[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, INDIANA UNIVERSITY]

Ortho-Substituted 2-Phenylquinolines[1]

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A series of 2-(*o*-halophenyl)quinolines (X = F, Cl, or Br) was prepared for the purpose of a preliminary investigation of hindered rotation. *o*-Haloacetophenones and -propiophenones were subjected to the Pfitzinger reaction to give 2-(*o*-halophenyl)cinchoninic acids and the corresponding 3-methyl compounds. Using *o*-halophenacyl acetates in the Pfitzinger reaction, 2-(*o*-halophenyl)-3-hydroxycinchoninic acids were obtained. The cinchoninic acids were decarboxylated to the corresponding 2-(*o*-halophenyl)quinolines which were, in turn, converted to the methiodides. An attempt was made at resolution by conversion of some of the methiodides to diastereoisomeric camphor sulfonates but no separation could be demonstrated. A comparison of the ultraviolet spectra of the methiodides of the 2-(*o*-halophenyl)quinolines and the corresponding ones with a methyl group in the 3-position did not show any differences which could be used to indicate hindered rotation.

Hindered rotation in the properly substituted biaryls and in a variety of other molecules has been a well established fact for a long time. The first attempt at the resolution of a heterocyclic-containing biaryl, 3-(2′-nitrophenyl)indole-2-carboxylic acid by Kermack and Slater.[3] Adams and students[4,5] resolved compounds such as *N*-(2′-carboxyphenyl)-2,5-dimethylpyrrole-3-carboxylic acid and *N*,*N*′-(2,2′,5,5′-tetramethyl)bipyrrole-3,3′-dicarboxylic acid but a substance without the hindering *ortho* groups, such as *N*-(3-carboxyphenyl)-2,5-dimethylpyrrole-3-carboxylic acid[6] could not be resolved. More recently, Webb[7] isolated one of the optical antipodes of 2,2′-(*N*,*N*′,3,3′,5,5′-hexamethyl)bipyrrole-4,4′-dicarboxylic acid. Biaryls in the furan series, such as 3-(2′-nitrophenyl)-2,5-dimethylfuran-4-carboxylic acid, have been separated into its optical isomers by Khawam and Brown.[8] Owen and Nord[9] have resolved biaryls such as 2-(2′-methyl-6′-nitrophenyl)thiophene-3-carboxylic acid as well as tetra *ortho*-substituted bithienyls.

Many of the earlier attempts at isolation of optically active biaryls in the pyridine series were unsuccessful[10-12]; 6,6′-diphenyl-3,3′-bipyridyl-2,2′,4,4′-tetracarboxylic acid[13] was resolved but it racemized rapidly. Breckenridge and co-workers[14] have reported more recently the successful resolution of compounds such as *N*-methyl-2-(2′-carbomethoxyphenyl)-3-carbomethoxypyridinium iodide and *N*,*N*′-dimethyl-3,3′-dicarbomethoxy-2,2′-bipyridinium diiodide.[15] There has been some investigation in the biquinolines. Bell and Morgan[16] tried the resolution of 8,8′-biquinoline and Crawford and Smyth[17] actually resolved 4,4′- and 5,5′-biquinoline. The hindrance to coplanarity in these examples with attributed to factors other than the size of the atoms. Similar resolutions have also been done in the biisoquinoline series.[18]

It was the purpose of this research to synthesize some arylquinolines having bulky groups in *ortho* positions and do a preliminary study of the resolution of some of these. The 2-arylquinolines were chosen because synthesis appeared to be simpler through either a Conrad-Limpach reaction or the Pfitzinger reaction or even by alkylation in the *alpha* position by a lithium aryl. After some preliminary work the Pfitzinger reaction seemed to offer the best method. The prerequisite *o*-haloaceto- and *o*-halopropiophenones were prepared essentially according to the procedure of Lutz.[19] The phenacyl acetates were obtained by the action of potassium acetate upon the phenacyl halides. The methyl phenacyl ethers were not used as the preparation of these was not highly successful. The Pfitzinger reaction proceeded smoothly with the phenacyl acetates and decarboxylation[20] of the cinchoninic

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acids offered no difficulty. However, the Pfitzinger reaction was unsuccessful with *o*-nitropropiophenone. The 3-methoxy-2-(*o*-halophenyl)quinolines were more conveniently prepared by methylation of the corresponding 3-hydroxy compounds. Except for the latter compounds, the methiodides were prepared by treatment of the quinoline compound with methyl sulfate and precipitation of the iodide by treatment of the aqueous methosulfate solution with potassium iodide.

On the basis of the accepted values for bond distances[21] used in the biphenyls, the *N*,3-dimethyl-2-(2′-chlorophenyl)quinolinium *d*-camphorsulfonate and the corresponding 3′-bromo- compound should have been resolvable. The overlap or hindrance value should be 0.22 Å for the 2′-chloro and 0.35 Å for the 2′-bromo compound. However, if interatomic distances are shorter as claimed by Hillemann,[22] or if one used the more generally accepted values, then the 2′-chloro compound would give no overlap while the 2′-bromo compound would give a 0.12 Å interference.

From the work on the hindered phenylfurans,[8] these substances seem to follow the biphenyls closely, but the ease of racemization and/or the isolation of only one optically active form of a pair in the case of the hindered thiophenes,[9] the pyrroles,[7] and phenylpyridines[15] would indicate that the interatomic distances must be different or the electron-releasing effect may allow coplanarity of the aryl rings.

It has been reported by Pickett, Walter, and France,[23] Rodebush,[24,25] and others that biphenyls exhibiting hindrance due to bulky groups in the *ortho* positions have ultraviolet spectra like that of the simple substituted benzene, while biphenyls in which free rotation occurs have different ultraviolet spectra. 2,2′,4,4′-6,6′-Hexamethylbiphenyl has an ultraviolet spectra like that of mesitylene while 4,4′-dimethylbiphenyl has a spectrum different from that of toluene. This is explained on the basis that in the latter biphenyl, the aromatic rings can become coplanar to allow reasonance between them while in the hindered biphenyl, the rings cannot become coplanar; therefore, the spectra are not altered because of resonance between the rings. Examples of this in the heterocyclic series have been reported. It has been shown that the ultraviolet spectra of 4,4′- and 5,5′-biquinoline[17] is like that of quinoline. Jean and Nord[26] found that the spectrum of 3-(2-methyl-6-nitrophenyl)-2,5-dimethylthiophene-4-carboxylic acid was similar to that of a composite of *m*-nitrotoluene and 2,5-dimethyl-3-thenoic acid while that of 3,3′,5,5′-tetranitro-2,2′-bithienyl was not like that of 3,5-dinitrothiophene.

With the above in mind, the ultraviolet spectra of a series of arylquinolines were studied. The spectra of the methiodides of 2-(2′-halophenyl)-quinolines, which should show no hindrance, were the same as for the methiodides of 3-methyl-2-(2′-halophenyl)quinolines. On the basis of this observation, even *N*,3-dimethyl-2-(2′-bromophenyl)quinolinium iodide did not show hindrance.

EXPERIMENTAL[27]

o-Fluorophenacyl bromide, o-chlorophenacyl bromide, and o-bromophenacyl bromide were prepared by the customary method[19] of bromination of the corresponding acetophenone. The 2,4-dinitrophenylhydrazone derivatives of these are summarized in Table I. The *phenacyl bromides* were converted to the *acetates* by the conventional procedure. These are summarized in Table II and the 2,4-dinitrophenylhydrazones in Table I.

TABLE I

2,4-DINITROPHENYLHYDRAZONE DERIVATIVES

$o\text{-}XC_6H_4\overset{\displaystyle NNHC_6H_3(NO_2)_2}{\overset{\|}{C}}CH_2Y$

X	Y	M.P., °	Formula	Analysis, % Calcd.	Found
F	Br	178–179	$C_{14}H_{10}BrFN_4O_4$	14.11[a]	14.39
Cl	Br	178–179	$C_{14}H_{10}BrClN_4O_4$	27.89[b]	27.75
Br	Br	174–175	$C_{14}H_{10}Br_2N_4O_4$	34.89[b]	34.81
F	CH_3CO_2	179–180	$C_{16}H_{13}FN_4O_6$	14.89[a]	15.14
Cl	CH_3CO_2	167–168	$C_{16}H_{13}ClN_4O_6$	14.27[a]	14.34
Br	CH_3CO_2	164–165	$C_{16}H_{13}BrN_4O_6$	18.28[b]	18.50

[a] Nitrogen. [b] Halogen.

TABLE II

ACETATE DERIVATIVES

$o\text{-}XC_6H_4COCH_2O_2CCH_3$

X	Yield, %	B.P., ° Mm.	Formula	Analysis, % Calcd.	Found
F	48	100 (0.1 mm.)	$C_{10}H_9FO_3$	C, 61.22	61.51
				H, 4.62	5.29
Cl	62	88 (0.05 mm.)	$C_{10}H_9ClO_3$	Cl, 16.67	16.70
Br	45	135–136 (0.1 mm.)	$C_{10}H_9BrO_3$	Br, 31.09	31.12

2-(2′-Fluorophenyl)-3-hydroxycinchoninic acid. To a refluxing solution of 100 ml. of 6*N* potassium hydroxide, 60 ml. of ethyl alcohol, and 9 g. (0.061 mole) of isatin was added dropwise a solution of 11 g. (0.056 mole) of *o*-fluorophenacyl acetate in 100 ml. of ethyl alcohol. After refluxing the solution for 9 hr., 150 ml. of distillate was removed and the residue was poured into a slurry of 300 g. of ice and 70 ml. of

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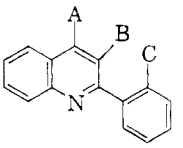
(27) Microanalyses performed by Miss Joanna Dickey of this department.

TABLE III

CINCHONINIC ACIDS AND QUINOLINES



A	B	C	Yield, %[a]	M.P., °	Formula	Halogen, % Calcd.	Halogen, % Found
CO_2H	H	F	63[b]	236 (dec.)	$C_{16}H_{10}FNO_2$	[c]	
$CO_2C_2H_5$	H	F	[b]	56.5–57	$C_{18}H_{14}FNO_2$	[d]	
H	H	F	40	[f]	$C_{15}H_{10}FN$	[e]	
CO_2H	CH_3	Cl	84[g]	310 (dec.)	$C_{17}H_{12}ClNO_2$	11.91	11.69
$CO_2C_2H_5$	CH_3	Cl	[h]	67–68	$C_{19}H_{16}ClNO_2$	10.88	10.81
H	CH_3	Cl	74[h]	89–90	$C_{16}H_{12}ClN$	13.97	13.66
CO_2H	CH_3	Br	78[g]	320 (dec.)	$C_{17}H_{12}BrNO_2$	23.36	22.96
$CO_2C_2H_5$	CH_3	Br	[h]	79–80	$C_{19}H_{16}BrNO_2$	21.59	21.60
H	CH_3	Br	33[i]	83.5–84.5	$C_{16}H_{12}BrN$	26.80	26.65
CO_2H	H	Cl	82[j]	266 (dec.)	$C_{16}H_{10}ClNO_2$	12.50	11.88
$CO_2C_2H_5$	H	Cl	[h]	81.5–82	$C_{12}H_{14}ClNO_2$	11.37	11.44
H	H	Cl	58[i]	79.5–80	$C_{16}H_{10}ClN$	14.79	14.72
CO_2H	H	Br	67[b]	240 (dec.)	$C_{16}H_{10}BrNO_2$	24.35	24.07
$CO_2C_2H_5$	H	Br	[b]	78.5–79	$C_{18}H_{14}BrNO_2$	22.43	22.57
H	H	Br	49[i]	72–73	$C_{15}H_{10}BrN$	28.13	28.25
CO_2H	OH	Cl	34[b,g]	204 (dec.)	$C_{16}H_{10}ClNO_2$	11.83	11.72
$CO_2C_2H_5$	OH	Cl	[b]	123–124	$C_{18}H_{14}ClNO_3$	10.79	11.05
H	OH	Cl	74[b]	232–233	$C_{15}H_{10}ClNO$	13.87	13.88
CO_2H	OH	Br	13[b]	205 (dec.)	$C_{16}H_{10}BrNO_3$	23.22	22.88
$CO_2C_2H_5$	OH	Br	[b,h]	135.5–136.5	$C_{18}H_{14}BrNO_3$	21.24	21.32
H	OH	Br	64[b]	244–245	$C_{15}H_{10}BrNO$	26.63	26.57
H	OCH_3	Cl	29[k]	125–125.5	$C_{16}H_{12}ClNO$	13.15	13.26
H	OCH_3	Br	40[b]	126–127	$C_{16}H_{12}BrNO$	25.44	25.21
Cl	Br	H	81[l]	134–135	$C_{15}H_9BrClN$	36.23	36.08
CH_3O	Br	H	45[m]	142–143	$C_{16}H_{12}BrNO$	25.44	25.82
HO	H	Br	20[b]	245–246	$C_{15}H_{10}BrNO$	26.62	26.67
Cl	H	Br	88[m]	140.5–141	$C_{15}H_9BrClN$	36.23	36.56
HO	Br	Br	53[m,n]	317–318	$C_{15}H_9Br_2NO$	42.32	42.57
Cl	Br	Br	75[m]	148–149	$C_{15}H_8Br_2ClN$	49.12	49.28

[a] Solvent for recrystallization. [b] Aqueous ethyl alcohol. [c] *Anal.* Calcd.: N, 5.24. Found: N, 5.36. [d] *Anal.* Calcd.: N, 4.74. Found: N, 4.82. [e] *Anal.* Calcd.: N, 6.38. Found: N, 6.48. [f] B.p., 127–129° at 0.02 mm.; n_D^{23} 1.6624. [g] Methyl cellosolve. [h] Aqueous acetone. [i] Petroleum ether (b.p. 30–60°). [j] Aqueous methyl cellosolve. [k] Aqueous methyl alcohol. [l] Acetone–ethyl alcohol. [m] Ethyl alcohol. [n] Nitromethane.

concd. hydrochloric acid. The yield of somewhat brown colored solid was 14.5 g. (91%) which melted with decomposition at 195°. Recrystallization from 70% ethyl alcohol gave a golden yellow colored solid which melted with decomposition at 197°.

Anal. Calcd. for $C_{16}H_{10}FNO_3$: N, 4.95. Found: N, 5.27.

The *ethyl ester*, prepared by direct esterification, was recrystallized from 50% ethyl alcohol; m.p. 109–109.5°.

Anal. Calcd. for $C_{18}H_{14}FNO_3$: N, 4.50. Found: N, 4.62.

2-(2′-Fluorophenyl)-3-hydroxyquinoline. To 50 ml. of boiling nitrobenzene was added 3 g. (0.011 mole) of 2-(2′-fluorophenyl)-3-hydroxycinchoninic acid; the solution was allowed to boil for about 5 min. After the solution cooled, it was extracted with three 50-ml. portions of 10% potassium hydroxide solution; the combined alkaline solution was extracted with two 75-ml. portions of ether. The alkaline solution was acidified with concd. hydrochloric acid to *p*H 6. The precipitated solid was collected by filtration and was recrystallized from 55% ethyl alcohol. The yield of tan colored needles was 2.25 g. (88%); m.p. 206–209°. Three recrystallizations from dilute ethyl alcohol raised the melting point to 209.5–210.5°.

Anal. Calcd. for $C_{15}H_{10}FNO$: N, 5.86. Found: N, 5.86.

N-Methyl-2-(2′-fluorophenyl)-3-methoxyquinolinium iodide. A solution of 0.86 g. (0.0036 mole) of 2-(2′-fluorophenyl)-3-hydroxyquinoline and 1 g. of sodium methoxide in 50 ml. of absolute methanol was refluxed for 22 hr. with 5 ml. of methyl iodide; then 25 ml. of distillate was removed. Absolute ether (200 ml.) was added to the residual liquid. The solid (0.51 g.) was recrystallized twice from absolute ethyl alcohol to give a yellow-orange substance which melted, with decomposition, at 187°.

Anal. Calcd. for $C_{17}H_{15}FINO$: I, 32.11. Found: I, 32.53.

2-(2′-Fluorophenyl)-3-methoxyquinoline. The ether-methanol filtrate from the isolation of the above methiodide was evaporated to 10 ml., then 100 ml. of water containing 2 g. of sodium thiosulfate was added to this residual solution. The solution was heated to boiling, then cooled, and the solid was collected by filtration. The substance was recrystallized from 70% ethyl alcohol, giving 0.46 g. of fine cream colored needles, m.p. 142–143°.

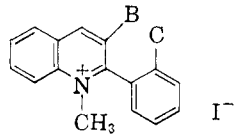
Anal. Calcd. for $C_{16}H_{12}FNO$: N, 5.53. Found: N, 5.65.

The other 2-(2′-halophenyl)-3-hydroxycinchoninic acids and 2-(2′-(halophenyl)-3-hydroxy- and -3-methoxyquinolines are summarized in Table III. The other 2-(2′-halophenyl)-3-methoxyquinoline methiodides are summarized in Table IV.

N,3-Dimethyl-2-(2′-fluorophenyl)quinolinium iodide. A solution of 1.5 g. of 2-(2′-fluorophenyl)-3-methylquinoline in 10 ml. of dimethyl sulfate was heated at 110° for 2 hr. After the solution cooled to room temperature, 40 ml. of absolute ether was stirred into it and the solid was removed

TABLE IV

METHIODIDE DERIVATIVES



B	C	Yield, %[a]	M.P., °	Formula	Halogen,[e] % Calcd.	Found
CH_3	Cl	81[b]	200–201	$C_{17}H_{15}ClIN$	41.04	40.91
CH_3	Br	92[b]	200–201	$C_{17}H_{15}BrIN$	46.99	46.56
OCH_3	Cl	56[c,d]	200 dec.	$C_{17}H_{15}ClINO$	39.44	39.02
OCH_3	Br	46[c,b]	194 dec.	$C_{17}H_{15}BrINO$	45.34	45.07
H	F	85[b]	198 dec.	$C_{16}H_{13}FIN$	34.75[f]	34.96[f]
H	Cl	70[d]	199 dec.	$C_{16}H_{13}ClIN$	42.55	42.33
H	Br	90[b]	213 dec.	$C_{16}H_{13}BrIN$	48.54	48.63

[a] Solvent for recrystallization. [b] Ethyl alcohol. [c] Prepared by the sodium methoxide–methyl iodide method. [d] Water. [e] Combined halogen content. [f] Iodine only.

by filtration. The crystalline methosulfate was washed with absolute ether. The solid was mixed with 25 ml. of water; then it was filtered and the filtrate was poured, with stirring, into a solution of 6 g. of potassium iodide in 10 ml. of water. The yellow colored solid was collected and after drying, it was recrystallized from absolute ethyl alcohol. The yield of deep yellow colored needles was 2.1 g. (85%), m.p. 240° (dec.).

Anal. Calcd. for $C_{17}H_{15}FIN$: I, 33.47. Found: I, 33.74.

The other methiodides are summarized in Table IV.

2-(2′-Chlorophenyl)-3-quinolinecarboxylic acid.[28] A solution of 38 g. (0.15 mole) of 2-(2′-chlorophenyl)-3-methylquinoline in 800 ml. of 30% sulfuric acid contained in a 3-l. three necked flask fitted with a stirrer, condenser, and a dropping funnel was heated to boiling. A 2-g. sample of manganese dioxide was added and a solution of 80 g. of chromic anhydride in 400 ml. of 30% sulfuric acid was added over a period of 2 hr. The refluxing was continued for 2 hr. The reaction mixture was poured into 18 l. of hot water. After it cooled somewhat, the solution was made alkaline with concd. ammonia water, then filtered through a sintered glass funnel, and finally evaporated to about 3 l. volume. The solution was acidified with acetic acid and the solid was collected. The yield was 24.5 g. (58%), m.p. 269° dec. The melting point could not be raised by recrystallization from 60% aqueous methyl cellosolve.

Anal. Calcd. for $C_{16}H_{10}ClNO_2$: Cl, 12.50. Found: Cl, 12.22.

The *ethyl ester* was prepared through the intermediate acid chloride and was recrystallized from aqueous acetone; m.p. 123–124°.

Anal. Calcd. for $C_{18}H_{14}ClNO_2$: Cl, 11.37. Found: Cl, 11.45.

2-(2′-Chlorophenyl)-3-quinolinecarboxyhydrazide. A solution of 10.4 g. (0.033 mole) of ethyl 2-(2′-chlorophenyl)-3-quinolinecarboxylate and 3 g. (0.094 mole) of freshly dried hydrazine in 2 ml. of absolute ethyl alcohol was refluxed for 16 hr. The solution was poured into 150 ml. of 2*N* hydrochloric acid, and then filtered and the filtrate made alkaline with sodium carbonate. The solid was collected. The crude hydrazide (8.3 g., 87%) melted at 200–204°. It was recrystallized from toluene; m.p. 205.5–206.5°.

Anal. Calcd. for $C_{16}H_{12}ClN_3O$: N, 14.12. Found: N, 14.29.

Ethyl N-[2-(2′-chlorophenyl)-3-quinolyl]urethan. A solution of 2.8 g. (0.0094 mole) of 2-(2′-chlorophenyl)-3-quinolinecarboxyhydrazide in 80 ml. of 1*N* hydrochloric acid was cooled to −4° and, while stirring, a solution of 2.1 g. of sodium nitrite in 30 ml. of water was added over a period of 20 min. After standing at room temperature for 10 min., the solid was collected and then was refluxed with 80 ml. of absolute ethyl alcohol until there was no further evolution of gas. Bright yellow crystals separated when the solution cooled. The crude substance (2 g., 65%), which melted at 150–152°, was recrystallized from ethyl alcohol yielding short needles which melted at 154.3–154.7°.

Anal. Calcd. for $C_{18}H_{15}ClN_2O_2$: N, 8.58. Found: N, 8.73.

The *methyl urethan* was obtained in 73% yield by an analogous procedure; it was recrystallized from methyl alcohol, m.p. 158–158.5°.

Anal. Calcd. for $C_{17}H_{13}ClN_2O_2$: N, 8.96. Found: N, 9.18.

2-(2′-Chlorophenyl)-3-aminoquinoline. A solution of 26.5 g. (0.085 mole) of methyl *N*-[2-(2′-chlorophenyl)-3-quinolyl]urethan was refluxed for 24 hr. with 250 ml. of concd. hydrochloric acid. Then it was concentrated in a vacuum to a small residue. The residue was diluted with 250 ml. of boiling water then made alkaline with sodium carbonate. The solid was collected, dried, and refluxed with 2 l. of ligroin (b.p. 63–99°). The solution was filtered and concentrated to one-half its volume, yielding cream colored needles (15 g., 69%) which melted at 99–101°. Recrystallization from ligroin raised the melting point to 101–102°.

Anal. Calcd. for $C_{15}H_{11}ClN_2$: N, 11.00. Found: N, 11.13.

The *acetyl* derivative was recrystallized from dilute alcohol, m.p. 171.5–172.5°.

Anal. Calcd. for $C_{17}H_{13}ClN_2O$: N, 9.44. Found: N, 9.58.

The *benzoyl* derivative was recrystallized from ethyl alcohol, m.p. 150.5–151.5°.

Anal. Calcd. for $C_{22}H_{15}ClN_2O$: N, 7.81. Found: N, 8.04.

The *picrate* was recrystallized from absolute ethyl alcohol, m.p. 188–189°.

Anal. Calcd. for $C_{21}H_{14}ClN_5O_7$: N, 14.48. Found: N, 14.44.

2,(2′-Chlorophenyl)-3-chloroquinoline.[28] A stirred solution of 15 g. (0.06 mole) of 2-(2′-chlorophenyl)-3-aminoquinoline in 300 ml. of concd. hydrochloric acid was cooled to −14° and was diazotized by the dropwise addition of 7.2 g. of potassium nitrite in 60 ml. of water. The solution was kept at −15° for 1.5 hr., then warmed to 25° for 30 min., heated quickly to 80°, and cooled rapidly to 25° again. This solution was poured into 420 g. of potassium carbonate in 500 ml. of water. The solid was collected by filtration, extracted with 10% potassium hydroxide, and recrystallized from absolute ethyl alcohol. The white solid (4.3 g., 26%), which melted at 143–145°, on further recrystallization melted at 147–147.5°.

Anal. Calcd. for $C_{15}H_9Cl_2N$: Cl, 25.87. Found: Cl, 25.76.

N,3-Dimethyl-2-(2′-chlorophenyl)quinolinium d-camphorsulfonate. A solution of 3.96 g. (0.01 mole) of *N*,3-dimethyl-

(28) H. John and H. Ottawa, *J. prakt. Chem.*, **131**, 266, 354 (1931).

2-(2′-chlorophenyl)quinolinium iodide in 50 ml. of hot 50% ethyl alcohol was added to a solution of 3.4 g. (0.01 mole) of silver *d*-camphorsulfonate dissolved in 20 ml. of 50% ethyl alcohol. The hot solution was filtered to remove the silver iodide and the filtrate was evaporated to dryness. The residue was dissolved in 50 ml. of chloroform, 200 ml. of absolute ether was added, and the solution was allowed to stand overnight in a refrigerator. The white solid (2.9 g.) melted at 188–190°. After recrystallization from absolute ether-chloroform and from acetone, the white granular solid melted at 190–191°.

Anal. Calcd. for $C_{27}H_{30}ClNO_4S$: C, 64.84; H, 6.05; S, 6.41; Cl, 7.09. Found: C, 64.39; H, 5.95; S, 6.37; Cl, 7.08.

All of the fractions in recrystallization of this substance gave the same optically inactive iodide when the aqueous solution of the *d*-camphorsulfonate salt was treated with potassium iodide. Also prepared by the same method were the *N*,3-dimethyl-2-(2′-chlorophenyl)quinolium *d*-α-bromo-π-camphorsulfonate, $[\alpha]_D^{28} = +47.3°$, and *N*,3-dimethyl-2-[2′-bromophenyl]quinolinium *d*-α-bromo-π-camphorsulfonate, $[\alpha]_D^{28} = +45.7°$, but it could not be demonstrated that either of these yielded diastereomers and no optical activity was demonstrated when they were reconverted to the iodides.

Ethyl o-bromobenzoylacetate (b.p. 116° at 0.4 mm.) was prepared from *o*-bromobenzoyl chloride and ethyl acetoacetate in a 41% yield using the method described for ethyl *p*-bromobenzoylacetate.[29] The 2-(*o*-bromophenyl)quinolines prepared from it are summarized at the bottom of Table III.

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(29) C. E. Kaslow and S. J. Nix, *Proc. Indiana Acad. Science*, **61**, 121 (1952).

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

9-Vinylacridine: Preparation and Some Reactions of It and Related Substances of Possible Application in the Synthesis of Acridine Amino Alcohols

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Dehydrobromination of 9-α-bromoethylacridine gives 9-vinylacridine (III). The structure is confirmed by reduction of 9-ethylacridane. 9-α-Bromoethylacridine and 9-β-bromoethylacridine as well as III react with piperidine to give 9-β-piperidinoethylacridine.

Some time ago we reported[1] the preparation of acridine amino alcohols of type I. We also wished to prepare II and IIa, but the effort failed because we were unable to prepare the 9-metalated acridine derivatives necessary to react with the appropriate amino aldehydes.[2] The reverse procedure (in which an amino organometallic compound reacts with acridine-9-aldehyde [V]) cannot be applied here as one- and two- carbon amino organometallic compounds cannot be prepared.[3]

There are other approaches to this synthetic problem, however, and it is the purpose of this paper to present a partial investigation of one of them, namely, the route employing 9-vinylacridine (III). The results presented here are incomplete. We have, however, discontinued this work some time ago, and, as there is no likelihood of its being resumed, we would like to present the results at this time.

In 1936, O. Eisleb reported[4] a number of acridine derivatives which might lead to the preparation of II. Acridine-9-carboxyaldehyde (V) was condensed with nitromethane to yield XIV. The latter could not be reduced to the desired amino alcohol. He also prepared 9-acetylacridine (XV), which was subsequently converted to both XVI and XVII. He was unable to convert either of these to the desired amino alcohol.

In 1940, Braz and Gortinskaya[5] reported the conversion of acridine-9-carboxylic acid to XVI *via* the diazo ketone. XVI was mentioned as an intermediate for the synthesis of possible antimalarial pharmaceuticals, but as none of its reactions were described, it is reasonable to assume that these workers encountered the same difficulty as did Eisleb. As Eisleb did not characterize XVI, it is not possible to compare his substance with that of the Russian scientists.

Subsequently, Braz and Kore[6] studied the reaction of XVI with piperidine and with diethyl-

(1) T. D. Perrine and L. J. Sargent, *J. Org. Chem.*, **14**, 533 (1949).

(2) T. D. Perrine, *J. Org. Chem.*, **18**, 1356 (1953).

(3) Wittig and Wetterling (*Annalen*, **557**, 193–201 (1947)) report that ylides such as $(CH_3)_3N^+$-CH_2: behave like organometallic compounds and add to carbonyl compounds. We have not investigated the application of ylides to this problem. The writer has also been informed (personal communication from Dr. E. M. Fry of this laboratory) that diethylaminomethyl methyl ether reacts with lithium metal to yield 1,2-bisdiethylaminoethane. This is a coupling product of the expected diethylaminomethyllithium, reminiscent of that encountered in the reaction of lithium with benzyl halides. Thus the dialkylaminomethyl lithium compound probably may have a transitory existence and might be trapped.

(4) O. Eisleb, *Medizin und Chemie*, Band III, Bayer, Leverkusen a.Rh., 1936, p. 41.

(5) G I. Braz and T. V. Gortinskaya, *J. Gen. Chem. (USSR)*, **10**, 1751 (1940); *Chem. Abstr.*, **35**, 4025[8].