TABLE I

HYDROLYSIS PRODUCTS OF METHYLTRIMETHOXYSILANE

$CH_3Si(OCH_3)_3:H_2O$ = 1:0.75

Fraction	Total vol. of flat, ml.	B.p., °C.	Mm.	$n^{30}D$	d^{30}_4[a]	Analyses, % Found C	H	Si	Mol. wt.	Calcd. C	H	Si	Mol. wt.	Molar refr. Found	Calcd.[b]	Formula
3	22.4	44.5	3	1.3834	1.024	32.5	8.2	24.8	226	31.8	8.0	24.8	226	51.5	52.0	$C_6H_{18}Si_2O_5$[d]
7	1.5	64	5	1.3909	1.100	27.3	7.2	31.4	260	26.6	6.8	31.2	270	58.3	58.2	$C_6H_{18}Si_2O_6$[e]
11	12.6	94	5	1.3894	1.062	30.6	7.9	27.4[c]	301	30.4	7.6	26.6	316	70.5	71.4	$C_8H_{24}Si_3O_7$[f]
21	5.9	74	0.2	1.3940	1.084	28.8	7.3	28.6	382	29.5	7.4	27.6	407	89.9	90.8	$C_{10}H_{30}Si_4O_7$[g]
28	3.0	103.5	0.2	1.3998	1.127	26.8	6.6	31.5	473	26.6	6.8	31.2	451	97.0	97.0	$C_{10}H_{30}Si_5O_{10}$[h]
33	1.5	137–141	0.2	1.4013	1.152	25.9	6.8		542	26.6	6.8		541	114.2	116.4	$C_{12}H_{36}Si_6O_{12}$[i]

[a] Determined with a Fisher–Davidson gravitometer. [b] R. O. Sauer, THIS JOURNAL, **68**, 954 (1946); E. L. Warrick, *ibid.*, **68**, 2455 (1946). [c] There is no obvious explanation for the poor correlation between calculated and found values for silicon in this case. Since the sample was taken from the middle of a good distillation "flat" and since other analytical data are in excellent agreement with "theory," there is little reason to doubt that an authentic sample of the linear trimer was obtained. The physical constants are in good agreement with those reported by Tamborski and Post.[5] [d] 1,3-Dimethyl-1,1,3,3-tetramethoxydisiloxane. [e] 1,3,5-Trimethoxy-1,3,5-trimethylcyclotrisiloxane. [f] 1,1,3,5,5-Pentamethoxy-1,3,5-trimethyltrisiloxane. [g] 1,1,3,5,7,7-Hexamethoxy-1,3,5,7-tetramethyltetrasiloxane. [h] 1,3,5,7,9-Pentamethoxy-1,3,5,7,9-pentamethylcyclopentasiloxane. [i] 1,3,5,7,9,11-Hexamethoxy-1,3,5,7,9,11-hexamethylcyclohexasiloxane.

100–118°, 18.9% OCH_3. The residue (16.7 g.) was a soft, weak gel, with 12.1% residual $-OCH_3$.

Hydrolysis with 0.75 Molar Equivalent of Water.—The initial reaction was carried out as described above, using 13.5 g. of water and 136.2 g. (1.0 mole) of methyltrimethoxysilane in 1000 ml. of benzene. After 0.9 hour, the equilibrium liquid temperature was 63.0° and the vapor temperature was 59.1°. Filtration removed 5.4 g. of gel. Solvents were removed rapidly under rough vacuum, leaving 68.3 g. of a liquid product. A rapid vacuum distillation yielded 54.9 g., boiling range 50° at 5 mm. to 208° at 1 mm. This product was redistilled in a spinning-band column. The distillation curve is shown in Fig. 1. The mid-cuts of the six distillation "flats" were analyzed, and these results are summarized in Table I.

Acknowledgment.—We are indebted to M. E. Hadsell for the spinning-band distillations, and to Mrs. Joyce Northrop and Mrs. Joan Martin for analyses.

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The Preparation of 3-Bromoquinoline Derivatives

BY SAMUEL W. TINSLEY[1]

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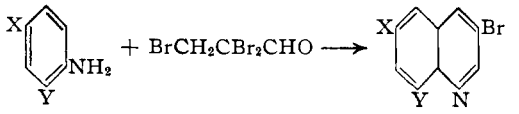
The preparation of substituted 3-bromoquinolines by the reaction of substituted anilines with 2,2,3-tribromopropanal[2] has been extended and the scope and limitations of the reaction have been investigated.

The preparation of 3-bromoquinolines by reaction of substituted anilines with 2,2,3-tribromopropanal was first undertaken to obtain nuclei from which potential antimalarial drugs might be prepared. Other 3-bromoquinolines have now been prepared in order to determine the general applicability of the reaction.

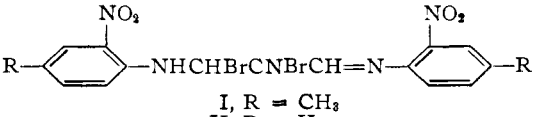
It has been confirmed that the reaction is most efficient with amines having substituents in one *ortho* and the *para* position. Thus 2,4-disubstituted anilines react to give the corresponding quinolines in yields of 30–80%, 65–80% usually being obtained.



It was reported previously[2] that *o*-nitroaniline yielded only 1% of the expected 3-bromo-8-nitroquinoline along with much larger amounts of 6-bromo-8-nitroquinoline and 3,6-dibromo-8-nitroquinoline. Bromination of the benzenoid ring also occurred with *p*-nitroaniline and anthranilic acid, although in these cases only the relatively insoluble dibromo compounds were isolated. However, with 2-methyl-5-nitroaniline, which also has an open *para* position, no bromination of the benzenoid ring occurred.

No identifiable products could be isolated by the action of the tribromoaldehyde on aniline, the three bromoanilines, 2-aminopyridine, 2-amino-4-nitrophenol or 2,5-dimethylaniline although definite, sometimes highly exothermic, reactions occurred in each case. In every instance black insoluble tars resulted. The tribromoaldehyde could not be induced to react with sulfanilic acid or 2-aminotoluene-5-sulfonic acid either under the usual conditions or by heating in the absence of solvent.

The reaction does not occur in such solvents as alcohol, ether or benzene. In the absence of solvent the tribromoaldehyde did react with 2-nitro-4-methylaniline to produce a light orange crystalline compound. This compound was converted readily to 6-methyl-8-nitroquinoline by warming in acetic acid. This intermediate was not characterized; however, analysis indicated I as a possible structure. This structure is quite similar to that postulated as an intermediate in the Skraup reaction.



I, R = CH_3
II, R = H

o-Nitroaniline also reacted in the absence of solvent to produce a small amount of crystalline intermediate whose analysis indicates a similar structure (II). It is interesting to note that cyclization of II in acetic acid yielded 3-bromo-8-nitroquinoline and no 3,6-dibromo-8-nitroquinoline or 6-bromo-8-nitroquinoline. One may speculate that such intermediates as I and II are formed by dehydrohalo-

(1) Carbide and Carbon Chemicals Co., South Charleston, West Virginia.

(2) R. H. Baker, S. W. Tinsley, D. Butler and B. Riegel, THIS JOURNAL, **72**, 393 (1950).

genation of the tribromoaldehyde, 1,4-addition of the amine to the resulting dibromoacrolein followed by anil-type condensation with another molecule of the amine. The conjugate addition of the amine followed by elimination of a group from the β-carbon is quite similar to the well known ethoxymethylenemalonic ester synthesis. The final products then might arise by the ring closure of such intermediates as I or II followed by dehydrobromination to the aromatic quinoline.

Experimental[3]

Preparation of 3-Bromoquinolines.—Except as noted the amine (0.04 mole) was dissolved in 100 ml. of glacial acetic acid at steam-bath temperatures and the tribromoaldehyde was added with stirring. The reaction was completed by continued heating for three hours. After cooling and filtering, the crude hydrobromide was stirred with ammonia and the product removed by filtration, dried and crystallized from alcohol.

The nitroquinolines were reduced to the corresponding amines by stannous chloride and hydrochloric acid in the usual way.

3-BROMOQUINOLINES

5	6	8	M.p.,[a] °C.	Yield, %	Formula	Nitrogen, % Calcd.	Found
	NO_2	Cl	203–204	64	$C_9H_4BrClN_2O_2$	9.75	9.95
	NO_2	OCH_3	219–220	78	$C_{10}H_7BrN_2O_3$	9.90	9.74
	NO_2	CH_3[b]	190–191	80	$C_{10}H_7BrN_2O_2$	10.49	10.37
	NO_2	Br[c]	218–219	41	$C_9H_4Br_2N_2O_2$	8.44	8.56
	C_6H_5	NO_2[d]	183–186	79	$C_{15}H_9BrN_2O_2$	8.72	8.83
	CH_3	NO_2	190	60	$C_{10}H_7BrN_2O_2$	10.49	10.67
	CH_3	CH_3	59–60	32	$C_{11}H_{10}BrN$	5.95	6.14
	Cl	COOH	237–238	72	$C_{10}H_5BrClNO_2$	4.90	5.09
	NO_2	NO_2	157[e]	40			
NO_2		OCH_3	212–213	50	$C_{10}H_7BrN_2O_3$	9.90	9.80

AMINES

5	6	8	M.p.,[a] °C.	Yield, %	Formula	Nitrogen, % Calcd.	Found
NH_2		OCH_3	171	71	$C_{10}H_9BrN_2O$	11.43	10.87
	C_6H_5	NH_2	121–122	80	$C_{15}H_{11}BrN_2$	9.36	9.78
	CH_3	NH_2	117–118	70	$C_{10}H_9BrN_2$	11.82	11.48
	NH_2	Cl	223	77	$C_9H_6BrClN_2$	10.89	11.02
	NH_2	OCH_3	224–225	77	$C_{10}H_9BrN_2O$	11.43	11.43
	NH_2	CH_3	141–142	72	$C_{10}H_9BrN_2$	11.82	12.23

[a] All m.p.'s were taken on a Fisher–Johns block. [b] W. O. Kermack and T. W. Wright, *J. Chem. Soc.*, 1421 (1935), reported m.p. 188–189° for the compound obtained by bromination of 6-nitro-8-methylquinoline which they deduced to be the 3-bromo derivative. [c] The structure of this compound was not proved. It was prepared from *p*-nitroaniline and the tribromoaldehyde. [d] This compound was prepared by two methods: in 15% yield by the reaction of the tribromoaldehyde with anthranilic acid; in 66% yield by the reaction of the tribromoaldehyde with *m*-bromoanthranilic acid. In each case the reactants were mixed and heated in the absence of solvent until reaction occurred. Acetic acid then was added and the solution was boiled for three hours and worked up as before. [e] G. Bendy, C. C. J. Culvenor, L. J. Goldsworthy, K. S. Kirby and R. Robinson, *J. Chem. Soc.*, 1130 (1950), report m.p. 157–158°.

Isolation of Intermediates.—2-Nitro-4-methylaniline (0.02 mole) was stirred with 2,2,3-tribromopropanal (0.01–0.02 mole) until a thick paste was obtained. This was warmed on a steam-bath for 30 minutes and the resulting hard mass crystallized from alcohol. The bright orange crystals melted 165–160°. The yield was 25%.

Anal. Calcd. for $C_{17}H_{16}Br_2N_4O_4$: C, 40.82; H, 3.22. Found: C, 41.11, 41.10; H, 3.43, 3.45.

When this compound was warmed in acetic acid, a mixture of 3-bromo-6-methyl-8-nitroquinoline and its hydrobromide precipitated. Stirring with ammonia and crystallizing from alcohol gave pure 3-bromo-6-methyl-8-nitroquinoline.

The intermediate was formed in the same way with *o*-nitroaniline. In this case the product was bright yellow, m.p. 180–181°. The yield was 12%.

Anal. Calcd. for $C_{15}H_{12}Br_2N_4O_4$: C, 38.16; H, 2.56. Found: C, 38.05, 38.46; H, 2.98, 2.71.

Warming this compound in acetic acid and working up in the usual way yielded 3-bromo-8-nitroquinoline, m.p. 120–122°, identified by mixed m.p. with authentic sample.[4]

(3) Analyses by Oakwold Laboratories, Alexandria, Va.

(4) C. R. Hauser, M. S. Bloom, A. S. Breslow, J. T. Adams, A. T. Amore and M. J. Weiss, THIS JOURNAL, **68**, 1544 (1946).

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The Oxidation of Stilbestrol in Alkali[1]

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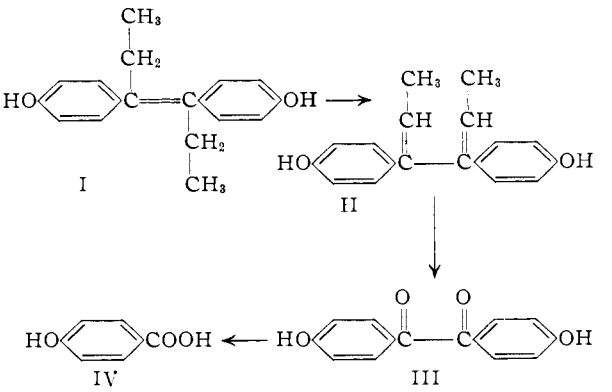
Aqueous neutral or alkaline solutions of diethylstilbestrol kept for two weeks at room temperature or in the cold become yellow in color and lose their estrogenic activity.[2] This instability is greater in the presence of air or oxidizing agents.[3] The isolation of the alkaline oxidation products of stilbestrol was undertaken by us after the crude reaction mixture was found to be effective in causing the release of pituitary gonadotropins.[4] The biological properties of several of the isolated oxidation products have been reported.[4b]

When "concentrated" solutions of stilbestrol (5 mg./cc.) in 0.02 *N* NaOH were oxygenated and allowed to stand at room temperature or refluxed, isodienestrol[5] was isolated in 17–33% yield; 10–27% of the stilbestrol was recovered unchanged. The oxidation of diethylstilbestrol (I) to isodienestrol (II) by the removal of two hydrogens indicates the initial mechanism whereby the estrogenic activity of alkaline stilbestrol solutions is lost on stand-



(1) This investigation was supported in part by research grant C-2161 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) B. Zondek and F. Sulman, *Endocrinol.*, **33**, 204 (1943).

(3) (a) A. E. Wilder-Smith and P. C. Williams, *Nature*, **156**, 718 (1945); (b) A. E. Wilder-Smith and P. C. Williams, *J. Endocrinol.*, **5**, 152 (1947); (c) F. L. Warren, F. Goulden and A. M. Robinson, *Biochem. J.*, **42**, 151 (1948).

(4) (a) O. W. Smith, private communication, 1945; (b) O. W. Smith and R. E. Vanderlinde, *Endocrinol.*, **49**, 742 (1951).

(5) (a) G. J. Hobday and W. F. Short, *J. Chem. Soc.*, 609 (1943); British Patent 566,581 (Jan. 4, 1945); (b) H. v. Euler and E. Adler, *The Svedburg (Mem. Vol.)*, 246 (1944); (c) J. F. Lane and L. Spialter, THIS JOURNAL, **73**, 4408 (1951).

(6) R. E. Vanderlinde and W. W. Westerfeld, *Federation Proc.*, **8**, 262 (1949).