



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.<sup>2</sup> 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  $\mu$  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<sup>8</sup> from cyclopropene and *m*-xylene also has a peak at 13.0  $\mu$ . 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.<sup>6</sup> 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.

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### Experimental<sup>7</sup>

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-dimethylpropio-phenone. The yield was 68%, b.p. 90–91° (16 mm.),  $n_D^{25}$  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.),  $n_D^{20}$  1.4998.

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

(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.

*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.),  $n_D^{25}$  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<sup>8</sup> 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.),  $n_D^{25}$  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°,  $n_D^{25}$  1.4965; (d) 25 g., 89.5–90°,  $n_D^{25}$  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,<sup>6</sup> 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<sup>9</sup> 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  $C_{12}H_{14}N_3O_6$ : C, 53.09; H, 6.24. Found: C, 53.01; H, 6.72.

(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.<sup>2</sup>

**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<sup>1</sup>

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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.<sup>2,3</sup> 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.<sup>3</sup> 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.

travenous 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.<sup>3</sup>

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 tro-

TABLE I

		UNSYMMETRIC BISQUATERNARY SALTS $\text{RN}^{\oplus}-(\text{CH}_2)_3-\text{NR}'_2\text{Br}^{\ominus}$				Analyses, %				Hypotensive activity, dose/% fall/durn. hr. <sup>c</sup>	
RN	NR' <sub>2</sub>	M.p., °C. <sup>a</sup>	Formula	C	Calcd. H	Br	C	Found H	Br <sup>b</sup>		
I Atropine	N(CH <sub>3</sub> ) <sub>2</sub>	207 <sup>f</sup>	C <sub>23</sub> H <sub>38</sub> Br <sub>2</sub> N <sub>3</sub> O <sub>3</sub>	50.18	6.95	29.04	50.36	7.03	29.22		1/30/1
II Tropine	N(CH <sub>3</sub> ) <sub>2</sub>	247 <sup>f</sup>	C <sub>14</sub> H <sub>20</sub> Br <sub>2</sub> N <sub>2</sub> O	41.80	7.52	39.74	42.03	7.71	39.47		2/30/1.5
III Tropine	NC <sub>4</sub> H <sub>8</sub> <sup>d</sup>	268 <sup>g</sup>	C <sub>18</sub> H <sub>22</sub> Br <sub>2</sub> N <sub>2</sub> O	44.87	7.53	37.32	44.93	7.23	36.93		0.5/25/0.2-1 <sup>h</sup> 1/40/3.5
IV Tropine	NC <sub>6</sub> H <sub>10</sub> <sup>e</sup>	>270 <sup>g</sup>	C <sub>17</sub> H <sub>24</sub> Br <sub>2</sub> N <sub>2</sub> O	46.16	7.75	36.14	46.50	7.53	36.02		1/30-60/0.1-0.2
V Tropinone	N(CH <sub>3</sub> ) <sub>2</sub>	204 <sup>f</sup>	C <sub>14</sub> H <sub>20</sub> Br <sub>2</sub> N <sub>2</sub> O	42.01	7.05	39.94	42.61	7.35	39.62		2/35/0.25
VI Tropane	N(CH <sub>3</sub> ) <sub>2</sub>	>270	C <sub>14</sub> H <sub>20</sub> Br <sub>2</sub> N <sub>2</sub>	43.53	7.83	41.38	43.38	7.95	41.02		1/40/3
VII N-Methylpiperidine	N(CH <sub>3</sub> ) <sub>2</sub>	268	C <sub>12</sub> H <sub>20</sub> Br <sub>2</sub> N <sub>2</sub>	40.01	7.85	44.37	40.48	7.85	44.11		1/30-50/0.1

<sup>a</sup> Melt with decomposition. <sup>b</sup> Ionic halogen determination (Volhard). <sup>c</sup> 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.* <sup>d</sup> Pyrrolidino group. <sup>e</sup> Piperidino group. <sup>f</sup> Gradually melts with decomposition starting at the temperature indicated. <sup>g</sup> With preliminary darkening. <sup>h</sup> 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 in-

pine 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 pH of blood follows from the extreme lability of tropinone methiodide under alkaline conditions.<sup>4</sup>

(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 cycloheptadionones (*cf.* J. Meinwald, S. L. Emerman, N. C. Yang and G. Büchi, *THIS JOURNAL*, **77**, 4401 (1955)).