absolute alcohol) and 2 g. of desyl chloride[8] were heated on a water-bath for about five minutes. After cooling 20 ml. of water was added and the mixture cooled in an ice-bath. The crystals which formed (2 g.) were recrystallized first from alcohol and then from petroleum ether (b.p. 50–60°), giving colorless needles m.p. 79°.

Anal. Calcd. for $C_{21}H_{18}OS$: C, 79.3; H, 5.6; S, 10.1. Found: C, 79.0; H, 5.7; S, 10.0.

o-Cresyl Desyl Sulfide (IIb).—This was prepared as in the case of IId; colorless crystals, m.p. 115°, were obtained from petroleum ether (b.p. 50–60°).

Anal. Calcd. for $C_{21}H_{18}OS$: C, 79.3; H, 5.6; S, 10.1. Found: C, 78.7; H, 5.7; S, 10.2.

Phenyl Desyl Sulfide[9] (IIa).—This was prepared like IId, m.p. 83–84°.

(8) A. M. Ward, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 159.

(9) W. A. Mitchel and S. Smiles, *J. Chem. Soc.*, 1529 (1933).

m-Cresyl Desyl Sulfide (IIc).—A solution of 1.9 g. of *m*-thiocresol in alcoholic sodium ethoxide (0.3 g. of sodium in 15 ml. of absolute alcohol) was treated with 3.5 g. of desyl chloride and heated on a water-bath for 10 minutes. Water (20 ml.) was added, the solution extracted with ether, the extract dried over anhydrous sodium sulfate and the ether removed. The oil obtained was washed several times with petroleum ether (b.p. 50–60°) and cooled. The colorless solid which separated was crystallized from alcohol (1.99 g., m.p. 63°).

Anal. Calcd. for $C_{21}H_{18}OS$: C, 79.3; H, 5.6; S, 10.1. Found: C, 79.6; H, 5.9; S, 10.0.

m-Cresyl desyl sulfide is insoluble in 5% aqueous sodium hydroxide solution and gives no color reaction in acetic acid with sodium nitrite.[6] When treated with concentrated sulfuric acid, a yellow-brown coloration was obtained, which turned violet in a few minutes.

CAIRO, EGYPT

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MISSOURI]

The Action of Aluminum Chloride on Alkylbenzenes. V

BY DOROTHY V. NIGHTINGALE AND JAMES M. SHACKELFORD[1]

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When 1,3-dimethyl-4-*n*-propylbenzene is warmed with aluminum chloride, the propyl group migrates to the 5-position without extensive isomerization. Under the same conditions, 1,3-dimethyl-4-isopropylbenzene yields 1,3-dimethyl-5-isopropylbenzene. The alkylation of *m*-xylene with *n*-propyl chloride yields 1,3-dimethyl-5-*n*-propylbenzene, 1,3-dimethyl-5-isopropylbenzene and a small amount of 1,3,4-trialkylbenzene.

Recent work from this Laboratory[2] has shown that when 1,3-dimethyl-4-*n*-butylbenzene was warmed with aluminum chloride, the *n*-butyl group migrated to the 5-position without extensive isomerization. This fact led us to repeat our earlier experiments with 1,3-dimethyl-4-*n*-propylbenzene.[3]

It has now been established by both chemical and spectroscopic evidence that the principal changes which take place when these trialkylbenzenes are warmed on a steam-bath with aluminum chloride are

1,3-dimethyl-4-*n*-propylbenzene (I) ⟶ 1,3-dimethyl-5-*n*-propylbenzene (II)

1,3-dimethyl-4-isopropylbenzene (III) ⟶ 1,3-dimethyl-5-isopropylbenzene (IV)

1,2,4-tri-*n*-propylbenzene (V) ⟶ 1,3,5-tri-*n*-propylbenzene (VI)

The migrating *n*-propyl group was not extensively isomerized as previously reported.

The identity of the rearrangement products II and IV was established by comparison of their infrared spectra with the spectra of authentic II[4] and with IV prepared by the alkylation of *m*-xylene with isopropyl chloride. Mixture melting points of the trinitro derivatives furnished the chemical evidence for the identity of the hydrocarbons. The spectrum of IV was nearly identical with that of IV from *m*-xylene and isopropyl chloride. Products II and IV contained 28 and 13%, respectively, of 1,3,4-trialkylbenzene.

Neither the spectrum of II nor the melting point data from the trinitro derivatives exclude the possible presence of some IV in the rearrangement product from I. The resolving power of our infrared spectrophotometer is not now sufficiently good to detect and determine IV in this product. Roberts and Brandenberger[5] have used isotopic tracer methods to demonstrate that the aluminum chloride catalyzed disproportionation of *n*-(β^{14}-C)-propylbenzene results in a partial isomerization of the *n*-propyl group. A known mixture which we prepared containing 15% of IV and 85% of II yielded the trinitro derivative of II which melted at 98.5–99.5° after two recrystallizations and was constant at 99.5–100° after the third recrystallization. Similar results were obtained from the nitration of a mixture containing 10% of 1,3-dimethyl-5-*sec*-butylbenzene and 90% of 1,3-dimethyl-5-*n*-butylbenzene. It is entirely possible that our product from the action of aluminum chloride on 1,3-dimethyl-4-*n*-butylbenzene[2] contained some 1,3-dimethyl-5-*sec*-butylbenzene.

The alkylation of *m*-xylene with *n*-propyl chloride yielded a mixture of II and IV in a ratio of about 1.8:1 based on the weights of the 1,3,5-trialkylbenzene fractions. They were identified by means of their trinitro derivatives.

The alkylation of *m*-xylene with isopropyl alcohol

(1) Abstracted from the dissertation submitted by J. M. Shackelford for the degree of Doctor of Philosophy, August, 1955.

(2) D. V. Nightingale and J. M. Shackelford, THIS JOURNAL, **76**, 5767 (1954).

(3) D. V. Nightingale and B. Carton, *ibid.*, **62**, 280 (1940).

(4) The authentic 1,3-dimethyl-5-*n*-propylbenzene, 99.3% pure, was kindly furnished to us by Dr. K. W. Greenlee of the American Petroleum Institute Research Project 45 (APIRP45), C. E. Boord, Director, a project of the Ohio State University Research Foundation; *J. Org. Chem.*, **19**, 923 (1945).

(5) R. M. Roberts and S. G. Brandenberger, *Chemistry and Industry*, 227 (1955).

and 85% sulfuric acid was repeated to compare the infrared spectrum of the product with that of III synthesized by the Grignard reaction and also with the spectrum of the trialkylbenzene obtained from *sec*-butyl alcohol and *m*-xylene under the same experimental conditions.[2] It contained 74% of 1,3,4-trialkylbenzene, 11% of 1,3,5-trialkylbenzene and perhaps 5% of *m*-xylene or 1,2,3-trialkylbenzene. In the spectrum of this isopropyl-*m*-xylene as well as in that of the *sec*-butyl-*m*-xylene obtained in the same way there is an absorption peak at 13.0 μ which is not present in the spectrograms of any of the other trialkylbenzenes prepared in these two investigations. Absorption in the 13.0 region is characteristic of *m*-xylene and also of 1,2,3-trialkylbenzenes, but the *m*-xylene should have been removed during fractionation.

The infrared spectrum of the trialkylbenzene prepared by Carton[3] from cyclopropene and *m*-xylene also has a peak at 13.0 μ. This product contains 81% of 1,3,4-trialkylbenzene and 11% of 1,2,3-trialkylbenzene or *m*-xylene with little or no 1,3,5-trialkylbenzene. Nitration of this mixture yielded nearly equal amounts of trinitro-*m*-xylene and a trinitro derivative, m.p. 104–106° after three recrystallizations. A mixture of this derivative and the trinitro derivative (m.p. 108.5–109°) of I melted at 105–106°. The formation of so much trinitro-*m*-xylene may be interpreted as an indication of the presence of some III in the mixture. Only trinitro-*m*-xylene was isolated from the nitration of authentic III and the isopropyl-*m*-xylene from *m*-xylene and isopropyl alcohol.

As a matter of interest, the rearrangement of 1,2,4-tri-*n*-propylbenzene (V) was carried out as described by Baddeley and Kenner.[6] The trialkylbenzene fraction so obtained formed a solid tribromotripropylbenzene, which indicated that this fraction contained mainly 1,3,5-tri-*n*-propylbenzene as stated by the authors. Bromination of V yielded an oil.

Acknowledgment.—The authors wish to thank the Oronite Chemical Co. for the *m*-xylene used in this and the preceding investigation.

Experimental[7]

Unless otherwise specified, the hydrocarbons were distilled on a medium bore Todd column at a reflux ratio of 8:1. A center cut of the main product was used for refractive index and the infrared spectrogram. The percentages of the trialkylbenzenes were determined from these spectrograms. The center cut was redistilled for an analytical sample.

1,3-Dimethyl-4-*n*-propylbenzene (I).—This was synthesized by the Wolff–Kishner reduction of 2,4-dimethylpropiophenone. The yield was 68%, b.p. 90–91° (16 mm.), $n^{25}D$ 1.4980. The hydrocarbon formed a trinitro derivative, m.p. 108.5–109°.

Anal. Calcd. for $C_{11}H_{13}N_3O_6$: C, 46.64; H, 4.64. Found: C, 46.35; H, 4.59.

The tribromo derivative was an oil.

1,3-Dimethyl-4-isopropylbenzene (III).—This was prepared by the reduction of dimethyl-(2,4-dimethylphenyl)-carbinol with hydrogen and copper–chromium oxide catalyst, b.p. 87–88° (17 mm.), $n^{20}D$ 1.4998.

Authentic 1,3-dimethyl-5-*n*-propylbenzene (II)[4] formed a trinitro derivative, m.p. 99–99.5°.

Anal. Calcd. for $C_{11}H_{13}N_3O_6$: C, 46.64; H, 4.64. Found: C, 46.84; H, 4.61.

The tribromo derivative of authentic II melted at 63–64°.

Anal. Calcd. for $C_{11}H_{13}Br_3$: C, 34.32; H, 3.43. Found: C, 33.99; H, 3.76.

1,3-Dimethyl-5-isopropylbenzene (IV).—This was synthesized from *m*-xylene and isopropyl chloride, b.p. 86–87° (18 mm.), $n^{25}D$ 1.4955. It contained 13% of 1,3,4-trialkylbenzene. The trinitro derivative melted at 115.5–116°.

Anal. Calcd. for $C_{11}H_{13}N_3O_6$: C, 46.64; H, 4.64. Found: C, 46.75; H, 4.79.

Alkylation of *m*-Xylene with *n*-Propyl Chloride.—In the usual equipment was placed 65 g. of *m*-xylene and 31 g. of aluminum chloride. To this mixture was added slowly with stirring 39 g. of *n*-propyl chloride at a temperature not exceeding 20°. After the addition was complete, the mixture stood overnight at room temperature and then the complex was decomposed with iced hydrochloric acid. The reaction product was isolated in the usual manner and fractionated at 16 mm.: (a) 11 g., 80–86°; (b) 4 g., 86–88°; (c) 18 g., 88–91°. Fraction a was identified by its trinitro derivative, m.p. 115–116°, as mainly 1,3-dimethyl-5-isopropylbenzene (IV). Fraction c was similarly identified as 1,3-dimethyl-5-*n*-propylbenzene (II). Its trinitro derivative melted at 98.5–99° and did not depress the melting point of the same derivative of authentic II.

Alkylation of *m*-Xylene with Isopropyl Alcohol.—The procedure of Kirrmann and Graves[8] was used. *m*-Xylene (200 ml.), 48 g. of isopropyl alcohol and 400 ml. of 85% sulfuric acid yielded 37 g. (27%) of hydrocarbon, b.p. 85–86° (15 mm.), $n^{24}D$ 1.5004. The trinitro derivative of this product melted at 177–178° and did not depress the melting point of trinitro-*m*-xylene (m.p. 177–178°).

Rearrangements with Aluminum Chloride.—The aluminum chloride was added to the hydrocarbon and the mixture was warmed with stirring on a steam-bath. After heating for four hours, the complex was decomposed with iced hydrochloric acid and the hydrocarbon was isolated in the usual manner.

1,3-Dimethyl-4-*n*-propylbenzene (I).—The product from 135 g. of hydrocarbon and 29 g. of aluminum chloride was fractionated at 16 mm.: (a) 22 g. up to 75°; (b) 5 g., 85–89°; (c) 10 g., 89–89.5°, $n^{22}D$ 1.4965; (d) 25 g., 89.5–90°, $n^{22}D$ 1.4965; (e) 12 g., 90–91°; (f) 12 g., 91–110°; (g) 20 g., 110–120°. Fraction a was identified by its trinitro derivative as mainly *m*-xylene. Fraction b was a mixture. The trinitro derivative of c and d melted at 99–99.5° and did not depress the melting point of the trinitro derivative (m.p. 99–99.5°) of authentic II. The trinitro derivative of e melted at 97–98° and a mixture with the same derivative of II melted at 97–98°.

1,3-Dimethyl-4-isopropylbenzene (III).—The product from 55 g. of hydrocarbon and 12 g. of aluminum chloride was similarly identified as IV, containing 13% of III. The trinitro derivative of the main fraction (19 g.) melted at 115–116° and did not depress the melting point of the derivative of IV obtained from the alkylation of *m*-xylene with isopropyl chloride.

1,2,4-Tri-*n*-propylbenzene (V).—The hydrocarbon was prepared as described by Baddeley and Kenner,[6] except that 4-*n*-propylpropiophenone and 2,5-di-*n*-propylpropiophenone was reduced with hydrogen and copper–chromium oxide catalyst. Bromination of V yielded an oil which was not analyzed. *p*-Di-*n*-propylbenzene formed tetrabromo-1,4-di-*n*-propylbenzene, m.p. 107–108°.

Anal. Calcd. for $C_{12}H_{14}Br_4$: C, 30.12; H, 2.95. Found: C, 29.29; H, 3.11.

The product from 29 g. of V and 10 g. of aluminum chloride was fractionated through a helix-packed column at 16 mm. and collected in five 10-ml. fractions as described by Baddeley and Kenner. The fraction distilling at 130–140° yielded a tribromo derivative, m.p. 112–113°, literature value[9] 111°. The percentages of carbon and hydrogen corresponded to those of tribromotripropylbenzene.

This fraction formed a trinitro derivative, m.p. 123–124°.

Anal. Calcd. for $C_{15}H_{21}N_3O_6$: C, 53.09; H, 6.24. Found: C, 53.01; H, 6.72.

(6) G. Baddeley and J. Kenner, *J. Chem. Soc.*, 303 (1935).

(7) The carbon and hydrogen analyses were by R. E. Bolin and R. L. Elliott.

(8) A. M. Kirrmann and M. Graves, *Bull. soc. chim.*, [5] **1**, 1494 (1934).

(9) G. Baddeley, G. Holt and W. Pickles, *J. Chem. Soc.*, 4162 (1952).

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.

COLUMBIA, MISSOURI

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

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

BY WESLEY L. ARCHER, CHESTER J. CAVALLITO AND ALLAN P. GRAY

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

	RN	NR'$_2$	M.p., °C.[a]	Formula	Analyses, % C (Calcd.)	H (Calcd.)	Br	C (Found)	H (Found)	Br[b]	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)).