way, after two crystallizations from benzene–petroleum ether mixture had m.p. 78°.

Anal. Calcd. for $C_{17}H_{24}N_2S$: C, 70.83; H, 8.33. Found: C, 70.63; H, 8.52.

N,N - Dimethyl - β - (6 - methylcyclohexenyl) - ethylamine (XXVIII).—A mixture of the above secondary amine (5 g.) and ethyl formate (7.5 g.) was heated in a sealed tube at 150° for nine hours. The resulting liquid was heated on a steam-bath under reduced pressure for *ca.* one hour to remove low boiling substances. The residual oil XXVII had a very intense amide band in the infrared at 6 μ.

The crude N-formyl derivative (10 g.) was reduced with lithium aluminum hydride (5.2 g.) in ether (600 cc.). After stirring for three hours at room temperature the mixture was refluxed for one hour. It was then cooled, decomposed with a saturated solution of sodium sulfate and worked up in the usual way. The oil left after removal of the benzene distilled at 72–74° (2.5 mm.) as a colorless mobile liquid. It was redistilled and the constant boiling fraction was collected at 70° (2.5 mm.).

Anal. Calcd. for $C_{11}H_{21}N$: C, 79.04; H, 12.57. Found: C, 78.77; H, 12.73.

The picrate, prepared in the usual way, was crystallized three times from dilute alcohol and had m.p. 118°.

Anal. Calcd. for $C_{17}H_{24}N_4O_7$: C, 51.51; H, 6.06. Found: C, 51.10; H, 6.03.

6-Methyl-1-vinylcyclohexene (XVI).—The tertiary amine XXVIII (11 g.) dissolved in benzene (30 cc.) was cooled in ice-water and to this was added with stirring methyl iodide (15 g.) dissolved in benzene (20 cc.). After the addition was complete, the flask was heated on a steam-bath for about 30 minutes; a fresh quantity of methyl iodide (7.5 g.) in benzene (20 cc.) was added and heating was continued for another 20 minutes. After cooling, the mixture was diluted with petroleum ether and filtered. The crude methiodide was washed three times with petroleum ether and then dried in the air; crude yield 20.5 g.

The crude methiodide (20 g.) was dissolved in methanol containing 10% water (480 cc.) and treated with vigorous stirring with freshly prepared silver oxide (from silver nitrate (13 g.) and sodium hydroxide (3.3 g.)). Stirring was continued overnight. The solution was filtered and the inorganic residue was washed three times with methanol. The filtrate was then carefully concentrated on the steam-bath. The residual viscous liquid was then heated in an oil-bath when decomposition started around 150°; water and an oily liquid distilled over. The cloudy distillate was extracted with ether, the ether extract was washed with water, dried, and the ether was evaporated in a current of nitrogen. The residual oil was distilled in a nitrogen atmosphere, b.p. 155–158°, yield 4.5 g. On redistillation the constant boiling fraction, b.p. 156°, was collected as a colorless, mobile liquid with a characteristic smell; $\lambda_{\max}^{C_2H_5OH}$ 232 mμ, $\epsilon_{\max}$ 20,000.

Anal. Calcd. for C_9H_{14}: C, 88.52; H, 11.47. Found: C, 88.70; H, 11.46.

5-Methyl-1,2,3,5,6,7,8,9-octahydronaphthalene-1,2-dicarboxylic Acid Anhydride (XXIX).—The diene XVI (2.5 g.) and maleic anhydride (4 g.) dissolved in benzene (25 cc.) were heated on a steam-bath for *ca.* 8 hours in an atmosphere of nitrogen. The clear solution was then concentrated, diluted with ether, and the ether solution was washed several times with water, dried, concentrated and cooled. The crystals (2.5 g.) were removed by filtration; the mother liquor on concentration gave a second crop of crystals (0.5 g.), making the total yield 3.0 g. After one recrystallization the adduct had m.p. 113° and gave no depression in melting point on admixture with the adducts obtained previously from the diene mixtures prepared from XX. The infrared spectra of the adducts were also identical in all respects.

CAMBRIDGE 38, MASS.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH]

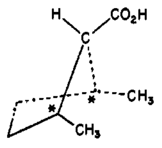
Stereoisomeric Quaternary Ammonium Derivatives of Tropine Having a Pseudoasymmetric Nitrogen Atom

BY STEPHEN P. FINDLAY

RECEIVED NOVEMBER 28, 1952

Tropine reacts with ethyl iodide to give tropine ethiodide which is identical with N-ethylnortropine methiodide obtained from N-ethylnortropine and methyl iodide. On the other hand N-ethylnortropine *n*-propiodide obtained from N-ethylnortropine and *n*-propyl iodide is different from N-*n*-propylnortropine ethiodide got from N-*n*-propylnortropine and ethyl iodide. This pair of isomeric iodides is convertible to the corresponding pair of bromides. The significance of these results is discussed. The nitrogen atom in these pairs of stereoisomeric halides is *pseudoasymmetric.*

Regarding optical activity in terms of asymmetric carbon atoms rather than in terms of asymmetry of the molecule as a whole has well known shortcomings.[1] One of these is that some symmetrically constituted, and hence optically inactive, molecules contain two or more asymmetric carbon atoms. A special case is the type of inactive compound in which a centrally located carbon atom is attached to four different groups: CXY(+)Z(−)Z. Such carbon atoms have been called *pseudoasymmetric*[2] which term may be applied to any atom attached tetrahedrally to four different groups two of which are the same except in being non-superposable and, therefore, optical opposites.[3] The α-carbon atom of the two inactive or *meso* forms of 2,5-dimethylcyclopentane-1-carboxylic acid (I and II) and C_3 of ribitol and xylitol are examples of pseudoasymmetric carbon atoms. Heretofore no examples of other atoms of this description appear to have been reported, although mention has been made of pseudoasymmetry of the nitrogen atom.[4]



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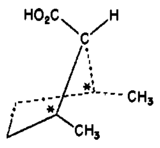

II

In connection with a study of the stereochemistry of the tropane alkaloids it was noticed that certain of the symmetrically constituted derivatives of this class should furnish compounds in which the nitro-

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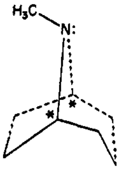
(1) *Cf.* G. Wittig, "Stereochemie," Akademische Verlagsgesellschaft, Leipzig, 1930, pp. 87–90.

(2) A. Werner originated this word to describe those central carbon atoms which possess certain of the properties of an asymmetric carbon atom without in effect being one. K. Freudenberg, "Stereochemie," Franz Deuticke, Leipzig and Vienna, 1933, p. 599.

(3) It will be necessary to modify this definition if examples of the type C(+)X(−)X(+)Y(−)Y also prove to be optically inactive.

(4) H. Gilman, "Organic Chemistry," Second Edition, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 417.

gen atom is pseudoasymmetric. For example, the nitrogen atom of tropane itself can conceivably exist in two arrangements (III and IV), although the non-resolvability of tertiary amines makes the isolation of either of these forms unlikely.[5] When these two configurations are stabilized by replacing the free electron pair with an element, *e.g.*, oxygen, or a radical other than methyl, two stereoisomeric products are possible. Thus there should be two tropane N-oxides (V and VI) and two ethiodides (VII and VIII). It is clear that in these three pairs the nitrogen atom, like the α-carbon of the *meso* forms of 2,5-dimethylcyclopentane-1-carboxylic acid, is attached to four different groups two of which are identical except in having opposite configurations, and hence it too is pseudoasymmetric.[6]



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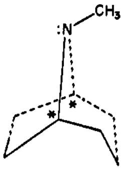

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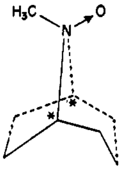

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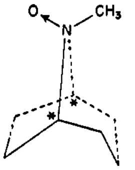

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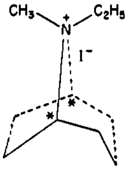

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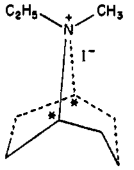
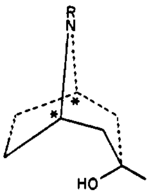
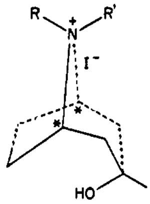


VIII

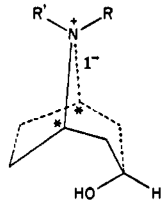
The amino alcohol tropine (IX, R = CH_3), rather than tropane, was selected as the starting material in the experiments hereinafter described because of its readier availability. The chief disadvantage of this choice is that the introduction of the hydroxyl group doubles the number of *meso* and optically active stereoisomers theoretically predicted for its sequence of atomic linkages. Therefore, in tropine the isolation of a pair of stereoisomeric ethiodides of the type above discussed would represent a partial rather than a complete study.



IX



X

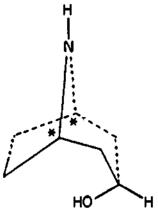


XI

It was thought probable that one or the other of the two possible *meso* forms of tropine ethiodide could be obtained according to the order in which the alkyl groups were attached to the nitrogen. Tropine (IX, R = CH_3) and ethyl iodide, heated in absolute alcohol about 60°, furnished tropine ethiodide (X or XI, R = CH_3, R′ = C_2H_5), $C_{10}H_{20}INO$, melting at 320°. N-Ethylnortropine (IX, R = C_2H_5) combined with methyl iodide under similar conditions also furnished a product melting at 320°. There was no depression of the melting point of a mixture of the two products. Tropine ethobromide, $C_{10}H_{20}BrNO$, and N-ethylnortropine methobromide, prepared from the iodides using silver bromide, both melted at 316°. It was therefore apparent that tropine ethiodide and N-ethylnortropine methiodide were identical.

To determine whether this result was to be generally expected attention was then directed to the stereoisomeric pair of the appropriate next higher homolog. N-Ethylnortropine (IX, R = C_2H_5), heated with excess *n*-propyl iodide in absolute alcohol about 60°, gave N-ethylnortropine *n*-propiodide (X or XI, R = C_2H_5, R′ = *n*-C_3H_7), $C_{12}H_{24}INO$, melting at 262°. On the other hand, N-*n*-propylnortropine (IX, R = *n*-C_3H_7), combined with excess ethyl iodide under similar conditions, yielded N-*n*-propylnortropine ethiodide (XI or X, R = C_2H_5, R′ = *n*-C_3H_7), $C_{12}H_{24}INO$, melting at 270.5°. The former compound, obtained pure in 44% yield, separated from absolute alcohol as flakes; the latter, obtained pure in 52% yield, crystallized from the same solvent as fine prisms. No other identifiable products were obtained from either reaction. Neither alkiodide seeded the other from solution. X-Ray diffraction patterns reveal a difference in crystal structure between the two compounds (see Experimental section). Shaken in aqueous solution with freshly prepared silver bromide the former gave N-ethylnortropine *n*-propobromide, $C_{12}H_{24}BrNO$, melting at 221°, and the latter N-*n*-propylnortropine ethobromide, $C_{12}H_{24}BrNO$, melting at 227.5–229°. The *n*-propobromide crystallized from absolute alcohol in flakes, the ethobromide as prisms from the same solvent. There is, therefore, little doubt concerning the non-identity of the two iodides.

N-Ethylnortropine and N-*n*-propylnortropine were made by reduction of the corresponding amides of nortropine (XII) with lithium aluminum hydride and then treated with the appropriate pure alkyl halide as above described. There appears to be no ambiguity about the course of either of these two kinds of reactions. It is therefore concluded that N-ethylnortropine *n*-propiodide and N-*n*-propylnortropine ethiodide and the corresponding bromides represent pairs of stereoisomeric quaternary ammonium halides in which the nitrogen atom is *pseudoasymmetric.*



XII

The failure to isolate the expected isomer of tropine ethiodide by the means which afford N-ethyl-

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(5) Reference 4, pp. 403–413.

(6) The unseparated optically active isomers of 2,5-dimethylcyclopentane-1-carboxylic acid also exist (J. Wislicenus, *Ber.*, **34**, 2565 (1901)). The two optically active tropane N-oxides and ethiodides, theoretically predicted, are on the other hand not likely to be obtained because ring strain prevents *trans*-fusion of the pyrrolidine–piperidine rings.

nortropine n-propiodide and its stereoisomer demonstrates that the N–CH_3 group of tropine reacts with ethyl iodide in a configuration opposite to that in which the N-alkyl groups of N-ethylnortropine and N-n-propylnortropine react with n-propyl iodide and ethyl iodide, respectively. Presumably the difference in stability between tropine ethiodide and its stereoisomer is sufficiently large to determine in which of two possible configurations the N–CH_3 will react, whereas for the next pair of stereoisomeric iodides this difference is not sufficiently large and hence the configuration here determines the product. Otherwise stated, it appears that in the first pair of reactions the thermodynamically favored product is obtained in each case, whereas in the second the kinetically favored product results in each case.

These observations are in some contrast to those made by Mills, Parkin, and Ward in their investigation of the configuration of the quaternary ammonium ion. They found that 4-phenyl-1-ethylpiperidine combined with methyl iodide to give a mixture of two geometrical isomers, α- and β-4-phenyl-1-methyl-1-ethylpiperidinium iodide, and that two products appeared to be formed from the reaction of 4-phenyl-1-methylpiperidine with ethyl iodide.[7] Similar results were obtained with 4-hydroxypiperidine. Evidently the rigid and prominent position of the nitrogen atom of tropine confers to it a special selectivity in reactions with alkyl halides.

Tropine (IX, R = CH_3) combined with ethyl iodide more quickly than N-n-propylnortropine (IX, R = n-C_3H_7). Also, N-ethylnortropine (IX, R = C_2H_5) reacted with methyl iodide much more quickly than with n-propyl iodide. These relative reactivities are to be expected from the results of kinetic studies of quaternary ammonium salt formation.[8]

N-Ethylnortropine n-propiodide and silver chloride gave the corresponding propochloride melting at 219° which was more difficult to purify than the propobromide. N-n-Propylnortropine ethiodide, similarly treated, furnished a mixture from which no pure product could be isolated.

Acknowledgments.—The writer is indebted to Mr. William C. White of this Institute for the X-ray diffraction patterns and to the Analytical Services Laboratory, directed by Dr. William C. Alford, for the analytical data herein recorded. He is also indebted to Dr. Karl Pfister of Merck and Company, Inc., of Rahway, N. J., for a generous sample of tropine hydrochloride. Finally, he is obliged to Dr. Lyndon F. Small for his interest and encouragement of this investigation.

Experimental[9]

Tropine.—A mixture of atropine (U.S.P.) (15.0 g.), water (55 ml.) and potassium hydroxide (6.0 g.) was refluxed 1.25 hours. The brown solution was cooled, mixed with more potassium hydroxide (8.0 g.), and extracted with ether (6 × 150 ml.). The extracts were dried 1–2 days over KOH and the solvent removed, the last traces *in vacuo*. On cooling to 0° the residue crystallized and was freed of colored impurities by sublimation at 60° (0.1 mm.); 6.3–6.4 g. (86–87%) of white prisms, m.p. 63–65.5° (reported[10] 63–64°).

Of the many methods for obtaining tropine the majority entail some sort of hydrolysis of a tropane alkaloid. The readily available *l*-hyoscyamine or its racemate, atropine, has been hydrolyzed with fuming hydrochloric acid,[11] aqueous barium hydroxide,[12,13] alcoholic sodium hydroxide,[14] water,[15] etc. It was difficult to decide which procedure to employ as only one was found in which the yield of tropine was mentioned. In this hyoscyamine (12 g.) furnished crude tropine (3 g.) in about 50% yield.[13]

Nortropine.[16]—Tropine (8.0 g., 0.0567 mole) was dissolved in water (80 ml.) and sodium hydroxide (20 g.) was added to the stirred solution. When the alkali had dissolved, a warm solution of potassium ferricyanide (112 g., 0.341 mole) in water (200 ml.) was added (one hour) dropwise with continuous stirring to the frothy mixture. The reaction mixture was kept about 15° during the addition and then allowed to rise to room temperature. Stirring was continued about 3 hours. During the addition the mixture became quite dark but lightened to orange in time (2–12 hours). After standing 4, 5, 6 or 7 days the solution, smelling of ammonia, was decanted from precipitated salts and continuously extracted with ether (1200 ml.) 48 hours. The dried extracts were concentrated to about 100 ml. and cooled to 0°. After several hours the crude crystalline nortropine was collected. After standing 4 days the yield was 3.6 g. (50%); after 5, 3.6 g. (50%); after 6, 4.1 g. (57%); after 7, 3.4 g. (47%). The crude nortropine from all four preparations melted at 150–160° (reported[17] 159–161°, 161°) and was used directly to prepare N-acetylnortropine. **Nortropine picrate**, prepared in alcohol, crystallized as small prisms, m.p. 169–171° (reported[17a] 170–171°).

No more nortropine was recoverable from the ethereal mother liquor from the six-day preparation. It was concentrated to a brown gum (2.6 g.) which was taken up in hot water and made neutral with picric acid (4.2 g.). On cooling a crystalline precipitate, contaminated with tarry and water-soluble by-products, was obtained. These impurities were largely eliminated by recrystallization from water. Two principal fractions were obtained (1.5 g., m.p. 280–282° and 0.5 g., m.p. 167–169°) and, in addition, small amounts of two other picrates, melting at 250–252° and above 300°. These salts were not further investigated.

N-Acetylnortropine.—Nortropine (2.0 g.), m.p. 150–160°, was dissolved in water (10 ml.) and acetic anhydride (1.6 ml.) added at such a rate that the temperature did not exceed 40°. After 20 minutes 3 *N* hydrochloric acid (5.0 ml.) was added and, after 5 minutes, saturated aqueous potassium carbonate (15 ml.). The amide was extracted with ether (6 × 100 ml.) and the extracts dried over K_2CO_3. The recovered oily amide crystallized slowly. It was freed of colored impurities by sublimation *in vacuo* (1.9 g.) and recrystallized three times from acetone: small prisms, m.p. 119–120° (reported[18] 124°).

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.87; H, 8.94. Found: C, 63.59; H, 8.90.

N-Ethylnortropine.—N-Acetylnortropine (1.2 g.), m.p. 118–120°, was placed in a soxhlet apparatus and extracted into a solution of 0.094 *M* lithium aluminum hydride (160 ml.) during 3 hours. After standing 24 hours the excess reducing agent was decomposed with ethereal ethyl acetate and the cold mixture shaken with a solution of Rochelle salt (4.5 g.), water (10 ml.) and saturated aqueous potassium carbonate (10 ml.). The white aqueous phase was extracted with more ether (3 × 50 ml.) and the combined extracts dried over potassium carbonate. The recovered, nearly colorless oil did not crystallize. It was obtained

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[7] W. H. Mills, J. D. Parkin and W. J. V. Ward, *J. Chem. Soc.*, 2613 (1927).

[8] (a) E. R. Thomas, *J. Chem. Soc.*, **103**, 595 (1913); (b) R. W. D. Preston and H. O. Jones, *ibid.*, **101**, 1931 (1912).

[9] All melting points are corrected.

[10] A. Orechoff and R. Konowalowa, *Ber.*, **67**, 1153 (1934).

[11] W. Lossen, *Ann.*, **131**, 43 (1864); **138**, 231 (1866).

[12] K. Kraut, *ibid.*, **128**, 280 (1863).

[13] A. Ladenburg, *ibid.*, **206**, 274 (1881); *Ber.*, **13**, 254 (1880).

[14] W. Will and G. Bredig, *ibid.*, **21**, 2777 (1888).

[15] R. A. Lapina and N. A. Preobrazhenskii, *C. A.*, **31**, 5366 (1937).

[16] *Cf.* T. D. Perrine, *J. Org. Chem.*, **16**, 1303 (1951).

[17] (a) A. Orechoff and R. Konowalowa, *Ber.*, **68**, 814 (1935); (b) F. H. Carr and W. E. Reynolds, *J. Chem. Soc.*, **101**, 946 (1912).

[18] M. Polonovski and M. Polonovski, *Bull. soc. chim.*, [IV] **41**, 1190 (1927).

crystalline by sublimation at 75° (0.1 mm.); 0.95 g. (86%), m.p. 70–77°. The sublimed material was recrystallized from benzene–ligroin; clusters of prisms, m.p. 76–78°. Recrystallized from acetone it separated as stout prisms, m.p. 78–79.5°.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04. Found: C, 69.59; H, 11.05.

N-*n*-Propylnortropine.—Nortropine (2.0 g., 0.0157 mole) was dissolved in water (6.0 ml.) and propionic anhydride (2.2 ml.), b.p. 165–166°, was added gradually (warming). After keeping overnight, the mixture was worked up in the same manner as for N-acetylnortropine. Crude N-propionylnortropine was not obtained crystalline by sublimation.

The crude amide was dissolved in dry tetrahydrofuran (50 ml.) and the solution added dropwise during one hour to a refluxing solution of tetrahydrofuran (75 ml.) and 1.5 *M* ethereal lithium aluminum hydride (15 ml.). After refluxing two hours more the excess reducing agent was decomposed with ethereal ethyl acetate and the reaction mixture shaken with a solution of Rochelle salt (10 g.) and excess potassium carbonate in water (50 ml.). The aqueous phase was extracted with ether (3 × 50 ml.) and the combined extracts dried over potassium carbonate. The solvents were removed, the last traces *in vacuo*, and the colorless oily residue neutralized with hydrochloric acid (13.3 meq.). The solution was concentrated to dryness *in vacuo* and the recovered crude N-*n*-propylnortropine hydrochloride recrystallized (6 times) to constant melting point from absolute alcohol in which it is extremely soluble; 0.24 g. (7.4%) of feathery prisms, m.p. 198–199°.

Anal. Calcd. for $C_{10}H_{20}ClNO$: C, 58.38; H, 9.81. Found: C, 58.31; H, 9.68.

The base regenerated from the remainder of the hydrochloride was converted to the hydrobromide which had approximately the same solubility in absolute alcohol. Three recrystallizations from absolute alcohol did not raise its melting point to a constant value. The purest fraction separated from absolute alcohol–ether as small, colorless prisms, m.p. 185–189°.

Anal. Calcd. for $C_{10}H_{20}BrNO$: C, 48.04; H, 8.06. Found: C, 47.98; H, 8.00.

Regenerated again the base (1.5 g.) was combined with the stoichiometric amount of picric acid and crystallized from absolute alcohol to constant melting point; yellow prisms, m.p. 145–147°.

Anal. Calcd. for $C_{16}H_{22}N_4O_8$: C, 48.28; H, 5.58. Found: C, 48.09; H, 5.59.

Tropine Ethiodide. (a) **From Tropine.**[19]—Tropine (0.24 g.) was dissolved in 1.0 ml. of an absolute alcoholic solution containing 0.37 ml. of ethyl iodide, b.p. 70–71°, and heated an hour at 57–59°. Most of the product soon separated as white crystals. From the cold mixture 0.45 g. (90%) of tropine ethiodide, m.p. 319° (evac. tube), was obtained. It was recrystallized from methanol–acetone and from absolute alcohol; small, irregularly shaped crystals, m.p. 320° (dec., evac. tube). The melting point is sharp but varies from 318 to 324° according to the rate of heating. Similarly, a mixture of tropine (0.91 g.), ethyl iodide (1.0 ml.) and absolute alcohol (10 ml.) refluxed 4 hours, yielded 1.7 g. (90%) of tropine ethiodide, m.p. 318°.

Anal. Calcd. for $C_{10}H_{20}INO$: C, 40.31; H, 6.78; I, 42.71. Found: C, 40.47; H, 7.17; I, 43.0.

(b) **From N-Ethylnortropine.**—N-Ethylnortropine (0.22 g.), m.p. 77–79°, was dissolved in 1.0 ml. of an absolute alcoholic solution containing 0.278 ml. of methyl iodide (Mallinckrodt Analytical Reagent). After a few moments at room temperature the methiodide began to separate. After two hours it was collected and washed with absolute alcohol; 0.37 g. (88%) of irregularly shaped crystals, m.p. 318.5° (dec., evac. tube) when determined simultaneously with the preceding preparation, m.p. 319°; mixed m.p. with tropine ethiodide, 320° (evac. tube).

Tropine Ethobromide. (a) **From N-Ethylnortropine Methiodide.**—N-Ethylnortropine methiodide (0.297 g.), m.p. 318.5°, from N-ethylnortropine, dissolved in distilled water, was shaken 6 hours with freshly precipitated and carefully washed silver bromide (about 1 g.). The filtrate from the silver halides was concentrated to dryness *in vacuo* to a white, crystalline residue; 0.21 g. (84%). The ethobromide was obtained pure by one recrystallization from absolute alcohol; prisms, m.p. 316° (dec., evac. tube), shrinkage at 311°. In an open capillary the bromide begins to discolor about 250°. There is very little discoloration below 310° in an evacuated capillary.

(b) **From Tropine Ethiodide.**—Tropine ethiodide (0.325 g.) shaken with silver bromide and worked up in similar manner afforded a product which separated from absolute alcohol as prisms melting at 316.5° (dec., evac. tube) when determined simultaneously with the previous preparation.

Anal. Calcd. for $C_{10}H_{20}BrNO$: C, 48.00; H, 8.05; Br, 31.94. Found: C, 48.12; H, 8.24; Br, 31.61.

N-Ethylnortropine *n*-Propiodide.—N-Ethylnortropine (0.73 g.), m.p. 78–79.5°, was dissolved in 3.0 ml. of an absolute alcoholic solution containing 1.24 ml. of *n*-propyl iodide, b.p. 100–101°, heated 5 hours at 55–60°, and cooled to room temperature. The product which separated was pure after one recrystallization from absolute alcohol; 0.10 g. of lustrous flakes, m.p. 262°.

Anal. Calcd. for $C_{12}H_{24}INO$: C, 44.32; H, 7.44; I, 39.02. Found: C, 44.58; H, 7.27; I, 39.28.

The mother liquors were heated 16 hours at 60–65°. On cooling and purifying the crystalline precipitate as before 0.36 g. of pure *n*-propiodide was obtained. The mother liquors were mixed with *n*-propyl iodide (2.0 ml.) and heated again (4 hours at reflux temperature). During this period the mixture became yellow. Evaporated to dryness it furnished a sticky, orange residue (0.80 g.) from which 0.21 g. of pure *n*-propiodide was recovered by fractional crystallization; total yield of pure N-ethylnortropine *n*-propiodide 0.67 g. (44%). The remainder of the mixture as indicated by analysis consisted of the *n*-propiodide contaminated with colored and resinous by-products.

N-Ethylnortropine *n*-Propobromide.—N-Ethylnortropine *n*-propiodide (0.19 g.) was dissolved in a little distilled water and shaken 12 hours with approximately 1 g. of freshly precipitated and thoroughly washed silver bromide. Worked up as in the case of tropine ethobromide, the mixture afforded the *n*-propobromide; lustrous flakes, m.p. 221–221.5°, from absolute alcohol–ether.

Anal. Calcd. for $C_{12}H_{24}BrNO$: C, 51.80; H, 8.70; Br, 28.72. Found: C, 51.90; H, 8.85; Br, 28.89.

N-Ethylnortropine *n*-Propochloride.—The *n*-propiodide (0.36 g.) was dissolved in distilled water and shaken 4 hours with a fourfold excess of silver chloride. The reaction mixture was worked as for tropine ethobromide. The crude *n*-propochloride was obtained pure by repeated recrystallization from absolute alcohol–ether; colorless prisms which separated in clusters, m.p. 219°.

Anal. Calcd. for $C_{12}H_{24}ClNO$: C, 61.64; H, 10.35; Cl, 15.17. Found: C, 61.40; H, 10.53; Cl, 15.24.

N-*n*-Propylnortropine Ethiodide.—N-*n*-Propylnortropine hydrochloride (0.915 g.), m.p. 196–199°, was treated with excess, nearly saturated aqueous potassium carbonate and extracted with ether (5 × 50 ml.). The recovered base, freed of traces of solvent, was dissolved in 3.0 ml. of an absolute alcoholic solution containing 0.98 ml. of ethyl iodide, b.p. 70–71°, and heated 3 hours at 57–60°. During the heating the product partially separated; 0.56 g. of needles, m.p. 270°. A smaller second crop was obtained; 0.20 g., total yield 0.76 g. (52%). After two recrystallizations from absolute alcohol the ethiodide was pure; fine needles, m.p. 270.5°. Unlike the tropine ethiodide, the melting points of this iodide and its stereoisomer are not perceptibly affected by the rate of heating. The yellowish-white, gummy residue from the mother liquors was dried on porous porcelain and recrystallized repeatedly from absolute alcohol, but no pure substance could be recovered. Added in small amount to a warm supersaturated solution of the lower-melting *n*-propiodide, the pure ethiodide did not effect precipitation of itself; and *vice versa*.

Anal. Calcd. for $C_{12}H_{24}INO$: C, 44.32; H, 7.44; I, 39.02. Found: C, 44.19; H, 7.36; I, 39.36.

N-*n*-Propylnortropine Ethobromide.—N-*n*-Propylnortropine ethiodide (60 mg.), m.p. 270–270.5°, was dissolved in a little distilled water and shaken with approximately 1 g. of silver bromide as described above. The recovered product separated from absolute alcohol–ether as fine, white prisms, m.p. 227.5–229°, shrinkage at 223°.

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[19] K. Kraut, *Ann.*, **133**, 87 (1865).

TABLE I[a]

N-Ethylnortropine *n*-propiodide		N-*n*-Propylnortropine ethiodide	
d	*d*	*d*	*d*
7.9 (M)	3.48 (M)	7.4 (MW)	3.09 (W)
7.4 (S)	3.34 (W)	6.8 (MS)	2.96 (W)
6.8 (W)	2.96 (MW)	4.9 (S)	2.89 (W)
5.1 (MS)	2.86 (MW)	4.7 (S)	2.43 (W)
4.9 (MS)	2.82 (MW)	4.5 (MW)	2.34 (W)
4.6 (MS)	2.48 (W)	4.3 (W)	2.29 (W)
4.5 (MS)	2.29 (W)	4.1 (W)	2.18 (W)
4.4 (W)	2.15 (W)	3.89 (MW)	1.89 (W)
4.2 (W)	2.11 (W)	3.79 (MW)	1.80 (W)
4.1 (W)	2.08 (W)	3.66 (W)	1.74 (W)
3.85 (M)	1.92 (W)	3.43 (M)	1.58 (W)
3.72 (W)	1.65 (W)	3.14 (W)	
3.60 (W)	1.55 (W)		

[a] *d* represents the interplanar spacings in Ångström units. S = strong, M = medium, W = weak.

Anal. Calcd. for $C_{12}H_{24}BrNO$: C, 51.80; H, 8.70; Br, 28.72. Found: C, 51.74; H, 8.49; Br, 28.89.

N-*n*-Propylnortropine Ethiodide and Silver Chloride.—The ethiodide (0.68 g.) in aqueous solution was shaken 15 hours with a fourfold excess of freshly prepared silver chloride. The yellowish-green product recovered from the solution freed of silver salts was recrystallized repeatedly from absolute alcohol–ether but no product of constant melting point was obtained. From the behavior of the mixture during recrystallization it appeared that at least two products were present. The last four recrystallizations in the attempted purification raised the melting point as follows: 225° to 249° to 252° to 257°.

X-Ray Diffraction Patterns.—The powder-wedge technique was employed, the sample being exposed in a cylindrical camera of 7.16 cm. radius to essentially CuKα radiation obtained from a copper anode X-ray tube with a nickel foil filter. The principal lines together with an estimate of their relative intensities are given in Table I.

BETHESDA, MARYLAND

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

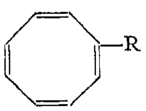
Cyclic Polyolefins. XXVI. Conversion of Cycloöctatetraenyl Phenyl Ketone to an Acyclic Tetraene*

BY ARTHUR C. COPE AND DAVID J. MARSHALL

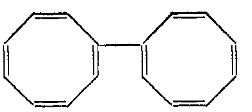
RECEIVED JANUARY 23, 1953

Cycloöctatetraenyllithium (I) has been converted to bicycloöctatetraenyl (II) by coupling in the presence of cobaltous chloride and to cycloöctatetraenyl phenyl ketone (III) by reaction with benzonitrile followed by hydrolysis of the intermediate imine. The ketone III was characterized by formation of a 1:1 complex with silver nitrate, a 2,4-dinitrophenylhydrazone, and by hydrogenation to benzylcycloöctane and to 1-cycloöctenyl phenyl ketone. Reduction of III with lithium aluminum hydride formed cycloöctatetraenylphenylcarbinol (V). On reaction with phenylmagnesium bromide, the ketone III underwent ring opening and yielded the acyclic ketone, 1,9-diphenylnona-2,4,6,8-tetraen-1-one (VI) (20%), identical with a sample prepared from 7-phenylhepta-2,4,6-trienal and acetophenone.

Further investigation of cycloöctatetraenyllithium (I), prepared by halogen–metal interchange from bromocycloöctatetraene and *n*-butyllithium,[1,2] showed the presence as a by-product in its preparation of a yellow, crystalline hydrocarbon that proved to be bicycloöctatetraenyl (II). By adding a catalytic amount of cobaltous chloride to an ether solution of I, a 24% yield of II was obtained, in a reaction analogous to the coupling of phenyllithium or *n*-butyllithium in the presence of cobaltous chloride.[3] The structure of II was established by quantitative hydrogenation to bicycloöctyl, which was identified by comparison with a sample prepared by a different method.[4]

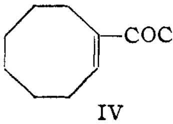


I, R = Li
III, R = COC_6H_5
V, R = $CH(OH)C_6H_5$



II

The reaction of the lithium compound I with benzonitrile at −70° formed an unstable imine that yielded cycloöctatetraenyl phenyl ketone (III) on hydrolysis (57% yield over-all from bromocycloöctatetraene). The ketone III was isolated by distillation as an orange liquid that solidified and melted at 38–39.5° after recrystallization. It formed a crystalline 1:1 complex with silver nitrate, from which the ketone could be regenerated, and a red 2,4-dinitrophenylhydrazone. Quantitative hydrogenation of the ketone III in the presence of 10% palladium on Norit resulted in absorption of six molar equivalents of hydrogen and formed benzylcycloöctane. Hydrogenation of III in the presence of 1% palladium on calcium carbonate yielded 1-cycloöctenyl phenyl ketone (IV), which was identified by comparison (through the 2,4-dinitrophenylhydrazone) with a sample prepared from 1-cyclooctenyllithium[2] and benzonitrile. Reduction of the ketone III with lithium aluminum hydride yielded cycloöctatetraenylphenylcarbinol (V) (89%), which was characterized by its infrared spectrum (bands at 2.78 and 2.93 μ) and by quantitative reduction in the presence of palladium on Norit with the absorption of five molar equivalents of hydrogen, forming benzylcycloöctane.



IV

Since III is a conjugated unsaturated ketone, it could react with a Grignard reagent either by addition to the carbonyl group to form a tertiary alcohol, or by addition to the conjugated system, form-

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* Supported in part by the Office of Naval Research under Contract N5ori-07822, Project Designation NR356-096.

[1] A. C. Cope and M. Burg, THIS JOURNAL, **74**, 168 (1952).

[2] A. C. Cope, M. Burg and S. W. Fenton, *ibid.*, **74**, 173 (1952).

[3] M. S. Kharasch, D. W. Lewis and W. B. Reynolds, *ibid.*, **65**, 498 (1943).

[4] A. C. Cope and F. A. Hochstein, *ibid.*, **72**, 2519 (1950).