The Preparation and Cyclization of Substituted 1-Anilino-3-halo-2-propanols and Their Conversion to Indoles

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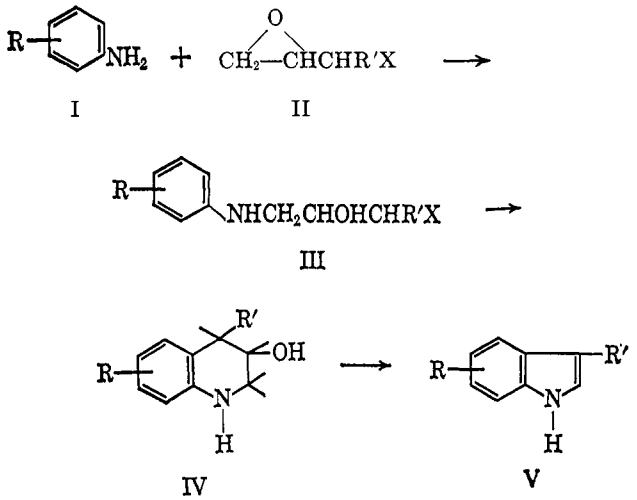
Substituted 1,2,3,4-tetrahydroquinolin-3-ols (IV) were prepared by cyclization of substituted 1-anilino-3-halo-2-propanols (III). General procedures for the preparation and cyclization of III are given. Because periodate oxidation of IV leads to substituted indoles (V), these procedures provide a general method for converting primary aromatic amines to indoles.

An attractive method for preparing substituted indoles involves a three-step synthesis: (1) reaction of primary aromatic amines with epihalohydrins to form substituted 1-anilino-3-halo-2-propanols (III), (2) cyclization of III to form 1,2,3,4-tetrahydroquinolin-3-ols (IV), and (3) periodate oxidation of the tetrahydroquinolinols to give indoles. The feasibility of the



synthesis was shown by the preparation of 5-methoxy and 5-methylindole from *p*-anisidine and *p*-toluidine, respectively.[1] The apparent simplicity of the reactions and the availability of the starting compounds made a more thorough study of the synthesis desirable. Therefore, we have investigated the addition and the cyclization reactions under a variety of conditions and have developed analytical techniques for following the course of the reactions.

The best general method for preparing III is that reported by Merchant, Choughuley, and Vaghani.[2] This involves condensing the amine and epihalohydrin in methanol with hydrochloric acid added as a catalyst. Because of the tendency for by-products to form and the variability in reaction rates, the reactions were analyzed by means of thin layer chromatography (t.l.c.). When a solution containing a 1 *M* concentration of amine and epihalohydrin was allowed to stand at room temperature, a maximum yield of III was usually obtained after about 4 days. Inasmuch as many of the products were oils, their recovery, storage, and characterization were facilitated by converting them to picrate salts. When direct conversion of the reaction products to picrates did not give pure picrates, alumina chromatography was used for purification. Table I gives yield and analytical data for the picrates of substituted 1-anilino-3-chloro-2-propanols prepared using acidic methanol.

When the primary amine is relatively soluble in warm water and seed crystals of the product are available, it is most convenient to carry out the reaction with the epihalohydrin in an aqueous system. For example, *p*-toluidine readily forms a pure addition compound with epichlorohydrin in water at 40–50°.[1] Table II summarizes the data on 3-substituted-1-*p*-toluidino-2-propanols prepared from *p*-toluidine and various epihalohydrins in aqueous systems, except for the reaction involving epifluorohydrin which was also carried out in acidic methanol.

For the cyclization of substituted 1-anilino-3-halo-2-propanols (III), solvents such as bromobenzene and *o*-dichlorobenzene gave the best results. The reaction frequently required several days at reflux temperature. The addition of at least a molar amount of tertiary amine prevented the formation of undesirable by-products and appeared to be essential in order to obtain reasonable yields. The extent of the cyclization was followed by oxidizing the tetrahydroquinolinols, as they were formed, to indoles (IV to V) and determining the amount of indole by means of acidic dimethylaminobenzaldehyde solution. Since the oxidation does not give a quantitative yield of indole, calibration curves were used to relate the extent of cyclization to the amount of indole as determined colorimetrically.

Because 1-*p*-toluidino-3-chloro-2-propanol is a readily obtainable crystalline compound, it was used for a study of the effect of varying the concentrations of the halo compounds and the tertiary base. Diethylaniline was the most commonly used tertiary base. Varying the molar ratio of diethylaniline to addition compound over the range from 1:1 to 12:1 had no marked effect on the yield. Pyridine was found to give about the same yield as diethylaniline while the yields were lower when triethylamine was used. When relatively dilute bromobenzene solutions (usually 0.0042 *M*) of addition compound were used, cyclization yields were over 80%. Higher concentrations led to lower per cent yields, the yield being about 50% at 0.042 *M*. In spite of this decrease in per cent yield the higher concentration was used for preparative work in order to obtain adequate amounts of compound.

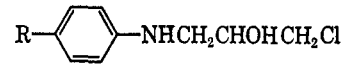
A comparison was made of the cyclization rates of 1-*p*-toluidino-3-halo-2-propanols derived from epifluorohydrin, epichlorohydrin, epibromohydrin, and epiiodohydrin in the presence of diethylaniline. The reactivity of the halides was clearly in the order I > Br > Cl > F.

(1) F. C. Pennington, M. Jellinek, and R. Thurn, *J. Org. Chem.*, **24**, 565 (1959); F. C. Pennington, L. J. Martin, R. E. Reid, and T. W. Lapp, *ibid.*, **24**, 2030 (1959).

(2) J. R. Merchant, A. S. V. Choughuley, and K. D. Vaghani, *Current Sci.* (India), **29**, 142 (1960).

TABLE I

SUBSTITUTED 1-ANILINO-2-CHLORO-2-PROPANOLS

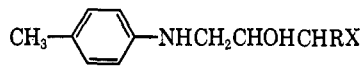


R	Yield, %	Picrate, m.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	75	171–174[a]							
o-CH_3	78	144–145	$C_{16}H_{17}N_4O_8Cl$	44.82	45.15	4.00	4.38	13.07	12.80
m-CH_3	77	123–125	$C_{16}H_{17}N_4O_8Cl$	44.82	45.01	4.00	3.93	13.07	13.05
p-CH_3	71	137–139[a]	$C_{16}H_{17}N_4O_8Cl$						
o-CH_3O	78	119–120	$C_{16}H_{17}N_4O_9Cl$	43.20	43.94	3.85	4.15	12.60	12.54
m-CH_3O	63	114–115	$C_{16}H_{17}N_4O_9Cl$	43.20	43.96	3.85	3.84	12.60	12.37
p-CH_3O	84	115–117	$C_{16}H_{17}N_4O_9Cl$	43.20	43.90	3.85	3.87	12.60	12.37
p-C_2H_5	69	103–106 (addition compd.)	$C_{17}H_{19}N_4O_8Cl$	46.11	46.40	4.32	4.39	12.65	12.57
p-C_6H_5	65	87–88[b]							

[a] See ref. 2. [b] N. N. Vorozhtosov, Jr., and S. I. Kutkevichus, *Zh. Obshch. Khim.*, **27**, 2152 (1957).

TABLE II

3-SUBSTITUTED 1-*p*-TOLUIDINO-2-PROPANOLS



R	X	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	F[a]		51–53 (picrate)	$C_{10}H_{14}NOF$	65.55	65.33	7.70	7.68	7.65	7.83
H	F	41	137–139	$C_{16}H_{17}N_4O_8F$	46.60	47.25	4.16	4.25	13.59	13.79
H	Cl	72	77–78[b]							
H	Br	61	83–83.5	$C_{10}H_{14}NOBr$	49.20	49.36	5.78	5.50	5.74	5.80
H	I	5	61–62.5	$C_{10}H_{14}NOI$	41.25	41.38	4.85	4.90	4.81	4.95
CH_3	Br	45	100.5–101.5	$C_{11}H_{16}NOBr$	51.17	51.37	6.25	5.99	5.43	5.55

[a] Epifluorohydrin was obtained from the Aldrich Chemical Co., Milwaukee, Wis. [b] See ref. 1.

It might appear from the relative cyclization rates that epibromohydrin or epiiodohydrin would be the best epihalohydrins to use, but, in general, the compounds derived from epichlorohydrin were the easiest to prepare in pure form. The compounds which we had isolated as picrates were converted to the free bases with lithium hydroxide prior to cyclization. Picrates could be cyclized directly, but the yields were very low.

For the preparative work either bromobenzene or *o*-dichlorobenzene were used as solvents, but, by using mixtures of 1,2,4-trichlorobenzene and bromobenzene, reaction temperatures could be adjusted over a wide range. Higher temperatures reduced reaction times, but above 180° decomposition appreciably decreased the yields. Table III summarizes the yield and analytical data for 1,2,3,4-tetrahydroquinolin-3-ols prepared using a concentration of 0.042 *M* and a 6:1 molar ratio of diethylaniline to III.

When 1-*p*-toluidino-3-chloro-2-propanol was cyclized without a tertiary base, the yield was very low (5–10%), and small amounts of 1,3-di-*p*-toluidino-2-propanol, apparently formed by the reaction of the addition compound with *p*-toluidine, were isolated. This compound was never isolated when a tertiary base was present. Since pyridine readily forms a quaternary ammonium salt with 1-*p*-toluidino-3-chloro-2-propanol under the reaction conditions, it suggests that the tertiary base prevents the decomposition of the addition compound by forming a salt. It is of interest that, when the pyridine salt was heated in bromobenzene, it readily cyclized. A comparable diethylaniline salt was not isolated.

Since we were interested in the conversion of the tetrahydroquinolinols to indoles, a number of oxidations to form indoles were carried out. Table IV summarizes the results of these experiments. Combined-yield data on the addition and cyclization and oxidation reactions indicate that in some cases the conversion of primary aromatic amines to indoles by this synthetic route is competitive with the Fischer indole synthesis in yield and in ease of preparation.

Experimental

Synthesis of Substituted 1-Anilino-3-halo-2-propanols (III) Using Acidic Methanol.—A solution of the aromatic amine and the epihalohydrin was prepared in which the concentration of both reactants was adjusted to 1 *M*. To 10 ml. of the reaction mixture was added 2 drops of concentrated hydrochloric acid, and the mixture was allowed to stand at room temperature. When analysis by t.l.c. showed that the reaction was nearly complete, the reaction mixture was poured into water, the acid was neutralized with sodium bicarbonate, and the product was extracted with benzene. The benzene was dried over sodium sulfate, and the benzene was removed *in vacuo*. The residual oil was treated with a saturated solution of picric acid in benzene. For the preparation of larger amounts of picrate, it was best to add the picric acid solution dropwise to a stirred benzene solution of the base. Frequently, the presence of impurities in the reaction product made it desirable to chromatograph the mixture on alumina prior to the formation of the picrate. The product was placed on the column in a concentrated benzene solution and eluted with benzene–ether and ether. The picrates were recrystallized from benzene for analysis.

Synthesis of Substituted 1-Anilino-3-halo-2-propanols (III) Using Water.—This procedure has been described previously.[1] Recrystallization was accomplished by using hexane or petroleum ether (b.p. 30–60°). Benzene–hexane was suitable for crystallizing larger amounts when the solubility in hexane was low. Products that are oils at room temperature may also be prepared

TABLE III

SUBSTITUTED 1,2,3,4-TETRAHYDROQUINOLIN-3-OLS

R	R′	R″	R‴	Reaction solvent	Reaction time, days	Yield, %	Recrystn. solvent	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	H	H	H	*o*-Dichlorobenzene	7	43	Petr. ether[a]	86–87[b]							
CH_3	H	H	H	Bromobenzene	3	50	Hexane	101.5–103[c]							
CH_3O	H	H	H	Bromobenzene	3		Benzene–hexane	73.5–74.5[c]							
C_6H_5	H	H	H	Bromobenzene	3	15	"Heptane"	109–111	$C_{15}H_{15}NO$	79.97	79.96	6.71	6.66	6.22	5.89
C_6H_5	H	H	H	Bromobenzene	2	Low	Benzene–hexane	78–78.5	$C_{11}H_{15}NO$	74.54	74.44	8.53	8.41	7.90	7.91
H	CH_3O	H	H	Bromobenzene	4	7[d]		145 dec.	$C_{10}H_{14}NO_2Br$	46.17	45.56	5.42	5.79	5.39	5.35
								57.5–59							
H	H	CH_3	H	*o*-Dichlorobenzene	3	38	Petr. ether	59–60	$C_{10}H_{13}NO$	73.59	73.38	8.03	7.99	8.58	8.63
H	H	CH_3O	H	Bromobenzene	4	48	Hexane	108–109	$C_{10}H_{13}NO_2$	67.02	67.30	7.31	7.29	7.82	7.65
CH_3	H	H	CH_3	Bromobenzene	1	13	Hexane	108–109.5	$C_{11}H_{15}NO$	74.54	74.44	8.53	8.59	7.90	7.81

[a] B.p. 30–60°. [b] G. Benz, C. C. J. Culvenor, L. J. Goldsworthy, K. S. Kirby, and R. Robinson, *J. Chem. Soc.*, 1130 (1950). [c] See ref. 1. [d] Isolated and characterized as the hydrobromide salt.

TABLE IV

SUBSTITUTED INDOLES

R	R′	R″	R‴	Yield, %	M.p., °C.	Lit. m.p, °C.
H	H	H	H	47 (picrate)	170 dec.	175[a]
CH_3	H	H	H	57 (picrate)	151–154 dec.	151[b]
OCH_3	H	H	H	(picrate)	145–148	145[c]
H	OCH_3	H	H	43 (picrate)	118–120 dec.	123[d]
CH_3	H	H	CH_3	70	73–74	74.5–75[e]
H	H	CH_3	H	52	82–83	82[f]
H	H	OCH_3	H	35 (picrate)	148–153 dec.	156[g]

[a] E. Hertel, *Ann.*, **451**, 191 (1926). [b] J. Raschen, *ibid.*, **239**, 226 (1887). [c] K. G. Blaikie and W. H. Perkin, Jr., *J. Chem. Soc.*, **125**, 322 (1924). [d] W. O. Kermack, W. H. Perkin, Jr., and R. Robinson, *ibid.*, **121**, 1879 (1922). [e] F. Mendlik and J. P. Wibant, *Rec. trav. chim.*, **50**, 91 (1931). [f] W. J. Boyd and W. Robson, *Biochem. J.*, 555 (1935). [g] K. G. Blaikie and W. H. Perkin, Jr., *J. Chem. Soc.*, **125**, 298 (1924).

by this procedure, but purification of the oil by chromatography is recommended.

Thin Layer Chromatographic Analysis.—Aluminum oxide with 5% calcium sulfate[3] was used as an absorbent and 15% (v./v.) hexane in acetone was used as the eluting solvent. The fumes from fuming nitric acid served as developing agent. In general, the primary amines moved the most rapidly, III moved less rapidly, and the disubstituted products moved least rapidly. The purity of picrates was estimated by treating the picrate with saturated lithium hydroxide and immediately extracting the addition compound with benzene. The benzene solutions were then analyzed. Although III may be hydrolyzed in basic solution, no hydrolysis was observed using this procedure.

Other Methods of Preparing III.—Early in our investigation it was hoped that one solvent might be suitable for both the addition and the cyclization reactions. Bromobenzene was chosen for study, and in this solvent the addition reaction proved to be very slow. For example, reaction of *p*-toluidine with epichlorohydrin at a concentration of 2.5 *M* required 2 to 3 weeks at room temperature. Kinetic studies using hydrogen bromide to titrate the unreacted epoxide revealed that there is an induction period.[4] With a 1 *M* bromobenzene solution the reaction was very slow for almost 10 days. Aniline exhibited a longer induction period and *p*-anisidine exhibited a shorter induction period. Raising the temperature led to undesirable side reactions. Reaction in dioxane was also very slow.

There are other procedures in the literature for the preparation of III[5] that we thought might be generally applicable. We followed these procedures and analyzed the products with t.l.c. In our experiments, the products appeared to be impure.[4]

Synthesis of 3-Bromo-1,2-epoxybutane.—This compound was conveniently prepared from crotyl alcohol by modifying the Petrov procedure.[6] The intermediate dibromide was not distilled but was converted directly to the epoxide by dehydrobromination. The dibromide, dissolved in an ether solution, was shaken at room temperature for 2 hr. with an equivalent amount of 1.7 *N* potassium hydroxide. The ether layer was separated, washed with water, and dried over magnesium sulfate. The ether was removed by distillation, and the residual oil was distilled and collected at 150–152°.

Analysis of Cyclization.—The procedure was adapted from that previously reported.[1] A 5% hydrochloric acid extract (3 ml.) from an aliquot (1 ml.) of the reaction mixture was added to the sodium metaperiodate solution (3 ml. of 1.28%) and sodium hydroxide solution (3 ml. of 6 *N*), and the mixture was distilled immediately. Most of the indole was collected in the

(3) Camag, Arthur H. Thomas Co., Philadelphia, Pa.

(4) O. Aniline and F. C. Pennington, reported at the Iowa Academy of Science Meeting, 1964; *Proc. Iowa Acad. Sci.*, to be published.

(5) J. B. McKelvey, B. S. Webre, and R. R. Benerito, *J. Org. Chem.*, **25**, 1424 (1960); H. R. Yale, E. J. Pribyl, W. Braker, F. H. Bergein and W. A. Lott, *J. Am. Chem. Soc.*, **72**, 3710 (1950).

(6) A. A. Petrov, *Zh. Obsch. Khim.*, **11**, 713 (1946).

first 5 ml. of distillate. The distillate was diluted to 10 ml. with ethanol, and further dilutions were made using 50% ethanol.

Aliquots (2 ml.) of the indole solution were treated with 1 ml. of 2.5% alcoholic dimethylaminobenzaldehyde and 1 ml. of 6 *N* hydrochloric acid. The indoles gave characteristic wine-violet colors (λ_{max} in the range of 570–585 mμ). Unreacted III also reacted with the periodate, and the amine formed was also steam distilled. The amine reacted with the Ehrlich reagent to give a yellow color (around 430 mμ). Therefore, it was possible to follow simultaneously the decrease in the concentration of III and the increase in the concentration of the tetrahydroquinolinol. Calibration curves were prepared by using solutions of the tetrahydroquinolinol of known concentrations in the analysis.

Cyclization Procedure.—The substituted 1-anilino-3-halo-2-propanol (III) was added to the reaction solvent together with the base (usually diethylaniline). The molar ratio of base to III was usually 6:1. When picrates were used for the cyclization, they were first treated with saturated lithium hydroxide and the addition compound was extracted with the reaction solvent. The solution was washed with water and dried with sodium sulfate before the addition of diethylaniline. Reaction mixtures were adjusted to about 0.042 *M* and then boiled under reflux. It was helpful to follow the course of the cyclization by the procedure outlined above even if calibration curves were not available in order to determine the best reaction time. Isolation was accomplished essentially by the procedure previously reported.[1] This involved extraction with 5% hydrochloric acid, neutralization with sodium hydroxide, extraction with benzene, and purification by means of alumina chromatography. The product was eluted with benzene–ether mixtures and ether. Evaporation of the eluates frequently gave very pure fractions while less pure fractions were recrystallized or converted to salts.

For kinetic experiments concentrations of addition compounds usually were adjusted to 0.0042 *M*. This gave cyclization yields of greater than 80%, but the concentrations were too low to make the procedure practical for most preparative purposes. The amount of III used at the concentration of 0.0042 *M* was only about 1 g./l. of solvent.

The effect of small amounts of water on the cyclization was negligible, but, if additional water was added, the yield was decreased. At the high temperatures used for the reaction the water tended to be carried up into the condenser. With larger amounts of water (1 ml./l.) a separate layer was present in the reaction mixture. This may have led to hydrolysis of the addition compound or to hydrolysis of an intermediate epoxide.

It is important to point out that tertiary bases, such as triethylamine, pyridine, γ-picoline, could be used in the cyclization. Pyridine salts of III could also be used. In the absence of base yields were very low and cyclization using 1-*p*-toluidino-3-chloro-2-propanol led to the formation of 1,3-di-*p*-toluidino-2-propanol, m.p. 113–115° (lit.[7] m.p. 113.5–114°). Positive identification of this product was established by analysis.

Anal. Calcd. for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.73; H, 7.52; N, 10.42.

Pyridine Salt of 1-*p*-Toluidino-3-chloro-2-propanol.—1-*p*-Toluidino-3-chloro-2-propanol (2.00 g.) was dissolved in pyridine (5 ml.), and the mixture was boiled under reflux for 1 hr. The mixture was cooled, and the yellow crystalline salt was recovered and washed with acetone. Addition of acetone to the mother liquor gave more product, 2.13 g. (76%). The compound, after recrystallization from acetone–methanol, had m.p. 192°.

Anal. Calcd. for $C_{15}H_{19}N_2OCl$: C, 64.62; H, 6.87; N, 10.05. Found: C, 64.36; H, 7.15; N, 9.77.

Oxidation of the Tetrahydroquinolinols to Indoles.—The procedure used was essentially that previously reported.[1] When the indole crystallized in the steam distillate, it was recovered by filtration and the mother liquor was extracted with ether. If purification proved necessary, alumina chromatography was effective.

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(7) B. J. Ludwig, W. A. West, and D. W. Farnsworth, *J. Am. Chem. Soc.*, **76**, 2893 (1954).

Metal Ion Decomposition of Hydroperoxides. III. Intermediates in Cobalt Salt Catalyzed Decomposition of *t*-Butyl Hydroperoxide[1a]

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Evidence for peroxy radical intermediates during the cobalt salt catalyzed decomposition of *t*-butyl hydroperoxide is given by electron spin resonance (e.s.r.) spectra and the effect of hydrogen atom donors on rate. Reactions of the peroxy radicals support a mechanism previously proposed. No evidence for peroxy radical–π-aromatic complexes was observed from kinetic or e.s.r. data. A deuterium isotope effect (k_H/k_D) of 1.93 was found for cobalt 2-ethylhexanoate catalyzed decomposition of *t*-butyl deuterioperoxide in chlorobenzene. In contrast, no isotope effect was observed with cobalt acetate catalysis in acetic acid-*d*. The isotope effects were rationalized in terms of the relative oxidation state of cobalt in the two systems. The effect of added 2-ethylhexanoic acid could not be solely explained on the basis of competition between the acid and hydroperoxide for cobalt ligand sites. It is suggested that the acid may not only compete for ligand sites, but that it may be hydrogen bonding the hydroperoxide and/or peroxy radicals.

Previously, a kinetic and product study of the catalytic decomposition of *t*-butyl hydroperoxide by cobalt acetate in acetic acid and by cobalt 2-ethylhexanoate in chlorobenzene was reported.[1a] The principal products, *t*-butyl alcohol and oxygen, were proposed to originate from the reactions between peroxy radicals and cobalt–hydroperoxide complexes.[1a,2] Further evidence for these intermediates is given. In addition, the question of peroxy radical–π-aromatic complexes, the mode of di-*t*-butyl peroxide formation, and the significance of a deuterium isotope effect with *t*-butyl deuterioperoxide is considered.

(1) (a) Part II: W. H. Richardson, *J. Am. Chem. Soc.*, **87**, 1096 (1965); (b) Department of Chemistry, San Diego State College.

(2) M. H. Dean and G. Skirrow, *Trans. Faraday Soc.*, **54**, 849 (1958).

Experimental

Materials.—Hydrocarbon solvents were distilled from calcium hydride and stored over the hydride. Cumene (Phillips, 99 mole %) was first purified by repeated extractions with concentrated sulfuric acid, concentrated sodium hydroxide, and water. The dried product was fractionated through a 30-in. glass helices