

tions, and the mean of the values is reported in the tables. No departures from Beer's law were observed except in the cases of cyclobutanone and cyclohexanone in methanolic hydrogen chloride solution, when only inflections or very broad maxima were observed.

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[CONTRIBUTION FROM STERLING-WINTHROP RESEARCH INSTITUTE]

### 3 $\alpha$ -(2-Diethylaminoethyl)-aminotropane and Related Compounds<sup>1,2</sup>

BY S. ARCHER, T. R. LEWIS AND M. J. UNSER

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Tropinone was reductively aminated in the presence of diethylaminoethylamine and the resulting triamine was quaternized to furnish a bismethiodide in which the secondary amine function was still present. The compound is a tropane and not a pseudotropane as was shown by converting 3 $\alpha$ -benzylaminotropane to the known 3 $\alpha$ -aminotropane. The corresponding triamine derived from pseudopelletierine was prepared by catalytic reduction of the Schiff base. Evidence is presented which lends additional support to the view that in the reductive amination process it is the Schiff base and not the carbinolamine which is hydrogenated. The triamines in the pseudo series were prepared by sodium-alcohol reduction of the Schiff bases from diethylaminoethylamine and tropinone or pseudopelletierine.

The proven clinical utility of "hexamethonium" in the control of malignant hypertension has stimulated further investigation of many bis 'onium types of peripheral ganglionic blocking agents.<sup>3</sup> More recently it has been shown by Cavallito and his co-workers<sup>4</sup> that by appropriate manipulation of the length of the chain separating the 'onium centers and the groups attached to the quaternary nitrogen atoms, it was possible to prepare hypotensive agents whose action was predominantly central rather than peripheral.

As a part of a chemical-pharmacological program, we have prepared a series of compounds of which the prototypes are the quaternary salts III and IV. Since the pharmacological aspects of this work already have been published,<sup>5</sup> we will confine our discussion to the more interesting chemical features of the joint endeavor.

The general method of synthesis is shown in the equation chart.

Since isomerism is possible at C-3 in the triamine I, it became necessary to establish which stereoisomer was formed in the reductive amination. Willstätter<sup>6</sup> prepared 3 $\beta$ -aminotropane by sodium-alcohol reduction of tropinone oxime. The same oxime furnished 3 $\alpha$ -aminotropane upon reduction with sodium amalgam. We were able to obtain 3 $\alpha$ -aminotropane by catalytic reduction of tropinone oxime. After our work was completed, a similar preparation was reported by Stoll.<sup>7</sup>

(1) A portion of this paper was presented at the XIV Congress for Pure and Applied Chemistry, Zurich, July, 1955.

(2) The configurations of the tropanes are designated according to the convention proposed by Fodor (ref. 10).

(3) *Inter alios*, cf. A. Marxer and K. Miescher, *Helv. Chim. Acta*, **34**, 924 (1951); J. Fakstorp, J. Christiansen and J. G. A. Pedersen, *Acta Chim. Scand.*, **7**, 184 (1953); F. Bergel, *Chimia*, **6**, 190 (1952); D. D. Libman, D. L. Pain and R. Stack, *J. Chem. Soc.*, 2305 (1952).

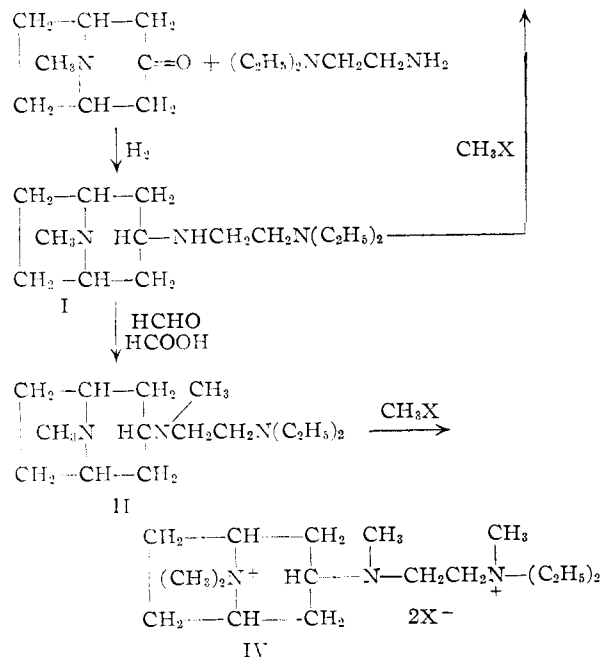
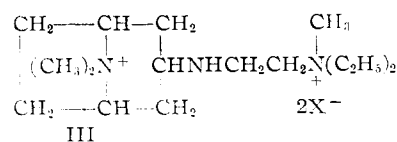
(4) C. J. Cavallito, A. P. Gray, T. B. O'Dell, C. Luna and M. D. Napoli, *J. Exp. Pharm. and Therapeutics*, **114**, 306, 317 (1955).

(5) H. E. Lape, D. J. Fort and J. O. Hoppe, *ibid.*, **116**, 462 (1956).

(6) R. Willstätter and W. Moller, *Ber.*, **31**, 1202 (1898).

(7) A. Stoll, E. Jucker and A. Ebnöther, *Helv. Chim. Acta*, **38**, 559 (1955).

Hydrogenation of tropinone affords tropine<sup>8</sup> which has been isomerized to pseudotropine under alkaline conditions.<sup>9</sup> Similarly, 3 $\alpha$ -aminotropane was isomerized to 3 $\beta$ -aminotropane with the aid of



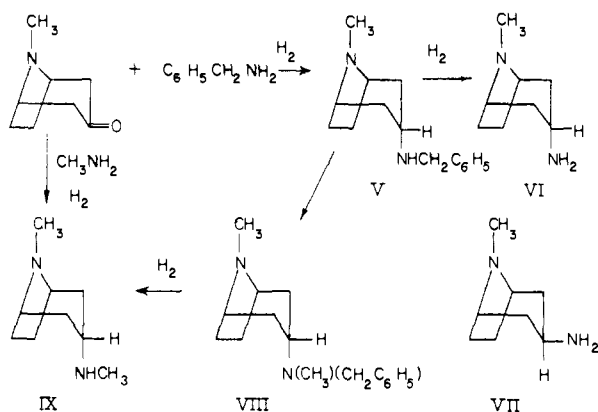
sodium amoxide.<sup>6</sup> The configuration of the tropanes has been established,<sup>10</sup> and in view of the marked similarities in preparation and isomerization of the two aminotropanes, it seems clear that

(8) L. R. Keagle and W. H. Hartung, *THIS JOURNAL*, **68**, 1608 (1946).

(9) R. Willstätter, *Ber.*, **29**, 930 (1896).

(10) G. Fodor and K. Nador, *J. Chem. Soc.*, 721 (1953).

3 $\alpha$ -troprylamine is best represented as shown in VI and 3 $\beta$ -aminotropane is VII.



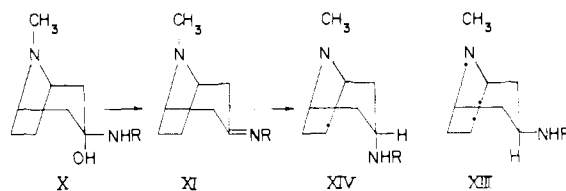
The reductive amination of tropinone in the presence of benzylamine led to 3 $\alpha$ -benzylaminotropane (V) which was catalytically hydrogenolyzed to give 3 $\alpha$ -aminotropane (VI). Thus the amine V is a member of the tropane group and by analogy the triamine I is also a member of the tropane and not the pseudotropane family.

The question whether it is the intermediate carbinolamine or the Schiff base which is hydrogenated in the reductive amination of ketones with primary amines, has never been completely answered. The consensus seems to be that it is the Schiff base that is hydrogenated.<sup>11</sup> Cope<sup>12</sup> found that in the reductive amination of carbonyl compounds with ethanalamine it was best to pre-reduce the platinum oxide catalyst in order to avoid induction periods. In our study of the preparation of the triamine I we were able to confirm this observation, but further investigation revealed that this induction period could be eliminated by pre-mixing the ketone and amine and that it was not necessary to pre-reduce the Adams catalyst. Furthermore if the platinum oxide were reduced and the reagents were added separately to the hydrogenation vessel containing the catalyst, the induction period re-appeared.

Since the conditions necessary to effect reductive amination would serve also to reduce tropinone to tropine, the above results are in harmony with the suggestion that the carbinolamine forms rapidly and protects the ketone from attack by hydrogen. This is followed by a slower dehydration to the Schiff base and, as soon as a sufficient quantity of this species is formed, hydrogenation begins.

Further support for this suggestion can be found in a consideration of the stereochemistry of the reduction process. Alder<sup>13</sup> has pointed out that addition to the carbonyl group of tropinone or pseudopelletierine takes place in the "exo" sense. On conformational grounds it would be expected that the larger group would occupy the less hindered equatorial positions.<sup>14</sup> For these reasons the car-

binolamine would be expected to have the structure X. Bonner<sup>15</sup> showed that hydrogenolysis of a carbon-oxygen bond proceeded with retention of configuration. Thus the amine which would be formed as the result of cleavage of the carbinolamine by hydrogen would be a 3 $\beta$ -aminotropane XIII.



This is contrary to the observed fact (see above). On the other hand, if it is the Schiff base XI which is reduced, one can predict the correct stereochemistry, XIV, by the invocation of Alder's principle<sup>13</sup> of "exo" addition of hydrogen.

We were unable to reductively aminate pseudopelletierine under conditions that were more strenuous than required for the tropinone series. It was found necessary to prepare and isolate the Schiff base<sup>16</sup> prior to catalytic hydrogenation in order to prepare the required 3-(2-dialkylaminoalkylamino)-9-methylgranatolines. The slow rate of formation of Schiff bases in the pseudopelletierine series is a reflection of the higher degree of hindrance that results from the interpolation of an additional methylene group in the bridge. Obviously, in this series it is not the carbinolamine which is being hydrogenated. The evidence adduced in this work lends further support to the belief that it is the Schiff bases and not the carbinolamines which are attacked by hydrogen in the reductive amination reaction.

In order to prepare the corresponding members in the pseudo series the ketimines derived from both tropinone and pseudopelletierine were reduced with the aid of sodium and either hexanol or ethanol. The mixture of triamines (I and its epimer at C-3) in the tropine series was separated as the phenylthioureaides. The  $\beta$ -form predominated in the ratio of 25:1. In the pseudopelletierine series metal-alcohol reduction afforded a mixture in which a very substantial amount of the normal (axial) isomer was present. This is in accord with the presumed greater hindrance at C-3 in the granatoline.<sup>17</sup>

The conversion of the triamine I to the methylated amine II was accomplished by the formaldehyde-formic acid methylation. Although Parham<sup>18</sup> showed that inversion at carbon does not accompany methylation in the Eschweiler-Clarke reaction, we thought it advisable to confirm this

(15) W. A. Bonner, J. A. Zderic and G. A. Casaletto, *THIS JOURNAL*, **74**, 5086 (1952).

(16) During the course of our work D. H. Norton, *et al.*, *J. Org. Chem.*, **19**, 1054 (1954), described a method for the isolation and reduction of aliphatic ketimines that was similar to ours.

(17) Reduction of hindered ketones in the carbocyclic series by metal-alcohols frequently furnishes axial carbinols (Barton, ref. 9). Alder (ref. 8) reported that reduction of pseudopelletierine afforded the equatorial isomer, but from inspection of the experimental details it is apparent that appreciable quantities of another substance were present in the crude reduction mixtures.

(18) W. E. Parham, W. T. Hunter, R. Hanson and T. Lahr *THIS JOURNAL*, **74**, 5646 (1952).

(11) W. S. Emerson, "Organic Reactions," Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 174.

(12) A. C. Cope and E. M. Hancock, *THIS JOURNAL*, **64**, 1503 (1942).

(13) K. Alder and A. A. Dortmann, *Ber.*, **86**, 1544 (1953).

(14) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

point since we were working in the thermodynamically less stable series. Accordingly, 3 $\alpha$ -benzylaminotropane (V) was converted to the methylated amine VIII. The latter was catalytically debenzylated to 3 $\alpha$ -methylaminotropane (IX). This same amine was prepared by reductive amination of tropinone in the presence of methylamine. Since it has been established that reductive amination furnishes  $\alpha$ -aminotropanes, it follows that no configurational change occurred in the Eschweiler-Clarke reaction.

Quaternization of the triamine I with methyl iodide proceeded rapidly and exothermically to yield a crystalline salt, the analysis of which indicated the formation of a bis-methiodide. That this substance was best represented by formula III follows from the analogous results obtained by Marxer and Miescher,<sup>3</sup> the fact that the infrared spectrum displayed a strong NH band and no significant absorption in the 4.0  $\mu$  region characteristic of ammonium salts.<sup>19</sup> Similarly the fully alkylated amine II furnished a bis-methobromide (IV, X = Br) when treated with methyl bromide.

Higher homologs of the triamine III were prepared by acylation of the secondary amine I with the appropriate anhydride and reduction of the corresponding amides with lithium aluminum hydride. Quaternization of these homologs proceeded at a noticeably slower rate in acetonitrile.

### Experimental<sup>20</sup>

**3 $\alpha$ -Aminotropane.**—A solution of 23 g. of tropinone oxime<sup>5</sup> in 150 ml. of methanol was reduced in the presence of 0.5 g. of Adams platinum oxide catalyst. After seven hours at 50° the reduction was stopped and the catalyst was filtered. After the solvent was removed, the residue furnished 5.5 g. of 3-aminotropane, b.p. 98–102° (20 mm.),  $n_D^{20}$  1.5018. A large high-boiling residue (ditropylamine?) was not investigated.

The above amine (0.5 g.) in 3 ml. of methanol was treated with 1.0 ml. of phenyl isothiocyanate. A crystalline solid separated almost immediately. The thiourea melted at 160–161°<sup>21</sup> after recrystallization from ethyl acetate.

*Anal.* Calcd. for C<sub>15</sub>H<sub>21</sub>N<sub>3</sub>S: N, 15.26. Found: N, 15.20.

The 3 $\beta$ -aminotropane prepared by sodium-amyl alcohol<sup>6</sup> reduction of tropinone oxime boiled at 104–106° (22 mm.),  $n_D^{20}$  1.4995, and furnished a thiourea, m.p. 173–175°.<sup>22</sup>

**3 $\alpha$ -Methylaminotropane.**—A solution of 45 g. of tropinone in 100 ml. of methanol was mixed with a solution of 40 ml. of 7.9 N methylamine in methanol. Adams catalyst was added and the mixture was heated to 50° to initiate the hydrogenation which then proceeded to completion in 90 minutes. The catalyst and solvent were removed and the residue was distilled to give a fraction, b.p. 59–60° (0.5 mm.), wt. 43.5 g.

*Anal.* Calcd. for C<sub>9</sub>H<sub>17</sub>N<sub>2</sub>: N, 18.3. Found: N, 17.6.

When a sample of the above amine was treated with excess alcoholic picric acid, a dipicrate separated which melted at 255° dec., after recrystallization from ethanol.

*Anal.* Calcd. for C<sub>9</sub>H<sub>15</sub>N<sub>2</sub>·2C<sub>6</sub>H<sub>3</sub>N<sub>3</sub>O<sub>7</sub>: neut. equiv., 306.2. Found: neut. equiv., 305.

The phenyl thiourea was prepared in methanol solution with the aid of phenyl isothiocyanate; m.p. 160–161° after recrystallization from ethyl acetate.

*Anal.* Calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>3</sub>S: N, 14.9. Found: N, 14.5.

(19) B. Witkop, *THIS JOURNAL*, **76**, 5597 (1954).

(20) Analyses were carried out under the supervision of Mr. K. D. Fleischer. The infrared spectra were determined under the supervision of Dr. F. C. Nachod. Melting points are corrected.

(21) Willstätter (ref. 5) reported the m.p. as 142–143° (typographical error?). Stoll (ref. 6) reported the m.p. was 153–154°.

(22) Willstätter (ref. 5) reported the m.p. to be 171–172°.

**3 $\alpha$ -Benzylaminotropane.**—A solution of 45 g. of tropinone and 32 g. of benzylamine in 80 ml. of ethanol was added to 1.5 g. of pre-reduced Adams platinum oxide suspended in 30 ml. of ethanol. Hydrogenation was complete in 3 hr. at 50°. The base, isolated in the usual way, boiled at 143–146° (0.05 mm.),  $n_D^{25}$  1.5445, yield 63%.

*Anal.* Calcd. for C<sub>15</sub>H<sub>22</sub>N<sub>2</sub>: N, 12.16. Found: N, 12.14.

**3 $\alpha$ -Benzylmethylaminotropane.**—Anhydrous formic acid (21.6 g.) was added slowly to 19.2 g. of benzylaminotropane. Then 8.4 ml. of 40% formalin was added, and the solution was heated on the steam-bath until gas evolution started. The source of heat was removed until the reaction had moderated. Heating was continued for 16 hr. The whole was poured into ice-water and the solution was made strongly alkaline with sodium hydroxide. The oil was taken up in ether, dried and distilled. The fraction with b.p. 126–129° (0.3 mm.) weighed 11.1 g.

This substance formed a dipicrate in ethanol, which melted at 230–232° after recrystallization from aqueous dimethylformamide.

*Anal.* Calcd. for C<sub>16</sub>H<sub>24</sub>N<sub>2</sub>·2C<sub>6</sub>H<sub>3</sub>N<sub>3</sub>O<sub>7</sub>: neut. equiv., 351. Found: neut. equiv., 350.<sup>23</sup>

When a solution of 4.3 g. of the above base in 30 ml. of dry ethanol was treated with 3.5 ml. of methyl iodide, crystals of the monomethiodide started to separate within 15 minutes. The whole was left overnight and filtered. The salt was crystallized from methanol, wt. 3.9 g., m.p. 233–237° dec.

*Anal.* Calcd. for C<sub>17</sub>H<sub>27</sub>IN<sub>2</sub>: I, 32.84; N, 7.25. Found: I, 32.55; N, 7.26.

**Catalytic Debonylation of 3 $\alpha$ -Benzylmethylaminotropane.** Ten grams of 3-benzylmethylaminotropane in 100 ml. of ethanol was hydrogenolyzed in the presence of 10% palladium-on-charcoal. Distillation of the oil that remained after removal of the catalyst and ethanol furnished an oil, b.p. 116–118° (18 mm.). When this base was treated with phenyl isothiocyanate in methanol, a phenyl thiourea separated which melted at 160–161°, after crystallization from ethyl acetate. When admixed with an authentic sample there was no depression in melting point.

**Catalytic Debonylation of 3 $\alpha$ -Benzylmethylaminotropane.**—In a similar fashion 22.8 g. of 3 $\alpha$ -benzylaminotropane was hydrogenated in the presence of 10% palladium-on-charcoal. The tropylamine that was formed boiled at 118–120° (43 mm.),  $n_D^{25}$  1.5014. The phenyl thiourea, m.p. 158–160°, did not depress the melting point of an authentic sample.

**3 $\alpha$ -(2-Diethylaminoethyl)-aminotropane.**—A solution of 30 g. of tropinone and 24 g. of diethylaminoethylamine in 100 ml. of dry ethanol was allowed to stand for 2 hr. During this time 1.2 g. of platinum oxide catalyst was reduced in 50 ml. of ethanol. The solution of the bases was added to the catalyst and the reduction which proceeded without delay was 80% complete in 1 hr. The mixture was heated to 50° to finish the reaction. After the usual work-up there was obtained 33.2 g. (66%) of the desired triamine, b.p. 111–115° (0.5 mm.).

In another experiment the catalyst was pre-reduced, and the tropinone and diethylaminoethylamine were added separately without mixing. In this case no reduction occurred at room temperature. The contents of the hydrogenation vessel were heated to 50° whereupon the required amount of hydrogen was consumed within the next few hours. There was obtained, in 70% yield, the desired base, b.p. 115–118° (0.5 mm.).

In our preferred procedure, 204 g. of tropinone and 174 g. of diethylaminoethylamine in 1 liter of methanol was allowed to stand overnight. The solution was added to 2.0 g. of Adams catalyst (*under nitrogen*), and the reduction was allowed to proceed at room temperature and 1000 p.s.i. Over 75% of the required amount of hydrogen was absorbed within the first hour at room temperature. The remainder was consumed at 60°. The triamine was collected at 99–101° (0.2 mm.), wt. 273 g.,  $n_D^{25}$  1.4842.

The phenyl thiourea was prepared by dissolving 3.8 g. of the above base in 30 ml. of methanol and treating the solution with 2.2 g. of phenyl isothiocyanate. After 1 hr. 5.0 g. of crystals was collected. Recrystallization from

(23) The neutral equivalent was determined by titrating the picric acid with sodium methoxide in anhydrous methanol. The value for the unmethylated base is 344.

ethanol and ethyl acetate furnished the pure compound, m.p. 168–170°, wt. 3.7 g.

*Anal.* Calcd. for C<sub>21</sub>H<sub>34</sub>N<sub>4</sub>S: N, 14.95; S, 8.56. Found: N, 14.96; S, 8.29.

The dipicrate prepared from two equivalents of picric acid in ethanol melted at 168–170° after crystallization from the same solvent.

*Anal.* Calcd. for C<sub>14</sub>H<sub>20</sub>N<sub>3</sub>·2(C<sub>6</sub>H<sub>3</sub>N<sub>3</sub>O<sub>7</sub>): N, 18.00; neut. equiv., 350. Found: N, 18.06; neut. equiv., 350.<sup>23</sup>

The tripicrate was prepared by (a) treating the base with excess picric acid in hot ethanol and recrystallizing the salt from aqueous dimethylformamide and (b) adding alcoholic picric acid to a hot alcoholic solution of the above dipicrate. In either case the derivative melted at 230–232°.

*Anal.* Calcd. for C<sub>14</sub>H<sub>20</sub>N<sub>3</sub>·3(C<sub>6</sub>H<sub>3</sub>N<sub>3</sub>O<sub>7</sub>): neut. equiv., 310. Found: neut. equiv., 307.<sup>23</sup>

**3-(N-2-Diethylaminoethyl)-tropinoneimine.**—A one-liter flask equipped with a water separator was charged with 69.5 g. of tropinone, 500 ml. of dry toluene and 500 mg. of fused zinc chloride. The mixture was refluxed for 1 hr. to remove traces of water (0.2 ml. was collected), and then 63.8 g. of diethylaminoethylamine was added. Reflux was resumed and in 12 minutes 50% of the theoretical amount of water was collected, and in 4 hr. the reaction was complete. On cooling, the mixture deposited a few crystals which were filtered off. The clear filtrate was distilled to yield 92.2 g. (78%) of the Schiff base, b.p. 117–131° (0.6 mm.), mainly at 128–131° (0.6 mm.).

A tripicrate, prepared in ethanol, melted at 184–185° after recrystallization from the same solvent.

*Anal.* Calcd. for C<sub>14</sub>H<sub>27</sub>N<sub>3</sub>·3(C<sub>6</sub>H<sub>3</sub>N<sub>3</sub>O<sub>7</sub>): neut. equiv., 308. Found: neut. equiv., 312.<sup>23</sup>

Hydrogenation of the Schiff base in the presence of Raney nickel catalyst occurred at 60° and 1,000 p.s.i. The oil that resulted after removal of the nickel and the ethanol was converted directly to the phenyl thioureide. The crude derivative melted at 167–169° and did not depress the m.p. of the sample prepared as above. No appreciable quantity of the isomeric base was present.

Similarly, reduction of 24.6 g. of the Schiff base in the presence of Adams catalyst (0.6 g.) occurred in 75 minutes at room temperature. Distillation afforded 21.5 g. (85%) of 3 $\alpha$ -(2-diethylaminoethyl)-aminotropane, b.p. 100–105° (0.2 mm.), *n*<sub>D</sub><sup>20</sup> 1.4832.

When 11.8 g. of the Schiff base in 100 ml. of dry ether was reduced with the aid of 2.0 g. of lithium aluminum hydride, there was obtained 7.8 g. of a colorless oil. This was converted to a crude phenyl thioureide, m.p. 166–169°, which did not depress the m.p. of the previously prepared sample.

**3 $\beta$ -(2-Diethylaminoethyl)-aminotropane.**—To a hot solution of 47.4 g. (0.2 mole) of the Schiff base in 375 ml. of absolute ethanol, 22.0 g. of freshly cut sodium was added in small pieces in a 2-hr. period. After all the metal had been added, the suspension was refluxed for 1 hr. The clear solution was cooled, and just enough concentrated hydrochloric acid was added slowly to neutralize the sodium ethoxide. The salt was removed by filtration, and the clear filtrate was concentrated to leave an oil which was dissolved in a small quantity of water. The desired amine was thrown out of the aqueous solution with solid potassium carbonate. It was collected with ether, dried and distilled to give a yellow base, b.p. 108–112° (0.3 mm.), wt. 26.5 g.

A solution of 11.1 g. of the above crude amine was dissolved in 75 ml. of methanol and treated with 6.75 g. of phenyl isothiocyanate in 25 ml. of methanol. The solution warmed slightly, but no crystals separated. The reaction mixture was left in the refrigerator overnight. The crystalline solid that deposited was collected on a filter, m.p. 165–168°, wt. 0.8 g. This compound did not depress the m.p. of the phenyl thioureide of 3 $\alpha$ -(2-diethylaminoethyl)-aminotropane.

The filtrate was concentrated to leave a yellow gum (wt. 17.4 g.) which was dissolved in 100 ml. of ethyl acetate. The solution was concentrated to 60 ml. and cooled. The crystals were filtered; wt. 12.7 g., m.p. 136–138°. After one recrystallization from ethyl acetate, the phenyl thioureide of 3 $\beta$ -( $\alpha$ -diethylaminoethyl)-aminotropane melted at 138–139.5°.

*Anal.* Calcd. for C<sub>21</sub>H<sub>34</sub>N<sub>4</sub>S: N, 14.95; S, 8.56. Found: N, 15.06; S, 8.38.

Addition of pentane to the filtrate caused the separation of an additional 2.6 g. of crystals, m.p. 110–115°. This was not further investigated.

A solution of 11.7 g. of the above phenyl thioureide, m.p. 136–138°, in 50 ml. of ethanol was mixed with 25 ml. of 8 *N* alcoholic hydrogen chloride and allowed to stand at room temperature for 2 hr. The solid that separated was filtered and a small portion was recrystallized from methanol. The compound, which proved to be the dihydrochloride of the phenyl thioureide, melted at 219–221°.

*Anal.* Calcd. for C<sub>21</sub>H<sub>34</sub>N<sub>5</sub>S·2HCl·H<sub>2</sub>O: S, 6.88; H<sub>2</sub>O, 3.87. Found: S, 6.80; H<sub>2</sub>O, 4.11.

The filtrate was concentrated, and the residue together with the above salt were dissolved in hot absolute alcohol; 25 ml. of 8 *N* alcoholic hydrogen chloride was added, and the solution was allowed to stand overnight. The crystals were filtered and the above process was repeated. The first and second crop of crystals were united (wt. 8.0 g.) and recrystallized from a large volume of ethanol to give the pure trihydrochloride, m.p. 268° dec.

*Anal.* Calcd. for C<sub>14</sub>H<sub>29</sub>N<sub>3</sub>·3HCl: C, 48.3; H, 9.22; Cl, 30.5. Found: C, 48.0; H, 9.33; Cl, 30.1.

**3 $\beta$ -(2-Diethylaminoethyl)-aminotropane Bis-methiodide.**—An aqueous solution of the above trihydrochloride was treated with potassium carbonate, and the liberated base was removed with the aid of ether and dried. Distillation furnished the free base, b.p. 117–119° (1.5 mm.), *n*<sub>D</sub><sup>20</sup> 1.4839.

One hundredth mole of the base (2.4 g.) was dissolved in 50 ml. of absolute ethanol; 2 ml. of methyl iodide was added, and the solution was allowed to stand at room temperature for 5 hr. The crystals (3.0 g.) were filtered and recrystallized from methanol, m.p. 270.5–271.5°.

*Anal.* Calcd. for C<sub>16</sub>H<sub>26</sub>N<sub>3</sub>I<sub>2</sub>: N, 8.03; I, 48.5. Found: N, 8.09; I, 48.4.

**3 $\alpha$ -( $\alpha$ -Diethylaminoethyl)-aminotropane Bis-methiodide.**—Six grams of the triamine I dissolved in 30 ml. of dry ethanol was chilled to 0°, and 3.5 ml. of methyl iodide was added. The solution was left at room temperature overnight. The solid which separated (wt. 10.4 g.) was crystallized from aqueous ethanol to give 7.5 g. of the bis-methiodide, m.p. 265–266°. The infrared spectrum (KBr pellet) showed a strong NH band.

*Anal.* Calcd. for C<sub>16</sub>H<sub>26</sub>I<sub>2</sub>N<sub>3</sub>: I, 48.5. Found: I, 48.2.

**N,N-Diethyl-N'-(3-[9-methylgranatany])-ethylenediamine Phenyl Thioureide.**—A solution of 15.7 g. of pseudopelletierine hemihydrate<sup>24</sup> in 100 ml. of dry toluene was refluxed under a water separator. The dried solution was treated with 12.0 g. of diethylaminoethylamine and 100 mg. of zinc chloride. After 4 hr. only 50% of the theoretical amount of water was collected and after 12 hr. only 83% (*cf.* the same reaction with tropinone). The mixture was distilled to give a small fore-run (b.p. 90–120°, 1.0 mm.) which contained pseudopelletierine and the main fraction, b.p. 130–135° (0.5 mm.), wt. 13.7 g. (57%). On redistillation the Schiff base boiled at 131–139° (0.7 mm.), *n*<sub>D</sub><sup>20</sup> 1.5050.

Reduction of 10.5 g. of the redistilled Schiff base in ethanol with 0.5 g. of Adams catalyst took 5 hr. at 60°. The triamine, isolated in the usual way, boiled at 116–122° (0.2 mm.) and weighed 9.0 g. (85%). On redistillation the base boiled at 128–130° (0.6 mm.), *n*<sub>D</sub><sup>20</sup> 1.4920.

When 600 mg. of the base was treated with 320 mg. of phenyl isothiocyanate, the corresponding phenyl thioureide separated, which melted at 188–190° after recrystallization from ethyl acetate.

*Anal.* Calcd. for C<sub>22</sub>H<sub>36</sub>N<sub>4</sub>S: N, 14.42; S, 8.25. Found: N, 14.49; S, 8.22.

**N,N-Diethyl-N'-(3-pseudo-[9-methylgranatany])-ethylenediamine Phenyl Thioureide.**—To a suspension of 7.5 g. of sodium sand in 175 ml. of refluxing toluene there was added over a 5.5-hr. period a solution of 20.5 g. of the Schiff base derived from pseudopelletierine and diethylaminoethylamine in 32.8 g. of 4-methyl-2-pentanol. After all had been added, the mixture was stirred for an additional half hour. The cooled reaction mixture was treated cautiously with 30 ml. of 10% sodium carbonate. The organic layer was separated, and the water layer was satu-

(24) A. C. Cope, *et al.*, *THIS JOURNAL*, **73**, 3416 (1951).

rated with potassium carbonate. The aqueous phase was extracted with benzene and the united organic portions were dried and distilled *in vacuo* to leave 22.8 g. of a residue. This was combined with 7.0 g. of a similar preparation, and the resulting 29.8 g. of mixed bases was dissolved in 100 ml. of ethanol and treated with 17.5 g. of phenyl isothiocyanate. After 1 hr. the mixture was chilled in ice and filtered. This was called fraction A. The filtrate was evaporated to leave a red oil which was called fraction B.

Fraction A was crystallized from a large volume of ethyl acetate. There deposited 20.3 g. of a phenyl thioureide, m.p. 189–191°, undepressed when mixed with the same derivative obtained from the triamine prepared by catalytic reduction of the Schiff base. The filtrate was concentrated to 300 ml. and cooled. The crop that separated weighed 2.0 g., m.p. 185–187°. The combined yield of the normal isomer was 22.3 g.

The above filtrate was further concentrated to 25 ml. On cooling 1.8 g. of the phenyl thioureide of the pseudo isomer, m.p. 133–135°, separated. Fraction B was dissolved in 50 ml. of ethyl acetate. On cooling 12.0 g. of the same isomer separated, m.p. 131–133°. The combined yield of the pseudo isomer was 13.8 g. Further crystallization from ethyl acetate raised the m.p. to 135–136°.

*Anal.* Calcd. for  $C_{22}H_{33}N_3S$ : N, 14.42; S, 8.25. Found: N, 14.70; S, 7.96.

**N,N-Diethyl-N'-(3-pseudo-[9-methylgranatany])-ethylenediamine Trihydrochloride.**—A suspension of 10.2 g. of the phenyl thioureide described directly above (m.p. 135–136°) in 100 ml. of absolute alcohol was mixed with 15 ml. of 8 N alcoholic hydrogen chloride and left overnight at room temperature. A small amount of insoluble material was removed by filtration and the filtrate was carefully treated with 150 ml. of dry ether to precipitate the crude trihydrochloride, wt. 9.1 g. After recrystallization from equal parts of methanol and ethanol, the salt melted at 264–267° dec.

*Anal.* Calcd. for  $C_{15}H_{31}N_3 \cdot 3HCl$ : C, 49.7; H, 9.45; Cl, 29.3. Found: C, 49.9; H, 9.54; Cl, 29.2.

The bis-methiodide was prepared from 2.6 g. of the trihydrochloride. The base was liberated from an aqueous solution of the salt with potassium carbonate and dissolved in ether. The dried ether solution was evaporated to an oil which was dissolved in 10 ml. of methanol. The solution was treated with 1.2 ml. of methyl iodide, left overnight and then filtered. The bis-quaternary salt was purified by crystallization from methanol; m.p. 270–272° dec.

*Anal.* Calcd. for  $C_{17}H_{37}I_2N_3$ : I, 47.2; N, 7.82. Found: I, 47.3; N, 7.88.

**3 $\alpha$ -(N-Diethylaminoethyl)-methylaminotropane.**—Sixty-nine grams of 3 $\alpha$ -(2-diethylaminoethyl)-aminotropane was cooled, and 76 ml. of 98% formic acid was added slowly. The solution was allowed to warm to room temperature before 29 ml. of 37% formalin was added. The solution was heated on the steam-bath for 17 hr., cooled, poured into ice-water and made strongly basic with 35% sodium hydroxide. The oil was removed and the aqueous layer was washed twice with methylene chloride. The united oil layers were dried over Drierite and distilled to give a fraction, b.p. 120–124° (0.9 mm.),  $n_D^{25}$  1.4873, which was taken as the methylated base, wt. 59.7 g.

Twenty grams of this base was dissolved in 250 ml. of absolute alcohol, and to it was added a freshly prepared solution of alcoholic hydrogen bromide to pH 3. The mixture was allowed to stand 18 hr. and was filtered. The trihydrobromide which weighed 34 g. was recrystallized from methanol. It was quite hygroscopic and melted unsharply in the range 135–145°.

*Anal.* Calcd. for  $C_{13}H_{31}N_3 \cdot 3HBr$ : C, 36.3; H, 6.91; Br, 48.3. Found: C, 35.9; H, 7.09; Br, 47.9.

The bis-methobromide was prepared by adding gaseous methyl bromide to 5.0 g. of the base in 50 ml. of acetonitrile for 4 minutes. The temperature rose from 23 to 30°, and the product started to separate during this time. After 3 hr. at room temperature the mixture was filtered and the salt was crystallized from isopropyl alcohol; wt. 4.4 g., m.p. 230–232° dec.

*Anal.* Calcd. for  $C_{17}H_{37}Br_2N_3$ : Br, 36.1. Found: Br, 35.7.

**3 $\alpha$ -(N-2-Diethylaminoethyl)-acetylaminotropane.**—A solution of 24 g. of N,N-diethyl-N'-(3-tropanyl)-ethylenediamine in 20 ml. of acetic anhydride was heated on the steam-bath for 2 hr. The mixture was allowed to stand overnight and then it was poured into ice-water. The solution was rendered strongly alkaline. The oil was taken up in benzene, dried by azeotropic distillation and then distilled to give 20.1 g. (73%) of a viscous oil, b.p. 143–150° (0.05–0.15 mm.),  $n_D^{25}$  1.4980.

A portion was converted to the dipicrate which melted at 194–195° after recrystallization from ethanol.

*Anal.* Calcd. for  $C_{16}H_{31}N_3O \cdot 2(C_6H_5N_3O_7)$ : N, 3.70. Found: N, 3.74.<sup>25</sup>

**3 $\alpha$ -(N-2-Diethylaminoethyl)-ethylaminotropane Bis-methiodide.**—The above amide (10.3 g.) was reduced in 100 ml. of dry ether with 4.0 g. of lithium aluminum hydride. The mixture was refluxed for 2 hr. after all the amide had been added. Excess reducing agent was destroyed with ethyl acetate followed by 10 ml. of water. The inorganic matter was filtered off and washed thoroughly with ether. The combined ethereal fractions were dried and distilled. The product boiled at 142° (2.0 mm.) and weighed 10.0 g.,  $n_D^{25}$  1.4845.

A solution of the base (470 mg.) in 10 ml. of acetonitrile was treated with 0.5 ml. of methyl iodide. No temperature rise was noted, but in two minutes crystals of the bis-methiodide started to separate. After 2.5 hr. the solid was collected and dried, wt. 630 mg., m.p. 217.5–219.5° dec.

*Anal.* Calcd. for  $C_{18}H_{39}I_2N_3$ : I, 46.0; N, 7.63. Found: I, 45.4; N, 7.74.

**3 $\alpha$ -(N-2-Diethylaminoethyl)-propionylaminotropane.**—3 $\alpha$ -(2-Diethylaminoethyl)-aminotropane (48 g.) was cooled under the tap as 50 ml. of propionic anhydride was added. The temperature rose to 70°. The mixture was allowed to stand for 2.5 hr. and then worked up as in the case of the lower homolog. The viscous propionyl derivative boiled at 160° (0.5 mm.),  $n_D^{25}$  1.4945, wt. 45.8 g.

The dipicrate prepared in ethanol melted at 173–176° after recrystallization from aqueous dimethylformamide.

*Anal.* Calcd. for  $C_{17}H_{33}N_3O \cdot 2(C_6H_5N_3O_7)$ : neut. equiv., 377. Found: neut. equiv., 373.<sup>23</sup>

**3 $\alpha$ -(N-2-Diethylaminoethyl)-propylaminotropane Bis-methiodide.**—One-tenth mole of the propionamide (29.5 g.) was reduced with 4.0 g. of lithium aluminum hydride in 100 ml. of ether. The mixture was worked up as in the previous case to furnish an oil, b.p. 119–126° (0.1 mm.),  $n_D^{25}$  1.4835, wt. 23.6.

Two grams of the above base in 30 ml. of acetonitrile was treated with 2.0 ml. of methyl iodide. The solution warmed noticeably, but crystals did not appear until about 10 minutes after the halide was added. The mixture was allowed to stand overnight, cooled to 5° and filtered. The salt was washed successively with acetonitrile, absolute alcohol and pentane; m.p. 193–195° dec.

*Anal.* Calcd. for  $C_{19}H_{41}I_2N_3$ : I, 44.9; N, 7.44. Found: I, 44.5; N, 7.56.

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(25) Acetic-perchloric acid titration of basic nitrogen.