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 (25 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

P. K. SRIVASTAVA AND M. SALEEM

Department of Chemistry, University of Roorkee, Roorkee, India

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*-$OC_2H_5C_6H_4$	$C_{17}H_{22}N_4OS\cdot HCl$	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

ELVIO BELLASIO AND GIANFRANCO CRISTIANI

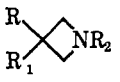
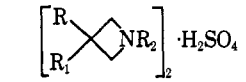
Research Laboratories of Lepetit S.p.A., Milan, Italy

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).

TABLE I

No.	R	R_1	R_2	Bp (mm) or mp, °C	Yield, %	Method	Formula	Analyses
1	n-C_3H_7	n-C_3H_7	CH_2CN	109 (7)	64	A	$C_{11}H_{20}N_2$	C, H, N
2	CH_3	C_6H_5	CH_2CN	100 (0.2)	73	A	$C_{12}H_{14}N_2$	C, H, N
3	C_2H_5	C_6H_5	CH_2CN	65–66[a]	70	A	$C_{13}H_{16}N_2$	N
4	n-C_4H_9	C_6H_5	CH_2CN	128 (0.4)	66	A	$C_{15}H_{20}N_2$	N
5	n-C_3H_7	n-C_3H_7	$(CH_2)_2NH_2$	95 (5)	55	B	$C_{11}H_{24}N_2$	C, H, N
6	CH_3	C_6H_5	$(CH_2)_2NH_2$	87 (0.2)	50	B	$C_{12}H_{18}N_2$	N
7	C_2H_5	C_6H_5	$(CH_2)_2NH_2$	97 (0.2)	61	B	$C_{13}H_{20}N_2$	N
8	n-C_4H_9	C_6H_5	$(CH_2)_2NH_2$	112 (0.4)	60	B	$C_{15}H_{24}N_2$	N
9	n-C_3H_7	n-C_3H_7	$(CH_2)_2NHC(NH)NH_2$	187–189[b]	91	C	$C_{24}H_{54}N_8O_4S$	C, H, N, S
10	CH_3	C_6H_5	$(CH_2)_2NHC(NH)NH_2$	239–240[b]	56	C	$C_{26}H_{42}N_8O_4S$	C, H, N, S
11	C_2H_5	C_6H_5	$(CH_2)_2NHC(NH)NH_2$	214–215[b]	87	C	$C_{28}H_{46}N_8O_4S$	C, H, N, S
12	n-C_4H_9	C_6H_5	$(CH_2)_2NHC(NH)NH_2$	151–154[b]	73	C	$C_{32}H_{54}N_8O_4S$	C, H, N, S
13	C_2H_5	C_6H_5	$C(NH)NH_2$	278–281[c]	79	D	$C_{24}H_{36}N_6O_4S$	C, H, N, S
14	n-C_4H_9	C_6H_5	$C(NH)NH_2$	240–241[d]	68	D	$C_{28}H_{44}N_6O_4S$	C, H, N, S

[a] From i-Pr_2O. [b] From H_2O. [c] From EtOH. [d] From i-PrOH.

None of these compounds (Table I) showed a significant degree of hypotensive activity.

Experimental Section[2]

3-Ethyl-3-phenyl-N-cyanomethylazetidine. Method A.—A mixture of 8.3 g of 3-ethyl-3-phenylazetidine,[1] 50 ml of Et_3N, and 3.9 g of chloroacetonitrile was refluxed for 2 hr. After cooling, 100 ml of Et_2O was added to the solution and the precipitate was filtered off. The filtrate was evaporated under reduced pressure and the residue was crystallized (i-Pr)$_2$O.[3]

3-Ethyl-3-phenyl-N-(β-aminoethyl)azetidines. Method B.—A mixture of 7.6 g of 3-ethyl-3-phenyl-N-cyanomethylazetidine, 350 ml of EtOH, and 14 ml of concentrated HCl was hydrogenated in the presence of 4 g of 10% Pd-C. The mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in a little H_2O and the solution was made alkaline (NaOH) and extracted (Et_2O). After evaporation the residue was distilled under reduced pressure.

3-Ethyl-3-phenyl-N-(β-guanidinoethyl)azetidine Sulfate. Method C.—A mixture of 4.1 g of 3-ethyl-3-phenyl-N-(β-aminoethyl)azetidine, 2.8 g of methylthiourea sulfate, and 20 ml of H_2O was stirred at room temperature for 1.5 hr. After standing overnight the mixture was refluxed for 0.5 hr and then evaporated under reduced pressure. The residue was crystallized from H_2O.

3-n-Butyl-3-phenyl-N-guanylazetidine Sulfate. Method D.—To a solution of 2.65 g of methylthiourea sulfate in 20 ml of H_2O, 3.6 g of 3-n-butyl-3-phenylazetidine[1] was added. The mixture was refluxed for 8 hr and then evaporated to dryness under reduced pressure. The residue was taken up in 50 ml of dioxane and the resulting solid was filtered and crystallized (i-PrOH).

(2) All melting points were taken on a Scaniameter capillary melting point apparatus and are uncorrected. Analyses are indicated only by the symbols of the elements. The analytical results were within ±0.3% of the theoretical values.

(3) All other N-(cyanomethyl)azetidines were distilled.

Book Reviews

Topics in Medicinal Chemistry. Volume 2. Edited by J. L. RABINOWITZ and R. M. MYERSON with 13 Contributors. John Wiley and Sons, Inc., New York, N. Y. 1968. xiii + 361 pp. 16 × 23.5 cm. $16.00.

Medicinal chemistry is concerned with the chemistry of medicinal products, their structure–activity relationships, their mode of action on a molecular level, and their metabolism. There is overlapping with pharmacology and biochemistry on the last two counts, but clearly, clinical implications are outside the field of medicinal chemistry. Clinical data can serve as background reading and can help medicinal chemists to visualize their contribution to the better health of patients. As suggested in the review of the first volume of this series [A. Burger, *J. Med. Chem.*, **10**, 1194 (1967)], the title of these collective monographs does not reflect their contents adequately.

The volume under discussion contains three reviews that are medicinal chemistry: J. M. Sprague's Diuretics (beautifully and authoritatively written as expected from this author); M. Gordon's Phenothiazine Drugs, an interesting account of the development and side-tracking of these compounds; and at least a portion of T. Rodman's Drugs Affecting Blood Coagulation and Clot Lysis, inevitably concerned with biochemical mechanisms of clotting (much of which may be found in any text on pharmacology, however). Of the remaining seven review articles, five are purely clinically oriented. One (S. Mudd, Staphylococcal Infection) makes good reading for microbiologists and immunologists, and the last one (J. H. Nodine, Computer Applications in Medicinal Chemistry) makes a bid for our field but fails to make the point, mostly because applications to regression analysis and molecular orbital calculations have been ignored. The author concentrates on interpretation of biological data and on literature retrieval, useful to medicinal chemists, to be sure, but certainly not medicinal chemistry *per se*.

With the exception of the articles by Sprague, Gordon, and Rodman, a medicinal chemist busy in drug design and the understanding of drug action will find little of immediate interest in this book. He may well thumb through it, however, to read about applications in other areas but will be hampered by the lack of effort of the editors to slant those topics toward his expertise, as implied by the title of the book.

UNIVERSITY OF VIRGINIA ALFRED BURGER
CHARLOTTESVILLE, VIRGINIA

Progress in Drug Research. Volume II. Edited by E. JUCKER. Birkhäuser Verlag, Basel and Stuttgart. 1968. 568 pp. 16.5 × 23.5 cm. Fr/DM 116.00.

The eleventh volume of this established and valuable series of monographs offers five review articles. Three of these are written from a distinct medicinal chemical viewpoint: Mescaline and