Derivatives.—The trinitro and tribromo derivatives were prepared as previously described.[2]

Infrared Spectrograms.—The absorption spectra were determined and interpreted by Dr. E. E. Pickett of the spectrographic laboratory of the University of Missouri and by J. M. Shackelford, on a Beckman infrared spectrophotometer, model IR-2, cell length 0.025 mm.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF IRWIN, NEISLER & CO.]

Bisammonium Salts. Unsymmetrical Derivatives of Tropane and Related Bases[1]

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RECEIVED SEPTEMBER 16, 1955

The preparation of unsymmetric bisammonium salts derived from tropane, tropine and tropinone is described. These are moderately active hypotensive agents in which the duration of action is related to the ease with which the compounds, on the basis of their chemical properties, would appear to undergo metabolic degradation.

Previous work from these laboratories has shown that potent hypotensive activity may be exhibited by unsymmetric bis-quaternary ammonium salts in which a small cationic head is joined by an alkylene chain to a ring nitrogen of a relatively large heterocyclic base.[2,3] In these series the heterocyclic basic moieties were essentially planar, bi- and tricyclic systems. It was shown that below certain limits in size, the large cationic head provided hypotensive activity of only very short duration. Compounds in which the large cationic head was derived from isoquinoline or N-alkyl tetrahydroisoquinoline were quite active; a pyridine analog was relatively inert.[3] In the present investigation tropane and several of its derivatives were used as the large cationic heads. These provided a fused ring system with a cage-like structure.

TABLE I

UNSYMMETRIC BISQUATERNARY SALTS $RN^{\oplus}-(CH_2)_3-\underset{CH_3}{\overset{|}{N^{\oplus}}}R'_2 2Br^{\ominus}$

	RN	NR′₂	M.p., °C.[a]	Formula	Analyses, % C Calcd.	H Calcd.	Br Calcd.	C Found	H Found	Br[b] Found	Hypotensive activity, dose/% fall/durn. hr.[c]
I	Atropine	$N(CH_3)_2$	207[f]	$C_{23}H_{38}Br_2N_2O_3$	50.18	6.95	29.04	50.36	7.03	29.22	1/30/1
II	Tropine	$N(CH_3)_2$	247[f]	$C_{14}H_{30}Br_2N_2O$	41.80	7.52	39.74	42.03	7.71	39.47	2/30/1.5
III	Tropine	NC_4H_8[d]	268[g]	$C_{16}H_{32}Br_2N_2O$	44.87	7.53	37.32	44.93	7.23	36.93	0.5/25/0.2–1[h] 1/40/3.5
IV	Tropine	NC_5H_{10}[e]	>270[g]	$C_{17}H_{34}Br_2N_2O$	46.16	7.75	36.14	46.50	7.53	36.02	1/30–60/0.1–0.2
V	Tropinone	$N(CH_3)_2$	204[f]	$C_{14}H_{28}Br_2N_2O$	42.01	7.05	39.94	42.61	7.35	39.62	2/35/0.25
VI	Tropane	$N(CH_3)_2$	>270	$C_{14}H_{30}Br_2N_2$	43.53	7.83	41.38	43.38	7.95	41.02	1/40/3
VII	N-Methylpiperidine	$N(CH_3)_2$	268	$C_{12}H_{28}Br_2N_2$	40.01	7.85	44.37	40.48	7.85	44.11	1/30–50/0.1

[a] Melt with decomposition. [b] Ionic halogen determination (Volhard). [c] In anesthetized dogs; values are: dose in mg. per kg./% maximum fall in blood pressure/duration in hours before return to pre-drug level. Pharmacological properties supplied by T. B. O'Dell, *et al.* [d] Pyrrolidino group. [e] Piperidino group. [f] Gradually melts with decomposition starting at the temperature indicated. [g] With preliminary darkening. [h] This derivative in a large number of dogs showed a wide variation in the duration of response.

In Table I are summarized the properties of these compounds, in which the linking chain is trimethylene. The trimethylammonium analogs do not vary markedly with respect to the degree of blood pressure fall induced immediately after intravenous administration in dogs, but the duration of the response varies over a wide range. The prerequisite of adequate size of the "large" cationic moiety is again evident upon comparison of the short action of an N-methylpiperidine derivative VII with the much longer action of the tropane analog VI. The compact tropane cationic head, furthermore, provides less active derivatives than the somewhat larger N-methyltetrahydroisoquinoline.[3]

Of interest are the significant decreases in duration of response evident upon proceeding from the tropane VI to tropine II to tropinone V derivative. These sharp differences are in accord with the presumable rates of *in vivo* degradation of these compounds; *i.e.*, the tropane salt would, of course, be most stable, whereas the tropinone derivative should be metabolized more rapidly than the tropine analog, which could undergo oxidation to the tropinone stage in the course of being transformed into inactive products. The suggested rapid destruction of the tropinone quaternary salt at the *p*H of blood follows from the extreme lability of tropinone methiodide under alkaline conditions.[4]

(1) Presented in part before the Division of Medicinal Chemistry at the 128th National Meeting of the American Chemical Society, Minneapolis, Minn., September 11–16, 1955.

(2) A. P. Gray, E. E. Spinner, D. C. Schlieper and C. J. Cavallito, THIS JOURNAL, **77**, 3533 (1955).

(3) A. P. Gray, W. L. Archer, D. C. Schlieper, E. E. Spinner and C. J. Cavallito, *ibid.*, **77**, 3536 (1955).

(4) *Cf.* R. Willstätter, *Ber.*, **29**, 393 (1896); G. Ciamician and P. Silber, *ibid.*, **29**, 490 (1896). Even when heated in aqueous sodium bicarbonate, the methiodide is rapidly degraded, the ultimate products being dimethylamine and neutral material recently shown to be a mixture of cycloheptadienones (*cf.* J. Meinwald, S. L. Emerman, N. C. Yang and G. Büchi, THIS JOURNAL, **77**, 4401 (1955)).

This instability is obviously to be expected of a β-quaternary ammonium substituted ketone. Thus, the initial step in the base-catalyzed decomposition of the tropinone derivative should lead to an α,β-unsaturated ketone intermediate.

Serving to underline the pronounced lability of the tropinone quaternary system in the presence of alkali is ultraviolet spectral evidence, which, incidentally, provides support for the formation of such an intermediate in the process of degradation. V is apparently stable in 95% ethanol solution; such solutions showed no change in absorption spectrum over a period of 48 hours. However, when the ultraviolet absorption was measured immediately after dissolving V at room temperature in 0.01 N (or even 0.001 N) sodium hydroxide in 95% ethanol, a new absorption maximum (228 mμ, log ϵ 4.00) had developed. This peak is in good agreement with that which would be expected for an α,β-unsaturated ketone with a single substituent in the β (or α) position.[5]

Tropane and tropine were prepared by known methods from tropinone. The bases were quaternized in a manner similar to that previously described[2,3] by refluxing in acetonitrile solution with a slight excess of the appropriate 3-bromopropyl quaternary ammonium bromide.[6] Fair yields (50–60%) of the unsymmetric bis-salts were obtained.

(5) R. B. Woodward, THIS JOURNAL, **63**, 1123 (1941).

(6) A. P. Gray, D. C. Schlieper, E. E. Spinner and C. J. Cavallito, *ibid.*, **77**, 3648 (1955).

Experimental[7]

Preparation of Intermediates.—Tropine was prepared by catalytic hydrogenation[8] of tropinone[9] or by the hydrolysis of atropine.[10] Dehydration of tropine in a sulfuric acid–acetic acid mixture, essentially as described by Ladenburg,[11] afforded a 70% yield of tropidine, b.p. 158–161°, n^{25}D 1.4860, picrate m.p. 289–290° dec. Tropane, b.p. 166–169°, n^{25}D 1.4732, picrate m.p. 284–285°, was prepared by hydrogenation of tropidine in methanol solution with Adams platinum oxide, in a similar manner to that described by Willstätter.[12]

The methods of preparation of the 3-bromopropyl quaternary ammonium bromides have been described earlier.[6]

Reaction of Tropine with 3-Bromopropyltrimethylammonium Bromide. Compound II.—A representative example will illustrate the procedures used for obtaining the salts listed in Table I. A solution of 33.6 g. (0.25 mole) of tropine and 68.0 g. (0.26 mole) of 3-bromopropyltrimethylammonium bromide in 300 ml. of acetonitrile was refluxed for 24 hours. The precipitate was recrystallized from ethanol–ethyl acetate to yield 63.0 g. (63%) of colorless crystals, melting at 247° and above with evolution of gas.

Ultraviolet absorption spectra were determined with a Beckman DU quartz spectrophotometer.

Acknowledgment.—The authors are indebted to the Messrs. Donald L. Miller and Dean F. Cortright of these laboratories for the ionic halogen determinations and for the measurements of ultraviolet spectra.

(7) Microanalyses were performed by the Clark Microanalytical Laboratories, Urbana, Illinois. Melting points were corrected for stem exposure.

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

(9) Winthrop–Stearns, Special Chemicals Division.

(10) S. P. Findlay, THIS JOURNAL, **75**, 3204 (1953).

(11) A. Ladenburg, *Ann.*, **217**, 118 (1883).

(12) R. Willstätter and E. Waser, *Ber.*, **43**, 1182 (1910).

DECATUR, ILLINOIS

[CONTRIBUTION FROM THE MALLINCKRODT CHEMICAL LABORATORIES, HARVARD UNIVERSITY]

The Kinetics of the Meerwein Reaction

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RECEIVED JULY 1, 1955

The Meerwein reaction has been studied kinetically. The similarity between this reaction and the Sandmeyer reaction is postulated to lie in the nature of the catalytic cuprous complex. The yields of the Meerwein reaction are found to be a critical function of the relative cupric, chloride and olefin concentrations.

It has been shown earlier[1] that the Meerwein and Sandmeyer reactions are related, in that both reactions are catalyzed by cuprous chloride. We have undertaken a kinetic study of the Meerwein reaction in order to attempt to elucidate the mechanism of this reaction and to compare it to the Sandmeyer reaction which already has been extensively studied.[2]

We examined the reaction of *p*-chlorobenzenediazonium chloride with acrylonitrile and with styrene in 65 volume per cent. acetone–water solutions at 24.8°. Cupric nitrate and lithium chloride and chloroacetate buffer were used in most runs. These systems were selected because of the high yields obtainable,[3] the ease of isolation and analysis of the products and the solubility of reactants and products at fairly high olefin and salt concentrations.

(1) J. Kochi, THIS JOURNAL, **77**, 5090 (1955).

(2) (a) W. Cowdrey and D. Davies, *J. Chem. Soc.*, **5**, S49 (1949); (b) E. Pfeil, *Angew. Chem.*, **65**, 155 (1953); *Ann.*, **562**, 163 (1949); **565**, 183 (1949).

(3) W. Brunner and H. Perger, *Monatsh.*, **79**, 187 (1948).

Although acetone is not required[4] when the reactions are catalyzed by cuprous chloride, we have found it convenient to investigate the reaction in aqueous acetone solutions because of the high catalytic effect of cuprous chloride in this medium. Moreover, side reactions involving azo compound formation and concomitant consumption of cuprous catalyst are either minimized or completely eliminated under these conditions.

Experimental

Materials. Acetone and crystalline ***p*-chlorobenzenediazonium chloride** were prepared pure in a manner described previously.[1] Standard aqueous solutions of the diazonium salt (1.42 M) were prepared using deionized water. Aliquots

(4) The "cupric chloride" reactions have been reported[5] to go in the absence of acetone. In the majority of these cases, however, we have found[6] that cuprous chloride is formed by the reduction of cupric chloride by the organic solvent used.

(5) (a) J. Rai and K. Mathur, *J. Indian Chem. Soc.*, **24**, 413 (1947); (b) O. Vogl and C. Rondestvedt, THIS JOURNAL, **77**, 3401 (1955); see also ref. 3.

(6) J. Kochi, THIS JOURNAL, **77**, 5274 (1955).