[CONTRIBUTION FROM THE GEORGETOWN UNIVERSITY MEDICAL CENTER]

Hypotensive Agents. IV.[1] Hydrogenated Dialkylaminoalkyl Isoindole Derivatives[2]

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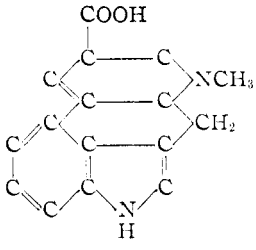
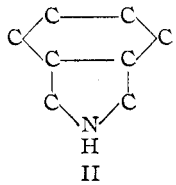
A series of hydrogenated dialkylaminoalkyl isoindole derivatives was prepared by the reduction of the appropriate dialkylaminoalkyl imides. These compounds have been found to possess marked hypotensive action.

As part of a continuing study of potential hypotensive compounds, we have studied the synthesis and physiological action of various hydrogenated N-substituted isoindole derivatives. On examination of the lysergic acid molecule, I, an isoindole ring system is noted, II. Since the isoindole structure is present in this substance, and some of its derivatives are potent pharmacologically active compounds, it was of interest to extend our work into this type of compound and to compare the activity of several members of this series. In this connection it has been reported that the isoindole-type analog, III, of "Dibenamine," IV, was inactive as a hypotensive agent.[4]



I



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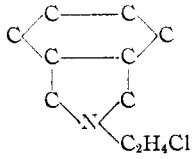

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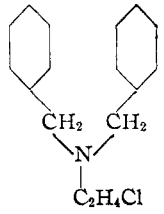
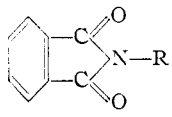


IV

Dihydroisoindole derivatives have been prepared by several different routes by various investigators. Tiffeneau and Fuhrer[5] obtained isoamyldihydroisoindole by the reaction of diisoamylamine and *o*-xylylene bromide. Similar reactions were carried out by von Braun, *et al.*,[6] in which isoindoline derivatives were prepared. By examination of the structure of possible intermediates it was believed that the various types of the hydrogenated isoindoles could be obtained by reduction of the corresponding imides of the various dicarboxylic acids. By means of electrolytic reduction of phthalimides some simple dihydroisoindoles[7-9] have been obtained in which case it has been shown that an intermediate phthalide may be isolated. Uffer and Schlitter[10] obtained dihydroisoindole itself by reduction of phthalimide with lithium aluminum hydride.

This route of preparation appeared to be the most direct and has been investigated to include N-substituted dialkylaminoalkyl isoindole derivatives in various hydrogenation states. Indeed, this method gave excellent results in several trial runs. The various imides that were used were those derived from phthalic, *cis*-Δ^4-tetrahydrophthalic, 3,6-endomethylene-*cis*-Δ^4-tetrahydrophthalic, 3,6-endoxy-*cis*-hexahydrophthalic, hexahydrophthalic, 3-methyl-3,6-endoxypentahydrophthalic, 5-methyl-*cis*-Δ^4-tetrahydrophthalic, cantharidin and quinolinic acid. These are shown in V through XIII, respectively, in which R represents dialkylaminoalkyl.



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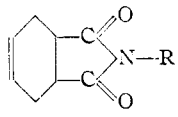

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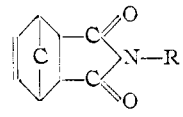

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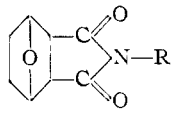
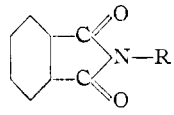
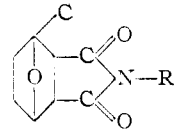


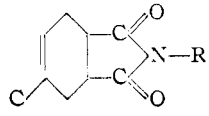
VIII



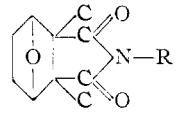
IX



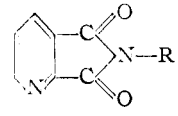
X



XI

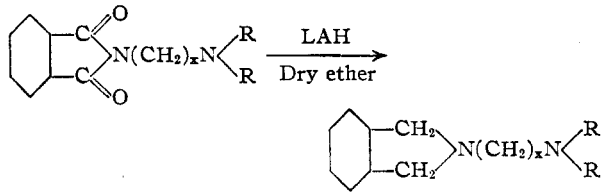


XII



XIII

These imides were readily obtained by reaction of the desired dialkylaminoalkylamines in equimolecular amounts with the anhydride at room temperature followed by heating at 160–170° for two hours. This period of heating is necessary to dehydrate and cyclize the initially formed amic acid to the imide. In all cases the imides were isolated in excellent yields by vacuum distillation The imides thus prepared and their constants are listed in Table I. The reduction of these imides was accomplished using an excess of lithium aluminum hydride in ether solution.



(1) For the first paper in this series see L. M. Rice, A. Popovici C. F. Geschickter and E. E. Reid, THIS JOURNAL, **74**, 3025 (1952).

(2) Supported (in part) by a research grant from the Geschickter Fund for Medical Research, Inc.

(3) Professor Emeritus, Johns Hopkins University, Baltimore. Md.

(4) M. Nickerson and W. S. Gump, *J. Pharmacol. Exptl. Therap.* **97**, 25 (1949).

(5) M. Tiffeneau and K. Fuhrer, *Bull. soc. chim.*, [4] **15**, 174 (1914).

(6) J. V. Braun and F. Zobel, *Ann.*, **445**, 247 (1925); J. V. Braun and A. Nelken, *Ber.*, **55B**, 2059 (1922).

(7) Bulei Sukural, *Bull. Chem. Soc. Japan*, **7**, 155 (1932).

(8) E. Hope and F. Lauskshear, *Proc. Chem. Soc.*, **29**, 224 (1913).

(9) E. W. Cook and W. G. France, *J. Phys. Chem.*, **36**, 2383 (1932).

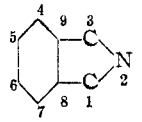
(10) A. Uffer and E. S. Schlittler, *Helv. Chim. Acta*, **31**, 1397 (1948).

TABLE I

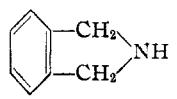
	N-Substitution	Formula	B.p. °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	HCl m.p., °C.	Ionic chlorine Calcd.	Ionic chlorine Found
			N-Dialkylaminoalkyl-Δ^4-tetrahydrophthalimides										
1	Diethylaminoethyl	$C_{14}H_{22}N_2O_2$	132–134	2	67.17	66.92	8.86	9.01	11.19	11.03	214–215	12.36	12.51
2	Dimethylaminopropyl	$C_{13}H_{20}N_2O_2$	140–144	2	66.07	66.20	8.53	8.44	11.86	11.55	172–173	13.00	13.04
3	Diethylaminopropyl	$C_{15}H_{24}N_2O_2$	162–165	3	68.15	68.34	9.15	8.98	10.60	10.27	114–116	11.79	11.88
4	Morpholinopropyl	$C_{15}H_{22}N_2O_3$	175–178	2	64.72	64.93	7.97	7.62	10.07	9.81	203–204	11.26	11.31
			N-Dialkylaminoalkyl-3,6-endomethylene-Δ^4-tetrahydrophthalimides										
1	Diethylaminoethyl	$C_{15}H_{22}N_2O_2$	142–144	2	68.75	69.05	8.46	8.39	10.68	10.69	219–220	11.87	11.96
2	Dimethylaminopropyl	$C_{14}H_{20}N_2O_2$	139–142[e]	2	67.71	67.91	8.06	8.12	11.28	11.00	206–207	12.45	12.41
3	Morpholinopropyl	$C_{16}H_{22}N_2O_3$	190–194	2	66.21	66.10	7.58	7.21	9.64	9.86	191–193	10.85	10.93
			N-Dialkylaminoalkyl-3,6-endoxyhexahydrophthalimides										
1	Dimethylaminoethyl[a]	$C_{12}H_{18}N_2O_3$[c]	140–145	0.5	60.48	60.65	7.61	7.31	11.76	11.90	244–245	12.91	13.06
			N-Dialkylaminoalkyl Quinolinimides										
1	Diethylaminoethyl	$C_{18}H_{17}N_3O_2$	155–160	3	63.14	63.24	6.93	7.14	16.99	16.47	.....	...	...
			N-Dialkylaminoalkyl Phthalimides										
1	Diethylaminoethyl[b]	$C_{14}H_{18}N_2O_2$[d]	140–143	2	68.27	68.35	7.37	7.52	11.37	11.28	232–233	12.50	12.58
2	Dimethylaminopropyl[b]	$C_{13}H_{16}N_2O_2$	140–145	2	67.22	67.06	6.94	6.75	12.06	11.99	206–207	13.19	13.32
3	Morpholinopropyl[b]	$C_{15}H_{18}N_2O_3$	173–177	2	65.67	65.40	6.61	6.74	10.21	10.11	247–248	11.41	11.44
			N-Dialkylaminoalkyl Hexahydrophthalimides										
1	Dimethylaminoethyl	$C_{12}H_{20}N_2O_2$	116–119	2	64.25	64.35	8.99	8.63	12.49	12.19	191–192	13.60	13.54
2	Diethylaminoethyl	$C_{14}H_{24}N_2O_2$	132–135	2	66.63	66.68	9.59	9.16	11.10	10.99	196–197	12.28	12.42
3	Dimethylaminopropyl	$C_{13}H_{22}N_2O_2$	130–132	2	65.51	65.33	9.31	9.10	11.76	11.67	176–177	12.90	13.06
4	Diethylaminopropyl	$C_{15}H_{26}N_2O_2$	150–153	2	67.63	67.45	9.84	9.69	10.52	10.40	123–124	11.71	11.81
5	Morpholinoethyl	$C_{14}H_{22}N_2O_3$	162–164	2	63.13	63.43	8.33	8.18	10.52	10.82	235–236	11.71	11.87
6	Morpholinopropyl	$C_{15}H_{24}N_2O_3$	173–177	2	64.26	64.54	8.63	8.44	9.99	10.03	162–163	11.19	11.20
7	Dibutylaminopropyl	$C_{19}H_{34}N_2O_2$	155–160	0.1	70.76	70.57	10.63	10.65	8.69	9.07	107–109	9.88	10.10
8	Dihexylaminoethyl	$C_{22}H_{40}N_2O_2$	170–175	0.2	72.48	72.26	11.06	10.81	7.68	7.98	.....	...	...
9	Diethylaminohexyl	$C_{18}H_{32}N_2O_2$	158–163	0.1	70.09	69.75	10.46	10.27	9.08	8.78	113–114	10.28	10.41
10	Piperidinoethyl	$C_{15}H_{24}N_2O_2$[f]	138–142	0.1	68.15	68.14	9.15	9.02	10.60	10.27	212–213	11.79	11.84
11	Diethylaminobutyl	$C_{16}H_{28}N_2O_2$	134–139	0.02	68.53	68.84	10.07	9.62	9.99	9.69	95–96	11.19	11.26
12	3-Diethylaminopropanol-2	$C_{15}H_{26}N_2O_3$	146–148	0.1	63.80	63.66	9.28	9.40	9.92	9.98	138	11.12	11.25
			N-Dialkylaminoalkyl-5-methyl-Δ^4-tetrahydrophthalimides										
1	Dimethylaminoethyl	$C_{13}H_{20}N_2O_2$	106–112	0.2	66.07	66.13	8.53	8.42	11.86	12.10	228–229	13.00	13.00
			N-Dialkylaminoalkyl-3-methyl-3,6-endoxyhexahydrophthalimides										
1	Dimethylaminoethyl	$C_{13}H_{20}N_2O_3$	124–130	0.2	61.88	61.74	7.99	8.07	11.10	11.12	260	12.28	12.38
			N-Dialkylaminoalkyl-1,2-dimethyl-3,6-endoxyhexahydrophthalimides										
1	Dimethylaminoethyl	$C_{14}H_{22}N_2O_3$[g]	135–145	0.4	63.13	63.14	8.33	8.24	10.52	10.30	276–277	11.71	11.90
			N-Dialkylaminoalkyl-3,6-dimethyl-3,6-endoxytetrahydrophthalimide										
1	Dimethylaminoethyl	$C_{14}H_{22}N_2O_3$	130–135	0.05	63.13	63.24	8.33	8.06	10.52	10.78	249–251	11.71	11.78

[a] *Anal.* Calcd.: O, 20.14. Found: O, 20.06. [b] Moore and Rapala, THIS JOURNAL, 68, 1657 (1946). [c] M.p. 55–56° [d] M.p. 45–46°. [e] M.p. 63–64°. [f] M.p. 50–51°. [g] M.p. 77–77.5°.

In all cases the imides, dissolved in anhydrous ether, were added at a rate just sufficient to maintain reflux. The reaction mixture was decomposed by slow dropwise addition of water until the ether ceased to reflux. The hydrogenated N-substituted isoindole derivatives thus prepared were isolated as colorless oils by vacuum distillation in excellent yields; except in the case of the pyridine analog which gave a lower yield. The reaction was clean cut and no appreciable amount of products from side reactions was evident. The dihydroisoindoles on standing rapidly developed colors ranging from cherry red to brown, as has been noted by previous investigators. The compounds were characterized as the dihydrochlorides and the dimethiodides. The naming of these compounds is in conformity with the Patterson Ring Index as is illustrated in the following example in which the numbers 8 and 9 had to be assigned to the two carbon atoms at the ring junctions



Octahydroisoindole



Isoindoline or dihydroisoindole

Thus various degrees of hydrogenation of the isoindole nucleus are readily available by this means and the reaction has wide applicability as shown in Table II.

The hypotensive activity and toxicity of our compounds were determined by Dr. Antoinette Popovici of our group. When screened on dogs for hypotensive action the following information was noted: The imides were not active when tested in the form of hydrochlorides. The isoindoles as such were very weak in hypotensive action. However, conversion to the dimethyl quaternary salts resulted in compounds with a low toxicity and a

TABLE II

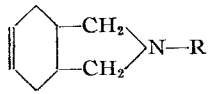
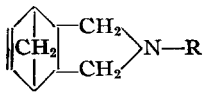
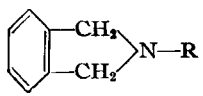
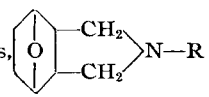
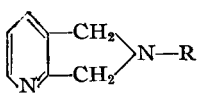
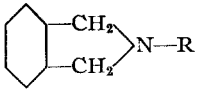
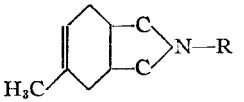
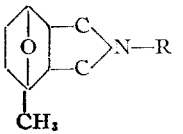
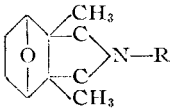
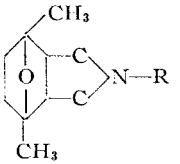
R	Formula	B.p. °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	HCl m.p., °C.	Analyses, % Ionic chlorine Calcd.	Ionic chlorine Found	Dimethiodide M.p., °C.	Dimethiodide Nitrogen Calcd.	Dimethiodide Nitrogen Found
N-Dialkylaminoalkyl-4,7,8,9-tetrahydroisoindolines, 															
Diethylaminoethyl	$C_{14}H_{26}N_2$	96–98	2	75.55	75.29	11.78	11.42	12.58	12.43	161–163	24.02	23.91	219–221	5.53	5.18
Dimethylaminopropyl	$C_{13}H_{24}N_2$	88–92	2	74.94	74.74	11.61	11.37	13.45	13.34	220–222	25.21	25.35	234–235	5.69	5.56
Diethylaminopropyl	$C_{15}H_{28}N_2$	106–108	2	76.21	76.17	11.94	11.69	11.85	11.70	137–138	22.93	23.07	228–229	5.60	5.50
Morpholinopropyl	$C_{15}H_{26}N_2O$	126–130	2	71.95	72.38	10.46	10.52	11.19	11.45	216–217	21.94	22.01	216–217	5.24	5.60
N-Dialkylaminoalkyl-4,7,8,9-tetrahydro-4,7-endomethanoisoindolines, 															
Diethylaminoethyl	$C_{15}H_{26}N_2$	122–124	2	76.91	77.19	11.17	10.99	11.94	11.95	175–176	23.08	22.97	208–210	5.40	5.16
Dimethylaminopropyl	$C_{14}H_{24}N_2$	91–94	2	76.28	76.54	10.93	10.85	12.73	12.33	244–246	24.18	24.12	278–280	5.56	5.45
Morphilinopropyl	$C_{16}H_{26}N_2O$	136–138	2	73.24	73.10	9.99	9.71	10.68	10.93	243–244	21.15	21.10	247–248	5.13	5.26
N-Dialkylaminoalkylisoindolines, 															
Diethylaminoethyl	$C_{14}H_{22}N_2$	101–104	2	77.01	76.87	10.15	9.76	12.83	12.54	234–235	24.35	24.18	193–194	5.58	5.51
Dimethylaminopropyl	$C_{13}H_{20}N_2$	120–123	3	76.42	76.12	9.87	9.40	13.71	13.41	246–247	25.58	25.37	237–238	5.74	5.88
Morpholinopropyl	$C_{15}H_{22}N_2O$	164–168	3	73.13	72.97	9.00	8.70	11.37	11.57	247–248	22.21	22.08	230–231	5.28	5.20
N-Dialkylaminoalkyl-4,7-endoxyoctahydroisoindoles, 															
Dimethylaminoethyl[a]	$C_{12}H_{22}N_2O$	98–101	0.6	68.53	67.78	10.54	10.28	13.32	13.37	265–267	25.04	24.99	231–233	5.67	5.75
6-Diethylaminoethyl-5,7-dihydro-2-pyrrolo[3,4-b]pyridine, 															
Diethylaminoethyl	$C_{13}H_{21}N_3$	145–155	2					19.16	18.99						

TABLE II (*Continued*)

R	Formula	B.p. °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	HCl m.p., °C.	Analyses, % Ionic chlorine Calcd.	Ionic chlorine Found	Dimethiodide M.p., °C.	Dimethiodide Nitrogen Calcd.	Dimethiodide Nitrogen Found
N-Dialkylaminoalkyl Octahydroisoindoles, 															
Dimethylaminoethyl	$C_{12}H_{24}N_2$	77–80	2	73.41	73.10	12.32	12.19	14.27	14.02	276–278	26.34	26.21	228–230	5.83	5.88
Diethylaminoethyl	$C_{14}H_{28}N_2$	93–96	2	74.93	75.01	12.58	12.21	12.48	12.23	177–178	23.85	23.77	222–223	5.51	5.24
Dimethylaminopropyl	$C_{13}H_{26}N_2$	85–88	2	74.22	74.10	12.46	12.20	13.32	13.22	236–237	25.03	24.84	246–247	6.08	5.71
Diethylaminopropyl	$C_{15}H_{30}N_2$	105–107	2	74.56	74.99	12.68	12.39	11.75	11.94	.....	22.78	22.82	224–225	5.36	5.56
Morpholinoethyl	$C_{14}H_{26}N_2O$	147–149	5	70.54	70.11	10.99	10.63	11.75	11.77	260–264	22.78	22.70	203–204	7.38[b]	7.40
Morpholinopropyl	$C_{15}H_{28}N_2O$	132–135	2	71.38	71.24	11.18	10.93	11.10	11.37	253–254	21.80	21.94	230–231	5.27	5.38
Dibutylaminopropyl	$C_{19}H_{38}N_2$	116–121	0.1	77.48	77.84	13.01	12.81	9.51	9.65	76–78	19.30	19.21		4.84	5.01
Dihexylaminoethyl	$C_{22}H_{44}N_2$	140–145	0.1	78.50	77.65	13.18	13.23	8.32	8.76	115–117	17.32	17.16	159–152	4.52	4.48
Diethylaminohexyl	$C_{18}H_{36}N_2$	110–120	0.1	77.07	76.99	12.92	12.63	9.99	9.71	203–204	20.06	29.18	230–231	4.96	5.02
Piperidinoethyl	$C_{15}H_{28}N_2$	103–107	0.1	76.21	76.29	11.94	11.69	11.85	11.70	300–302	22.93	22.82	249–250	5.38	5.32
Diethylaminobutyl	$C_{16}H_{32}N_2$	83–87	0.02	76.12	76.50	12.78	12.64	11.10	10.87	198–199	21.80	21.34	201–202	47.33	46.98[c]
3-Diethylaminopropanol-2	$C_{15}H_{30}N_2O$	105–115	0.1	70.81	71.30	11.89	11.96	11.01	11.20	196–198	21.66	21.30	155–156	47.15	46.89[c]
N-Dialkylaminoalkyl-6-methyl-4,7,8,9-tetrahydroisoindoline, 															
Dimethylaminoethyl	$C_{13}H_{24}N_2$	78–85	0.1	74.94	74.65	11.61	11.38	13.45	13.48	262–263	25.39	25.17	203–205	5.69	5.58
N-Dialkylaminoalkyl-4-methyl-4,7-endoxypentahydroisoindoline, 															
Dimethylaminoethyl	$C_{13}H_{24}N_2O$	100–105	0.2	69.60	69.38	10.78	10.61	12.49	12.19	237	23.86	23.94	231–233	5.51	5.45
N-Dialkylaminoalkyl-8,9-dimethyl-4,7-endoxytetrahydroisoindoline, 															
Dimethylaminoethyl	$C_{14}H_{26}N_2O$	110–115	0.2	70.54	70.30	10.99	10.82	11.75	11.80	264–265	22.78	22.66	206–207	5.36	5.44
N-Dialkylaminoalkyl-4,7-dimethyl-4,7-endoxytetrahydroisoindoline 															
Dimethylaminoethyl	$C_{14}H_{22}N_2O$	94	0.2	70.54	70.42	10.99	10.53	11.75	11.40	249–250	22.78	22.87	258–260	48.61	48.30[c]

[a] *Anal.* Calcd.: O, 7.61. Found: O, 8.10. [b] Monomethiodide. [c] Iodine analyses.

very potent hypotensive action. Most of these compounds were active in doses of 3 mg./kg. We will publish a fuller account of the pharmacology of these compounds separately.

Experimental

General Preparation of N-Dialkylaminoalkyl Imides and Their Reduction.—The preparation of diethylaminoethyl hexahydrophthalimide and its reduction will illustrate the procedure followed.

(a) **Diethylaminoethyl Hexahydrophthalimide.**—Into a flask fitted with a reflux condenser was placed 0.40 mole of hexahydrophthalic anhydride. With cooling and intermittent shaking 0.41 mole of diethylaminoethylamine was slowly added. After the reaction had subsided, the reaction mixture was allowed to cool to room temperature and then was heated in an oil-bath maintained at 175° for two hours. The resulting crude product was fractionated in vacuum and the pure imide was obtained as a colorless oil which boiled at 132–135° (2 mm.) in 81% yield.

(b) **Reduction.**—In a 2-liter 3-necked flask fitted with a mercury sealed stirrer, dropping funnel and a long condenser to which a calcium chloride tube was attached were placed 19 g. of lithium aluminum hydride and 1 liter of absolute ether. After solution had been effected, a solution of 50 g. of diethylaminoethyl hexahydrophthalimide dissolved in 200 ml. of absolute ether was added dropwise with rapid stirring. The rate of addition was adjusted so that the reaction mixture refluxed gently. During the addition a fine suspension of solid precipitated. After the addition was completed, the stirring was continued under reflux for two hours and the mixture allowed to stand overnight. The flask was cooled in an ice-bath and, with vigorous stirring, the reaction mixture was decomposed by the dropwise addition of water. The addition of the water was regulated so that reflux was just maintained; and then 10 cc. in excess was added at the end. After decomposition the mixture was stirred an additional hour and filtered with suction. The inorganic precipitate was well pressed and washed with 3 portions of ether. After drying over sodium sulfate, the ether was stripped and the residue distilled in vacuum. There was obtained 41 g. (92%) of material boiling at 77–80° (2 mm.).

The methiodides were prepared in the usual way employing absolute alcohol as a solvent.

The hydrochlorides were produced in the usual way by means of alcoholic hydrogen chloride.

Acknowledgment.—We are indebted to the Schwarzkopf Microanalytical Laboratories, Middle Village, Long Island, N. Y., for the microanalyses. We wish to express our thanks to Carbide and Carbon Chemicals Company for generous supplies of materials and to the Sharples Chemicals, Inc., for a generous gift of 3,6-endoxyhexahydrophthalic anhydride.

WASHINGTON 7, D. C.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

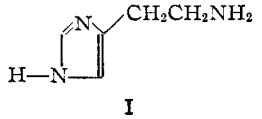
1,2,4-Triazole Analogs of Histamine

BY C. AINSWORTH AND R. G. JONES

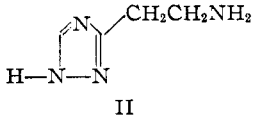
RECEIVED JUNE 11, 1953

3-β-Aminoethyl-1,2,4-triazole and several of its derivatives have been synthesized and tested for pharmacological activity. The parent compound and, to a lesser degree, 3-β-benzylaminoethyl-, 3-β-isopropylaminoethyl- and 3-β-acetamidoethyl-1,2,4-triazole have typical histamine-like activity. Furthermore, these compounds are effective orally.

A number of compounds patterned after histamine (I) have been synthesized and tested in this Laboratory.[1] The object of this work has been to find substances possessing useful physiological activities without the undesirable effects of histamine. The compounds so far examined have been nitrogen heterocycles carrying the β-aminoethyl side chain.[2] Most activity has been found in compounds with small, unsubstituted rings (*e.g.*, thiazole and pyrazole).[1,2c,3] In this paper we describe the preparation and properties of 3-β-aminoethyl-1,2,4-triazole (II) and some of its derivatives.

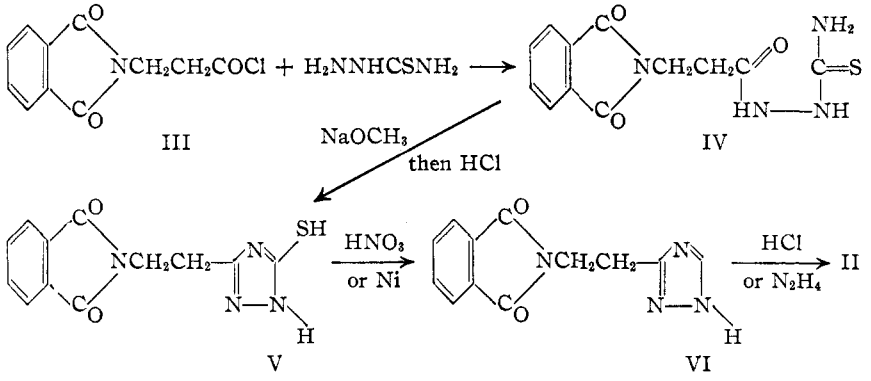


I



II

The method of synthesizing II is outlined by the accompanying series of reactions



The acyl thiosemicarbazide IV was obtained from the readily available acid chloride III[4] and thiosemicarbazide in dry pyridine.[5] Compound IV was cyclized with sodium methylate in alcohol and V was isolated in good yields after acidification of the reaction mixture. Removal of the mercapto group of V was best accomplished by oxidation with nitric acid.[6] Raney nickel desulfurization proved less satisfactory. For optimum yields in the nitric

(1) H. M. Lee and R. G. Jones, *J. Pharmacol. Exptl. Therap.*, **95**, 71 (1949).

(2) (a) R. G. Jones, THIS JOURNAL, **71**, 383 (1949); (b) R. G. Jones, E. C. Kornfeld and K. C. McLaughlin, *ibid.*, **72**, 3539 (1950); (c) R. G. Jones, E. C. Kornfeld and K. C. McLaughlin, *ibid.*, **72**, 4526 (1950).

(3) R. G. Jones and M. J. Mann, *ibid.*, **75**, 4048 (1953).

(4) S. Gabriel, *Ber.*, **41**, 242 (1908).

(5) This method of synthesis was described by E. Hoggarth, *J. Chem. Soc.*, 1160 (1949).

(6) R. G. Jones, THIS JOURNAL, **71**, 644 (1949).