The hydrochloride was prepared in the usual way employing alcoholic hydrogen chloride and after recrystallization melted at 300–301°.

Anal. Calcd. for $C_{18}H_{34}N_2Cl_2$: Cl, 20.30. Found: Cl, 20.25.

The dimethiodide was prepared employing a large excess of alcohol in the usual way with methyl iodide, and after recrystallization from methanol melted 269.5–271°.

Anal. Calcd. for $C_{20}H_{38}N_2I_2$: I, 45.29; Found: I, 45.23.

Preparation of Bis-1,6-(perhydroisoindolyl)-hexane.—This was prepared in a manner analogous to that of the ethane base above. The free base was collected at 160–165° at 0.05 mm.

Anal. Calcd. for $C_{22}H_{40}N_2$: C, 79.45; H, 12.12; N, 8.42. Found: C, 79.63; H, 12.01; N, 8.15.

The hydrochloride was prepared in the usual way and melted at 203–204°.

Anal. Calcd. for $C_{22}H_{42}N_2Cl_2$: Cl, 17.49. Found: Cl, 17.54.

The dimethiodide prepared as above melted at 249° on recrystallization from methanol.

Anal. Calcd. for $C_{24}H_{46}N_2I_2$: I, 41.18. Found: I, 41.10.

WASHINGTON 7, D. C.

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

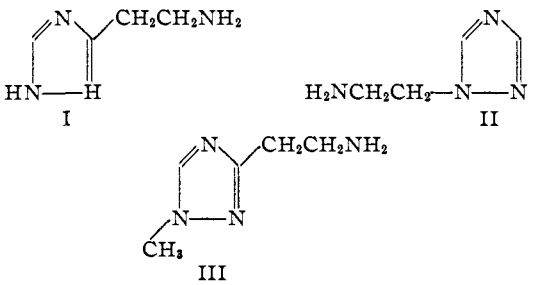
Isomeric and Nuclear-substituted β-Aminoethyl-1,2,4-triazoles

BY C. AINSWORTH AND R. G. JONES

RECEIVED AUGUST 13, 1954

1β-Aminoethyl-1,2,4-triazole (II), 1γ-aminopropyl-1,2,4-triazole (XIV), 3β-aminoethyl-1-methyl-1,2,4-triazole (III), 5β-aminoethyl-1-methyl-1,2,4-triazole (IV), 3β-aminoethyl-4-methyl-1,2,4-triazole (V) and 3β-aminoethyl-4-phenyl-1,2,4-triazole (VI) have been synthesized and tested pharmacologically. Only III and IV possessed histamine-like activity. An improved method for the synthesis of 1,2,4-triazole is described. Alkylation of a 3-alkyl-1,2,4-triazole (3β-phthalimidoethyl-1,2,4-triazole) with methyl iodide was found to give both the 3-alkyl-1-methyl and the 5-alkyl-1-methyl compounds.

3β-Aminoethyl-1,2,4-triazole (I) possessed unusually high histamine-like activity when tested on isolated muscle strips, on blood pressure and on gastric secretion.[1] Branching, shortening or lengthening of the side chain or alkylation of the amino group generally decreased or abolished activity.[2] Several additional variations of the basic structure I have been made with the hope of finding compounds having improved hypotensive action. The purpose of this communication is to describe the synthesis and preliminary pharmacology of a structural isomer of I, 1β-aminoethyl-1,2,4-triazole (II), and compounds III-VI in which the ring-nitrogen atoms carry substituents.



The starting material for the preparation of II was 1,2,4-triazole. This has been synthesized in low yields by heating hydrazine salts with formamide.[3] Better yields (up to 30%) were obtained by mixing one mole of hydrazine hydrate with two moles of formamide and distilling rapidly at atmospheric pressure. During this process, however, a large quantity of ammonia was evolved and diformylhydrazine was obtained as a by-product. In fact, if the mixture was heated slowly, all the ammonia was lost and diformylhydrazine was the only product. In order to avoid this loss of ammonia the reactants were heated in an autoclave. Thus 70–80% yields of 1,2,4-triazole were obtained by heating diformylhydrazine with excess ammonia or by heating a mixture of hydrazine, formamide and ammonia in an autoclave at 200° for 24 hours.[4]

Alkylation of 1,2,4-triazole has been shown to give exclusively the 1-substituted compounds.[5] Accordingly, ethyl 1,2,4-triazole-1-acetate (VII) was synthesized from ethyl bromoacetate and the sodium derivative of 1,2,4-triazole. Compounds VIII, IX and X were prepared from VII. Although VII readily underwent reduction with lithium aluminum hydride to give X, attempts to reduce the amide IX to the amine II were without success.

The condensation of the sodium derivative of 1,2,4-triazole with N-bromomethyl-, β-bromoethyl- and γ-bromopropylphthalimides gave, respectively, compounds XI, XII and XIII. Hydrolysis of XII afforded the desired 1β-aminoethyl-1,2,4-triazole (II), and hydrolysis of XIII gave XIV, the next higher homolog of II.

Alkylation of the sodium derivative of 3β-phthalimidoethyl-1,2,4-triazole with methyl iodide gave two products. After hydrolysis to remove the phthalyl group, the products were separated through their picrates and were found to be 3β-aminoethyl-1-methyl-1,2,4-triazole (III) and 5β-aminoethyl-1-methyl-1,2,4-triazole (IV). The ratio of III to IV was about 1 to 2, and none of the

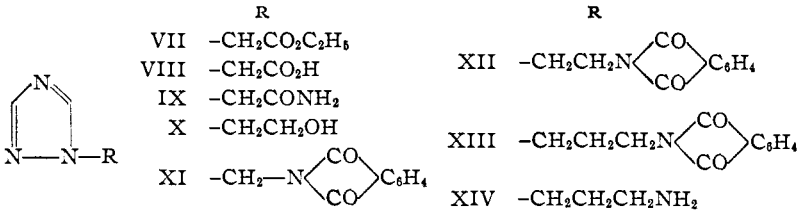
(1) C. Ainsworth and R. G. Jones, THIS JOURNAL, **75**, 4915 (1953).

(2) C. Ainsworth and R. G. Jones, *ibid.*, **76**, 5651 (1954).

(3) (a) G. Pellizzari, *Gazz. chim. ital.*, **24**, 222 (1894); *Ber.*, **27(R)**, 801 (1894); (b) H. H. Strain, THIS JOURNAL, **49**, 1995 (1927).

(4) This method was developed by Dr. D. E. Morrison and J. J. Traverso.

(5) M. R. Atkinson and J. B. Polya, *J. Chem. Soc.*, 141 (1954).

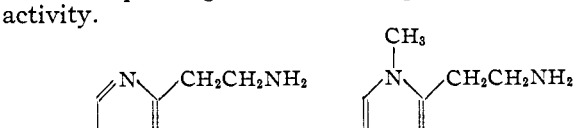


third possible isomer 3β-aminoethyl-4-methyl-1,2,4-triazole (V) was obtained. The structures of the methylated products III and IV were established by independent and unequivocal syntheses of III and V. Compound III was prepared from β-phthalimidopropionyl chloride and 2-methylthiosemicarbazide[6] by the same sequence of reactions described for the preparation of I.[1] In like manner compound V was prepared from β-phthalimidopropionyl chloride and 4-methylthiosemicarbazide. Compound V differed from either of those obtained by reaction of methyl iodide with 3β-phthalimidoethyl-1,2,4-triazole, whereas compound III was identical with the one obtained in lower yield from the methyl iodide reaction.

3β-Aminoethyl-4-phenyl-1,2,4-triazole (VI) was prepared in the same way as V except that 4-phenylthiosemicarbazide served as starting material.

Compounds II, III, IV, V, VI, and XIV were tested pharmacologically, but only III and IV were found to have any measurable histamine-like activity.[7] In the muscle strip assay they had about $^1/_{400}$ the activity of histamine acid phosphate or about $^1/_{70}$ that of the parent compound I. The action of III in lowering the blood pressure of the cat was about $^1/_{700}$ that of histamine acid phosphate, but, surprisingly, IV was much more active. In the cat-blood pressure test, IV appeared to have about $^1/_{100}$ the potency of histamine acid phosphate. When given to hypertensive dogs by mouth, IV caused a fall in blood pressure that lasted for many hours. After one or two doses, however, the dogs became insensitive to the drug, *i.e.*, the blood pressures returned to high levels and were unaffected by further doses of IV. This refractoriness lasted for several days.

An interesting structure–activity relationship between compounds III, IV and V and the corresponding imidazole compounds XV and XVI can be pointed out. Thus V and its imidazole counterpart XVI[7] are inactive, whereas III like the corresponding imidazole compound XV[7] has activity.



Acknowledgments.—The authors are grateful to W. L. Brown, H. L. Hunter, G. M. Maciak and Gloria Beckman for the microanalyses, and to Dr. H. M. Lee and associates and J. H. Tilden of these laboratories for permission to report the results of pharmacological tests.

(6) A. H. Greer and G. B. L. Smith, THIS JOURNAL, **72**, 874 (1950).
(7) H. M. Lee and R. G. Jones, *J. Pharmacol.*, **95**, 71 (1949).

Experimental[8]

N,N'-Diformylhydrazine. (a) **Hydrazine Hydrate and Formic Acid.**[9]—A solution of 50 ml. of hydrazine hydrate and 150 ml. of 98–100% formic acid was heated overnight on the steam-bath. The solvents were removed by heating under reduced pressure and 100 ml. of ethanol was added. The solid which separated was collected and air-dried, m.p. 160° (lit.[10] m.p. 159–160°). The yield was 60%.

(b) **Hydrazine Hydrate and Formamide.**—A solution of 25 ml. (0.5 mole) of hydrazine hydrate and 45 g. (1 mole) of formamide was warmed on the steam-bath for two hours. It was treated the same as described in (a) and N,N'-diformylhydrazine was isolated in 80% yield.

1,2,4-Triazole.—A mixture of 95 g. (1.08 moles) of N,N'-diformylhydrazine and 500 ml. of liquid ammonia was heated in a steel pressure vessel at 200° for 24 hours. After removal of the ammonia the residue was extracted with hot ethyl acetate. The extract was evaporated and the residue distilled under reduced pressure, b.p. 124° (5 mm.). The yield was 70–80%. A sample was recrystallized from ethyl acetate, m.p. 120° (lit.[3b] m.p. 120–121°).

The picrate was recrystallized from water and obtained as needles, m.p. 168° (lit.[5] m.p. 168°).

Ethyl 1,2,4-Triazole-1-acetate (VII).—To a solution formed from 69 g. (1.0 mole) of 1,2,4-triazole, 23 g. (1.0 g. atom) of sodium and 500 ml. of ethanol was added, dropwise with stirring, 184 g. (1.1 mole) of ethyl bromoacetate. After standing at room temperature overnight the mixture was concentrated to 300 ml. and sodium bromide was removed by filtration. The filtrate was distilled under diminished pressure and 125 g. (81%) of ethyl 1,2,4-triazole-1-acetate was obtained as a colorless liquid, b.p. 110° (0.5 mm.), $n^{25}D$ 1.470.

Anal. Calcd. for $C_6H_9N_3O_2$: N, 27.08. Found: N, 26.72.

A one-gram sample of the ester was heated under reflux with 10 ml. of 6 *N* hydrochloric acid for two hours. The solvent was removed under reduced pressure and the residue was recrystallized from methanol–ether. 1,2,4-Triazole-1-acetic acid hydrochloride separated as prismatic needles, m.p. 165–167°. The analytical sample was dried under reduced pressure for six hours at room temperature.

Anal. Calcd. for $C_4H_5N_3O_2 \cdot HCl$: N, 25.69. Found: N, 25.54.

The above hydrochloride, dried under reduced pressure for two hours at 78°, was converted to the free amino acid VIII, m.p. 203–204°.

Anal. Calcd. for $C_4H_5N_3O_2$: N, 33.06. Found: N, 33.27.

1,2,4-Triazole-1-acetamide (IX).—A solution of 39 g. (0.25 mole) of ethyl 1,2,4-triazole-1-acetate and 50 ml. of methanol was treated with 500 ml. of methanol saturated with ammonia at room temperature. After standing overnight the solvent was removed under reduced pressure. The residue was recrystallized from methanol and 26 g. (82% yield) of 1,2,4-triazole-1-acetamide was obtained as shiny plates, m.p. 185–186°.

Anal. Calcd. for $C_4H_6N_4O$: C, 38.09; H, 4.80; N, 44.43. Found: C, 38.04; H, 4.83; N, 44.53.

The amide with lithium aluminum hydride in tetrahydrofuran, heated under reflux for two hours, gave unchanged amide and a small quantity of an unidentified oil.

A sample of 1,2,4-triazole-1-acetamide was treated with hypochlorite in the usual manner. The only product isolated from the reaction mixture was 1,2,4-triazole. The yield was 71%.

1β-Hydroxyethyl-1,2,4-triazole Hydrochloride (X).—To a solution of 15.5 g. (0.1 mole) of ethyl 1,2,4-triazole-1-acetate and 500 ml. of ether was added 3.8 g. (0.1 mole) of lithium aluminum hydride suspended in 200 ml. of ether. After heating under reflux for two hours, 20 ml. of 50% methanol–water was added. The mixture was filtered and the filter cake was extracted with 200 ml. of methanol and then twice

(8) Melting points were taken on a Fisher–Johns block and recorded as read.
(9) This method was suggested by Dr. Q. F. Soper.
(10) G. Schofer and N. Schwan, *J. prakt. Chem.*, **51**, 182 (1895).

with 100-ml. portions of hot water. The combined extracts were taken to dryness and the residue was dissolved in 100 ml. of ethanol. Dry Ice was added and this mixture was taken to dryness by heating under reduced pressure. The residue was extracted with ethanol which was evaporated and about 10 g. of oil remained. The hydrochloride was formed in alcohol and the salt was recrystallized from methanol–ether and obtained as needles, m.p. 125–127°.

Anal. Calcd. for $C_4H_7N_3O\cdot HCl$: C, 32.12; H, 5.39; N, 28.09. Found: C, 31.91; H, 5.08; N, 28.03.

1-Phthalimidomethyl-1,2,4-triazole (XI).—To a solution formed from 2.3 g. (0.1 g. atom) of sodium, 200 ml. of ethanol and 7 g. (0.1 mole) of 1,2,4-triazole was added, with stirring, 24 g. (0.1 mole) of N-bromoethylphthalimide.[11] The mixture was heated under reflux overnight and the salt was removed by filtration. The filtrate was concentrated to 50 ml., and the solid which formed on cooling was recrystallized from 95% ethanol and obtained as plates, m.p. 179–180°. The yield was 9.3 g. (41%).

Anal. Calcd. for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.53; N, 24.55. Found: C, 58.14; H, 3.61; N, 24.35.

A solution of 1-phthalimidomethyl-1,2,4-triazole and 6 *N* hydrochloric acid was heated under reflux for two hours. 1,2,4-Triazole hydrochloride, identical with authentic material, was isolated.

A sample of 1-phthalimidomethyl-1,2,4-triazole in ethanol and 96% hydrazine was heated under reflux for one hour. The solvents were removed by heating under reduced pressure and the residue was extracted with hot benzene. The addition of petroleum ether caused a solid to separate. It was obtained as needles, m.p. 120°, and was identical with 1,2,4-triazole.

1β-Phthalimidoethyl-1,2,4-triazole (XII).—By the same method used above 1β-phthalimidoethyl-1,2,4-triazole was prepared from 1,2,4-triazole and Nβ-bromoethylphthalimide. It was recrystallized from 95% ethanol and obtained as plates, m.p. 169–170°. The yield was 40%.

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.74; H, 4.36; N, 22.49.

1β-Aminoethyl-1,2,4-triazole Dihydrochloride (II).—A sample of 1β-phthalimidoethyl-1,2,4-triazole was hydrolyzed with 6 *N* hydrochloric acid under the same conditions reported for the preparation of 3β-aminoethyl-1,2,4-triazole dihydrochloride.[1] 1β-Aminoethyl-1,2,4-triazole dihydrochloride was recrystallized from methanol–ether and obtained as prisms, m.p. 182–183°.

Anal. Calcd. for $C_4H_8N_4\cdot 2HCl$: N, 30.28; Cl, 38.32. Found: N, 30.00; Cl, 38.60.

1γ-Aminopropyl-1,2,4-triazole Dihydrochloride (XIV).—By the same methods used above 1γ-phthalimidopropyl-1,2,4-triazole (XIII) was prepared from 1,2,4-triazole and Nγ-bromopropylphthalimide.[12] It was recrystallized from water and obtained as prisms, m.p. 115–116°. The yield was 32%. The analytical sample was dried overnight under reduced pressure at 100°.

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72. Found: C, 61.11; H, 4.75.

1γ-Aminopropyl-1,2,4-triazole dihydrochloride was recrystallized from methanol–ether and obtained as prisms, m.p. 218–220° (capillary).

Anal. Calcd. for $C_5H_{10}N_4\cdot 2HCl$: N, 28.14. Found: N, 28.08.

3β-Aminoethyl-1-methyl-1,2,4-triazole (III).—1-(β-Phthalimidopropionyl)-2-methylthiosemicarbazide was prepared from β-phthalimidopropionyl chloride and 2-methylthiosemicarbazide[6] according to the procedure reported for the preparation of 1β-phthalimidopropionylthiosemicarbazide.[1] It was recrystallized from water and obtained as prisms, m.p. 241–242° dec. The yield was 30%.

Anal. Calcd. for $C_{13}H_{14}N_4O_3S$: C, 50.98; H, 4.61. Found: C, 51.01; H, 4.79.

1-Methyl-3-(β-phthalimidoethyl)-1,2,4-triazole-5-thiol was prepared by cyclization of 1-(β-phthalimidopropionyl)-2-methylthiosemicarbazide using sodium methylate in a manner similar to that used for the preparation of 1β-phthalimidoethyl-1,2,4-triazole-5-thiol.[1] It was recrystallized from acetic acid and obtained as plates, m.p. 240°. The yield was 62%.

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

(12) S. Gabriel and J. Weiner, *ibid.*, **21**, 2671 (1888).

Anal. Calcd. for $C_{13}H_{12}N_4O_2S$: C, 54.15; H, 4.20; S, 11.12. Found: C, 53.86; H, 4.02; S, 11.15.

The mercapto group of 1-methyl-3-(β-phthalimidoethyl)-1,2,4-triazole-5-thiol was removed by nitric acid oxidation according to the method for obtaining 3β-phthalimidoethyl-1,2,4-triazole.[1] 1-Methyl-3-(β-phthalimidoethyl)-1,2,4-triazole was obtained in 70% yield, m.p. 195–196°.

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72. Found: C, 61.23; H, 4.68.

A sample of 1-methyl-3-(β-phthalimidoethyl)-1,2,4-triazole was hydrolyzed with 6 *N* hydrochloric acid under the same conditions reported for the preparation of 3β-aminoethyl-1,2,4-triazole dihydrochloride.[1] 3β-Aminoethyl-1-methyl-1,2,4-triazole dihydrochloride was a hygroscopic white solid, m.p. 175–178°. It was best purified through the corresponding dipicrate.

Anal. Calcd. for $C_5H_{10}N_4\cdot 2HCl$: C, 30.16; H, 6.08. Found: C, 29.97; H, 5.98.

3β-Aminoethyl-1-methyl-1,2,4-triazole dipicrate was recrystallized from water and obtained as prisms, m.p. 212–213°.

Anal. Calcd. for $C_{17}H_{16}N_{10}O_{14}$: C, 34.94; H, 2.76; N, 23.97. Found: C, 35.00; H, 2.65; N, 24.01.

3β-Aminoethyl-4-methyl-1,2,4-triazole (V).—By the same methods used above 1-(β-phthalimidopropionyl)-4-methylthiosemicarbazide was prepared from β-phthalimidopropionyl chloride and 4-methylthiosemicarbazide. It was recrystallized from water and obtained as plates, m.p. 202–203° dec. The yield was 35%.

Anal. Calcd. for $C_{13}H_{14}N_4O_3S$: N, 18.29. Found: N, 18.13.

4-Methyl-3-(β-phthalimidoethyl)-1,2,4-triazole-5-thiol was recrystallized from 1:3 ethanol–water mixture and obtained as prisms, m.p. 230°. The yield was 59%.

Anal. Calcd. for $C_{13}H_{12}N_4O_2S$: C, 54.15; H, 4.20. Found: C, 54.00; H, 4.30.

4-Methyl-3-(β-phthalimidoethyl)-1,2,4-triazole was recrystallized from water and obtained as plates, m.p. 219–220°. The yield was 63%.

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72. Found: C, 60.70; H, 4.91.

3β-Aminoethyl-4-methyl-1,2,4-triazole dihydrochloride was recrystallized from a methanol–ether mixture and obtained as plates, m.p. 190–194°.

Anal. Calcd. for $C_5H_{10}N_4\cdot 2HCl$: C, 30.16; H, 6.08. Found: C, 29.98; H, 6.18.

The dipicrate of 3β-aminoethyl-4-methyl-1,2,4-triazole was recrystallized from water and obtained as prismatic needles, m.p. 207–208°.

Anal. Calcd. for $C_{17}H_{16}N_{10}O_{14}$: C, 34.94; H, 2.76; N, 23.97. Found: C, 35.06; H, 2.89; N, 24.21.

3β-Aminoethyl-4-phenyl-1,2,4-triazole (VI).—By the same methods described above 1-(β-phthalimidopropionyl)-4-phenylthiosemicarbazide was prepared from β-phthalimidopropionyl chloride and 4-phenylthiosemicarbazide. It was recrystallized from acetic acid–water, m.p. 199–200° dec. The yield was 60%.

Anal. Calcd. for $C_{18}H_{16}N_4O_3S$: C, 58.68; H, 4.38. Found: C, 58.44; H, 4.54.

4-Phenyl-3-(β-phthalimidoethyl)-1,2,4-triazole-5-thiol was recrystallized from 50% acetic acid–water mixture and obtained as prisms, m.p. 230–232°. The yield was 43%.

Anal. Calcd. for $C_{18}H_{14}N_4O_2S$: C, 61.70; H, 4.03. Found: C, 61.76; H, 4.19.

4-Phenyl-3-(β-phthalimidoethyl)-1,2,4-triazole was recrystallized from water and obtained as prisms, m.p. 175–177°. The yield was 40%.

Anal. Calcd. for $C_{18}H_{14}N_4O_2$: C, 67.91; H, 4.43. Found: C, 67.73; H, 4.56.

3β-Aminoethyl-4-phenyl-1,2,4-triazole dihydrochloride was recrystallized from methanol–ether and obtained as plates, m.p. 205–207°. The yield was almost quantitative.

Anal. Calcd. for $C_{10}H_{12}N_4\cdot 2HCl$: C, 45.99; H, 5.40; Cl, 27.15. Found: C, 45.73; H, 5.49; Cl, 27.13.

3β-Phthalimidoethyl-1,2,4-triazole and Methyl Iodide.—To a stirred solution formed from 0.7 g. (0.03 g. atom) of sodium, 100 ml. of ethanol and 7.3 g. (0.03 mole) of 3β-

phthalimidoethyl-1,2,4-triazole[1] was added, dropwise, 1.9 ml. (0.03 mole) of methyl iodide. After standing at room temperature overnight the solvent was removed and the residue in 100 ml. of 6 *N* hydrochloric acid was heated under reflux for six hours. The phthalic acid which separated on cooling was removed, and the filtrate was taken to dryness by heating under reduced pressure. The residue was dissolved in 50 ml. of ethanol and treated with 2.4 g. (0.06 mole) of sodium hydroxide. After the solvent was evaporated the solid was extracted with 25 ml. of ethanol, and this solution was treated with 13.8 g. (0.06 mole) of picric acid dissolved in 100 ml. of ethanol. The picrate which formed on cooling was collected and extracted with 100 ml. of boiling water. The insoluble material remaining was dissolved in 300 ml. of boiling water and on cooling 2.2 g. of solid separated as prisms, m.p. 212–213°.

Anal. Calcd. for $C_{17}H_{16}N_{10}O_{14}$: C, 34.94; H, 2.76; N, 23.97. Found: C, 35.00; H, 2.65; N, 24.01.

The compound was shown to be identical with 3β-aminoethyl-1-methyl-1,2,4-triazole dipicrate by mixed melting point determination and comparison of infrared absorption curves.

The 100-ml. hot-water extract of the crude picrate mixture was concentrated to 50 ml. and on cooling 5 g. of 5β-aminoethyl-1-methyl-1,2,4-triazole dipicrate separated as needles, m.p. 180–182°.

Anal. Calcd. for $C_{17}H_{16}N_{10}O_{14}$: C, 34.94; H, 2.76; N, 23.97. Found: C, 34.96; H, 2.73; N, 24.02.

The infrared absorption curve of this dipicrate was different from the above and also that of 3β-aminoethyl-4-methyl-1,2,4-triazole dipicrate.

5β-Aminoethyl-1-methyl-1,2,4-triazole dihydrochloride (IV) was obtained from the dipicrate in the usual manner. It was very hygroscopic.

Anal. Calcd. for $C_5H_{10}N_4 \cdot 2HCl$: C, 30.16; H, 6.08. Found: C, 29.91; H, 6.32.

INDIANAPOLIS, INDIANA

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

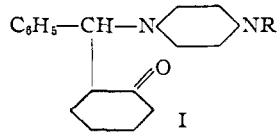
The Addition of Secondary Amines to Some α-Benzal Ketones

BY RICHARD BALTZLY, EMIL LORZ, PETER B. RUSSELL AND FRANCES M. SMITH

RECEIVED AUGUST 23, 1954

The addition of a number of secondary amines to cyclic and open-chain analogs of benzalcyclohexanone has been studied. In these systems the steric requirements of the amine appear to be quite critical, only cyclic amines and methyl secondary amines adding well. Ease of addition also can be correlated to some extent to recent theories of ring strain.

Monoquaternary salts of hexahydrobenzhydrylpiperazines exhibit marked spasmolytic action of an atropine-like nature.[1] Since the obvious preparation of the ditertiary amines (*e.g.*, N-hexahydrobenzhydryl-N′-methylpiperazine), required as precursors, through reaction of the appropriate halide and an N′-alkylpiperazine is rather unsatisfactory, an alternative preparation was sought. A possible route was seen in the addition of an alkylpiperazine to benzalcyclohexanone which should afford an amino ketone I possessing the desired carbon skeleton. Conversion of I to desired compounds of



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physiological interest has been accomplished and will be the subject of a separate communication.

During the exploratory stage of this work it was found that the addition of amines to the benzalcyclohexanone system was influenced markedly by various factors, largely steric in character, and a study of these factors appeared to have some general interest. Accordingly a variety of secondary amines were allowed to act on benzalcyclohexanone and the addition of certain of these amines to various other cyclic and non-cyclic α-benzal ketones was also studied.

The results of these experiments are shown in Tables I and II. The general procedure was to mix the amine and unsaturated ketone, close the flask and allow the mixture to stand at room temperature. The reaction mixtures tended to become more viscous and to acquire brownish colors, and these changes had an inverse relationship. In certain cases after one to three days the reaction mixture solidified. In these cases excellent yields were obtained and little color developed. In other experiments, especially with diethylamine, the color deepened greatly, the viscosity was unaltered and the yields were extremely poor.

TABLE I

ADDITION OF VARIOUS SECONDARY BASES TO BENZALCYCLOHEXANONE

Base	Yield.[a] %	Base	Yield. %
Piperidine	80–90[a]	1,2,5-Trimethylpiperazine	0–3[d]
N-Methylpiperazine	80–90[a]	Pyrrolidine	70[c]
N-Ethylpiperazine	60[b]	Dimethylamine	40[c,e]
Morpholine	50[c]	Benzylmethylamine	35[c]
2-Methylpiperidine	0[d]	Diethylamine	1–5[d]

[a] Isolated as crystalline ketone. [b] Estimated as basic fraction after reduction. Crystalline aminoalcohols separated. [c] Estimated by reduction to give a non-crystalline but analytically pure mixture of aminoalcohols. [d] Estimated as crude basic fraction after reduction. [e] Carried out in ether.

It seemed likely that the color arose through de-aldolization followed by subsequent recondensation. It was found that when styryl isopropyl and *t*-butyl ketones, in which further condensation is impossible or at least unlikely, were compared with benzalacetone, the two former compounds showed no increase in color while benzalacetone showed some. The yields in the three condensations were quite similar. It seems probable therefore that the development of color may arise from de-aldolization and recondensation, but that it does not necessarily indicate a great diminution of yield. In the case of the cyclopentanone derivatives, however, the rather intense color is accompanied by a poor yield.

(1) R. Baltzly, W. S. Ide, E. Lorz and P. B. Russell, in preparation.