[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

1-Ethyl-4-(3-tropanyl)-tetrahydro-1H-1,4-benzodiazepine

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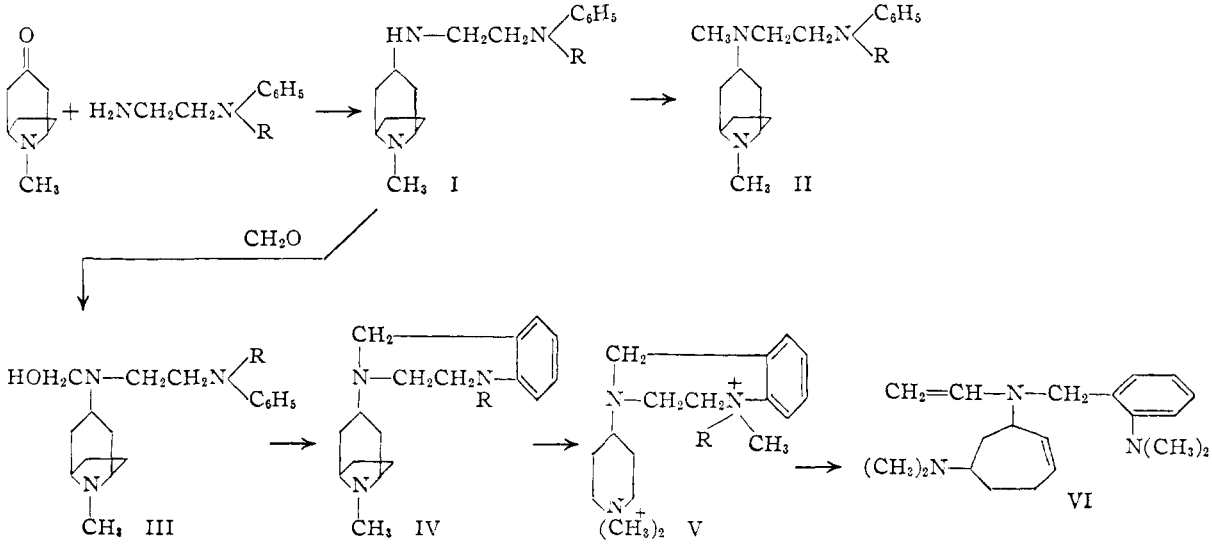
Reductive amination of tropinone in the presence of N-ethyl-N-phenylethylenediamine afforded N-ethyl-N-phenyl-N'-(3-tropanyl)-ethylenediamine. Treatment of this triamine with formaldehyde and formic acid led to the title compound rather than N-ethyl-N-phenyl-N'-methyl-N'-(3-tropanyl)-ethylenediamine. The latter base was prepared by formylation of the diazepine precursor with formic acid followed by lithium aluminum hydride reduction of the resulting formamide.

In a previous paper[1] the preparation of the bismethobromide of N,N-diethyl-N'-methyl-N'-(3-tropanyl)-ethylenediamine was described. Lape, Fort and Hoppe[2] studied the hypotensive effects of this salt and a series of related compounds in anesthetized dogs and found that they depressed blood pressure by both a peripheral and central action. an effective hypotensive agent showing a typical biphasic response characteristic of a drug which exerted both peripheral and central actions. However, subsequent preparations revealed sufficient differences in potency, pattern and duration of action to warrant a more careful chemical investigation.



At the time our work had started central vasodepressive action of quaternary ammonium salts had not been demonstrated, but in the course of our studies, Cavallito and O'Dell found this pharmacological property to be present in a number of bisquaternary ammonium compounds.[3]

Since this central action seemed to be associated with the presence of aromatic rings in the molecule, we decided to prepare quaternary salts of N-ethyl-N-phenyl-N'-methyl-N'-(3-tropanyl)-ethylenediamine. To this end tropinone was reductively aminated with N-ethyl-N-phenylethylenediamine, and the resulting triamine I (R = Et) was subjected to Eschweiler–Clarke methylation in the hope of obtaining the base II (R = Et). A high-boiling viscous oil was obtained whose analysis agreed with that required for the methylated base II (R = Et) and a fair amount of polymeric material which tended to decompose on distillation. The oil furnished a mono- and bis-methiodide with acceptable analyses, and the latter proved to be

It seemed that the base I was behaving anomalously in the methylation reaction. Accordingly, the triamine I (R = Et) was formylated with formic acid whereupon a high-boiling N-formyl derivative was formed which was induced to crystallize. Reduction of the formamide with lithium aluminum hydride furnished a relatively fluid base of the correct analytical composition, which on treatment with methyl iodide afforded a methiodide. This salt was different in both chemical and physical properties from the previously described bismethiodide and also showed a different vasodepressive response.

To simplify chemical studies we carried out our degradative work on the lower homolog, N-methyl-N-phenyl-N'-(3-tropanyl)-ethylenediamine, I (R = CH_3). Under Eschweiler–Clarke conditions this triamine furnished a very viscous base also, accompanied by the usual polymeric material. This base also gave a bismethiodide. Electrometric titration of the monomethiodide of IV (R = Et) indicated that the aromatic amine had not been quaternized while a similar titration on the bismethiodide V (R = CH_3) showed that an aliphatic tertiary amine was still present. In view of the reluctance of the 3-aminotropanes to undergo methylation, it was con-

(1) S. Archer, T. R. Lewis and M. J. Unser, THIS JOURNAL, 79, 4194 (1957).

(2) H. Lape, D. Fort and J. O. Hoppe, *J. Pharm. and Exp. Therapeutics*, 116, 462 (1956).

(3) C. J. Cavallito, A. P. Gray and T. B. O'Dell, *Arch. Internat. Pharmacodyn.*, 101, 38 (1955); T. B. O'Dell, C. Luna and M. D. Napoli, *J. Exp. Pharm. and Therapeutics*, 114, 306, 317 (1955).

cluded that the aromatic and heterocyclic nitrogen atoms were quaternary.

A compound of structure II (R = CH_3) contains 3 N-methyl groups whereas the diazepine IV has only two. The viscous oil obtained from I (R = CH_3) yielded only two such groups in an N-methyl determination, and on the basis of this observation and the non-identity of the Eschweiler–Clarke product and the lithium aluminum hydride product obtained in the ethyl series, it was provisionally concluded that viscous bases were indeed tetrahydro-1H-1,4-benzodiazepines represented by formula IV.

Further support for this conclusion was obtained by means of a Hofmann degradation of the bismethohydroxide of V. The sole basic product was isolated as a dipicrate, the composition of which was in agreement with that required of a dipicrate of the vinylamine VI. A careful search in the reaction mixture for dimethylaniline proved fruitless. The latter is an expected product if the base were represented by the open chain formula II.

Apparently the function of the concentrated formic acid was to furnish an acidic medium for the cyclization of the intermediate methylol derivative III. When concentrated hydrochloric acid was substituted, a small yield of diazepine V resulted together with a large amount of polymeric material. In dilute formic or hydrochloric acid the yield of the cyclic base V increased at the expense of the polymer. When the *p*-tolyl analog of I (R = CH_3) was treated with formaldehyde in concentrated formic acid, a high yield of the corresponding diazepine was obtained with little polymer. This result indicated that the intermolecular condensation was taking place primarily at the *p*-position in the triamine I.

Apparently the methylol intermediate III (or an ion or its equivalent species) can undergo three reactions in concentrated formic acid. First, it may attack the *o*-position of the aromatic amine intramolecularly to form a tetrahydro-1H-1,4-benzodiazepine. Second, it may attack the *p*-position of another molecule to furnish a polymer. The chemical evidence to establish these paths has been presented. Evidence for the third course, namely, reduction of the intermediate III to give the base II, has been obtained from the biological side. The characteristic biphasic vasodepressive response of V (R = Et) prepared by the formaldehyde–formic acid path could not be duplicated by the same salt made with the aid of formaldehyde and dilute hydrochloric acid nor by the bismethiodide of the open chain base II (R = Et) prepared by the lithium aluminum hydride reduction of the N-formyl derivative of the base I (R = Et). However, mixtures of the latter two compounds did duplicate qualitatively the dose–response pattern. On this basis it was concluded that some N-methylation did accompany ring closure under Eschweiler–Clarke conditions.

Experimental[4]

N-Ethyl-N-phenylethylenediamine.—A mixture of 224 g. of bromoethylphthalimide and 222 g. of ethylaniline in 550 ml. of xylene was refluxed 10 hr. The solid that separated was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was boiled under reflux with a solution of 271 ml. of concentrated hydrochloric acid and 45 ml. of water for 6 hr., cooled and filtered. The filtrate was made alkaline with aqueous potassium hydroxide and the oil that separated was removed with benzene. The dried solution was concentrated, and after two distillations there was obtained 58 g. of the desired base, b.p. 97–99° (0.2 mm.), n^{25} 1.5625.[5]

Anal. Calcd. for $C_{10}H_{16}N_2$: N, 17.06. Found: N, 16.87.

N-Methyl-N-phenylethylenediamine.—The above procedure furnished 51 g. of the base, b.p. 100–102° (0.15 mm.), starting with 224 g. of bromoethylphthalimide and 196 g. of methylaniline. The picrate, which was prepared in and recrystallized from ethanol, melted at 174–175°.[5]

N-Ethyl-N-phenyl-N'-(3-tropanyl)-ethylenediamine.—A solution of 41 g. of N-ethyl-N-phenylethylenediamine and 35 g. of tropinone in 100 ml. of ethanol was allowed to stand overnight before being hydrogenated in a Parr apparatus in the presence of 0.5 g. of Adams platinum oxide. After 1 hr. the reduction was complete. The catalyst was removed by filtration and the filtrate was distilled to yield the triamine, b.p. 164–165° (0.25 mm.), n^{25} 1.5551, wt. 54 g. (76%).

Anal. Calcd. for $C_{18}H_{29}N_3$: N, 14.62. Found: N, 14.30.

N-Methyl-N-phenyl-N'-(3-tropanyl)-ethylenediamine.—In a similar fashion 51.5 g. of tropinone and 50.6 g. of N-methyl-N-phenylethylenediamine gave after reduction 65 g. of the triamine, b.p. 163–171° (0.1 mm.). On redistillation the oil boiled at 169–171° (0.1 mm.), n^{25} 1.5595.

Anal. Calcd. for $C_{17}H_{27}N_3$: N, 15.37. Found: N, 15.27.

1-Ethyl-4-(3-tropanyl)-tetrahydro-1H-1,4-benzodiazepine.—In a typical experiment 31.2 g. of N-ethyl-N-phenyl-N'-(3-tropanyl)-ethylenediamine was cooled in an ice-bath and treated with 28.1 g. of 98% formic acid. After the solution had warmed to room temperature, 10.9 ml. of 37% formalin was added. The whole was heated on the steam-bath for 18 hr., cooled and poured into ice-water. The solution was made strongly alkaline with 35% sodium hydroxide. The oil was extracted with ether, dried and distilled. A viscous oil was obtained which boiled at 178–180° (0.7 mm.). The residue which weighed 7.5 g. decomposed when attempts were made to distil it.

When 29 g. of the triamine was heated with 25 ml. of concentrated hydrochloric acid and 8.2 ml. of formalin and the mixture worked up as above, there was obtained only 2.7 g. of the diazepine, b.p. 160–163° (0.04 mm.), and a residue which weighed 17.3 g.

The same amount of triamine, 26.5 ml. of formic acid, 10 ml. of 37% formalin and 500 ml. of water was kept at 95° for 16 hr. and processed as above. There was obtained 18.7 g. of the diazepine, b.p. 178–183° (0.7 mm.), and only 5.4 g. of non-volatile materials.

The infrared spectra of the three samples were virtually identical. The last sample was redistilled for analysis, b.p. 171–175° (0.2 mm.).

Anal. Calcd. for $C_{19}H_{29}N_3$: C, 76.21; H, 9.76; N, 14.03. Found: C, 76.19; H, 9.54; N, 13.90.

1-Methyl-4-(3-tropanyl)-tetrahydro-1H-1,4-benzodiazepine.—Forty-seven grams of N-methyl-N-phenyl-N'-(3-tropanyl)-ethylenediamine was treated successively with 42.5 ml. of 98% formic acid and 16.5 ml. of formalin and heated overnight on the steam-bath. After the usual work-up there was obtained 18.7 g. of the diazepine, b.p. 188–190° (0.7 mm.). On redistillation (slower rate) the base boiled at 180–182° (0.7 mm.).

Anal.[6] Calcd. for $C_{18}H_{27}N_3$: 2N-CH_3, 10.4; 3N-CH_3, 16.8. Found: N-CH_3, 10.5.

(4) Analyses were carried out under the supervision of Mr. K. D. Fleischer. NAP refers to the perchloric acid titration of amines or their picrates in glacial acetic acid. Infrared spectra were determined under the supervision of Dr. F. C. Nachod.

(5) J. V. Braun, *et al.*, *Ber.*, **70B**, 979 (1937), reported the b.p. of N-ethyl-N-phenylethylenediamine as 148–150° (20 mm.) and of N-methyl-N-phenylethylenediamine as 100–112° (0.3 mm.); picrate, m.p. 174°.

(6) Analysis carried out by the Schwarzkopf Laboratories.

Quaternization of 1-Ethyl-4-(3-tropanyl)-tetrahydro-1H-1,4-benzodiazepine. A. Monomethiodide.—A solution of 15.5 g. of the diazepine IV (R = Et) and 16 g. of methyl iodide was allowed to stand overnight at room temperature. The crystals that separated were filtered off and then were leached with boiling ethanol. The hot suspension was filtered and the insoluble residue reserved (see below). The filtrate, on cooling, deposited the monomethiodide which after recrystallization from alcohol melted at 227–228.5° dec., wt. 6.0 g.

Anal. Calcd. for $C_{20}H_{34}IN_3$: N, 9.48; I, 28.6. Found: N, 9.51; I, 28.6.

Electrometric titration was carried out by dissolving 200 mg. of the above salt in 20 ml. of 0.1 *N* hydrochloric acid and titrating with 0.1 *N* sodium hydroxide. The two inflection points occurred at *p*H 3.57 and 6.74.

B. Bismethiodide.—The alcohol-insoluble fraction which was reserved in the above experiment crystallized nicely from water, m.p. 266–267° dec. Analysis indicated that it was the bismethiodide.

Anal. Calcd. for $C_{21}H_{37}I_2N_3$: I, 43.4; N, 7.18. Found: I, 43.2; N, 7.22.

1-Methyl-4-(3-tropanyl)-tetrahydro-1H-1,4-benzodiazepine Bismethiodide.—A mixture of 7.5 g. of the diazepine IV (R = CH_3), 8.2 ml. of methyl iodide and 35 ml. of absolute ethanol was allowed to stand at room temperature overnight. The crystalline solid was collected on a filter and leached several times with boiling ethanol. The insoluble fraction melted at 253–253.5° dec. after three crystallizations from water; wt. 5.2 g. Electrometric titration showed an inflection point at *p*H 7.02.

Anal. Calcd. for $C_{20}H_{35}I_2N_3$: N, 7.36; I, 44.4. Found: N, 7.41; I, 44.2.

Hofmann Degradation of 1-Methyl-4-(3-tropanyl)-tetrahydro-1H-1,4-benzodiazepine Bismethiodide.—Fifty grams of IRA-400 resin[7] was converted to the hydroxide form, and then an aqueous solution of 8.2 g. of the above methiodide was passed through the column. The halogen-free eluate was concentrated to remove most of the water, and the residue was distilled at atmospheric pressure. An aliquot of the distillate gave a weakly positive Tollens test and a small precipitate with Brady reagent indicating that some acetaldehyde was formed. The remainder of the aqueous solution was treated with alcoholic picric acid. The picrate which separated melted at 193–194° after one crystallization from ethanol. When distillation at atmospheric pressure ceased, the pressure was lowered to 1 mm. and heating was continued. The distillate was treated with picric acid and the picrate which separated melted at 193–194° after crystallization from ethanol and did not depress the melting point of the sample obtained previously. The analytical data were in agreement with those required for dipicrate of the vinylamine VI.

Anal. Calcd. for $C_{20}H_{31}N_3 \cdot 2(C_6H_3N_2O_7)$: C, 49.8; H, 4.83; N_{AP}, 5.44.[4] Found: C, 50.2; H, 4.60; N_{AP}, 5.32.

N-Methyl-N-phenyl-N′-formyl-N′-(3-tropanyl)-ethylenediamine.—To a solution of 88.2 g. of N-methyl-N-phenyl-N′-tropanyl)-ethylenediamine in 200 ml. of toluene there was added 88.2 ml. of 98% formic acid. The mixture was boiled under reflux overnight, poured into ice-water and then made strongly alkaline with 35% sodium hydroxide. The layers were separated and the aqueous phase was back extracted with benzene. The united organic layers were concentrated and the residue was distilled at 187–196° (0.2 mm.), wt. 48 g. On standing the viscous oil solidified. After recrystallization from ether it melted at 95–97°.

Anal. Calcd. for $C_{18}H_{27}N_3O$: N_{AP}, 9.25. Found: N_{AP}, 9.25.[4]

N-Ethyl-N-phenyl-N′-formyl-N′-(3-tropanyl)-ethylenediamine.—In a similar way 20 g. of N-ethyl-N-phenyl-N′-(3-tropanyl)-ethylenediamine was treated with 16.5 ml. of formic acid in 150 ml. of toluene. The whole was refluxed overnight and worked up as in the immediately preceding case. There was obtained 13.5 g. of a viscous oil, b.p. 197–202° (0.08 mm.), which crystallized after manipulation under hexane. After recrystallization from the same solvent the amide melted at 105–107°.

Anal. Calcd. for $C_{19}H_{29}N_3O$: N_{AP}, 8.88. Found: N_{AP}, 8.84.[4]

N-Ethyl-N-phenyl-N′-methyl-N′-(3-tropanyl)-ethylenediamine.—Ten grams of lithium aluminum hydride was stirred in 200 ml. of ether while a solution of the formyl derivative (25 g.) in 100 ml. of ether was added dropwise. The mixture was left overnight and then ethyl acetate and 20 ml. of water were added to decompose the reagent and complex. The inorganic material was filtered and washed with ether. The combined ether fractions were concentrated and the residue was dried azeotropically with benzene. Distillation furnished a relatively mobile oil, b.p. 159–164° (0.5 mm.). Upon redistillation it boiled at 182–187° (1.5 mm.), n^{25} 1.5518, wt. 10 g.

Anal. Calcd. for $C_{19}H_{31}N_3$: N, 13.9. Found: N, 13.3.

The bismethiodide was prepared from 3.0 g. of the above base and 5 ml. of methyl iodide in 20 ml. of ethanol. The mixture was boiled under reflux for 5 hr. and filtered hot. The insoluble salt melted at 228.5–230° dec.

Anal. Calcd. for $C_{21}H_{37}I_2N_3$: N, 7.18; I, 43.4. Found: N, 7.22; I, 43.2.

N-Methyl-N-phenyl-N′-methyl-N′-(3-tropanyl)-ethylenediamine.—In the same manner, 24.4 g. of N-methyl-N-phenyl-N′-formyl-N′-(3-tropanyl)-ethylenediamine was reduced with the aid of 10 g. of lithium aluminum hydride to give 17.6 g. of the base II (R = CH_3), b.p. 165–168° (0.1 mm.), $n^{25}D$ 1.5560.

Anal. Calcd. for $C_{18}H_{29}N_3$: N, 14.6. Found: N, 14.4.

The bismethiodide was prepared by first converting the base to the bismethobromide with the aid of methyl bromide in alcohol and then dissolving this salt in water. Treatment of the solution of this base with aqueous potassium iodide caused the desired bismethiodide to separate. It was purified by recrystallization from water.

Anal. Calcd. for $C_{20}H_{35}I_2N_3$: I, 44.4; N, 7.36. Found: I, 44.0; N, 7.40.

N-Methyl-N-(*p*-tolyl)-N′-(3-tropanyl)-ethylenediamine.—A solution of 125 g. of N-methyl-N-(*p*-tolyl)-ethylenediamine and 117 g. of tropinone in 400 ml. of absolute alcohol was allowed to stand overnight before being reduced in the presence of Adams catalyst (2.0 g.) at room temperature and 1000 p.s.i. The reaction mixture was worked up in the usual way to furnish, after two distillations, 134 g. of the desired base, b.p. 164–167° (0.3 mm.), n^{25} 1.5533.

Anal. Calcd. for $C_{18}H_{29}N_3$: N, 14.62. Found: N, 14.40.

1,7-Dimethyl-4-(3-tropanyl)-tetrahydro-1H-1,4-benzodiazepine.—The above base (44.3 g.) was cooled and treated successively with 40 ml. of 98% formic acid and 15.5 ml. of formalin. The mixture was heated on the steam-bath overnight and then worked up in the usual way. There was obtained 35.2 g. of the viscous diazepine, b.p. 180–183° (0.1 mm.), and 6.0 g. of a non-volatile residue.

Anal. Calcd. for $C_{19}H_{29}N_3$: N, 14.03. Found: N, 14.31.

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(7) J. Weinstock and V. Boekelheide, THIS JOURNAL, **75**, 2546 (1953).