TABLE II

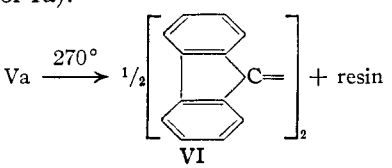
Va, R = C_6H_5, R′ = H, R″ and R‴ = 9-fluorenylidene ($C_{13}H_8$)
b, R = $C_6H_4NO_2$-*o*, R′ = H, R″ and R‴ = $C_{13}H_8$
c, R = $C_6H_4NO_2$-*m*, R′ = H, R″ and R‴ = $C_{13}H_8$
d, R = $C_6H_4NO_2$-*p*, R′ = H, R″ and R‴ = $C_{13}H_8$
e, R = $C_{16}H_9$, R′ = H, R″ and R‴ = $C_{13}H_8$

TABLE III

I	V	Time of reacn., hr.	M.p., °C.	Yield, %	Solvent for cryst.[f]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Ia[a]	Va	10	172	81	A	$C_{21}H_{15}NO_2$[g]	80.5	80.4	4.8	4.8	4.5	4.4
Ib[b]	Vb	8	191–192	76	B	$C_{21}H_{14}N_2O_4$	70.4	70.4	3.9	3.7	7.8	7.6
Ic[c]	Vc	8	180	71	B	$C_{21}H_{14}N_2O_4$	70.4	70.2	3.9	3.8	7.8	7.7
Id[d]	Vd	6	193	78	B or C	$C_{21}H_{14}N_2O_4$	70.4	70.3	3.9	3.9	7.8	7.7
Ie[e]	Ve	12 and kept 4 days at room temp.	151	56	B	$C_{31}H_{19}NO_2$[h]	85.1	85.0	4.3	4.1	3.2	3.2

[a] "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., 1932, p. 405. [b] J. Thiele, *Ber.*, **32**, 1294 (1899). [c] K. H. Slotta and G. Szyszka, *ibid.*, **68**, 189 (1935). [d] Van der Lee, *Rec. trav. chim.*, **44**, 1809 (1924). [e] It was obtained after the method described for the preparation of nitrostyrene, in deep orange crystals from benzene or glacial acetic acid, m.p. 188–189° (red melt). *Anal.* Calcd. for $C_{15}H_{11}NO_2$: C, 79.1; H, 4.0. Found: C, 79.1; H, 3.9. E. Bograchov (THIS JOURNAL, **66**, 1612 (1944)) gave m.p. 177° for the same substance. [f] A, benzene and light petroleum (b.p. 40–60°); B, benzene; C, xylene. [g] Mol. wt., 313; found: mol. wt. (Rast), 308. [h] Calcd. mol. wt., 437; mol. wt. (Rast), 431.

The cyclopropane derivatives V (listed in Table II) are colorless and soluble in hot alcoholic potassium hydroxide. The molecular weight of Va is in agreement with the calculated value. When Va is heated to 270° it decomposes to give $\Delta^{9,9'}$-bifluorene (VI)[3] and an unidentified resin (probably the polymer of Ia).



VI

3,4-Methylenedioxy-B-nitrostyrene (I, R = 3,4-CH_2O:C_6H_3; R′ = H) and 6-nitro-3,4-methylenedioxy-B-nitrostyrene (I, R = 3,4-CH_2O:$C_6H_2NO_2$[6]; R′ = H) are stable or almost stable toward the action of 9-diazofluorene under the given experimental conditions. Similarly, Ia and Ic are recovered essentially unchanged when treated with a benzene solution of diphenyldiazomethane.

Experimental

General Procedure.—To a solution of 1 g. of Ia in 30 ml. of dry benzene, was added 1.5 g. of 9-diazofluorene[4] in 20 ml. of dry benzene. The reaction mixture was then refluxed, whereupon the deep red color faded. The reaction products (Va-Ve) were processed as follows (*cf.* Table III).

The crystals that separated on cooling the reaction mixture in the case of Va, Vb and Vd, were collected and recrystallized. Concentration of the benzene mother liquors gave further crops of the reaction product.

The benzene was evaporated and the oily residue, that remained in the case of Vc, was washed several times with cold light petroleum ether (b.p. 40–60°). The solid that formed was separated and recrystallized.

The mixture of the yellow and orange crystals that separated on cooling the benzene reaction mixture in the case of Ve was filtered off and the yellow crystals were separated mechanically and recrystallized.

The 2-aryl-3-nitrospiro-(cyclopropane-1,9′-fluorene) (Va-Ve) listed in Table II were similarly prepared. They give green color with concentrated sulfuric acid; Ve gives a bluish-green color. They are almost insoluble in hot aqueous potassium hydroxide, but soluble in alcoholic potassium hydroxide solution (*ca.* 35%) giving yellow solution in the case of Va and Ve, brown in the case of Vb, orange in the case of Vc and violet in the case of Vd. In general, they are soluble in hot benzene or chloroform, but are sparingly soluble in cold ethyl alcohol and light petroleum ether (b.p. 40–60°).

A solution of 1 g. of each of 3,4-methylenedioxy-B-nitrostyrene[5] and 6-nitro-3,4-methylenedioxy-B-nitrostyrene[5] in 20 ml. of dry benzene was treated with 1.5 g. of 9-diazofluorene in 20 ml. of benzene. The reaction mixture was refluxed for 12 hours. On cooling, starting nitroölefin was recovered essentially unchanged.

Thermal Decomposition of Va.—Va (0.5 g.) was heated for one hour at 270–280° (bath temp.) in a test-tube shaped vessel (Pyrex glass) which was connected during pyrolysis to a working oil vacuum pump. The reaction vessel was then allowed to cool in a vacuum. The bottom of the reaction vessel contained a brownish-red residue which was extracted several times with boiling ether. After concentration of the ethereal extract to about one ml., light petroleum (b.p. 40–60°) was added dropwise at room temperature till turbidity occurred. A reddish-brown substance separated which was dissolved in a very small amount of hot benzene. After adding a saturated solution of picric acid and keeping aside overnight, orange crystals separated, which proved to be the picrate of VI.

Diphenyldiazomethane and Ia.—One gram of Ia in 20 ml. of dry benzene was treated with diphenyldiazomethane[6] (prepared from 1.5 g. of benzophenone hydrazone and 3 g. of yellow mercuric oxide suspended in 30 ml. of dry benzene). The mixture was refluxed for three hours, during which the deep color faded. The benzene solution was evaporated and the solid residue was washed several times with cold ether (*ca.* 25 ml.). The insoluble product was identified as starting material; diphenylketazine[6] was isolated from the ether solution.

The above experiment was repeated and the reaction mixture was allowed to stand at room temperature for 72 hours in the presence of 0.5 ml. of methyl alcohol. On working out the reaction mixture as above, Ia and diphenylketazine were isolated.

Similarly, Ic was recovered essentially unchanged when treated with diphenyldiazomethane as described in the case of Ia.

(3) *Cf.* the decomposition of 7,8-9′,9′-fluorenyleneacenaphthene at 280° into VI and acenaphthylene (A. Schönberg, A. Mustafa and N. Latif, THIS JOURNAL, **75**, 2267 (1953)).

(4) A. Schönberg, W. Awad and N. Latif, *J. Chem. Soc.*, 1368 (1951).

(5) H. Burten and J. A. Duffield, *ibid.*, 78 (1949).

(6) H. Staudinger and A. Gaule, *Ber.*, **49**, 1897 (1916).

DEPARTMENT OF CHEMISTRY
FACULTY OF SCIENCE
THE CAIRO UNIVERSITY
CAIRO, EGYPT

Serotonin Analogs. The Synthesis of 5-Dimethylaminoindoles

BY ELLIOTT SHAW

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Derivatives of 5-aminoindole have been prepared[1] and shown to be effective antagonists of the

(1) E. Shaw and D. W. Woolley, THIS JOURNAL, **75**, 1877 (1953).

naturally occurring vasoconstrictor, serotonin, a 5-hydroxyindole.[2,3] In a continuation of the study of the relation of antimetabolite activity to structure among the aminoindoles, the effect of alkylation of the 5-amino group was investigated. Such bases had not previously been prepared. A monomethyl derivative readily was obtained on reduction of a 5-formamidoindole with lithium aluminum hydride. A 5-dimethylamino derivative of 2-methyl-3-ethylindole was obtained from the 5-amino compound by methylation with dimethyl sulfate in aqueous sodium bicarbonate suspension[4] to the quaternary methyl stage, followed by removal of one methyl group with sodium propylate. Although attempts to stop the methylation at the dimethylamino stage were made, quaternary base and unreacted starting material were usually found. The demethylation was effectively accomplished by refluxing the quaternary chloride with excess sodium *n*-propylate in 1-propanol for yields of 80%. Pyrolysis of the quaternary chloride at reduced pressure also provided the dimethylaminoindole, but in lower yield (50%). This same process was applied to other 5-aminoindoles which were thus converted to the dimethylamino compounds by methylation to the quaternary stage with dimethyl sulfate followed by demethylation (Table I). 2-Methyl-3-β-hydroxyethyl-5-dimethylaminoindole so obtained was converted to the 3-β-chloroethylindole by means of thionyl chloride.

The amines used as starting materials for methylation were obtained from the nitroindoles by hydrosulfite reduction[1] or by catalytic reduction with palladium-on-charcoal. Catalytic reduction was more convenient for the preparation of large amounts of amines and was used in spite of occasional evidence of contamination of the products by dihydroindole formation. However, attempts to reduce exclusively to the dihydroindole stage by means of large amounts of either palladium or platinum catalysts did not succeed at the pressures used.

The amino- and alkylaminoindoles were not obviously unstable in the course of preparatory procedures. However, in the high dilutions used in biological work certain changes, presumably oxidative, took place. More than one type of alteration appeared possible. For example, 5-amino- or 5-methylaminoindoles gave deep green and violet colors, respectively, with ferric chloride, probably due to their oxidation to quinone imine structures.[5] Under similar treatment 5-dimethylaminoindoles formed only an orange complex which decolorized in strong acid. However, 2-methyl-3-ethyl-5-dimethylaminoindole was unstable for other reasons. It underwent conversion to a yellow fluorescent derivative in aqueous and organic solvents. The resultant product could be crystallized and its structure is under investigation. Apparently the instability was related to the hydrogen on the ring nitrogen since its replacement by a methyl group led to increased stability.

The 5-dimethylaminoindoles were found to be considerably more powerful antiserotonins than the 5-aminoindoles described earlier[1-3] as will be reported in detail elsewhere.

Acknowledgment.—The author acknowleges the assistance of Miss Caryl Carter in carrying out the experimental work. 2-Methyl-3-ethyl-5-nitroindole was generously supplied by Dr. Karl Pfister of Merck and Co.

Experimental[6]

2-Methyl-3-ethyl-5-nitro-7-chloroindole.—2-Chloro-4-nitrophenylhydrazine was prepared[7] and converted in aqueous acetic acid to the methyl *n*-propyl ketone hydrazone, m.p. 74–76° (aq. alcohol).

Anal. Calcd. for $C_{11}H_{14}O_2N_3Cl$: C, 51.67; H, 5.46. Found: C, 51.88; H, 5.54.

The hydrazone was converted to the indole by the Fischer rearrangement in concentrated hydrochloric acid as described in (1). When the crude product was chromatographed on alumina with benzene as a solvent, the initial band eluted was the desired material obtained in a yield of 10%, m.p. 173–176°. The nitroindole separated from alcohol as needles, m.p. 175–176°.

Anal. Calcd. for $C_{11}H_{11}O_2N_2Cl$: C, 55.35; H, 4.65. Found: C, 55.02; H, 4.65.

2-Methyl-3-β-hydroxyethyl-5-nitroindole.—2-Methyl-3-β-chloroethyl-5-nitroindole[1] (3.0 g.) in glacial acetic acid (20 ml.) was refluxed with anhydrous sodium acetate (2.0 g.) for three hours. The acetic acid was removed by distillation under reduced pressure, and the residue neutralized with 20% aqueous potassium hydroxide. More alkali (10 ml.) was then added plus ethanol (25 ml.) and the solution refluxed for two hours. After removal of the solvent the residue was thinned with water, collected on a filter and washed free of inorganic salts. A recrystallization from aqueous alcohol, during which the first small pigmented precipitate was discarded, yielded 2.1 g., 76%, of yellow needles, m.p. 158–159°.

Anal. Calcd. for $C_{11}H_{12}O_3N_2$: C, 60.00; H, 5.49. Found: C, 60.43; H, 5.39.

1,2-Dimethyl-3-ethyl-5-nitroindole.—Anhydrous toluene (600 ml.) was placed in a 3-neck 1-l. flask provided with stirrer, reflux condenser and gas inlet tube. When a nitrogen atmosphere had been provided, granular sodium hydride (4.2 g.) was introduced. The system was protected from moisture by means of a drying tube and a positive nitrogen pressure. A hot suspension of 2-methyl-3-ethyl-5-nitroindole (36 g.) in toluene (200 ml.) was added. Since a sodium salt did not form, dimethylformamide (20 ml.) was introduced. A vigorous evolution of gas occurred with rapid formation of the dark red sodium salt of the nitroindole. This change soon reached completion and methyl iodide (30 g.) was added. The suspension was warmed to about 60° after which the methylation proceeded by itself eventually decolorizing the mixture as the sodium salt reacted. After four hours, absolute alcohol (10 ml.) was added to help decompose unreacted hydride. Finally the sodium iodide was filtered off and washed with toluene.[8] The filtrate was concentrated to a small volume, thinned with benzene to permit filtration of a final insoluble sediment which was discarded. Crystallization was brought about by the gradual addition of ligroin (70 ml.) to the benzene solution (100 ml.) with chilling. The crystals so obtained, when stirred with boiling absolute ethanol (100 ml.), did not dissolve but underwent conversion to a voluminous, insoluble mass of yellow needles which were collected on cooling to yield 22.5 g., 77%, m.p. 111–113°. Material of this quality was used for catalytic reductions. The analytical sample, obtained from benzene and hexane had, m.p. 115–116°.

Anal. Calcd. for $C_{12}H_{14}O_2N_2$: C, 66.05; H, 6.47. Found: C, 66.35; H, 6.51.

(2) D. W. Woolley and E. Shaw, THIS JOURNAL, **74**, 2948 (1952).

(3) D. W. Woolley and E. Shaw, *J. Biol. Chem.*, **203**, 69 (1953).

(4) S. Hunig, *Ber.*, **85**, 1056 (1952).

(5) These bases are derivatives of *p*-phenylendiamine which undergoes ready dehydrogenation to a quinone imine. *Cf.* R. Willstätter and A. Pfannenstiel, *Ber.*, **37**, 4605 (1904).

(6) All melting points are uncorrected and were taken in a copper block.

(7) E. Votocek and L. Rys, *Collection Czechoslov. Chem. Communs.*, **1**, 346 (1929); *cf. C. A.*, **23**, 4679 (1929).

(8) Since the sodium iodide may still contain sodium hydride, it must be disposed of with great care in order to avoid fire.

TABLE I

SOME 5-AMINOINDOLES, 5-DIMETHYLAMINOINDOLES AND RELATED QUATERNARY SALTS

Indole	Method	M.p., °C.	Yield, %	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-Methyl-3-ethyl-5-dimethylamino-	D	100–102	80	77.27	8.97	13.86	77.15	9.23	13.96
5-trimethylammonium picrate	B	185–187	81	53.82	5.42		53.74	5.09	
5-trimethylammonium chloride	C	179–181	77	64.41	9.12		64.49	8.79	
2-Methyl-3-ethyl-5-amino-7-chloro-	[a]	206–208	50	63.30	6.28	13.43	63.49	6.30	13.49
2-Methyl-3-ethyl-5-dimethylamino-7-chloro-, picrate	D[b]	202–203	24	48.99	4.76		49.05	4.61	
5-trimethylammonium picrate	B	230–231	70	49.95	4.83	14.57	49.95	4.68	14.45
2-Methyl-3-β-hydroxyethyl-5-amino-	A	186–188	70	69.44	7.42	14.73	69.22	7.26	14.62
2-Methyl-3-β-hydroxyethyl-5-dimethylamino-	D	101–102	65	71.52	8.31	12.84	71.60	8.37	13.16
5-trimethylammonium dipicrate	B	164–165	84	45.16	3.94		45.48	3.95	
5-trimethylammonium chloride	C	207–209	84	62.65	7.91		62.51	8.10	
1,2-Dimethyl-3-ethyl-5-amino-	A	63–64	90	76.54	8.57		76.53	8.32	
1,2-Dimethyl-3-ethyl-5-dimethylamino-	D[b]	84–85	79	77.72	9.32	12.95	77.93	9.39	13.13
trimethylammonium picrate	B	207–209	93	54.77	5.69	15.21	54.99	5.55	14.95
2-Methyl-3-β-chloroethyl-5-dimethylamino-, picrate		188–189	72	48.99	4.76		48.72	4.49	

[a] Prepared by hydrosulfite reduction, *cf.* ref. 1. [b] In these cases, the quaternary picrate was converted to the chloride which was not purified, but dried and demethylated. The yield is calculated on the picrate.

The same product was obtained when the method used earlier was applied.[1] The above procedure was more convenient and offered higher yields. Alkylation at the ring nitrogen was assumed by analogy with the earlier example in which the structure of the product was proved.

2-Methyl-3-ethyl-5-formamidoindole.—The 5-aminoindole (15 g.), 98% formic acid (170 ml.) and acetic anhydride (5 ml.) were warmed in a boiling water-bath for two hours. The formic acid was removed by distillation under reduced pressure. The product precipitated as a gum on addition of water to the residue. Crystallization was induced by stirring the gum with a small amount of methanol together with sufficient aqueous potassium hydroxide added dropwise to maintain alkalinity. Finally, more water was cautiously added to complete crystallization, and the crude amide was filtered and recrystallized from aqueous alcohol, yielding 11 g., 63%, m.p. 153–157°. This was used for reduction without further treatment. For analysis, recrystallization from ethyl acetate and hexane gave a sample of m.p. 155–157°.

Anal. Calcd. for $C_{12}H_{14}ON_2$: C, 71.28; H, 6.96. Found: C, 71.15; H, 7.01.

2-Methyl-3-ethyl-5-methylaminoindole.—The 5-formamidoindole (5 g.) in dry ether (500 ml.) was partially dissolved by refluxing and a slurry of lithium aluminum hydride (3 g.) in dry ether (500 ml.) was added. After the mixture had been stirred for 20 hours, the excess hydride was decomposed with water or ethyl acetate, followed by 10% sodium hydroxide (100 ml.). The ether layer was then separated, and the amine extracted from it with several portions (50 ml. each) of 2 *N* hydrochloric acid. When the acid extracts were combined and made alkaline, the product crystallized. It was filtered, and washed with water to give 2.7 g., m.p. 145–148°, 57%. The analytical sample from ethyl acetate and hexane had m.p. 147–149°.

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.58; H, 8.57; N, 14.89. Found: C, 76.93; H, 8.50; N, 14.92.

2-Methyl-3-ethyl-5-(1′-pyrrolidyl)-indole.—2-Methyl-3-ethyl-5-succinimidoindole was first prepared. A mixture of 2-methyl-3-ethyl-5-aminoindole (5 g.) and succinic anhydride (3.2 g.) was heated *in vacuo* at 135° and 20 mm. for 45 minutes. The cold melt was partitioned between ethyl acetate and aqueous sodium carbonate. From the dried organic layer on concentration, pure crystalline imide, 3 g., 40%, m.p. 175–177°, was obtained. Additional cruder material could be isolated from the filtrate. The m.p. of the first crop was unchanged after crystallization.

Anal. Calcd. for $C_{15}H_{16}O_2N_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.18; H, 6.29; N, 11.02.

The succinimido derivative was reduced exactly as described above for the preparation of 2-methyl-3-ethyl-5-methylaminoindole. The 5-pyrrolidylindole was obtained in a 56% yield after recrystallization from aqueous alcohol and melted at 92–94°.

Anal. Calcd. for $C_{15}H_{20}N_2$: C, 78.93; H, 8.83; N, 12.27. Found: C, 78.86; H, 8.94; N, 12.14.

A. 5-Aminoindoles by Catalytic Reduction. 2-Methyl-3-ethyl-5-aminoindole.—After a number of trials, the following method was found to be best. The nitro compound (25 g.) was suspended in absolute alcohol (150 ml.) and shaken with 5% palladium-on-charcoal (0.40 g., Baker and Co.) at an initial hydrogen pressure of 60 lb. As soon as the theoretical pressure drop occurred (about 30 min.) the solution was rapidly filtered with suction while still hot. Chilling the filtrate yielded 14.6 g., 68%, m.p. 148–149°.[1] Addition of water to the mother liquor gave further crops but of poorer quality.

2-Methyl-3-β-hydroxyethyl-5-aminoindole.—To avoid partial reductions it was found necessary to reduce the nitro compound (5 g.) in absolute alcohol (100 ml.) as above but with more palladized charcoal (0.9 g.). The resultant suspension was heated before filtration and concentrated to a small volume for crystallization. Analyses and physical properties are in Table I.

1,2-Dimethyl-3-ethyl-5-aminoindole.—The nitro compound reduced readily under the conditions given above for the 3-β-hydroxyethyl derivative. The alcohol was removed from the filtrate *in vacuo*, and the residual sirup soon crystallized, m.p. 60–62°. Distilled *in vacuo* for analysis, a small sample gave m.p. 63–64°. The entire residue was thus pure enough for further use. This was not the case in the preparation of the amines above which lack the 1-methyl group and which must be purified by crystallization from the filtrates obtained by catalytic reduction.

B. Methylation to the Quaternary Stage of 2-Methyl-3-ethyl-5-aminoindole.—2-Methyl-3-ethyl-5-aminoindole (5 g.) and sodium bicarbonate (11 g.) were stirred in water (50 ml.) as dimethyl sulfate (12 ml.) was added during 15 minutes. There was a slight evolution of heat and gradual solution of the indole. The solution was finally brought to 65° to decompose unreacted dimethyl sulfate, acidified with 6 *N* hydrochloric acid, and added to a hot solution of picric acid (7 g.) in ethanol (100 ml.). The picrate so obtained was recrystallized from alcohol.

Quaternary Ammonium Picrates of Other Aminoindoles.—The procedure given above was used without change for 1,2-dimethyl-3-ethyl-5-aminoindole and for 2-methyl-3-ethyl-5-amino-7-chloroindole. In the case of 2-methyl-3-β-hydroxyethyl-5-aminoindole, however, the quaternary ammonium salt precipitated as a dipicrate. For best results, therefore, after methylation of 5 g. as described above, the acidified solution was added to a hot solution of picric acid (14.5 g.) in 20% aqueous alcohol (350 ml.).

C. Conversion of Quaternary Picrate to Quaternary Chloride.—The quaternary picrate (16 g.) from 2-methyl-3-ethyl-5-aminoindole was dissolved in a warm mixture of 2 *N* hydrochloric acid (200 ml.) and acetone (200 ml.) and the picric acid was extracted with toluene (300 ml.). The aqueous phase was concentrated *in vacuo* to a sirup. Repeated concentration with additions of *t*-butyl alcohol induced crystallization and the residue was recrystallized from absolute alcohol by addition of ether, yielding 7.0 g. The

product dried for one hour at 100° contained alcohol of crystallization.

D. Demethylation by Sodium Propylate. 2-Methyl-3-ethyl-5-dimethylaminoindole.—The quaternary ammonium chloride (10 g.) was refluxed with a solution of sodium (4 g.) in *n*-propyl alcohol (250 ml.) for 17 hours. After removal of most of the solvent under reduced pressure, water was added and residual propanol distilled out also under reduced pressure. Finally the water-insoluble oil remaining crystallized and was filtered. The dimethylamino compound so obtained was recrystallized from a concentrated alcoholic solution by slow addition of a little water.

The 5-dimethylaminoindole also was obtained from the 5-aminoindole without purification of the intermediate quaternary salts. Instead of precipitation of a picrate, concentration of the acidified methylation mixture was carried out. The saline residue was carefully dried by repeated concentration with absolute alcohol and final heating *in vacuo* at 50° and 1 mm. This material was then subjected to sodium propylate demethylation as described above. From 20 g. of 2-methyl-3-ethyl-5-aminoindole 19 g. of the 5-dimethylamino compound, m.p. 97–100°, was obtained for an over-all yield of 82%.

2-Methyl-3-β-chloroethyl-5-dimethylaminoindole Picrate.—To 2-methyl-3-β-hydroxyethyl-5-dimethylaminoindole (1.0 g.) dissolved in chloroform (50 ml.) was added a solution of thionyl chloride (1.2 ml.) in chloroform (50 ml.) in one portion. The mixture was refluxed for 45 minutes, then concentrated under reduced pressure with several additions of alcohol. The residue in a little alcohol was added to 5% alcoholic picric acid (60 ml.). The crystals that separated together with a second crop obtained on cautious addition of water were combined and recrystallized from 90% acetone to give 1.5 g., 72%, m.p. 188–189° with slow heating. The m.p. was quite variable with the rate of heating. The Beilstein test for halogen was strong.

THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH
NEW YORK, N. Y.

A Study of the Chlorination of Fluorinated Aliphatic Ethers[1]

BY J. D. PARK, BUCK STRICKLIN AND J. R. LACHER

RECEIVED OCTOBER 30, 1953

Previous papers[2,3] described the photochemical monochlorination of some fluorinated aliphatic ethers. The present paper reports (with some correction of previous data) a complete study of the products isolated in the stepwise photochemical chlorination of CH_3–O–CF_2CFClH and CH_3CH_2–O–CF_2CFClH in the liquid phase. The chlorination of CH_3–O–CF_2CFClH went easily and stepwise to CCl_3–O–CF_2CFClH then, after some lag, to CCl_3–O–CF_2CFCl_2. Although not all possible chlorinated products of C_2H_5–O–CF_2CFClH could be isolated, experimental results indicated that chlorination proceeded in a similar manner. Chlorination first gave the α- and β-monochlorinated ethers, CH_3CHCl–O–CF_2CFClH and CH_2ClCH_2–O–CF_2CFClH in a ratio of 3:1.

It was previously reported[2] that chlorination of C_2H_5–O–CF_2CFClH in a similar manner, yielded CH_3CCl_2–O–CF_2CFClH (2 parts) and CH_2ClCH_2–O–CF_2CFClH (1 part). The α-chloro ether obtained in the present work was found, by means of physical properties and infrared absorption spectra, to be identical with the compound reported to be CH_3CCl_2–O–CF_2CFClH. Since repeated chlorine analyses and molar refraction indicated the major fraction to be a monochlorinated product, it now appears that actually CH_3CHCl–O–CF_2-$CFClH$ was obtained instead of the dichlorinated ether.

Continued chlorination of either CH_3CHCl–O–CF_2CFClH or CH_2ClCH_2–O–CF_2CFClH yielded successively $CH_2ClCHCl$–O–CF_2CFClH and $CHCl_2CHCl$–O–CF_2CFClH. Further chlorination gave a mixture of higher chlorinated products which distilled over a range of 65–94° at 10 mm. pressure, with no constant-boiling flat, while the index of refraction rose from 1.4300 to 1.4575. Although the tetra- and pentachlorinated compounds could not be isolated from this high-boiling mixture, cleavage with aluminum chloride, as described below, showed it contained no products resulting from the replacement of the H-atom located in the fluoroalkyl portion of the ether.

Finally, chlorination was allowed to proceed to completion to yield CCl_3CCl_2–O–CF_2CFCl_2.

These chlorinated ethers proved to be stable compounds undergoing none of the reactions to which alkyl and chloroalkyl ethers are usually susceptible. They did not undergo hydrolysis to esters in the presence of sulfuric acid by the method of Young and Tarrant.[4] The ethers did undergo cleavage with aluminum chloride and aluminum bromide to yield a mixture of alkyl and acyl halides. These cleavage reactions were used extensively in the identification of the chlorinated products.

Experimental

The photochemical liquid-phase chlorination was carried out by bubbling chlorine through the liquid through a sintered glass distributor. The chlorinations proceeded smoothly with evolution of sufficient heat to cause refluxing. However, the reactions became slower as the ether became more highly chlorinated. In each case chlorine was passed into the ether until the gain in weight of the ether indicated that one additional chlorine had been introduced into the molecule. The product was washed with water, dried and fractionated in a precision fractionating column.

Proof of the point of attack of chlorine was found by cleavage of the ethers with aluminum chloride in the following manner. For example: CH_3–O–CF_2CFClH upon treatment with aluminum chloride yielded a mixture of methyl chloride, methyl fluoride, $CFClHCOF$ and $CFClHCOCl$. The acid halides were identified by formation of the known N-phenyl-α-chloro-α-fluoroacetamide,[4] m.p. 86–87°.

Anal. Calcd. for C_8H_7FClNO: C, 51.25; H, 3.76; N, 7.53; Cl, 18.90. Found: C, 51.55; H, 3.86; N, 7.53; Cl, 18.86.

The above methyl halides were identified after separation by low temperature distillation.

It was found, on subsequent use of the above reaction, that the more highly chlorinated the ether the more it resisted cleavage with aluminum chloride. In general, the period of reaction, the temperature at which reaction occurred and the amount of reagent required to bring about effective cleavage increased as the number of chlorine atoms increased. Aluminum bromide was also effective in splitting the chlorinated ethers.

The fact that N-phenyl-α-chloro-α-fluoroacetamide was obtained from all the chlorinated ethers except CCl_3-O-CF_2CFCl_2 and CCl_3CCl_2-O-CF_2CFCl_2 indicated that the stepwise chlorination proceeded in accord with the directive influence of the $-CF_2-$ cluster. Cleavage of the fully chlo-

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