3-Hydroxy-16,17-seco-16-norestra-1,3,5(10)-trien-17-oic Acid (1b).—The hydrogenolysis of the benzyl group of 1.00 g of **10** was accomplished as described in the preparation of **11**. The solid residue was crystallized from Me_2CO–*n*-C_6H_{14} to give 0.63 g (84%) of **1b**, mp 195–198° (evac tube). The analytical sample was obtained from C_6H_6 as thick needles, mp 198.5–200.5° (evac tube), $[\alpha]D$ +69° (EtOH). *Anal.* ($C_{17}H_{22}O_3$) C, H.

Doisynolic Acid (1a).—Doisynolic acid was prepared by the method of Heer and Miescher.[4] From 4.0 g of estrone there was obtained, after four crystallizations from MeOH–H_2O and one from Me_2CO–*n*-C_6H_{14}, 0.179 g of colorless needles, mp 198.5–200° (evac tube), $[\alpha]D$ +105° (*c* 0.470, EtOH) [lit.[4] mp 199–200°, $[\alpha]D$ +102° (*c* 0.475, in EtOH)].

Acknowledgments.—The authors are indebted to Drs. Leslie A. Freiberg, Wayne Cole, and Paul Kurath for helpful discussions, and to Dr. R. E. Mauer and Thomas Kallal for biological evaluation. We are also grateful to Brigitte Fruehwirth, Evelyn Baker, Ruth Stanaszek, Victor Rauschel, and David Williamson for spectroscopic and analytical services.

New Compounds

An Aziridinone Derived from 1-Aminoadamantane

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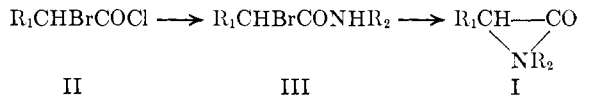
Received August 29, 1968

Although the physiological properties of aziridines have been extensively investigated, especially in connection with the nitrogen mustards, there is no report in the literature regarding the biological properties of aziridinones. We report here the preparation of an aziridinone (I), which is a derivative of 1-aminoadamantane, a compound in which there has been a considerable pharmacological interest since its antiviral activity was discovered.[2]



R_1 = *t*-Bu
R_2 = 1-adamantyl ($C_{10}H_{15}$)

Experimental Section[3]

N-(1-Adamantyl)-2-bromo-3,3-dimethylbutyramide (III).—A solution of 1.00 g (8.6 mmoles) of 3,3-dimethylbutyric acid in $SOCl_2$ (1.0 ml) was refluxed for 30 min and excess $SOCl_2$ was removed under reduced pressure at 30°. The acid chloride was dissolved in 2.3 ml of CCl_4 and refluxed with Br_2 (0.53 ml, 9.6 mmoles) for 2.5 hr. The resulting bromo acid chloride was treated gradually with an ice-cold solution of 1.31 g (8.6 mmoles) of 1-aminoadamantane and 1.14 g (11 mmoles) of Et_3N in 60 ml of CH_2Cl_2. The reaction mixture was then treated with H_2O, extracted with CH_2Cl_2, and the combined CH_2Cl_2 layers were washed (5% HCl, 5% NaOH, H_2O, saturated NaCl solution) and dried (Na_2SO_4). The solvent was removed *in vacuo* to give crude III, which was recrystallized from heptane to furnish 2.30 g (82% over-all) of crystals, mp 182–183°. *Anal.* ($C_{16}H_{26}BrNO$) C, H, Br, N.

1-(1-Adamantyl)-3-*t*-butylaziridinone (I).—A solution of 1.00 g (3.1 mmoles) of III in 150 ml of dry Et_2O was stirred with 0.55 g (4.9 mmoles) of KO-*t*-Bu at 0° for 15 min (progress of the reaction was followed by ir spectroscopy). The reaction mixture was filtered through a sintered-glass funnel and the filtrate was removed under reduced pressure at room temperature. The solid residue was recrystallized from heptane to afford 0.51 g (68%) of the aziridinone **I**: mp 82–83°; ir, 1830 cm^{-1}; nmr, τ 7.32 (1 H, s), 7.73–8.42 (15 H, m), 9.02 (9 H, s). *Anal.* Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.46; H, 10.07; N, 5.55.

(1) Recipient of a Graduate Traineeship from the National Science Foundation.

(2) W. L. Davies, R. R. Grunert, R. F. Haff, J. W. McGahen, E. M. Neumayer, M. Paulshock, J. C. Watts, T. R. Wood, E. C. Hermann, and C. E. Hoffmann, *Science*, **144**, 862 (1964).

(3) Melting points were taken on a Mel-Temp apparatus and are uncorrected. Ir spectra were obtained in $CHCl_3$ on a Perkin-Elmer spectrophotometer, Model 337, and nmr spectra were recorded in CCl_4 as solvent on a Varian A-60 instrument (TMS as internal standard). Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Some Aromatic Fluorine Compounds

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Received August 14, 1968

Fluorination of carcinogenic aminoazo dyes greatly enhances the activity of these compounds except when the sites involved in carcinogenesis are blocked by substitution with the halogen.[1,2] As these sites are on the diamine ring, various difluoroanilines are required for synthesis of the dyes. This communication reports some observations and new compounds of interest which have arisen during attempts to prepare 2,3-difluoroaniline.

Experimental Section[3]

2-Chloro-3-fluoronitrobenzene.—2,3-Dinitroaniline[4] (162 g) was suspended in HCl (5.5 *N*, 490 ml) and a solution of $NaNO_2$ (100 g) in H_2O (120 ml) was added slowly with constant stirring, the temperature being maintained below 0° by the addition of solid CO_2 to the mixture. The mixture was stirred for a further 30 min and then a slight excess (204 g) of solid sodium fluoroborate was added slowly with constant stirring. After a further 30 min, the precipitate was filtered off under vacuum, washed with a small volume of chilled saturated sodium fluoroborate solution, and allowed to dry in the dark. The product, **2-chloro-3-nitrobenzenediazonium fluoroborate,** was a bright yellow solid (193 g, 80%) which darkened upon exposure to light. The diazonium salt was dried further in a desiccator (NaOH, silica gel) and then decomposed by intimately mixing small portions (10 g) with washed, dried sand (20 g) in a 500 ml round-bottomed flask fitted with a condenser and heating carefully in an oil bath.

(1) J. A. Miller, E. C. Miller, and G. C. Finger, *Cancer Res.*, **13**, 93 (1953).

(2) J. A. Miller, E. C. Miller, and G. C. Finger, *ibid.*, **17**, 387 (1957).

(3) Melting points are corrected and were determined in a capillary tube; boiling points are uncorrected. Analyses were performed by the CSIRO Australian Microanalytical Service.

(4) K. H. Pausacker and J. G. Scroggie, *J. Chem. Soc.*, 1897 (1955).

Decomposition occurred at 187° with evolution of dense white fumes, and droplets of a dark brown oil collected in the flask and condenser. The oil was extracted with acetone (three 100-ml portions) and steam distilled to give a yellow oil in 15% yield, bp 235–236°. *Anal.* ($C_6H_3ClFNO_2$) C, H, Cl, N; F: calcd, 10.8; found, 10.1.

2-Chloro-3-fluoroaniline.—2-Chloro-3-fluoronitrobenzene (19.6 g) was heated under reflux (15 min) with $SnCl_2$ (118 g) and HCl (11 *N*, 180 ml). The solution was then basified with NaOH (2 *N*) and extracted with $CHCl_3$ (four 100-ml portions) to yield 12.5 g (77%) of a clear colorless oil, bp 212–215°.

2-Chloro-3-fluoroacetanilide.—2-Chloro-3-fluoroaniline was acetylated with Ac_2O–NaOAc to give colorless needles, mp 131–132° (from EtOH). *Anal.* (C_8H_7ClFNO) C, H, F, N; $COCH_3$: calcd, 22.9; found, 22.4.

2,6-Dinitrofluorobenzene.—Another attempted method of preparation of 2,3-difluoroaniline involved the initial preparation of 2,6-dinitrofluorobenzene, which was accomplished by two routes different from those previously reported.[5-7]

(**a**) Fluorobenzene (251 g) was heated (2 hr) on a water bath with constant stirring with a mixture of H_2SO_4 (36 *N*, 1.5 l.) and fuming H_2SO_4 (20%, 300 ml). The reaction mixture was cooled to 0° and solid KNO_3 (750 g) was added slowly, the temperature being maintained between 40 and 60°. The solution was then heated at 110° (20 hr) and poured onto ice and the white precipitate was filtered off under vacuum; after being pressed dry, the precipitate was heated under reflux (7.5 hr) with H_2SO_4 (18 *N*, 1.9 l.) and the reaction mixture was poured onto ice and extracted (Et_2O, four 200-ml portions). Evaporation of the dried (Na_2SO_4) ether extract yielded 104 g (22%) of a yellow, steam-volatile oil, bp 288–290° dec. *Anal.* ($C_6H_3FN_2O_4$) C, H, F, N.

(**b**) 3,5-Dinitro-4-chlorobenzenesulfonic acid (60 g), prepared by the method of Schultz,[8] was heated with anhydrous KF (31 g), DMF (100 ml), and C_6H_6 (100 ml) until the temperature of the distillate was 120° in order to dehydrate the system. The mixture was then heated under reflux (10 hr), brown fumes being evolved throughout. The DMF was then removed under reduced pressure and the residue was heated under reflux (8 hr) with H_2SO_4 (7 *N*, 1.25 l.). Extraction with $CHCl_3$ (four 100-ml portions) gave a yellow, steam-volatile oil, bp 288–290° dec, in 22% yield.

2-Fluoro-3-nitroaniline.—2,6-Dinitrofluorobenzene (28.5 g) was heated under reflux (30 min) with $SnCl_2$ (90 g), HCl (3 *N*, 540 ml), and EtOH (130 ml).[9] The reaction mixture was basified with 2 *N* NaOH and extracted (Et_2O, seven 200-ml portions) to give (11.2 g, 43%) yield when crystallized from petroleum ether (bp 40–60°) as orange needles, mp 99–100°. *Anal.* ($C_6H_3FN_2O_2$) C, H, N; F: calcd, 12.2; found 12.7.

Acknowledgments.—This work was mainly supported by grants from the Anti-Cancer Council of Victoria, of which P. E. Hughes was the W. J. Kilpatrick Fellow. Jill M. Blunck is in receipt of a Research Scholarship from the University of Melbourne.

(5) R. E. Parker and T. O. Read, *J. Chem. Soc.*, 3149 (1962).
(6) J. F. K. Wilshire, *Aust. J. Chem.*, **20**, 2809 (1967).
(7) N. N. Vorozhtsov, Jr., V. A. Sokolenko, and G. G. Yakobson, *Izv. Sibirsk. Otd Akad. Nauk. SSSR*, 87 (1962); *Chem. Abstr.*, **59**, 1507 (1963).
(8) H. P. Schultz in "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p 364.
(9) J. J. Blanksma, W. J. van den Broek, and D. Hoegen, *Rec. Trav. Chim.*, **65**, 329 (1946).

Synthesis of Some Antithyroid Compounds. I

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Received July 29, 1968

Various 1-arylformamidino-1-arylthiocarbamide hydrochlorides have been synthesized for biological testing since these compounds might prove to be antithyroid drugs due to their facile oxidation into the corresponding heterocyclic bases.

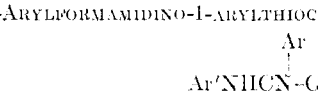
Experimental Section

Following the general technique for the reaction as worked out by earlier workers,[1-4] it has been found possible to prepare many substituted 1-arylformamidino-1-arylthiocarbamide hydrochlorides (I) by the interaction of arylcyanamides with the appropriate thiocarbamides.

1-Phenylformamidino-1-phenylthiocarbamide Hydrochloride.—Equimolecular quantities of phenylcyanamide (6 g) in dry Et_2O and 1-phenylthiocarbamide (8 g) dissolved in acetone were mixed and dry HCl was passed through the mixture for a few minutes. A colorless crystalline product separated which was filtered and washed freely (warm Me_2CO, Et_2O) (mp 158°). It could not be crystallized as it decomposed on boiling with any common solvent.

Similarly other substituted formamidinothiocarbamide hydrochlorides have been prepared and the results are summarized in Table I.

TABLE I
1-ARYLFORMAMIDINO-1-ARYLTHIOCARBAMIDE HYDROCHLORIDE (I)



No.	Ar′	Ar	Formula[a]	Yield, %	Mp, °C
1	C_6H_5	C_6H_5	$C_{14}H_{14}N_4S\cdot HCl$	92	157–158
2	C_6H_5	*p*-$CH_3C_6H_4$	$C_{15}H_{16}N_4S\cdot HCl$	90	153–155
3	C_6H_5	*m*-$CH_3C_6H_4$	$C_{15}H_{16}N_4S\cdot HCl$	88	135–137
4	C_6H_5	*o*-$CH_3C_6H_4$	$C_{15}H_{16}N_4S\cdot HCl$	90	142
5	C_6H_5	*p*-$OC_2H_5C_6H_4$	$C_{16}H_{18}N_4OS\cdot HCl$	85	133–135
6	C_6H_5	*p*-ClC_6H_4	$C_{14}H_{13}ClN_4S\cdot HCl$	85	150–151
7	C_6H_5	*p*-BrC_6H_4	$C_{14}H_{13}BrN_4S\cdot HCl$	80	148–150
8	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	$C_{15}H_{15}ClN_4S\cdot HCl$	78	152
9	*p*-ClC_6H_4	*m*-$CH_3C_6H_4$	$C_{15}H_{15}ClN_4S\cdot HCl$	75	125
10	*p*-ClC_6H_4	*p*-$OC_2H_5C_6H_4$	$C_{16}H_{17}ClN_4OS\cdot HCl$	70	148–150
11	*p*-Cl-C_6H_4	C_6H_5	$C_{14}H_{13}ClN_4S\cdot HCl$	85	125–126
12	*p*-Cl-C_6H_4	*p*-ClC_6H_4	$C_{14}H_{12}Cl_2N_4S\cdot HCl$	80	124–125
13	*p*-Cl-C_6H_4	*m*-ClC_6H_4	$C_{14}H_{12}Cl_2N_4S\cdot HCl$	78	115
14	*p*-Cl-C_6H_4	*p*-BrC_6H_4	$C_{14}H_{12}BrClN_4S\cdot HCl$	75	118–121
15	*p*-$OC_2H_5C_6H_4$	*o*-$CH_3C_6H_4$	$C_{17}H_{20}N_4OS\cdot HCl$	70	117–119
16	*p*-$OC_2H_5C_6H_4$	*p*-$CH_3C_6H_4$	$C_{17}H_{20}N_4OS\cdot HCl$	70	145
17	*m*-$CH_3C_6H_4$	*p*-ClC_6H_4	$C_{15}H_{15}ClN_4S\cdot HCl$	75	143–144
18	*m*-$CH_3C_6H_4$	*p*-BrC_6H_4	$C_{15}H_{15}BrN_4S\cdot HCl$	70	127–128
19	*m*-$CH_3C_6H_4$	*m*-ClC_6H_4	$C_{15}H_{15}ClN_4S\cdot HCl$	75	127
20	*m*-$CH_3C_6H_4$	*m*-$CH_3C_6H_4$	$C_{16}H_{18}N_4S\cdot HCl$	90	126–127
21	*m*-$CH_3C_6H_4$	C_6H_5	$C_{15}H_{16}N_4S\cdot HCl$	85	141
22	*m*-$CH_3C_6H_4$	*p*-$OC_2H_5C_6H_4$	$C_{17}H_{20}N_4OS\cdot HCl$	70	143
23	*m*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	$C_{16}H_{18}N_4S\cdot HCl$	88	145–146
24	*o*-$CH_3C_6H_4$	*p*-$OC_2H_5C_6H_4$	$C_{17}H_{20}N_4OS\cdot HCl$	65	136

[a] The analytical values for N, S, and equivalent weight for all the compounds were found in agreement with the value calculated for I. All compounds were water soluble and could not be crystallized without decomposition.

Acknowledgment.—Authors are grateful to Professor Wahid U. Malik for providing necessary laboratory facilities.

(1) C. P. Joshua, V. K. Verma, and K. S. Suresh, *Tetrahedron Letters*, 663 (1961).
(2) C. P. Joshua, *J. Sci. Ind. Res.* (India), **21B**, 588 (1962).
(3) S. N. Pandeya, *Indian J. Chem.*, **1**, 525 (1963).
(4) P. K. Srivastava, *ibid.*, **1**, 432 (1963).

N-(β-Guanidinoethyl)- and N-Guanylazetidines

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Received August 30, 1968

This communication deals with the synthesis of a series of 3,3-disubstituted N-(β-guanidinoethyl)azetidines[1] and 3,3-disubstituted N-guanylazetidines (Table I).

(1) E. Testa, L. Fontanella, and G. F. Cristiani, *Ann. Chem.*, **626**, 114 (1959).