cdot 2HCl$	11.67	11.84
2	Ethyl	Isopropyl	219–221	$C_{18}H_{27}N_3O\cdot 2HCl$	11.22	11.14
3	*n*-Propyl	*n*-Propyl	188–190	$C_{19}H_{29}N_3O\cdot 2HCl$	10.81	10.72
4	*n*-Propyl	Isopropyl	130	$C_{19}H_{29}N_3O\cdot 2HCl$	10.82	10.6
5	Isopropyl	Isopropyl	220–223	$C_{19}H_{29}N_3O\cdot 2HCl$	10.82	10.91
6	*n*-Propyl	*s*-Butyl	117	$C_{20}H_{31}N_3O\cdot 2HCl$	10.44	10.37
7	Isopropyl	Isobutyl	130–133	$C_{20}H_{31}N_3O\cdot 2HCl$	10.44	10.3
8	*n*-Butyl	Isobutyl	168–170	$C_{21}H_{33}N_3O\cdot 2HCl$	10.1	10.03
9	Isobutyl	Isobutyl	191–193	$C_{21}H_{33}N_3O\cdot 2HCl$	10.1	10.2
10	Isobutyl	*s*-Butyl	141–143	$C_{21}H_{33}N_3O\cdot 2HCl$	10.1	10.0
11	Isobutyl	1-Methylbutyl	140–143	$C_{22}H_{35}N_3O\cdot 2HCl$	9.77	9.62
12	Isobutyl	Cyclopentyl	196–198	$C_{22}H_{33}N_3O\cdot 2HCl$	9.81	9.74
13	*n*-Amyl	*n*-Amyl	125	$C_{23}H_{37}N_3O\cdot 2HCl$	9.46	9.66
14	Isoamyl	Isoamyl	163–165	$C_{23}H_{37}N_3O\cdot 2HCl$	9.46	9.36

TABLE IV

2-METHYL-6-METHOXY-8-(R_1R_2-AMINOALKYLAMINO)-QUINOLINES

Compound No. 3 was prepared from the disubstituted aminoalkyl chloride hydrochloride.

	8-Substituent	M. p., °C.	Formula	N analyses, % Calcd.	Found
1	β-Isopropylisobutylaminoethylamino	185–188	$C_{20}H_{31}N_3O\cdot 2HCl$	10.44	10.6
2	β-*s*-Butylisobutylaminoethylamino	184–186.5	$C_{21}H_{33}N_3O\cdot 2HCl$	10.1	10.0
3	β-Diisobutylaminoethylamino	226–228	$C_{21}H_{33}N_3O\cdot 2HCl$	10.1	9.96
4	γ-Diisobutylaminopropylamino	168–171	$C_{22}H_{35}N_3O\cdot 2HCl$	9.77	9.60

in vacuo. Yields varied from 30 to 60% based on the amount of halohydrin used. Disubstituted amino alkanols derived from propylene chlorohydrin were prepared in a similar manner.

Disubstituted Aminoalkyl Chlorides.—These were prepared essentially by the method of Magidson, *et al.* Those disubstituted aminoalkyl chlorides which formed crystalline hydrochlorides upon evaporation of the solvent were recrystallized from ethanol–ether and used as the hydrochlorides in the subsequent condensations. If no crystalline hydrochlorides were formed, the crude mixture was dissolved in a little water, made alkaline with sodium hydroxide and the liberated base taken up in ether. After drying over anhydrous magnesium sulfate, the ether was removed through a small glass helices packed column and the residual material distilled *in vacuo*. The disubstituted aminoalkyl chlorides formed colorless liquids having a rather pleasant odor. They appeared for the most part to be relatively stable compounds.

Substituted 8-Aminoquinolines.—The condensation reactions were carried out in the following manner: A mixture of 0.1 mole of 6-methoxy-8-aminoquinoline, 0.11 mole of the disubstituted aminoalkyl chloride hydrochloride or of the free disubstituted aminoalkyl chloride and 60 cc. of absolute ethanol was refluxed on an oil-bath at 110–115° for approximately forty-eight hours. The resulting solution was then poured into 300 cc. of water and the mixture made strongly alkaline with sodium hydroxide. After cooling, the liberated base was taken up in ether and the ethereal solution dried over anhydrous magnesium sulfate. The ether was removed by evaporation on the steam-bath and finally by warming *in vacuo* on the steam-bath. The residual liquid was distilled *in vacuo* from a Claisen flask heated on an oil-bath at a pressure of less than 1 mm. A small quantity of unchanged 6-methoxy-8-aminoquinoline was obtained in the first fraction. A small intermediate fraction is collected before the main fraction is taken. The free bases are obtained as viscous yellow oils.

The free base was dissolved in 50–100 cc. of absolute ethanol and converted to the dihydrochloride by saturation with dry hydrogen chloride. Upon addition of anhydrous ether and subsequent cooling to 0°, the dihydrochlorides crystallize. Recrystallization was effected from ethanol-ether. The dihydrochlorides form yellow or orange colored crystals. The yields varied from 40–70%.

The same procedure was used in the preparation of derivatives of 2-methyl-6-methoxy-8-aminoquinoline.

For analysis the dihydrochlorides were dried *in vacuo* at 100° for one hour.

Summary

Sixty-two new derivatives of 8-aminoquinolines have been described. These cover compounds

having β-disubstituted aminoethyl, α-methyl-β-disubstituted aminoethyl and γ-disubstituted aminopropyl side chains.

INDIANAPOLIS, INDIANA RECEIVED JUNE 14, 1944

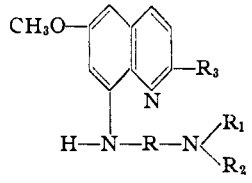
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Derivatives of 6-Methoxy-8-aminoquinoline and 2-Methyl-6-methoxy-8-aminoquinoline. II

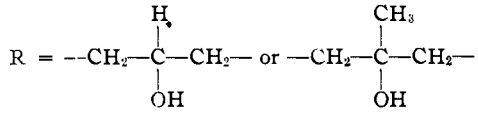
BY EWALD ROHRMANN AND H. A. SHONLE

There have been comparatively few substituted 8-aminoquinolines reported containing a free hydroxyl group in the side chain.[1,2] Magidson and Strukov[2] observed that the compound 6-methoxy-8-(β-hydroxy-γ-diethylaminopropylamino)-quinoline was highly active but was somewhat more toxic than the corresponding desoxy compound.

The present work was undertaken in order to obtain a better correlation between compounds of the type prepared by Magidson and Strukov[2] and the corresponding desoxy derivatives. The present paper concerns the preparation of quinoline derivatives of the type



where R_1 and R_2 = alkyl, cycloalkyl or alkene



and R_3 = H or CH_3.

The dialkylaminohydroxyalkyl chlorides which were coupled with 6-methoxy-8-aminoquinoline or 2-methyl-6-methoxy-8-aminoquinoline to yield the desired quinoline derivatives were prepared by treating epichlorohydrin or β-methylepichlorohydrin with the desired secondary amine in a suitable solvent such as ethanol. In most cases, the reaction proceeds readily at room temperature. In many cases the dialkylaminohydroxyalkyl chlorides can be purified by distillation, but this is not necessary since the crude reaction mixture may be used directly. Certain of the dialkylaminohydroxyalkyl chlorides such as the β-hydroxy-γ-diethylaminopropyl chloride and the β-hydroxy-γ-piperidinopropyl chlorides tend to decompose rather vigorously on vacuum distillation and this procedure for these compounds should be avoided.

Coupling of the dialkylaminohydroxyalkyl chlorides with the desired quinoline nucleus was carried out by refluxing in ethanol solution at 110–115° for two days. The yield of product varied from 40 to 65%. The reaction products were purified by distillation *in vacuo* and subsequent conversion to the dihydrochlorides.

These compounds have been tested in ducklings infected with *Plasmodium lophurae* by Mr. C. L. Rose of these Laboratories. Full details of the activities and toxicities of these compounds will be reported later.

The details of the preparation and properties of the secondary amines used in this work will be published at a later date in THIS JOURNAL.

We wish to thank Miss Shirley Crandall and the late Mr. J. T. Bryant of these Laboratories for the micro Dumas analyses reported herein. We also wish to thank Mr. R. D. Stayner for his assistance in the preparation of 6-methoxy-8-aminoquinoline and 2-methyl-6-methoxy-8-aminoquinoline.

Experimental[3]

6-Methoxy-8-aminoquinoline.—This was prepared by the usual Skraup synthesis[4] from 1-amino-2-nitro-6-methoxybenzene and the resulting 6-methoxy-8-nitroquinoline reduced with iron and hydrochloric acid.[5] The product was purified by distillation *in vacuo*.

2-Methyl-6-methoxy-8-aminoquinoline.—This was prepared essentially by the method described by Mathur and Robinson.[6] The nitro compound was reduced with iron and hydrochloric acid.[5] The product was purified by distillation *in vacuo*.

Dialkylaminohydroxyalkyl Chlorides.—To a solution of 0.25 mole of secondary amine dissolved in 25 cc. of ethanol and cooled to 20° was added 0.25 mole of epichlorohydrin or β-methylepichlorohydrin. The mixture may become warm spontaneously and external cooling may be required. This was particularly so with the lower alkyl amines and with the piperidines. The mixture was allowed to stand at about 25–30° overnight. The reaction mixture may be used directly in the subsequent condensation or in some cases it may be purified by distillation *in vacuo*. Distillation *in vacuo* is not advisable if the secondary amine is a rather reactive one, such as diethyl, methyl, *n*-propyl, pyrrolidine or the piperidines. The yields are about 70–75%.

Condensation with 8-Aminoquinolines.—A mixture of 0.1 mole of 6-methoxy-8-aminoquinoline or 2-methyl-6-methoxy-8-aminoquinoline and approximately 0.11 mole of the dialkylaminohydroxyalkyl chloride (a considerable excess does not appear to be detrimental to the reaction) was dissolved in 60 cc. of absolute ethanol and the solution refluxed on an oil-bath at a temperature of 110–115° for

(1) British Patent 267,169 (1927); German Patents 486,079, 488,945 (1942).

(2) Magidson and Strukov, *Arch. Pharm.*, **271**, 369 (1933).

(3) All melting points are uncorrected.

(4) Magidson and Strukov, *Arch. Pharm.*, **271**, 359 (1933).

(5) West, *J. Chem. Soc.*, **127**, 494 (1925).

(6) Mathur and Robinson, *ibid.*, 1520 (1934).