considerably, but 20 g. of product (XIX) boiling at 101° (100 mm.) was obtained (19.9% yield); infrared spectrum: bands at 1610, 1650, 2960, and 3350 cm.$^{-1}$; n.m.r. spectrum showed a single peak for a hydroxyl H, a single peak for 2(—CH_3), and a series of peaks corresponding to a vinylic hydrogen split by a cross-ring —CH_2— and resplit by an adjacent —CH_2—.

Anal. Calcd. for $C_7H_8F_4O$: C, 45.6; H, 4.35; F, 41.3. Found: C, 45.85; H, 4.38; F, 40.95.

2-(3,3,4-Trifluoro-4-chloro-1-cyclobutenyl)isopropyl Alcohol (XV).—A 2-l. steel bomb containing 600 g. (7.15 moles) of 3-methyl-1-butyn-3-ol (XIII) and 5 ml. of "Terpene B" inhibitor was chilled in a Dry Ice bath and then evacuated. A 610-g. sample (5.25 moles) of trifluorochloroethylene was bled in, and the bomb was heated at 160° for 24 hr. On cooling, bleeding off gases, and opening, 1110 g. of brown liquid was obtained. This was steam distilled to yield 676.3 g. (after drying over magnesium sulfate) of steam volatile material. Vapor phase chromatography showed this to be 70% pure adduct XV. The yield was thus 45%. The product had the following properties: b.p. 97–98° (38 mm.); $d^{25}{}_{25}$ 1.468; n^{26}D 1.4198; infrared spectrum: bands at 1610, 2960, and 3350 cm.$^{-1}$; n.m.r. spectrum showed single peaks for a hydroxyl H and a methyl H, and a series of peaks corresponding to a vinylic hydrogen split once by a cross-ring —CFCl— and split again by an adjacent —CF_2—.

Anal. Calcd. for $C_7H_8ClF_3O$: C, 42.0; H, 4.00; Cl, 17.7; F, 28.5. Found: C, 41.83; H, 3.77; Cl, 18.99; F, 28.93.

1-Isopropenyl-3,4,4-trifluoro-3-chloro-1-cyclobutene (XVI).—About 50 g. (0.25 mole) of the above 2-(3,3,4-trifluoro-4-chloro-1-cyclobutenyl)isopropyl alcohol was added dropwise with stirring into 130 ml. of concentrated sulfuric acid previously cooled to 5° in an ice bath. The temperature was maintained at 5–15° throughout the addition. Afterwards the temperature was allowed to rise to 20° for 2.5 hr., at which time it was poured into 500 g. of ice with stirring. A black tar resulted which was extracted several times with dichloromethane (a process which proved very messy and tedious). The extracts were dried over anhydrous magnesium sulfate and then stripped to a volume of about 75 ml. The product was distilled at 38-mm. pressure. A 12-g. sample of XXI (27% yield) was obtained, boiling at 61–65° (38 mm.), n^{26}D 1.4304; infrared spectrum: bands at 1588 and 1635 cm.$^{-1}$. Sharts and Roberts[8] reported this compound earlier and listed properties as follows: infrared bands at 1588 and 1635 cm.$^{-1}$, b.p. 60–65° (32–37 mm.), n^{25}D 1.4288–1.4295.

Attempted Diels–Alder Reactions of 2,2′-Dimethoxy-3,3,3′,3′-tetrafluorobicyclobutenyl (VIIIa). A. With Maleic Anhydride.—A 2.38-g. sample (0.01 mole) of the above "dibox" compound (VIIIa) and 1.5 g. (0.015 mole) of maleic anhydride were refluxed with 50 ml. of toluene for 55 hr. At the end of the reflux period, a small amount of black solid was filtered off. The filtrate, on cooling, yielded 0.45 g. of bright yellow needles. Infrared spectra (see Table I) showed this to be identical with 2,2′-diethoxy-3,3′-diketobicyclobutenyl (IXa) prepared by sulfuric acid hydrolysis of the same starting material.

B. With Tetracyanoethylene.—A 2.38-g. sample (0.01 mole) of XIIIa and 1.30 g. of tetracyanoethylene (0.01 mole) were dissolved separately in 10 ml. portions of tetrahydrofuran and the two solutions were then mixed. No colored π-complex was observed. A day later the solvent was stripped *in vacuo*. The residual solid was found to be a mixture of the two starting materials. There was no indication of any reaction having occurred.

Acknowledgment.—The authors wish to express their appreciation to the Minnesota Mining and Manufacturing Company, St. Paul, Minnesota, and the U. S. Army Quartermaster Research and Engineering Command, Natick, Massachusetts, under Scientific Project Officer, Dr. Malcolm C. Henry, for their partial support of this work.

The Synthesis and Properties of 1,1-Dimethylindolium Perchlorate, an N-Quaternized Indole

R. L. HINMAN AND J. LANG

The Union Carbide Research Institute, Union Carbide Corporation, Tarrytown, New York

Received December 26, 1963

1,1-Dimethylindolium perchlorate (IVb), the first example of an N-quaternized indole, has been prepared *via* the sequence: isatin, 3-hydroxyindoline (I), 1,1-dimethyl-3-hydroxyindolinium chloride (II), 3-chloro-1,1-dimethylindolinium chloride (III), and dehydrochlorination of the last compound to the indolium salt. The ultraviolet spectrum of IVb bears a striking resemblance to those of indene and styrene. The indolium salts are powerful methylating agents, attacking even chloride ion at room temperature. Dehydrochlorination of III can also be effected by chloride ion. Both reactions are favored by nonpolar media.

In the course of our investigations of the protonation of indoles[1a,b] and pyrroles,[1c,d] it became desirable to know the general characteristics of the ultraviolet spectra of N-protonated indoles. Although N-protonated salts have been isolated,[1a,b] the principal conjugate acid of an indole in solution in strong acids is the 3-protonated isomer.[1b] A model for the N-protonated species was prepared, therefore, in the form of 1,1-dimethylindolium perchlorate (IVb), the first example of an N-quaternized salt of an indole. This report describes the synthesis of the indolium salt and some of its rather remarkable properties as a methylating agent.[2]

Since indoles undergo alkylation—like protonation—on carbon,[3] the double bond of the indolium salt was formed after quaternization of the ring nitrogen. This was accomplished *via* the reaction sequence shown in the accompanying chart. 3-Hydroxyindoline had been prepared previously[4] by reduction of isatin with lithium aluminum hydride. Since the yields were consistently low (12–14% as compared to a reported[4] yield of 21%), other methods of synthesis of this key compound were examined. Indoxyl is an obvious choice as a precursor, but attempts to reduce it selectively have been largely unsuccessful.[4] Our attempts to reduce indoxyl O-acetate with lithium aluminum hydride, sodium borohydride, sodium dithionite, or by catalytic hydrogenation at 3 atm. over

---

(1) (a) R. L. Hinman and J. Lang, *Tetrahedron Letters*, **21**, 12 (1960); (b) R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, **84**, 2534 (1963); (c) E. B. Whipple, Y. Chiang, and R. L. Hinman, *ibid.*, **85**, 26 (1963); (d) Y. Chiang and E. B. Whipple, *ibid.*, **85**, 2763 (1963).

(2) Two examples of pyrrolium salts have been reported [(a) R. Lukeš and J. Trojánek, *Collection Czech. Chem. Commun.*, **18**, 454 (1953); and (b) O. Achmatowicz, S. Achmatowicz, and W. J. Rodwald, *Rocznicki Chem.*, **35**, 497 (1961)], but demethylation was observed only incidentally and under relatively severe conditions.

(3) See, for example, W. C. Sumpter and F. M. Miller, "The Chemistry of Heterocyclic Compounds with Indole and Carbazole Systems," Interscience Publishers, Inc., New York, N. Y., 1954, p. 32.

(4) E. Giovannini and T. Lorenz, *Helv. Chim. Acta*, **40**, 1553 (1957).

platinum oxide in methanol, under neutral, acidic, or basic conditions, were all unsuccessful.[5]

Conversion of the quaternary indolinol (II) to the chloride (III) was readily effected with thionyl chloride, but dehydrochlorination of III was more difficult to achieve because of the facile demethylation of the indolium salt. When an excess of base such as ammonia or triethylamine was used, a sizeable portion of the product was converted to 1-methylindole, as shown by changes in the ultraviolet spectra (Table I). Although demethylation could be suppressed by keeping the per cent conversion low, separation of starting material from product and from by-product ammonium salts proved exceedingly difficult. When it was discovered that *even chloride ion caused demethylation*, these methods were abandoned.

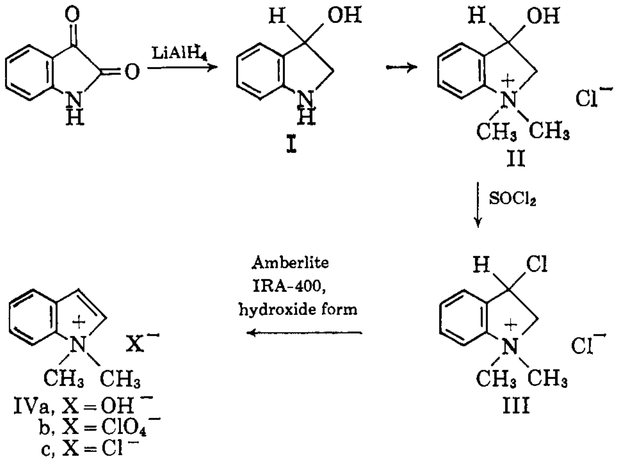


TABLE I

ULTRAVIOLET SPECTRA OF 1,1-DIMETHYLINDOLIUM PERCHLORATE AND RELATED COMPOUNDS IN 95% ETHANOL[a]

3-Chloro-1,1-dimethylindolinium chloride (III)	216 sh (6840)	249 sh (170) 254 (230) 260 (260) 267 sh (170)	
1,1-Dimethylindolium perchlorate (IVb)	215 (15600)	250 (8700)	278 (350) 282 (350) 288 (230)
Indene[b]	220 sh (9340)	249 (9340)	280 (480) 285 sh (240) 290 sh (140)
$C_6H_5CH{=}CH_2$[c]		248 (14600)	273 (770) 282 (760) 291 (530)
$C_6H_5CH{=}CHCH_3$[c]		251 (17300)	284 (960) 293 (620)
$C_6H_5CH{=}CH\overset{+}{N}(CH_3)_3$ Br^-[d]		247 (15300)	

[a] Wave lengths are given in mμ; values of ε are in parentheses.
[b] T. W. Campbell, S. Linden, S. Godshalk, and W. G. Young, *J. Am. Chem. Soc.*, **69**, 880 (1947).
[c] C. G. Overberger and D. Tanner, *ibid.*, **77**, 369 (1955).
[d] W. E. Truce and J. A. Simms, *J. Org. Chem.*, **22**, 762 (1957).

It was finally found that dehydrochlorination could be carried out efficiently by merely passing the chloro derivative (III) down a strongly basic ion-exchange column in the hydroxide form. The indolium hydroxide (IVa) was recognized by its characteristic ultraviolet spectrum (Table I), from which the virtual absence of 1-methylindole was also apparent. Titration of the resulting solution of indolium hydroxide with perchloric acid gave the desired salt in the form of its perchlorate. The relatively low nucleophilicity of this anion permitted isolation of the product (IVb) in high yield.

The anticipated structure of IVb was supported by elemental analysis, an ultraviolet spectrum which resembled those of indene and styrene (Table I), and the n.m.r. spectrum, which showed a complex pattern in the vinyl region of total area equal to that of a single sharp peak at τ 6.38, assigned to the six N-methyl protons.[6] Confirmation of the structure was obtained by demethylation with sodium hydroxide, from which the picrate of 1-methylindole was isolated in 54% yield, based on the indolium perchlorate.

The ultraviolet spectrum of 1,1-dimethylindolium perchlorate shows a striking resemblance (Table I) to that of styrene, and, especially in the intensity of the 250-mμ band, to that of indene, in which the cyclic *cis* configuration has the usual effect on intensity of absorption. In addition to the position and intensity of the principal bands, the similarity of the fine structure in the 280-mμ region is especially noteworthy. The spectrum of the β-styryltrimethylammonium cation also resembles that of styrene (Table I). On the other hand, no similarity can be found between the ultraviolet spectrum of 1,1,2-trimethylpyrrolium iodide, $\lambda_{\max}^{\mathrm{EtOH}}$ 213 mμ ($\epsilon_{\max}$ 13,700),[2b] and that of cyclopentadiene, $\lambda_{\max}^{\mathrm{EtOH}}$ 235 mμ ($\epsilon_{\max}$ 4000).[7,8]

The remarkably facile demethylation of indolium salts in the presence of even weak nucleophiles such as chloride ion, which undoubtedly has the formation of the aromatic ring system as its driving force, is illustrated by the experiments under controlled conditions summarized in Table II. Stronger nucleophiles such as amines, acetate ion, and hydroxide ion were, of course, more effective than chloride, but as shown in the table the demethylation process was in all cases highly solvent-dependent. The effect of medium on the rate of demethylation suggests that this reaction should be considered as a simple bimolecular displacement reaction in which charge is cancelled. As is typical of this class of reaction,[9] an increase in rate accompanies a decrease in the polarity of the medium. It should be noted, however, that the system is unique as a case in which an amine is a particularly good leaving group.

That even weaker nucleophiles than chloride might effect demethylation was suggested by the slow demethylation of the indolium perchlorate in tetrahydrofuran,

---

(5) Reduction of indoxyl derivatives has been achieved *via* the N-acetyl derivatives [J. R. Johnson and J. H. Andreen, *J. Am. Chem. Soc.*, **72**, 2862 (1950)], but, under the conditions of deacetylation the hydroxyindoline was converted to an indole, making the method useless for our work.

(6) The infrared spectrum had four peaks of weak intensity in the 1620–1710-cm.$^{-1}$ region; it is not known which of these arises from the double-bond stretching vibration.

(7) J. D. Idol, C. W. Roberts, and E. T. McBee, *J. Org. Chem.*, **20**, 1743 (1955).

(8) The similarity of the ultraviolet spectra of benzene and of anilinium salts is well known, although the relationship does not appear to hold as well when the anilinium salt bears groups in the *para* position capable of significant resonance interaction with the ring [L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **69**, 2714 (1947)].

(9) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 345 ff.

TABLE II

EFFECT OF SOLVENT AND ATTACKING NUCLEOPHILE ON RATES OF DEMETHYLATION AND DEHYDROCHLORINATION OF IVb AND III[a]

Source of added nucleophile[c]	Solvent[d]	Product[e]	Rate	
		1,1-Dimethylindolium Perchlorate (IVa)[b]		
	A			No reaction after 25 hr.
	AT	M	Very slow	Very slight reaction after 25 hr.
LiCl	A			No reaction after 25 hr.
LiCl	AT	M	Slow	About one-third complete after 25 hr.
NaOH	A	M	Medium	Almost complete after 25 hr.
NaOH	AT	M	Fast	Complete in 1 hr.
		3-Chloro-1,1-dimethylindolinium Chloride (III)[f]		
	A			No reaction after 25 hr.
	AT	I + M	Very slow	Slight reaction after 6 hr.
LiCl	A			No reaction after 25 hr.
LiCl	AT	I + M	Very slow	Slight reaction after 25 hr.
NaOH	A	I	Very fast	Almost complete within 30 min.
		M	Medium	Complete after 25 hr.
NaOH	AT	I	Very fast	Complete in less than 35 min.
		M	Fast	Complete in more than 35 min., but less than 1.5 hr.

[a] All reactions carried out at 23° in quartz cuvettes and followed by changes in the ultraviolet spectra by means of a Beckman DK-2 recording spectrophotometer. [b] Concentration 6.7×10^{-3} *M*. [c] In all cases the concentration of the added salt was ten times that of the quaternary salt. [d] A = methanol, AT = a 1:2 mixture of methanol and tetrahydrofuran (v./v.). [e] M = 1-methylindole, I = indolium cation. These products were easily recognized by their ultraviolet spectra which differ greatly from each other and from that of the indolinium salt (III). [f] Concentration 6.9×10^{-3} *M*.

which is reminiscent of the methylation of ethers by oxonium salts.[10] However, acetamide, cyclohexanone, and butyrolactone, which are alkylated by oxonium cations,[10b] did not react with IVb under the conditions of Table II, and sufficient material was not available for comparison under the conditions (neat reactants) usually used with the oxonium compounds.

The available data do not permit exact comparison of the ease of demethylation of indolium and pyrrolium salts. 1,1-Dimethylpyrrolium hydroxide appeared to undergo demethylation easily in aqueous solution at room temperature,[2a] indicating a higher order of reactivity than that of the indolium hydroxide. On the other hand, 1,1,2-trimethylpyrrolium acetate, chloride, and iodide have been isolated,[2b] the last salt under conditions (evaporation of an acetone solution) which would favor demethylation of the indolium structure prepared in our work. Although an unusual substituent effect may be responsible for the increased stability of the second pyrrolium salt, the unusual method of synthesis and the failure of the ultraviolet correlation noted above leave some doubt as to the identity of the salt.

Attention is also called to the data in Table II on the dehydrochlorination of 3-chloro-1,1-dimethylindolinium chloride (III), from which two significant points emerge: dehydrochlorination can be effected by chloride ion, and elimination is much faster than demethylation.[11] Since the effect of the medium was much more pronounced in the demethylation step, media could be selected so that build-up of the indolium salt could be observed in the ultraviolet, followed by slower conversion of the latter to 1-methylindole (Table II). Moreover, the markedly different rates and different responses to medium made it possible to select a solvent system (methanol–water, 4:1) such that demethylation of the indolium salt did not occur to an appreciable extent during dehydrochlorination on a preparative scale. No conditions were found under which isolation of the indolium chloride (IVc) could be carried out without the occurrence of extensive demethylation.

In none of the work on dehydrochlorination was any evidence found to indicate the intrusion of ring opening by elimination. Such a reaction is probably precluded by the acidity of the hydrogens β to the halogen, which would be high compared to those of more common aralkyl halide systems which undergo base-catalyzed elimination reactions. The same reasoning leads to the prediction that the C_β–H bond would be more completely broken than the C–Cl bond in the transition state,[12] which would, in turn, favor displacement on hydrogen in the chloride-ion-catalyzed elimination rather than attack on carbon in the "merged elimination–substitution" type of mechanism proposed for other cyclic systems.[13]

The cyclic systems described in this report offer particular advantages for kinetic studies of displacement reactions with an amine as the leaving group, since these processes take place at convenient rates at or near room temperature, and can be followed with ease by spectrophotometric methods. The indolium system can probably be extended also to studies of the mechanism of elimination with the amine as leaving group since that process may be encountered with alkyl groups larger than methyl on the quaternized nitrogen. The close relationship of the indole system to vinylamines generally[14] suggests that these proc-

---

[10] (a) H. Meerwein, U. Eisenmenger, and H. Matthiae, *J. prakt. Chem.*, **566**, 150 (1950); (b) H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodt, and J. Spille, *Chem. Ber.*, **89**, 2060 (1956).

[11] Elimination must precede demethylation since 1,1-dimethylindolinium chloride itself is stable under all conditions studied.

[12] See the chapter by D. J. Cram, "Steric Effects in Organic Chemistry," M. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 345, 346.

[13] D. N. Kevill, P. H. Hess, P. W. Foster, and N. H. Cromwell, *J. Am. Chem. Soc.*, **84**, 983 (1962); N. H. Cromwell, D. N. Kevill, and G. A. Coppens, Abstracts, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963, p. 8M.

[14] R. L. Hinman and E. R. Shull, *J. Org. Chem.*, **26**, 2339 (1961).

esses will be encountered very widely when the appropriate N-quaternized vinylamines are available.

A number of other methods of synthesis of indolium salts were tried without success. Attempted dehydration of 1,1-dimethyl-3-hydroxyindolinium chloride (II) with 9 *M* hydrochloric acid caused no appreciable change in the ultraviolet spectrum after 48 hr., including 12 hr. of heating on the steam bath, and II was also unreactive towards boron fluoride etherate in glacial acetic acid. The positive charge probably hindered either protonation of the hydroxyl or formation of a carbonium ion at the 3-position, which would also account for the report that 3-hydroxyindoline (I), when pure, resists attack by concentrated hydrochloric and sulfuric acids.[4,15]

Hydrogen bromide in acetic acid reacted with compound II, but produced unidentifiable materials. With sodium acetate in acetic anhydride, 1-methylindole was obtained. Dehydration to the indolium salt apparently took place but was followed immediately by demethylation by the highly nucleophilic acetate ion. Thermal dehydration of II, either solid or in solution, yielded only 1-methylindole.

Attempted dehydrogenation of 1,1-dimethylindolinium chloride (V) with either chloranil or 10% palladium on carbon in refluxing xylene, yielded mixtures in which only starting material and indolic substances could be recognized.

Several attempts were also made to prepare the 3-chloro intermediate (III) by direct chlorination of 1,1-dimethylindolinium chloride (V), but the latter compound was completely resistant to *t*-butyl hypochlorite in chloroform, acetic acid, or neat *t*-butyl hypochlorite under irradiation with ultraviolet light for periods up to 2.5 hr., and to chlorine in a 1:1 mixture of carbon tetrachloride and acetic acid during 1 hr. of irradiation by ultraviolet light at 25°. The positively charged nitrogen probably inhibits attack by chlorine molecule or atom and *t*-butoxy radical, all of which are electron-seeking species.[16]

Experimental[17]

3-Hydroxyindoline.—The procedure was similar to that reported previously[4] but the yields were only 12–14% as compared to the reported value of 21%. Indole and indigo were the major products. In one experiment, decreasing the isatin–lithium aluminum hydride mole ratio from 0.6 to 0.24 was accompanied by a marked decrease in the yield. The highest melting point obtained was 92–93°, lit.[4] m.p. 96°. The infrared spectrum had a strong band at 3220–3225 cm.$^{-1}$ and other prominent bands at 2970, 2890, 1610, 1490, 1475, 1478, 1325, 1317, 1255, 1204, 1062, 933, 923, 813, 787, and 741 cm.$^{-1}$. The ultraviolet spectrum in 95% ethanol showed $\lambda_{\max}$ 241 and 295 mμ, ($\epsilon_{\max}$ 7200 and 2100, respectively).

1,1-Dimethyl-3-hydroxyindolinium Iodide.—To a chilled, stirred solution of 1.93 g. (0.014 mole) of 3-hydroxyindoline in 110 ml. of acetone was added 20.5 g. (0.14 mole) of methyl iodide, followed by 4.01 g. (0.029 mole) of potassium carbonate. After the mixture had come to room temperature, it was stirred for 2 hr. and filtered. The solid was mixed with about 100 ml. of 95% ethanol and heated on the steam bath for 15 min. The mixture was filtered, and the filtrate was evaporated *in vacuo*, yielding 4.16 g. of a white solid. The acetone filtrate was evaporated almost to dryness under reduced pressure, leaving a brown paste which was recrystallized from 95% ethanol, from which three crops were obtained, totalling 1.49 g. of fine ivory-colored crystals. The combined crops, which contained inorganic salts, were used in the subsequent step without further purification.

1,1-Dimethyl-3-hydroxyindolinium Chloride (II).—A solution of 1.66 g. of the impure methiodide, obtained as described above, in 60 ml. of a 4:1 (v./v.) mixture of ethanol and water was passed down a column of Amberlite resin IRA-400 in the chloride form and eluted with 80% ethanol until the eluent no longer gave a positive silver nitrate test. The eluent was evaporated under reduced pressure, and the residue was triturated with absolute ethanol and filtered. After concentration of the filtrate, ether was added until a precipitate appeared. The mixture was heated to effect solution and then chilled, producing 0.52 g. of ivory crystals, which, after washing with a cold ethanol–ether mixture, melted at 190–191° dec. A second crop (33 mg.) was obtained by concentration of the filtrate and addition of ether. The total yield was 48%. Two recrystallizations from an ethanol–ether mixture afforded an analytical sample, m.p. 201.5° dec. The infrared spectrum (potassium bromide) had a strong band at 3220 cm.$^{-1}$ and other prominent bands at 1473, 1075, 984, and 770 cm.$^{-1}$. The ultraviolet spectrum (95% ethanol) showed $\lambda_{\max}$ 246 sh, 252, 258, and 266 mμ ($\epsilon_{\max}$ 150, 210, 250, and 200, respectively). In water, an additional band at $\lambda_{\max}$ 206 mμ ($\epsilon_{\max}$ 8300) was observed.

Anal. Calcd. for $C_{10}H_{14}ClNO$: C, 60.05; H, 7.07; Cl, 17.76; N, 7.02. Found: C, 60.04; H, 7.05; Cl, 17.81; N, 7.14.

3-Chloro-1,1-dimethylindolinium Chloride (III).—To a stirred mixture of 1.31 g. (0.0065 mole) of 1,1-dimethyl-3-hydroxyindolinium chloride in 15 ml. of chloroform in an ice bath was added 7.14 g. (0.060 mole) of thionyl chloride. The mixture was allowed to warm to room temperature and, after all the solid had dissolved (about 10 min.), it was heated to 65°. When the reaction appeared from the ultraviolet spectrum to be complete (about 45 min.), the yellow solution was concentrated under a stream of nitrogen. Ether was added to the residual yellow oil and the white solid which formed was filtered and washed with ether. Recrystallization from an ethanol–ether mixture afforded 1.22 g. (85%) of white crystals, m.p. 165–167° dec.; two additional crops were collected to give a total yield of 1.26 g. (88%). Three recrystallizations from a methanol–ether mixture, afforded an analytical sample, m.p. 168° dec. The infrared spectrum showed major bands at 3010, 2930, 1480, 1475, 1460, 1450, 1270, 1140, 982, 943, 882, 876, 856, 773, and 699 cm.$^{-1}$. The ultraviolet spectrum is given in Table I. In water an additional shoulder at 209 mμ (ϵ 7400) was observed.

Anal. Calcd. for $C_{10}H_{13}Cl_2N$: C, 55.06; H, 6.01; Cl, 32.51; N, 6.42. Found: C, 55.06; H, 5.67; Cl, 32.53; N, 6.54.

1,1-Dimethylindolium Perchlorate (IVb).—A solution of 0.31 g. (0.0014 mole) of 3-chloro-1,1-dimethylindolinium chloride in 20 ml. of an 80% methanol–water mixture was passed down a column of Amberlite resin IRA-400 in the hydroxide form, and eluted with the same solvent. Six fractions of an average volume of 12 ml. were collected, of which the first four contained a substance with an ultraviolet spectrum resembling that of indene. The fractions containing this material, which was assumed to be **1,1-dimethylindolium hydroxide**, were combined, and 0.1 *M* perchloric acid was added until the solution was neutral to pHydrion paper. The neutralized solution was concentrated to a slurry under reduced pressure and the slurry was taken up in absolute ethanol. Concentration of this solution yielded 0.26 g. (75%) of a white solid, m.p. 185–186° dec. Further concentration of the filtrate yielded a second crop to give a total yield of 83%. An analytical sample, m.p. 185–186° dec., was obtained by two recrystallizations from a methanol–ether mixture.

Anal. Calcd. for $C_{10}H_{12}ClNO_4$: C, 48.89; H, 4.93; Cl, 14.43; N, 5.70. Found: C, 48.57; H, 5.03; Cl, 14.31; N, 6.00.

The infrared spectrum (potassium bromide) had the following major peaks (in cm.$^{-1}$): 3070 (s), 1470 (s), 1427 (m), 1406 (m), 1050–1120 (vs, ClO_4^-), 950 (s), 872 (s), 784 (s), 763 (vs), 767 (vs), and 738 (s). In the double-bond region were the following bands of weak intensity: 1708, 1656, 1638, and 1620 cm.$^{-1}$. An n.m.r. spectrum in perdeuterio dimethyl sulfoxide had a multiplet at τ 1.6–1.9, a multiplet at τ 2.2–2.5, and a sharp singlet at τ 6.38, with relative areas of 1:2:3, respectively. The ultraviolet spectrum is given in Table I.

---

(15) A solution of 0.01 mmole of 1,1-dimethyl-3-hydroxyindolinium chloride in 10 ml. of 1 *M* aqueous sodium hydroxide was stable for 3 days at room temperature. Pure 3-hydroxyindoline (I) has also been shown to be stable under similar conditions.

(16) C. Walling and B. B. Jacknow, *J. Am. Chem. Soc.*, **82**, 6113 (1960).

(17) Melting points are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Model 21 spectrophotometer equipped with sodium chloride optics, and n.m.r. spectra were obtained with a Varian A-60 spectrometer, using tetramethylsilane as an internal standard.

1-Methylindole from 1,1-Dimethylindolium Perchlorate.—To 2 ml. of methanol was added 108 mg. (0.44 mmole) of the perchlorate followed by 8 ml. of water and 10 ml. of 1 *M* aqueous sodium hydroxide. The solution was heated for a total of 17.5 hr. at 53–75° over a period of 2 days, until ultraviolet spectra showed no remaining indolium salt. At the end of this time the solution was cloudy and the odor of 1-methylindole was very strong. The mixture was extracted with ether and the ether extract dried over sodium sulfate and concentrated *in vacuo* to a volume of about 2 ml. To the residue was added a few milliliters of ethanol followed by about 5 ml. of a warm ethanolic solution containing 109 mg. of picric acid. The long red needles of picrate which formed after cooling were collected in two crops, giving a total yield of 85 mg. (54%). Two recrystallizations from ethanol did not change the melting point. A mixture melting point with an authentic sample of the picrate of 1-methylindole, m.p. 143–145° dec., lit.[18] m.p. 144–145° dec., was not depressed.

Anal. Calcd. for $C_9H_9N \cdot C_6H_3N_3O_7$: C, 50.00; H, 3.36; N, 15.55. Found: C, 50.05; H, 3.23; N, 15.52.

---

[18] K. T. Potts and J. E. Saxton, *J. Chem. Soc.*, 2641 (1954).

New Thyroxine Analogs. Halogen Derivatives of 3-Carbethoxy-5-hydroxy-2-methylbenzofuran

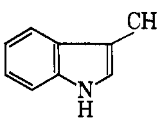
C. A. GIZA AND R. L. HINMAN

The Union Carbide Research Institute, Union Carbide Corporation, Tarrytown, New York

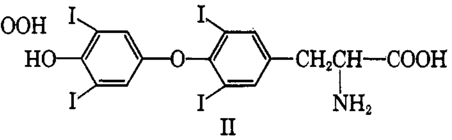
Received October 16, 1963

In an effort to combine the structural features of the plant growth hormone, indole-3-acetic acid, and the mammalian hormone, thyroxine, a number of mono and dihalo derivatives of the title compound (III) have been synthesized. Chlorination and bromination were achieved by use of the elemental halogens, whereas only a combination of iodine and morpholine, of a wide variety of reagents examined, was suitable for iodination. Bromination and iodination of III yielded the 6-monosubstituted derivatives, but chlorination afforded primarily the 4-monochloro derivative. Mercuration also occurred at the 4-position, affording a route to the 4-iodo derivative. Deiodination was readily effected by zinc and acetic acid without ring cleavage, but chlorine was not removed by this procedure. Iodine at the 4-position was especially labile toward base, and by the use of potassium cyanide in dimethyl sulfoxide a remarkably selective removal of a 4-iodo group was achieved while a 6-iodo was untouched. The 4,6-dihalo derivatives of III formed methanol- and water-insoluble salts with alkyl and alicyclic amines, as did many simple di-*o*-halophenols. Since mono-*o*-halophenols did not form such salts, the reaction is of value for identification and separation purposes. The 4- and 6-monoiodo derivatives of III showed thyromimetic activity.

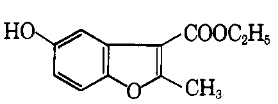
Recent demonstrations in this laboratory of living systems in which the plant growth hormone indole-3-acetic acid ("auxin," I) and the mammalian hormone thyroxine (II) show similar types of behavior[1] suggested that interesting physiological activity might be found in a synthetic hormone having the structural features of both I and II. The 4,6-diiodo derivative IX of the title compound (III) approaches this hybrid form, the 2,3-double bond taking the place of the second benzene ring of II. This hydroxybenzofuran is also related to α-tocopherol (IV), one of the E vitamins. The known antioxidant character of IV[2] and the suggestion that antioxidant activity and hormonal behavior may be related in a general way[3,4] were additional reasons for choosing this system. Finally, these hydroxybenzofurans appeared to be readily accessible by condensation of *p*-benzoquinones with β-keto esters and β-diketones.[5–8]



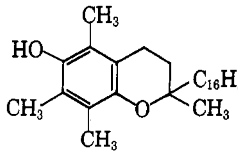
I



II



III



IV

There were few examples of the 2,3-disubstituted 5-hydroxybenzofurans in the literature prior to the recent work of Grinev, Terentyev, *et al.*,[5–7] and Bernatek, *et al.*[5,6,8] These authors have not discussed halogenation of this system, although the former group did describe the synthesis of two 6,7-dichloro derivatives by condensation of 2,3-dichlorobenzoquinone with the appropriate β-keto ester.[9] The earlier representatives of the series include 2-methyl-3-carbethoxy-, 2,3-dimethyl-, 2,3-diphenyl-, and 2,3-benzo-5-hydroxybenzofuran (2-hydroxydibenzofuran). Reactions of the last compound with bromine have been reported.[10] A compound, $C_{12}H_9Cl_3O_4$, obtained from the condensation of chloroanil with the sodium derivative of ethyl acetoacetate, is said[5b] to be the 4,6,7-trichloro derivative of III.

A description of the chlorination, bromination, and iodination of 3-carbethoxy-5-hydroxy-2-methylbenzo-

---

[1] S. M. Siegel, F. Porto, and P. Frost, *Arch. Biochem. Biophys.*, **82**, 330 (1959); S. M. Siegel and P. Frost, *Proc. Natl. Acad. Sci. U. S.*, **45**, 1379 (1959).

[2] See, for example, "Handbook of Food and Agriculture," F. C. Blanck, Ed., Reinhold Publishing Co., New York, N. Y., 1955, pp. 243, 253, 286, 592; also "Autoxidation and Antioxidants," Vol. I, W. O. Lundberg, Ed., Interscience Publishers, Inc., New York, N. Y. 1962, pp. 1069–1084.

[3] S. M. Siegel, F. Porto, and P. Frost, *Physiol. Plantarum*, **12**, 727 (1959).

[4] S. M. Siegel and F. Porto, "Plant Growth Regulation," R. Klein, Ed., Iowa State University Press, Ames, Iowa, 1961, pp. 341–353.

[5] (a) H. von Pechmann, *Chem. Ber.*, **21**, 3005 (1888); (b) M. Ikuta, *J. prakt. Chem.*, [2]**45**, 65 (1892); (c) A. N. Grinev, P. B. Khvar, and A. P. Terentyev, *J. Gen. Chem. USSR*, **27**, 1172 (1957), and earlier papers; (d) E. Bernatek and T. Ledaal, *Acta Chem. Scand.*, **12**, 2053 (1958); (e) V. J. Grinšteins and V. A. Slavinskaya, *Latvijas Valsts. Univ. Kim. Fak. Zinatniskie Raksti*, **22**, 119 (1958); *Chem. Abstr.*, **53**, 7090*d* (1959).

[6] (a) E. Bernatek, *Acta Chem. Scand.*, **10**, 273 (1956); (b) A. N. Grinev, P. B. Khvar, and A. P. Terentyev, *J. Gen. Chem. USSR*, **27**, 897 (1957).

[7] A. N. Grinev, L. A. Bukhtenko, and A. P. Terentyev, *ibid.*, **29**, 927 (1959).

[8] E. Bernatek, *Acta Chem. Scand.*, **7**, 677 (1953).

[9] A. N. Grinev, N. K. Venevtseva, and A. P. Terentyev, *J. Gen. Chem. USSR*, **28**, 1900 (1958).

[10] H. Gilman and P. R. Van Ess, *J. Am. Chem. Soc.*, **61**, 1365 (1939).