Expt. 20.—The reaction mixture was poured into water, extracted with diethyl ether and, after drying, the ether was removed by distillation under reduced pressure. The residue was recrystallized from petroleum ether; the 6.8 g. of ethyl α-oximinopropionate obtained had m.p. and mixed m.p. 94.5°. From the petroleum ether mother liquors 8.7 g. of a high-boiling, orange liquid was obtained which, on attempted rectification, gave no ethyl α-nitropropionate.

The Reaction of Propyl Pseudonitrole with Sodium Nitrite.—Propyl pseudonitrole was prepared in 42% yield by treating the sodium salt of 2-nitropropane, in aqueous methanol, at −15°, with nitrosyl chloride. The precipitate was isolated by filtration, washed with water, with absolute ethanol, and then air-dried (in the dark). The white powder melted with decomposition to a blue liquid at 74–75°, lit. m.p. 76°.[19]

To 600 ml. of DMF in a flask equipped with a sealed stirrer was added 50 g. of propyl pseudonitrole (0.42 mole). A small aliquot (A) was removed to observe color changes. Urea (40 g.) was then added and, once again, an aliquot (B) removed. Finally 36 g. of sodium nitrite (0.52 mole) was added after which the mixture was allowed to stir in the dark.

COLOR CHANGES OBSERVED AT ROOM TEMPERATURE

Time, hr.	Aliquot A	Aliquot B	Reaction mixture
0	Deep blue	Deep blue	Deep blue
3	Deep blue	Deep blue	Deep blue-gr.
15	Deep blue	Deep blue	Light yellow
40	Deep blue	Deep green	.....
65	Pale green	Light yell.	.....
75	Pale yellow	Light yell.	.....

After 15 hr. the reaction mixture was subjected to a vacuum of 10 mm. for 3 hr.; traps held at −80° were interposed between the pump and the reaction product. The 25 g. of a very pale yellow liquid which collected in the traps was rectified. The first material to distil was a pale yellow liquid, b.p. 21°, probably N_2O_4 + NO_2, which was lost by accident. After a very small interfraction (b.p. 21–52°) there was obtained 18.2 g. (76% yield) of acetone, b.p. 52–54°, $n^{20}D$ 1.3586–1.3589. The 2,4-dinitrophenylhydrazone (89% yield) had m.p. 124–125°, mixed m.p. with an authentic sample 124–125°.

Isolation of Cyclopentyl Pseudonitrole from the Reaction of Cyclopentyl Bromide with Sodium Nitrite.—Cyclopentyl bromide, 45 g. (0.3 mole), was treated with sodium nitrite in the manner described for the preparation of 4-nitroheptane from 4-iodoheptane[3] (reaction time 7 hours). The blue petroleum ether extracts were concentrated *in vacuo* and the deep blue residual liquid was allowed to stand at −5°. White crystals precipitated out and the intensity of the blue color diminished considerably. At the end of a week the pale blue solution was filtered and the white solid collected (see below). (The filtrate, on rectification, gave a 32% yield of nitrocyclopentane and a 12% yield of cyclopentyl nitrite.) When the white crystals were recrystallized from diethyl ether there was obtained 2.2 g. (5% yield) of white crystals, m.p. 89.5–90.5° (sealed tube). At the melting point the solid formed a blue liquid which decomposed on further heating.

Anal. Calcd. for $C_5H_8N_2O_3$: C, 41.66; H, 5.59; N, 19.93. Found: C, 41.61, 41.56; H, 5.70, 5.86; N, 20.01, 20.28.

LAFAYETTE, INDIANA

(19) V. Meyer, *Ann.*, **175**, 120 (1875).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, NORTHWESTERN UNIVERSITY DENTAL SCHOOL]

Some New Halogen-substituted Pressor Amines of the Synephrine Type[1]

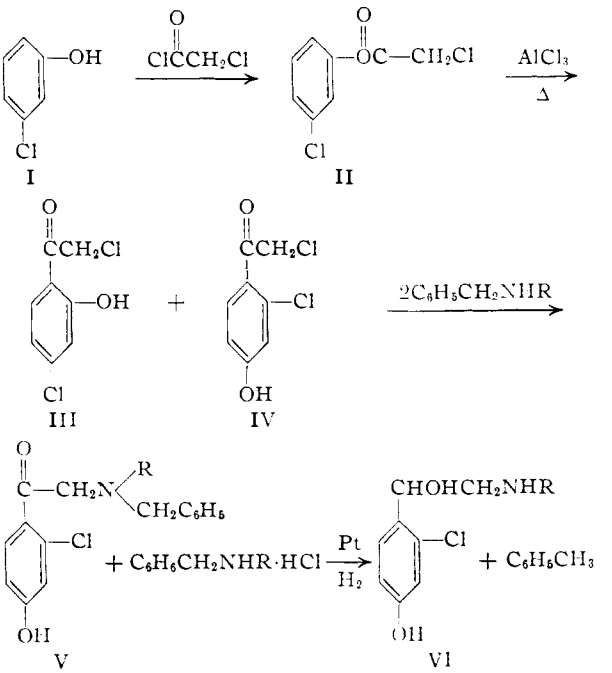
BY J. A. CARBON AND L. S. FOSDICK

RECEIVED MAY 25, 1955

2-Chloro-4-hydroxy-α-(methylaminomethyl)-benzyl alcohol hydrochloride and the corresponding N-ethyl compound have been prepared and their physical properties described. Pharmacological testing of these compounds has shown that the halogen atom in the 2-position greatly reduces vasopressor activity.

Even though epinephrine has long been used in conjunction with local anesthetics as a vaso-constricting agent, other compounds which would possess high vaso-constrictor properties, but which would be free from the undesirable side effects of epinephrine have been sought. Many substituents have been introduced into the aromatic nucleus of epinephrine, but the introduction of halogen atoms has received comparatively little attention.

This work is an extension of the early work of Hansen,[2a] and later of Fosdick, Fancher and Urbach,[2b] on the preparation of halogen-substituted synephrine derivatives. These workers prepared some 3-chloro- and 3-fluoro-4-hydroxy-α-(alkylaminomethyl)-benzyl alcohol hydrochlorides and showed that the halogen atom in the 3-position reduced the pressor activity to $^1/_{400}$ that of epinephrine. The effect of fluorine in the aromatic ring of a pressor amine compared favorably with chlorine in the same position, but both were inferior to a hydroxyl group in this respect. The reaction scheme used was



(1) This paper is derived from part of the thesis submitted for partial fulfillment of the Ph.D. degree.

(2) (a) H. L. Hansen, THIS JOURNAL, **59**, 280 (1937); (b) L. S. Fosdick, O. E. Fancher and K. F. Urbach, *ibid.*, **68**, 840 (1946).

The starting material, *m*-chlorophenol (I), was synthesized from commercial *m*-chloroaniline by diazotization and subsequent thermal decomposition using a method modified from that of Fieser and Thompson.[3] The substance thus obtained was esterified by refluxing with a slight excess of chloroacetyl chloride in the absence of any solvent to form *m*-chlorophenyl chloroacetate (II).

The Fries rearrangement of II occurred only with great difficulty and with poor yields. Since only the *p*-hydroxy isomer IV was desired, the reaction was attempted at room temperature using nitrobenzene as solvent. This method has been shown to yield predominantly the *para*-isomers with several nuclear substituted phenyl acetates,[4] but with the closely related compound, *m*-cresyl acetate, only the *o*-hydroxy isomer is obtained using the above conditions.[5] This method gave little or no product with II, even when allowed to stand for two days at room temperature in nitrobenzene solution containing a slight molar excess of anhydrous aluminum chloride. Attempts to run the reaction at higher temperatures were also unsatisfactory due to extensive polymer formation.

Since all attempts to carry out successfully the Fries reaction in nitrobenzene failed, the reaction was attempted in carbon disulfide, a method previously used with success by Hartung, *et al.*[6] This method has also been used to produce 3-chloro- and 3-fluoro-4-hydroxy-ω-chloroacetophenone from *o*-chloro- and *o*-fluorophenyl chloroacetate by Hansen.[2] With it, we obtained a mixture of 4-chloro-2-hydroxy-ω-chloroacetophenone (III) and 2-chloro-4-hydroxy-ω-chloroacetophenone (IV), which were separated by steam distillation, making use of the fact that *o*-hydroxy aromatic ketones are volatile with steam while the *p*-hydroxy isomers are not. The structures of the two isomers were proved by ring closure of III in sodium acetate solution to form 6-chloro-3(2H)-benzofuranone,[7] and by methylation and oxidation of IV to form 2-chloro-4-methoxybenzoic acid,[8] both of which have been previously prepared.

The condensation of IV with the N-alkylbenzyl amines, and the subsequent catalytic debenzylation and reduction were carried out according to a general method first mentioned in Canadian Patent 318,488 and later extended by Baltzly and Buck.[9,10]

The compounds were tested for vaso-pressor activity by intravenous injection of an aqueous solution into dogs anesthetized with Nembutal. Blood pressure was recorded directly from the carotid artery, and the rise in blood pressure was compared to that produced by a standard solution of epinephrine.

Using this testing procedure, compound VI (R = CH_3) displayed a pressor activity only $^1/_{400}$–$^1/_{500}$ that of epinephrine, while the corresponding ethyl derivative (VI, R = C_2H_5) was even weaker, being only $^1/_{600}$ as active as epinephrine. Duration of action was slightly prolonged with the ethyl derivative, however. From the fact that synephrine (*p*-$OHC_6H_4CHOHCH_2NHCH_3$) is approximately $^1/_{50}$ as active as epinephrine, it appears that chlorine substitution in the 2-position of this type of compound has the effect of reducing the pressor activity approximately by a factor of ten.

(3) L. F. Fieser and H. T. Thompson, THIS JOURNAL, **61**, 376 (1939).

(4) K. W. Rosenmund and W. Schnurr, *Ann.*, **460**, 77 (1928).

(5) A. H. Blatt, *Chem. Revs.*, **27**, 413 (1940).

(6) W. H. Hartung, J. C. Munch, E. Miller and F. Crossley, THIS JOURNAL, **53**, 4149 (1931).

(7) R. Kuhn and H. R. Hensel, *Ber.*, **84**, 557 (1951).

(8) F. Ullmann and C. Wagner, *Ann.*, **355**, 368 (1907).

(9) R. Baltzly and J. S. Buck, THIS JOURNAL, **62**, 164 (1940).

(10) R. Baltzly and J. S. Buck, *ibid.*, **65**, 1984 (1943).

Experimental

***m*-Chlorophenyl Chloroacetate** (II).—*m*-Chlorophenol (100 g., 0.78 mole) was mixed with 100 g. (0.89 mole) of chloroacetyl chloride and refluxed until evolution of hydrogen chloride had ceased (about five hours). After cooling, the solution was diluted with an equal volume of ether, extracted with two small portions of 1 *N* KOH, and the ether layer dried over anhydrous $MgSO_4$. The ether was then removed and the dark oil distilled under vacuum to yield 90 g. (56%) of a colorless oil, b.p. 145–148° (11 mm.). This purification was usually not carried out, the crude reaction mixture being used directly for the Fries reaction.

Anal. Calcd. for $C_8H_6O_2Cl_2$: C, 46.86; H, 2.95. Found: C, 46.77; H, 2.91.

4-Chloro-2-hydroxy-ω-chloroacetophenone (III).—The crude reaction mixture prepared from 96.4 g. (0.75 mole) of *m*-chlorophenol and 102 g. (0.90 mole) of chloroacetyl chloride as directed above was slowly added to a suspension of 120 g. (0.90 mole) of anhydrous aluminum chloride in 500 ml. of carbon disulfide contained in a three-neck flask fitted with a thermometer, reflux condenser and dropping funnel. The resulting dark green solution was refluxed until HCl evolution had practically ceased (about 2 hours), and the carbon disulfide then removed *in vacuo*. The heavy black oil was slowly brought up to 135–140° and maintained there for an additional 2 hours. After cooling, the thick black mass was decomposed by the addition of 1500 ml. of dilute HCl, and the resulting mixture distilled with steam. The yellow oil which rapidly solidified as it came over was isolated by suction filtration and dried in a vacuum desiccator. Upon recrystallization from petroleum ether (60–70°), it appeared as 17.0 g. (11%) of light yellow needles, m.p. 74–75°. This compound is sparingly soluble in cold petroleum ether, soluble in hot petroleum ether, and extremely soluble in ethanol or benzene.

Anal. Calcd. for $C_8H_6O_2Cl_2$: C, 46.86; H, 2.95. Found: C, 47.04; H, 2.89.

2-Chloro-4-hydroxy-ω-chloroacetophenone (IV).—The aqueous phase of the residue from the above steam distillation was decanted off from a quantity of black oil and cooled overnight in the refrigerator. A quantity of light yellow crystals were thus deposited, which were filtered off with suction and dried in the air. Further quantities of this material were obtained by extraction of the black oil with several large portions of boiling water, decantation, and cooling in the refrigerator. The combined solids were recrystallized from a benzene–petroleum ether (60–70°) mixture, to obtain 32 g. (21%) of long, light yellow needles, m.p. 117–118°. This compound is soluble in ethanol or benzene, slightly soluble in hot water, and insoluble in cold water or petroleum ether.

Anal. Calcd. for $C_8H_6O_2Cl_2$: C, 46.86; H, 2.95. Found: C, 47.05; H, 2.85.

Proof of Structure of III by Conversion to 6-Chloro-3(2H)-benzofuranone.—Two grams (0.01 mole) of III was dissolved in 30 ml. of hot ethanol containing 5 g. of sodium acetate. The bright red solution was boiled for 15 minutes and then poured into 200 ml. of ice-water. The light red precipitate was filtered off with suction, washed with water, and dried in the air. Upon recrystallization from cyclohexane it appeared as 1.5 g. (88%) of light yellow prisms, m.p. 120–121°. The recorded melting point for 6-chloro-3(2H)-benzofuranone is 123°.[7]

Anal. Calcd. for $C_8H_5O_2Cl$: C, 56.99; H, 2.98. Found: C, 57.13; H, 2.81.

The **semicarbazone**, synthesized in the usual manner, was obtained as a yellow microcrystalline solid from ethanol. This compound melted at 217–220°, which agrees well

with the recorded melting point of 220° for 6-chloro-3(2H)-benzofuranone semicarbazone.[7]

Proof of Structure of IV by Conversion to 2-Chloro-4-methoxybenzoic Acid.—Two grams (0.01 mole) of IV was dissolved in 50 ml. of water containing 2 g. of NaOH and heated to the refluxing temperature. Methyl sulfate (2.5 g., 0.02 mole) was added slowly and the refluxing continued for 2 hours. At the end of this time, a solution of 8 g. of $KMnO_4$ in 100 ml. of water was added slowly and the refluxing continued for an additional hour. The manganese dioxide was then filtered off with suction, washed with water, and the combined filtrates made strongly acidic with concd. HCl. After cooling overnight in the refrigerator, the light yellow solid was filtered off with suction and recrystallized from dilute ethanol to yield 0.8 g. (42%) of short colorless needles, m.p. 204–205° with sublimation. The recorded melting point of 2-chloro-4-methoxybenzoic acid is 208° with sublimation.[8]

Anal. Calcd. for $C_8H_7O_3Cl$: C, 51.49; H, 3.78. Found: C, 51.61; H, 3.50.

2-Chloro-4-hydroxy-ω-(benzylmethylamino)-acetophenone Hydrochloride (V, R = CH_3).—2-Chloro-4-hydroxy-ω-chloroacetophenone (IV) (3.5 g., 0.017 mole) was added as a powder to 4.1 g. (0.034 mole) of N-benzylmethylamine[11] dissolved in an anhydrous mixture of 150 ml. of ether and 50 ml. of dioxane. The resulting red solution was shaken mechanically until crystals of N-benzylmethylamine hydrochloride were seen to form (about 5 hours) and then left to stand at room temperature for 3 days. The precipitated secondary amine hydrochloride was filtered off with suction and washed with a little dry ether. Absolute ethanol, saturated with dry HCl, was added dropwise to the combined filtrates until the yellow precipitate just began to redissolve. After the addition of 100 ml. of dry ether, the mixture was chilled in the refrigerator and the precipitate isolated by suction filtration. This substance was dissolved in a small quantity of absolute methanol, decolorized with Norit, and precipitated with dry ether to obtain 4.3 g. (78%) of colorless leaflets, m.p. 145–150° dec.

Anal. Calcd. for $C_{16}H_{17}Cl_2O_2N$: N, 4.29; ionic Cl, 10.87. Found: N, 4.18; ionic Cl, 10.73.

2-Chloro-4-hydroxy-ω-(benzylethylamino)-acetophenone Hydrochloride (V, R = C_2H_5).—This substance was prepared in a similar manner using 3.5 g. (0.017 mole) of IV and 4.6 g. (0.034 mole) of N-benzylethylamine.[11] The product was obtained as 3.0 g. (52%) of almost colorless leaflets, m.p. 177–180° dec.

Anal. Calcd. for $C_{17}H_{19}Cl_2O_2N$: N, 4.12; ionic Cl, 10.42. Found: N, 3.90; ionic Cl, 10.36.

2-Chloro-4-hydroxy-α-(methylaminomethyl)-benzyl Alcohol Hydrochloride (VI, R = CH_3).—Two grams (0.0061 mole) of V (R = CH_3) were placed in the hydrogenation flask with 40 ml. of absolute methanol and 0.1 g. of Adams catalyst and hydrogenated at a pressure of 47 lb./sq. in. at room temperature. At the completion of the reaction (about 5 hours), the catalyst was filtered off and the methanol removed *in vacuo*. The remaining oily solid was dissolved in a small quantity of hot acetone, separated from insoluble oils by decantation, and slowly cooled to 0°. The product was thus obtained as colorless prisms, m.p. 160–161°, with a yield of 1.0 g. (69%).

Anal. Calcd. for $C_9H_{13}Cl_2O_2N$: N, 5.88; ionic Cl, 14.89. Found: N, 5.69; ionic Cl, 14.91.

2-Chloro-4-hydroxy-α-(ethylaminomethyl)-benzyl Alcohol Hydrochloride (VI, R = C_2H_5).—This compound was prepared in the same manner from 2.0 g. (0.0059 mole) of V (R = C_2H_5), and was obtained as 0.98 g. (65%) of colorless prisms from absolute methanol-ether, decomposing at 160–170°.

Anal. Calcd. for $C_{10}H_{15}Cl_2O_2N$: N, 5.55; ionic Cl, 14.06. Found: N, 5.46; ionic Cl, 13.89.

CHICAGO 11, ILLINOIS

(11) The N-alkylbenzylamines were prepared from the corresponding N-benzylidenealkylamines by catalytic reduction using a palladium-on-charcoal catalyst.

COMMUNICATIONS TO THE EDITOR

DEUTERIUM ISOTOPE EFFECTS ON THE AIR OXIDATION OF CUMENE

Sir:

In spite of the large body of data on the air oxidation of hydrocarbons,[1] no direct evidence has been presented that would indicate the nature of the termination reaction. The reaction $2RO_2\cdot \rightarrow ROOR + O_2$ is the most common proposal. The kinetically important propagation reaction of air oxidations is much better understood and is accepted as involving the formation of alkyl radicals by reaction of alkyl peroxy radicals with hydrocarbons. The stabilization of free radicals by resonance[2] is well established, but evidence for hyperconjugative resonance stabilization rests mostly on addition reactions to C=C bonds.[2] The relative reactivities of toluene and cumene toward various free radicals[3] indicate that adjacent methyl groups can affect the rate by as much as a factor of 18.9, but this is complicated by polar effects. In the oxidation of ring substituted cumenes, polar substituents have a small effect with a ρ value of -0.4.[4]

In order to learn more about the stabilization of free radicals and the nature of the chain terminating step, the rates of oxidation of cumene and β-deutero cumenes were determined. To the extent that hyperconjugative stabilization is important the rates should be slower for the deuterated compound.[5] On the other hand, if the chain terminating step involved breaking a C–H bond this step should be greatly inhibited and the net result would be an increase in the rate of oxidation.

The deuterocumene was prepared from deuteroacetone and phenylmagnesium bromide. The resulting carbinol was dehydrated with iodine catalyst and the olefin hydrogenated to cumene using Adams catalyst with methanol as the solvent. The cumene was washed with concentrated sulfuric acid and distilled before use in the oxidation experiments. Two different samples of deuterocumene were prepared and analyzed by optical density measurements in the 3.4 μ region on a

(1) L. Bateman, *Quarterly Reviews*, **8**, 147 (1954).

(2) G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, New York, N. Y., 1955, pp. 381–476.

(3) G. A. Russell and H. C. Brown, THIS JOURNAL, **77**, 4578 (1955).

(4) G. A. Russell, Abstracts of Papers, 128th Meeting Am. Chem. Soc., Minneapolis, Minn., **128**, 18-O (1955).

(5) E. S. Lewis and C. E. Boozer, THIS JOURNAL, **76**, 791 (1954).