[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

3-Aminoalkyl-1,2,4-triazoles

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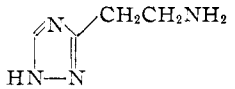
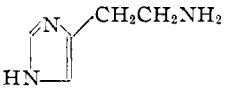
RECEIVED JUNE 4, 1954

Nine new 3-aminoalkyl-1,2,4-triazoles have been prepared. These include the aminomethyl compound, three aminopropyl derivatives and several β-N-alkyl- and N,N-dialkylaminoethyl derivatives. Some pharmacological activities of these compounds have been observed.

3-β-Aminoethyl-1,2,4-triazole[1] (I) was of particular interest because of its prolonged depressive effect on mammalian blood pressure when given either parenterally or orally. Both in chemical structure and in biological activity, I resembles histamine (II). Although on a weight basis II is more intensely active than I in lowering blood pressure, the duration of action of I is much longer. Furthermore, II is not active when given orally.[2]



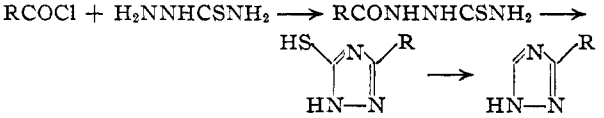
I



II

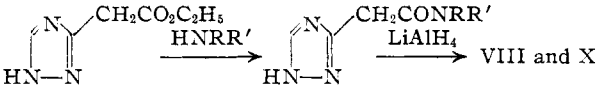
A number of derivatives of I in which the nitrogen of the side chain carried acetyl or alkyl groups retained, in part, the physiological activity of the parent compound. It was of interest, therefore, to make further variations in the structure of I to see if the desirable effects could be retained and the undesirable effects, such as stimulation of gastric secretion, could be eliminated. This paper describes the preparation and physiological activities of several homologs of I wherein the side chain has been shortened, lengthened and branched, and the nitrogen of the side chain has been substituted with methyl and ethyl groups.

The nine new compounds together with some preliminary pharmacological observations are presented in Table I. Compounds III–VII in which the amino group on the side chain is primary, were prepared by the same general method as previously described for the synthesis of I.[1] The synthetic procedure is illustrated by the accompanying sequence of reactions.

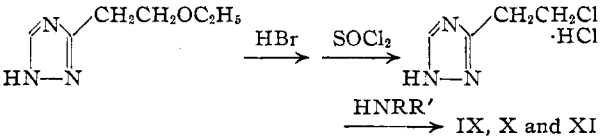


During the transformations, the amino function in the side chain R was protected as a phthalimido group.

Two methods were developed for the synthesis of the N-alkylated compounds VIII–XI. The first of these consisted of reducing the appropriate amides with lithium aluminum hydride in tetrahydrofuran. The amides were prepared from ethyl (1,2,4-triazolyl-3)-acetate which, in turn, was obtained from ethyl malonyl chloride and thiosemicarbazide by the series of reactions outlined above.



The second method involved the reaction of an amine with 3-β-chloroethyl-1,2,4-triazole. This latter compound was obtained by the general triazole synthesis above starting from β-ethoxypropionyl chloride and thiosemicarbazide.



A third method of obtaining 3-β-dimethylaminoethyl-1,2,4-triazole (X) was the methylation of I with formaldehyde–formic acid mixture.

Pharmacological Activities.—The results of preliminary pharmacological observations of compounds III–XI are summarized in Table I. The spasmogenic effect on isolated muscle strips, and the effect on blood pressure of anesthetized cats were determined as outlined previously.[3] Variations of the ethyl side chain of I either by shortening, lengthening or introducing substituents (branching) are seen to reduce or abolish activity. These observations parallel those with histamine homologs where it has been shown that shortening the ethyl side chain to methyl[4] or lengthening it to propyl[5] reduces or abolishes activity.

The N-alkyl and N,N-dialkyl derivatives (VIII–XI) are less active than the parent compound I. Similarly, the corresponding alkyl derivatives of histamine are much less active than is histamine itself.[6] In addition to the pharmacological tests reported in Table I, the N-methyl derivatives VIII and X were tested in hypertensive dogs. Large oral doses (about 100 mg. per kg. of body weight) caused marked and prolonged lowering of the blood pressure, but the effect was accompanied by tachycardia.

Acknowledgment.—The authors are grateful to W. L. Brown, H. L. Hunter, G. M. Maciak and Gloria Beckmann for the microanalyses. The pharmacological tests were carried out by Dr. H. M. Lee and associates, and J. H. Tilden.

(1) C. Ainsworth and R. G. Jones, THIS JOURNAL, **75**, 4915 (1953).

(2) J. J. Abel and S. Kubota, *J. Pharmacol. Exptl. Therap.*, **13**, 243 (1919). In addition these authors concluded that histamine is present in appreciable quantity in some foods and most likely is consumed in the daily diet.

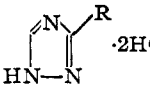
(3) H. M. Lee and R. G. Jones, *ibid.*, **95**, 71 (1949).

(4) A. J. Ewins, *J. Chem. Soc.*, **99**, 2052 (1911).

(5) S. Akabori and T. Kaneko, *J. Chem. Soc. Japan*, **53**, 207 (1932); *C. A.*, **27**, 293 (1933).

(6) C. F. Huebner, R. A. Turner and C. R. Scholz, THIS JOURNAL, **71**, 3942 (1949), concluded that spasmogenic activity of N-alkyl and N,N-dialkyl derivatives of histamine was inversely proportional to the size of the alkyl group.

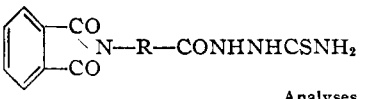
TABLE I

3-AMINOALKYL-1,2,4-TRIAZOLE SALTS  ·2HCl or ·H_2SO_4

No.	R	Yield, %	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Pharmacological effects[e] Smooth muscle[f]	Blood pressure[g]
III	CH_2NH_2	80[a]	263–265	$C_3H_6N_4 \cdot 2HCl$	21.07	21.22	4.71	4.69	0	0
IV	$CH(NH_2)CH_3$	82[b]	182–183	$C_4H_8N_4 \cdot 2HCl$	25.96	25.68	5.45	5.34	0	0
V	$CH(CH_3)CH_2NH_2$	20[c]	218–220	$C_5H_{10}N_4 \cdot H_2SO_4$	26.78	26.62	5.40	5.51	1/700–1/600	1/1200–1/600
VI	$CH_2CH(CH_3)NH_2$	25[d]	225–227	$C_5H_{10}N_4 \cdot H_2SO_4$	26.78	27.04	5.40	5.72	1/400	0
VII	$(CH_2)_3NH_2$	84[a]	172–174	$C_5H_{10}N_4 \cdot 2HCl$	30.16	30.00	6.08	5.93	0	0
VIII	$CH_2CH_2NHCH_3$	70[a]	175–178	$C_5H_{10}N_4 \cdot 2HCl$	30.16	30.40	6.08	6.30	1/20–1/10	1/50–1/25
IX	$CH_2CH_2NHC_2H_5$	65[a]	158–160	$C_6H_{12}N_4 \cdot 2HCl$	33.81	33.58	6.62	6.65	1/140	1/125
X	$CH_2CH_2N(CH_3)_2$	85[a]	155–157	$C_6H_{12}N_4 \cdot 2HCl$	33.81	33.68	6.62	6.70	1/30–1/20	1/40
XI	$CH_2CH_2N(C_2H_5)_2$	83[a]	152–155	$C_8H_{16}N_4 \cdot 2HCl$	39.84	39.72	7.52	7.58	1/800	0

Recrystallization solvent: [a] methanol–ether; [b] ethanol–ether; [c] ethanol; [d] 5% water–ethanol. [e] Activity less than one-thousandth that of histamine acid phosphate is reported as 0. [f] Isolated guinea pig ileum strip. Histamine acid phosphate = 1. [g] Anesthetized cat. Histamine acid phosphate = 1.

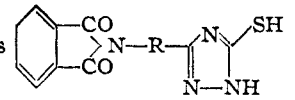
TABLE II

1-SUBSTITUTED THIOSEMICARBAZIDES 

R	Yield, %	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_2	43[b]	232–234[f]	$C_{11}H_{10}N_4O_3S$	47.47	47.53	3.62	3.70
$CHCH_3$	41[c]	135–137	$C_{12}H_{12}N_4O_3S \cdot H_2O$	46.44	46.43	4.55	4.43
$(CH_2)_3$	30[c]	208–210[f]	$C_{13}H_{14}N_4O_3S$	50.98	50.62	4.61	4.60
CH_2CHCH_3[a]	68[d]	183–184	$C_{13}H_{14}N_4O_3S$	50.98	50.85	4.61	4.76
$CH(CH_3)CH_2$	43[e]	210–212[f]	$C_{13}H_{14}N_4O_3S$	50.98	51.19	4.61	4.76

[a] 1-β-Phthalimidoisobutyryl thiosemicarbazide. Recrystallization solvent: [b] acetic acid; [c] water; [d] 95% ethanol; [e] acetic acid–water. [f] Melted with decomposition.

TABLE III

3-SUBSTITUTED-1,2,4-TRIAZOLE-5-THIOLS 

R	Yield, %	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Sulfur Calcd.	Sulfur Found
CH_2	50[b]	293–294	$C_{11}H_8N_4O_2S$	50.76	50.92	3.10	2.93	12.32	12.64
$CHCH_3$	52[b]	289–290	$C_{12}H_{10}N_4O_2S$	52.55	52.35	3.67	3.72	11.68	11.88
$(CH_2)_3$	56[c]	235–237	$C_{13}H_{12}N_4O_2S$	54.15	54.15	4.20	4.24	11.12	10.98
CH_2CHCH_3[a]	30[c]	247–248	$C_{13}H_{12}N_4O_2S$	54.15	54.34	4.20	4.32	11.12	10.96
$CH(CH_3)CH_2$	30[d]	285–286	$C_{13}H_{12}N_4O_2S$	54.15	54.49	4.20	4.32	11.12	10.87

[a] 3-β-Phthalimidoisopropyl-1,2,4-triazole-5-thiol. Recrystallization solvent: [b] water; [c] ethanol–water; [d] acetic acid–water.

Experimental[7]

Phthalimidoacid Chlorides.—Phthalimidoacetyl chloride,[8] α-phthalimidopropionyl chloride[9] and γ-phthalimidobutyryl chloride[10] were prepared from the corresponding acids and thionyl chloride.

β-phthalimidobutyric acid was obtained in 90% yield by heating equimolar quantities of *dl*-β-aminobutyric acid and phthalic anhydride at 180° for two hours. A sample was recrystallized from benzene–petroleum ether; m.p. 120–122°.

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.97; H, 4.62; N, 6.26.

β-Phthalimidobutyryl chloride was prepared in 92% yield from the acid and thionyl chloride; m.p. 75°.

Anal. Calcd. for $C_{12}H_{10}ClNO_3$: N, 5.57. Found: N, 5.60.

β-Phthalimidoisobutyric acid was obtained from β-aminoisobutyric acid[11] and phthalic anhydride; m.p. 165° from ethanol–water.

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.99; H, 4.73; N, 6.00.

β-Phthalimidoisobutyryl chloride was prepared from the acid and thionyl chloride. It was purified by distillation under reduced pressure; b.p. 190° at 5 mm.

Anal. Calcd. for $C_{12}H_{10}ClNO_3$: N, 5.57. Found: N, 5.32.

1-Substituted Thiosemicarbazides (Table II).—These compounds were prepared from appropriate acid chlorides and thiosemicarbazide in dry pyridine according to the procedure reported for the preparation of 1-β-phthalimidopropionyl thiosemicarbazide.[1]

3-Substituted-1,2,4-triazole-5-thiols (Table III).—The cyclic thiols were prepared from the above thiosemicarbazides and sodium methylate in a manner similar to that used for the preparation of 3-β-phthalimidoethyl-1,2,4-triazole-5-thiol.[1]

(7) Melting points were taken on a Fisher–Johns block and recorded as read.

(8) S. Gabriel, *Ber.*, **40**, 2649 (1907).

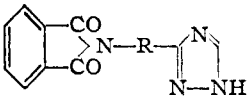
(9) S. Gabriel, *ibid.*, **41**, 248 (1908).

(10) S. Gabriel and J. Colman, *ibid.*, **41**, 517 (1908).

(11) M. A. Pollack, THIS JOURNAL, **65**, 1335 (1943).

TABLE IV

3-PHTHALIMIDOALKYL-1,2,4-TRIAZOLES



R	Yield, %	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
CH_2	50	270–272	$C_{11}H_8N_4O_2$	57.89	57.97	3.53	3.60	24.55	24.65
$CHCH_3$	40	195–196	$C_{12}H_{10}N_4O_2$	59.50	59.29	4.16	4.33		
$(CH_2)_3$	35	155–156	$C_{13}H_{12}N_4O_2$	60.93	61.19	4.72	4.97	21.87	21.90
CH_2CHCH_3[a]	55	210–212	$C_{13}H_{12}N_4O_2$	60.93	61.00	4.72	4.83	21.87	21.64
$CH(CH_3)CH_2$	50	199–200	$C_{13}H_{12}N_4O_2$	60.93	60.69	4.72	4.88	21.87	21.72

[a] 3-β-Phthalimidoisopropyl-1,2,4-triazole.

3-Phthalimidoalkyl-1,2,4-triazoles (Table IV).—These compounds were obtained by removal of the mercapto group of the above 3-substituted-1,2,4-triazole-5-thiols by nitric acid oxidation according to the method for obtaining 3-β-phthalimidoethyl-1,2,4-triazole.[1] All of the compounds were recrystallized from water.

1-Carbethoxyacetylthiosemicarbazide.—To a suspension of 20 g. (0.21 mole) of thiosemicarbazide in 100 ml. of dry pyridine at 0° was added, with stirring over a two-hour period, 30 g. (0.20 mole) of ethyl malonyl chloride.[12] The solution was allowed to stand at room temperature for three days. The pyridine was removed by heating under reduced pressure and the resulting oil was dissolved in 150 ml. of hot methanol. The solid which formed after cooling was collected and air dried. Recrystallization of the product from water produced 15 g. (37% yield) of 1-carbethoxyacetylthiosemicarbazide which formed as plates; m.p. 182°.

Anal. Calcd. for $C_6H_{11}N_3O_3S$: C, 35.12; H, 5.40; N, 20.48. Found: C, 35.19; H, 5.51; N, 20.27.

3-Carbethoxymethyl-1,2,4-triazole-5-thiol.—To a solution made by dissolving 1.2 g. (0.05 g. atom) of sodium in 100 ml. of absolute ethanol was added 10 g. (0.05 mole) of 1-carbethoxyacetylthiosemicarbazide. The mixture was heated under reflux overnight and then the alcohol was removed by heating under reduced pressure. The resulting solid was dissolved in 100 ml. of water, and to this solution was added 9 ml. of 6 *N* hydrochloric acid. The solid which formed was collected and was washed with water. The 3-carbethoxymethyl-1,2,4-triazole-5-thiol was recrystallized from water and obtained as plates; m.p. 192–194°. The yield was 5 g. (55%).

Anal. Calcd. for $C_6H_9N_3O_2S$: C, 38.49; H, 4.85. Found: C, 38.34; H, 4.73.

A sample of the ester was hydrolyzed with warm 1 *N* sodium hydroxide solution. 5-Carboxymethyl-1,2,4-triazole-5-thiol was obtained from water as prisms; m.p. 225–229° dec.

Anal. Calcd. for $C_4H_5N_3O_2S$: C, 30.18; H, 3.17; N, 26.40. Found: C, 29.91; H, 3.28; N, 26.71.

Ethyl (1,2,4-Triazolyl-3)-acetate.—A stirred mixture of 10 g. (0.05 mole) of 3-carbethoxymethyl-1,2,4-triazole-5-thiol, 50 ml. of ethanol and about 25 g. of Raney nickel was heated under reflux four hours. The nickel was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. Recrystallization from a small volume of ethanol gave 4 g. (48% yield) of ethyl (1,2,4-triazolyl-3)-acetate as prismatic needles; m.p. 82–83°.

Anal. Calcd. for $C_6H_9N_3O_2$: C, 46.44; H, 5.85; N, 27.08. Found: C, 46.18; H, 5.61; N, 27.17.

α-(1,2,4-Triazolyl-3)-acetamide was prepared by treating the ester with alcoholic ammonia. It crystallized from ethyl acetate as prisms; m.p. 148–149°.

Anal. Calcd. for $C_4H_6N_4O$: C, 38.09; H, 4.80; N, 44.43. Found: C, 38.15; H, 4.94; N, 44.21.

α-(1,2,4-Triazolyl-3)-N-methylacetamide.—A solution of 3.9 g. (0.025 mole) of ethyl (1,2,4-triazolyl-3)-acetate in 5 ml. of methanol was saturated with dry methylamine at 0° and allowed to stand overnight. The solid (3.0 g., 86% yield) which separated was collected and a sample was recrystallized from 50% methanol–ethanol; m.p. 180°.

(12) D. S. Breslow, E. Baumgarten and C. R. Hauser, THIS JOURNAL, **66**, 1286 (1944).

Anal. Calcd. for $C_5H_8N_4O$: C, 42.85; H, 5.75; N, 39.98. Found: C, 42.88; H, 6.03; N, 39.98.

α-(1,2,4-Triazolyl-3)-N,N-dimethylacetamide.—A solution of 3.9 g. (0.025 mole) of ethyl 1,2,4-triazolyl-3-acetate in 5 ml. of methanol was saturated at 0° with dry dimethylamine and was allowed to stand over the week-end. The solvent was removed under reduced pressure and the residue recrystallized from 5 ml. of ethanol. The amide (2.5 g., 70% yield) was obtained as prisms; m.p. 103–104°.

Anal. Calcd. for $C_6H_{10}N_4O$: C, 46.74; H, 6.54; N, 36.34. Found: C, 46.46; H, 6.71; N, 36.34.

3-β-Methylaminoethyl-1,2,4-triazole Dipicrate.—A suspension of 1.4 g. (0.01 mole) of α-(1,2,4-triazoyl-3)-N-methylacetamide and 1 g. of $LiAlH_4$ in 100 ml. of anhydrous tetrahydrofuran was heated under reflux for 48 hours. Five ml. of 50% aqueous methanol was added and the mixture was filtered. The filter cake was extracted twice with 100-ml. portions of methanol and twice with 100-ml. portions of water. The combined filtrates were concentrated to dryness under reduced pressure. The resulting residue was dissolved in 100 ml. of ethanol and this solution was saturated with carbon dioxide. After removal of the alcohol by heating under reduced pressure, the residue was extracted with two 50-ml. portions of ethanol. This alcoholic solution was concentrated to 25 ml. and was treated with 4.6 g. (0.02 mole) of picric acid dissolved in 50 ml. of hot ethanol. The dipicrate which separated on cooling was collected and recrystallized from water. It was obtained as feathery needles; m.p. 159–160°. The yield was 1.5 g. (26%).

Anal. Calcd. for $C_{17}H_{16}N_{10}O_{14}$: C, 34.94; H, 2.76; N, 23.97. Found: C, 34.90; H, 2.82; N, 23.75.

3-β-Dimethylaminoethyl-1,2,4-triazole Dipicrate. (a) Lithium Aluminum Hydride Reduction of α-(1,2,4-Triazolyl-3)-N,N-dimethylacetamide.—A mixture of 2.5 g. (0.016 mole) of α-(1,2,4-triazolyl-3)-N,N-dimethylacetamide, 2.5 g. of lithium aluminum hydride and 100 ml. of tetrahydrofuran was heated under reflux for two days. The product (80% yield) was isolated as the dipicrate in a manner similar to that described above for 3-β-methylaminoethyl-1,2,4-triazole. It was recrystallized from water and obtained as flat needles; m.p. 181–182°.

Anal. Calcd. for $C_{18}H_{18}N_{10}O_{14}$: C, 36.13; H, 3.03; N, 23.41. Found: C, 35.97; H, 2.78; N, 23.32

(b) 3-β-Chloroethyl-1,2,4-triazole Hydrochloride and Dimethylamine.—A solution of 1 g. of 3-β-chloroethyl-1,2,4-triazole hydrochloride (see below) and 5 ml. of dimethylamine was stored in a pressure bottle for one week. After removing the excess amine the residue was dissolved in ethanol and treated with 2.7 g. of picric acid in ethanol solution. The crystalline solid which formed weighed 2.7 g. (76% yield). A sample was recrystallized from water and obtained as needles; m.p. 180–182°.

The melting point was not depressed after admixture with the picrate obtained by procedure (a).

(c) 3-β-Aminoethyl-1,2,4-triazole and Formaldehyde–Formic Acid.—A solution of 2.2 g. (0.02 mole) of 3-β-aminoethyl-1,2,4-triazole,[1] 10 ml. of 37% formaldehyde and 20 ml. of 98% formic acid was heated under reflux for two hours. The solution was evaporated to dryness by heating under reduced pressure, and the residue was dissolved in 20 ml. of water. After the solution had been neutralized with ammonium hydroxide, it was treated with 9.2 g. (0.04 mole) of picric acid dissolved in 50 ml. of hot ethanol. The dipicrate

which separated on cooling was collected and recrystallized from water. It was obtained as flat needles; m.p. 181–182°. The yield was 7.2 g. (60%).

Anal. Calcd. for $C_{18}H_{18}N_{10}O_{14}$: C, 36.13; H, 3.03; N, 23.41. Found: C, 36.10; H, 3.31; N, 23.42.

The picrates obtained by procedures a, b and c showed identical absorption in the infrared.

3-β-Ethoxyethyl-1,2,4-triazole-5-thiol.—To a suspension of 100 g. (1.1 moles) of thiosemicarbazide in 1 l. of dry pyridine was added with stirring 136 g. (1.0 mole) of β-ethoxypropionyl chloride.[13] After standing overnight most of the pyridine was removed by heating under reduced pressure. One liter of ethanol and then 123 g. (2.2 moles) of sodium methylate were added and the solution was heated on the steam-bath overnight. The solvent was removed under reduced pressure and the residue was dissolved in 1 l. of water. After the addition of 6 *N* hydrochloric acid to *p*H 1 the solution was concentrated under reduced pressure to a volume of 500 ml. The solid which formed was collected and air-dried. The product was extracted with absolute ethanol to separate it from sodium chloride. After removal of the alcohol 52 g. (30% yield) of solid remained. A sample was recrystallized from ethyl acetate and obtained as plates; m.p. 166–167°.

Anal. Calcd. for $C_6H_{11}N_3OS$: C, 41.61; H, 6.40; N, 24.27. Found: C, 41.79; H, 6.22; N, 24.55.

3-β-Ethoxyethyl-1,2,4-triazole.—To a solution of 50 ml. of concentrated nitric acid and 100 ml. of water containing a few crystals of sodium nitrite was added with stirring 47 g. (0.27 mole) of 3-β-ethoxyethyl-1,2,4-triazole-5-thiol. The temperature was maintained near 50° during the addition. After cooling, the solution was made basic with sodium carbonate and then was concentrated to dryness by heating under reduced pressure. The residue was extracted with absolute ethanol. The alcohol was evaporated by heating on the steam-bath and the resulting oil was distilled under reduced pressure. A colorless liquid was obtained; b.p. about 130° (0.5 mm.); $n^{25}D$ 1.4785. The yield was 25 g. (66%).

Anal. Calcd. for $C_6H_{11}N_3O$: C, 51.04; H, 7.85; N, 29.77. Found: C, 50.65; H, 7.90; N, 29.56.

3-β-Chloroethyl-1,2,4-triazole Hydrochloride.—A solution of 14.1 g. (0.1 mole) of 3-β-ethoxyethyl-1,2,4-triazole and 200 ml. of 48% aqueous hydrobromic acid was heated under reflux overnight. The solvent was removed by heating under reduced pressure, and the residue was treated with 100 ml. of thionyl chloride. After heating under reflux for two hours the excess thionyl chloride was evaporated under reduced pressure. The solid residue was washed with dry benzene. It was recrystallized from ethanol–ether mixture and obtained as white plates; m.p. 120°. The yield was 7.1 g. (42%).

Anal. Calcd. for $C_4H_6ClN_3 \cdot HCl$: C, 28.60; H, 4.20; N, 25.01. Found: C, 28.97; H, 4.35; N, 24.86.

3-β-Ethylaminoethyl-1,2,4-triazole Dipicrate.—A solution of 2 g. (0.012 mole) of 3-β-chloroethyl-1,2,4-triazole hydrochloride and 5 ml. of ethylamine was allowed to stand in a stoppered bottle at room temperature for one week. The excess amine was removed by heating under reduced pressure and the residue in 10 ml. of 95% ethanol was added to 5.5 g. of picric acid dissolved in 25 ml. of ethanol. The product which formed on cooling was recrystallized from water and obtained as prismatic needles; m.p. 161°. The yield was 2.2 g. (30%).

Anal. Calcd. for $C_{18}H_{18}N_{10}O_{14}$: C, 36.13; H, 3.03; N, 23.41. Found: C, 36.00; H, 2.70; N, 23.68.

3-β-Diethylaminoethyl-1,2,4-triazole Dipicrate.—This picrate was obtained from 2 g. of 3-β-chloroethyl-1,2,4-triazole hydrochloride and 5 ml. of diethylamine in a manner similar to that described above for the preparation of 3-β-ethylaminoethyl-1,2,4-triazole dipicrate. It was recrystallized from ethanol and obtained as prisms; m.p. 160°. The yield was 2.5 g. (33%).

Anal. Calcd. for $C_{20}H_{22}N_{10}O_{14}$: C, 38.34; H, 3.54. Found: C, 37.93; H, 3.42.

3-Aminoalkyl-1,2,4-triazole Salts (Table I).—Compounds III to VII were prepared by the hydrolysis of the corresponding phthalimido compounds (Table IV) with 6 *N* hydrochloric acid.[1] The hydrochlorides of 3-β-aminopropyl-1,2,4-triazoles were hygroscopic and were converted to the sulfates in the usual manner.

Compounds VIII–XI were obtained from the corresponding picrates according to the procedure reported for the preparation of 3-β-isopropylaminoethyl-1,2,4-triazole dihydrochloride.[1]

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(13) N. A. Milas, U. S. Patent 2,369,157 [*C. A.*, **39**, 5044 (1945)].

[CONTRIBUTION FROM THE DEPARTMENTS OF AGRICULTURAL CHEMISTRY AND HORTICULTURE, MICHIGAN STATE COLLEGE]

The Nature of an Oxidation Product of 3-Indoleacetic Acid[1–3]

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RECEIVED OCTOBER 14, 1953

The colored product obtained by the reaction of 3-indoleacetic acid with ferric ion in an acidic solution is N-hydroxy-3-indoleacetic acid and may be formed by the hydrolysis of an intermediate resulting from the oxidation of the unsubstituted nitrogen in the indole ring.

Salkowski[4] first reported a qualitative test for 3-indoleacetic acid, in which a red color developed when ferric chloride was added to a solution of 3-indoleacetic acid in the presence of mineral acids. Later Mitchell and Brunstetter[5] placed this qualitative color reaction on a quantitative basis. Tang and Bonner[6] and Gordon and Weber[7] have modified this original quantitative procedure, the latter using ferric chloride–perchloric acid solution for color development. Further investigations in this Laboratory resulted in the isolation of a colored amorphous solid upon treatment of 3-indoleacetic acid with a solution of ferric chloride–perchloric acid.

Bonner[8] suggested that the color develops from a complex between 3-indoleacetic acid and ferric ion in acid solution. However color can be produced by a variety of oxidizing agents some of which contain no metal ions. An examination of the colored product disclosed that it was completely free of iron. These observations, along with the presence of iron II in the reaction solution, suggested that the colored species is derived from the oxidation of 3-indoleacetic acid. In addition to 3-indoleacetic acid, other indole derivatives (indole, ethyl-

(1) Journal Article No. 1561 of the Michigan Agricultural Experiment Station.

(2) This investigation was supported by the Horace H. Rackham Research Endowment.

(3) Presented before the Division of Organic Chemistry at the 124th Meeting of the American Chemical Society, Chicago, Ill., 1953.

(4) E. Salkowski, *Z. physiol. Chem.*, **9**, 23 (1885).

(5) J. W. Mitchell and B. C. Brunstetter, *Bot. Gaz.*, **100**, 802 (1939).

(6) Y. W. Tang and J. Bonner, *Arch. Biochem.*, **13**, 11 (1947).

(7) S. A. Gordon and R. P. Weber, *Plant Physiology*, **26**, 192 (1951).

(8) J. Bonner, "Plant Biochemistry," Academic Press, Inc., New York, N. Y., 1950, p. 442.