Summary

1. The botanical origin of the active alkaloid of tube curare, *d*-tubocurarine chloride, has been established as *Chondodendron tomentosum* Ruiz and Pavon, N. O. Menispermaceae.

2. Procedures are described for the isolation of crystalline *d*-tubocurarine chloride from the desiccated extracts of freshly gathered plant material.

3. In addition to the physiologically active quaternary base there were isolated from this curare four tertiary bases: *d*-isochondodendrine and *d*-isochondodendrine dimethyl ether, neither heretofore reported as constituents of tube curare, a third alkaloid provisionally identified as *l*-curine and a new base for which the name *d*-chondocurine is proposed. The latter was shown to be of the "bebeerine" type of bisbenzylisoquinoline alkaloid and to yield a quaternary salt of high physiological potency.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

The Polybromination of Alkylbenzenes[1]

BY G. F. HENNION AND JAMES G. ANDERSON

Introduction

No generally satisfactory method exists for the preparation of solid derivatives of the alkyl- and polyalkylbenzenes, useful both for identifying and locating the positions of alkyl substituents.[2] Nitration, sulfonation, mercuration and acetamino or benzamino substitution, valuable when applied to simple alkylbenzenes, frequently give trouble when used with the higher or polysubstituted homologs. The difficulties may be ascribed to side reactions such as oxidation, rearrangement, partial or complete alkyl group replacement, and to formation of isomers. Since the benzene nucleus is amenable to complete bromination in good yield and under mild conditions, a study has been made of polybromination as a possible means of derivatizing alkylbenzenes. This method has been used previously to derivatize various polymethylbenzenes, though open to criticism because mixtures of isomers frequently show no significant depressions in melting point.[3,4] The literature of nuclear polybromination, especially of higher alkylbenzenes, is confusing. Bodroux[5] early stated that 2-ethyl-*p*-xylene and 5-*t*-butyl-*m*-xylene gave the corresponding tetrabromoxylenes and concluded that bromination at zero degrees in the presence of aluminum powder causes the loss of all alkyl groups larger than methyl. This was indicated also by the work of Auwers,[6] who reported that *p*-cymene gave pentabromotoluene, and of Klages[7] who obtained tetrabromo-*o*-xylene from 4-isopropyl-*o*-xylene. On the other hand, Klages and Keil[8] brominated a variety of polyethyl- and ethylmethylbenzenes without loss of ethyl groups, and Chichibabin[9] cited the preparation of pentabromo-*n*-propylbenzene from the hydrocarbon by the same method.

For this study the procedure of Auwers,[6] namely, use of liquid bromine with a small amount of aluminum powder at zero degrees, was first applied to a wide variety of alkylbenzenes. It was found that secondary and tertiary alkyl groups are replaced in the reaction whereas methyl and ethyl groups are retained. Thus *p*-cymene, *p*-*s*-butyltoluene and *p*-*t*-butyltoluene gave pentabromotoluene; *s*-amyl-benzene, *t*-amylbenzene, *p*-diisopropylbenzene, *p*-di-*s*-amylbenzene, etc., gave hexabromobenzene. With compounds containing primary alkyl groups longer than ethyl, tarry products were formed, indicating partial attack of the primary chains.

The use of iron as a catalyst, previously used for polybromination in only a few cases,[10] was then explored. The iron catalyzed reactions were somewhat less vigorous; secondary and tertiary alkyl groups again brominolyzed off the benzene ring while primary groups seemingly were unaffected. Even when the two types of groups were contained on the same ring, the primary ones were retained and the others displaced. The procedure was applied to forty-five alkylated benzenes, eight alkylhalobenzenes, and two haloalkylbenzenes without encountering exception to this rule. The results are listed in Table I. The study was then extended to synthetic mixtures of certain isomeric alkylbenzenes. When the isomers contain a primary alkyl group and a secondary (or tertiary) one, respectively, the two characteristic polybromo derivatives may be recovered. For example, it is possible to detect 10% or less of *n*-propylbenzene in isopropylbenzene in this way. Many other mixtures of known isomers were analyzed equally well.

Study of the Fisher–Hirschfelder scale models of polybromoalkylbenzenes indicated that the selective replacement of secondary and tertiary

(1) Preliminary report, THIS JOURNAL, **66**, 1801 (1944).
(2) Nightingale, *Chem. Rev.*, **25**, 344 (1939).
(3) Meyer and Meyer, *Ber.*, **52**, 1250 (1919).
(4) Smith and Moyle, THIS JOURNAL, **55**, 1680 (1933).
(5) Bodroux, *Bull. soc. chim.*, [3] **19**, 888 (1898).
(6) Auwers, *Ber.*, **38**, 1707 (1905).
(7) Klages, *ibid.*, **39**, 2312 (1906).
(8) Klages and Keil, *ibid.*, **36**, 1632 (1903).
(9) Chichibabin, *J. Russ. Phys.-Chem. Soc.*, **26**, 43 (1894); *Bull. soc. chim.*, [3] **12**, 1220 (1894).
(10) Qvist, *et al.*, *Acad. Aboensis Math. Phys.*, **14**, no. 1, 3 (1942); *C. A.*, **38**, 5205 (1944).

TABLE I

PRODUCTS OF THE IRON-CATALYZED POLYBROMINATION OF ALKYLBENZENES

Reagent		
Formula	Compound	Product
C_8H_{10}	Ethylbenzene	Pentabromoethylbenzene
C_8H_{10}	*o*-Xylene	Tetrabromo-*o*-xylene
C_8H_{10}	*m*-Xylene	Tetrabromo-*m*-xylene
C_8H_{10}	*p*-Xylene	Tetrabromo-*p*-xylene
C_9H_{12}	*n*-Propylbenzene	Pentabromo-*n*-Pr-benzene
C_9H_{12}	Isopropylbenzene	Hexabromobenzene
C_9H_{12}	Mesitylene	Tribromomesitylene
$C_{10}H_{14}$	*n*-Butylbenzene	Pentabromo-*n*-Bu-benzene
$C_{10}H_{14}$	*s*-Butylbenzene	Hexabromobenzene
$C_{10}H_{14}$	*t*-Butylbenzene	Hexabromobenzene
$C_{10}H_{14}$	*p*-Cymene	Pentabromotoluene
$C_{11}H_{16}$	*n*-Amylbenzene	Pentabromo-*n*-amylbenzene
$C_{11}H_{16}$	2-*s*-Amylbenzene	Hexabromobenzene
$C_{11}H_{16}$	3-*s*-Amylbenzene	Hexabromobenzene
$C_{11}H_{16}$	*t*-Amylbenzene	Hexabromobenzene
$C_{11}H_{16}$	*p*-*s*-Butyltoluene	Pentabromotoluene
$C_{11}H_{16}$	*p*-*t*-Butyltoluene	Pentabromotoluene
$C_{11}H_{16}$	*p*-Ethyl-*i*-Pr-benzene	Pentabromoethylbenzene
$C_{12}H_{18}$	*p*-*s*-Amyltoluene	Pentabromotoluene
$C_{12}H_{18}$	*p*-*t*-Amyltoluene	Pentabromotoluene
$C_{12}H_{18}$	*p*-Diisopropylbenzene	Hexabromobenzene
$C_{12}H_{18}$	*sym*-Triethylbenzene	*sym*-Tribromo-tri-Et-benzene
$C_{12}H_{18}$	4-*s*-Butyl-*m*-xylene	Tetrabromo-*m*-xylene
$C_{12}H_{18}$	5-*s*-Butyl-*m*-xylene	Tetrabromo-*m*-xylene
$C_{12}H_{18}$	5-*t*-Butyl-*m*-xylene	Tetrabromo-*m*-xylene
$C_{13}H_{18}$	*p*-Cyclohexyltoluene	Pentabromotoluene
$C_{13}H_{20}$	*p*-Ethyl-*s*-amylbenzene	Pentabromoethylbenzene
$C_{14}H_{22}$	*s*-Octylbenzene	Hexabromobenzene
$C_{14}H_{22}$	*p*-Di-*n*-butylbenzene	Tetra-Br-*p*-di-*n*-Bu-benzene
$C_{14}H_{22}$	*p*-Diisobutylbenzene	Tetra-Br-*p*-di-*i*-Bu-benzene
$C_{14}H_{22}$	*p*-Di-*s*-butylbenzene	Hexabromobenzene
$C_{14}H_{22}$	*p*-Di-*t*-butylbenzene	Hexabromobenzene
$C_{14}H_{22}$	*p*-*n*-Butyl-*i*-Bu-benzene	Tetra-Br-*n*-Bu-*i*-Bu-benzene
$C_{14}H_{22}$	*p*-*n*-Butyl-*s*-Bu-benzene	Pentabromo-*n*-butylbenzene
$C_{14}H_{22}$	*p*-*n*-Butyl-*t*-Bu-benzene	Pentabromo-*n*-butylbenzene
$C_{14}H_{22}$	*p*-Isobutyl-*s*-Bu-benzene	Pentabromoisobutylbenzene
$C_{14}H_{22}$	*p*-Isobutyl-*t*-Bu-benzene	Pentabromoisobutylbenzene
$C_{14}H_{22}$	*p*-*s*-Butyl-*t*-Bu-benzene	Hexabromobenzene
$C_{15}H_{24}$	*p*-*s*-Octyltoluene	Pentabromotoluene
$C_{16}H_{26}$	*p*-*s*-Octylethylbenzene	Pentabromoethylbenzene
$C_{16}H_{26}$	*p*-Di-*s*-amylbenzene	Hexabromobenzene
$C_{19}H_{32}$	*p*-*s*-Dodecyltoluene	Pentabromotoluene
$C_{20}H_{34}$	*p*-Ethyl-*s*-dodecylbenzene	Pentabromoethylbenzene
$C_{22}H_{38}$	*p*-Di-*s*-octylbenzene	Hexabromobenzene
$C_{25}H_{44}$	*p*-*s*-Octadecyltoluene	Pentabromotoluene
C_8H_9Br	β-Phenylethyl bromide	β-(Penta-Br-phenyl)ethyl bromide
$C_9H_{11}Cl$	*p*-Isopropylchlorobenzene	Pentabromochlorobenzene
$C_9H_{11}Br$	γ-Phenyl-*n*-Pr-bromide	γ-(Penta-Br-phenyl)-*n*-Pr bromide
$C_{10}H_{13}Br$	*p*-Bromo-*s*-butylbenzene	Hexabromobenzene
$C_{10}H_{13}Br$	*p*-Bromo-isobutylbenzene	Pentabromoisobutylbenzene
$C_{10}H_{13}Br$	2-Bromocymene	Pentabromotoluene
$C_{10}H_{13}Cl$	*p*-Chloro-*s*-butylbenzene	Pentabromochlorobenzene
$C_{11}H_{15}Cl$	*p*-Chloro-*s*-amylbenzene	Pentabromochlorobenzene
$C_{11}H_{15}Br$	*p*-Bromo-*s*-amylbenzene	Hexabromobenzene
$C_{11}H_{15}I$	*p*-Iodo-*s*-amylbenzene	Pentabromoiodobenzene

alkyl groups cannot be explained on steric considerations alone. The replacements more likely depend on the electron releasing tendencies of the alkyl groups. Since the order of electron release is tertiary > secondary > primary, only the latter groups must be bound to the benzene ring firmly enough to resist the bromine–ferric bromide reagent. That the primary groups are not so inert in the aluminum bromide reaction was shown by further treatment of pentabromo-*n*-butylbenzene with bromine and aluminum powder. A tarry product was obtained from which both hexabromobenzene and unreacted *n*-butyl compound were recovered.

While the original hope of developing bromination to derivatize alkylbenzenes of all types (*i. e.*, without loss of alkyl groups) was not realized, the present findings afford a valuable diagnostic approach for studying the fate of alkyl groups in alkylation and rearrangement reactions. Ten of the compounds are new; the analyses are given in Table II along with the various melting points. Attempts to oxidize pentabromoalkyl- and tetrabromodialkylbenzenes to the corresponding polybromocarboxylic acids have been fruitless. The oxidation products recovered after reaction with nitric or chromic acids melted over wide temperature ranges and were analytically in very poor agreement with the expected products.

TABLE II

MELTING POINTS AND ANALYTICAL DATA

Compound	M. p., °C. Obs.	Lit.	Bromine, % Obs. [a]	Calcd.
Hexabromobenzene	319–321	316		
Pentabromochlorobenzene	297–298	299–300	100.1[b]	
Pentabromoidobenzene	315–316		100.5[b]	
Pentabromotoluene	284–286	283–285		
Tetrabromo-*o*-xylene	260–261	258–260		
Tetrabromo-*m*-xylene	250–251	247–248		
Tetrabromo-*p*-xylene	251–252	248–250		
Tribromomesitylene	224–225	224		
sym-Tribromo-tri-Et-benzene	102–103	105–106		
Pentabromoethylbenzene[c]	137–138.5		79.7	79.81
Pentabromo-*n*-Pr-benzene	94.5–95	96–97	77.52	77.63
Pentabromo-*n*-Bu-benzene	76.5–77.5		75.5	75.57
Pentabromoisobutylbenzene	75.5–76		75.5	75.57
Pentabromo-*n*-amylbenzene	80–80.5		73.56	73.62
Tetrabromo-*p*-di-*n*-Bu-benzene	121.5–122.5		63.2	63.18
Tetrabromo-*p*-di-*i*-Bu-benzene	145–146.5		63.3	63.18
Tetrabromo-*p*-*n*-Bu-*i*-Bu-benzene	98–99		63.4	63.18
β-(Penta-Br-phenyl)-ethyl bromide	130–130.5		82.6	82.73
γ-(Penta-Br-phenyl)-*n*-Pr-bromide	113.5–114.5		80.58	80.78

[a] Average of duplicate Parr bomb determinations. [b] Percentage of theoretical silver halide. [c] Previously stated to be tetrabromoethylbenzene by Klages and Allendorff, *Ber.*, **31**, 1005 (1898).

Experimental

Alkylbenzenes.—Most of the compounds used were available from previous studies.[11] *m*-Xylene and *sym*-triethylbenzene were from the du Pont Company, while the 4-*s*-butyl-*m*-xylene was obtained through the kindness of Dr. Dorothy Nightingale.[12] Ethylbenzene, *n*-propylbenzene, mesitylene, β-phenylethyl bromide, γ-phenylpropyl bromide, 2-bromocymene and *p*-bromoisobutylbenzene were purchased from the Eastman Kodak Company.

Bromination.—A 25-ml., round-bottom flask was immersed in a bath of crushed ice and charged with 7 ml. of

(11) Hennion, *et al.*, THIS JOURNAL, **62**, 1145 (1940); **63**, 2603 (1941); **64**, 2751 (1942); **65**, 1001, 1603 (1943).

(12) Nightingale, Radford and Shanholtzer, *ibid.*, **64**, 1662 (1942).

bromine and about 0.2 g. of C. P. iron powder. A weighed amount (about 1 ml.) of alkylbenzene was then added over a period of an hour. The mixture was stirred periodically, allowed to remain in the ice-bath for an additional hour, and then removed for evaporation of the excess bromine. When practically free of bromine, the residue was thoroughly washed with water and finally with sodium carbonate solution. A few products were gummy at this stage and it was found desirable to wash these with warm sodium thiosulfate solution. The samples were air-dried and purified by repeated crystallization. Hexabromobenzene and pentabromotoluene were crystallized from chlorobenzene, β-(pentabromophenyl)-ethyl bromide and γ-(pentabromophenyl)-*n*-propyl bromide from isopropyl alcohol. The other compounds were crystallized from ethyl alcohol. Use of decolorizing carbon in the second crystallization usually resulted in nearly colorless well defined crystals. Each product was prepared many times and commonly from different sources (*cf.* Table I). The yields averaged about 60% of the theoretical. Melting points were taken with a 360° thermometer calibrated against a set of fractional-degree partial immersion thermometers; the values may be considered equivalent, therefore, to corrected melting points.

Mixtures.—Synthetic mixtures, *e. g.*, *n*-propyl- with isopropylbenzene, isobutyl- with *t*-butylbenzene, etc., were brominated, washed, and dried as described above. The crude product was extracted several times with small portions of boiling 95% alcohol. Extracts were combined and concentrated by boiling to the beginning of crystallization; on cooling, the polybromoalkylbenzene deposited and was purified by repeated crystallization. The original residue was then taken up in hot chlorobenzene and the hexabromobenzene worked up in the usual manner.

Summary

1. A study has been made of the nuclear polybromination of fifty-five alkyl- and polyalkylbenzenes. Bromination with liquid bromine in the presence of iron powder at zero degrees substituted the benzene ring completely with replacement of all secondary and tertiary alkyl groups. Primary alkyl groups were not affected.

2. Mixtures of the two types of alkylbenzenes, one containing replaceable and the other nonreplaceable alkyl groups, were found to behave normally; each compound gave its own characteristic polybromo derivative.

3. Ten new polybromoalkylbenzenes are described.

NOTRE DAME, INDIANA RECEIVED NOVEMBER 29, 1945

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Some Compounds Containing the Trifluoromethyl Group

BY H. GILMAN, L. TOLMAN, F. YEOMAN, L. A. WOODS, D. A. SHIRLEY AND S. AVAKIAN

Incidental to some studies on fluorine-containing organic compounds, it appeared that certain special properties of trifluoromethyl types warranted their examination as antimalarials. Among the compounds first examined, two simple ones showed positive action in avian malaria: *m*-trifluoromethylphenol and *m*-trifluoromethylaniline. Subsequent tests showed these compounds to have a doubtful activity, and then no essential activity. Of the other compounds tested the only one with activity is *m*-trifluorophenylarsonic acid, and the specific contribution of the trifluoromethyl group to such activity is uncertain. The patent literature describes 4-(4′-diethylamino-1-methylbutylamino)-7-(trifluoromethyl)-quinoline,[1] 4-acetylamino-3′,5′-bis-(trifluoromethyl)-benzene-sulfonanilide,[2a] 4-nitro-3′,5′-bis-(trifluoromethyl)-benzenesulfonanilide[2a] and 4-amino-3′,5′-bis(trifluoromethyl)-benzenesulfonanilide.[2a] These compounds were very probably examined for antimalarial action. In addition, a mono-fluoride has been reported: 2-methoxy-6-fluoro-9-(4-diethylaminobutylamino)-acridine,[2b] and this showed no activity.

The preparation of γ-diethylaminopropyl γ-(*m*-trifluoromethylanilino)-propyl sulfide and its dihydrochloride were described recently.[3]

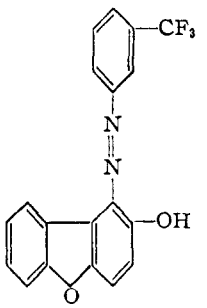
(1) Andersag, Breitner and Jung, German Patent 683,692 (1939); *C. A.*, **36**, 4973 (1942).

(2) (a) Behnisch, Klarer and Mietzsch, U. S. Patent 2,248,911 (1941); *C. A.*, **35**, 6738 (1941); (b) Magidson and Travin, *J. Gen. Chem.*, U. S. S. R., **11**, 243 (1941); *C. A.*, **35**, 7965 (1941).

(3) Gilman and Tolman, THIS JOURNAL, **67**, 1847 (1945).

Experimental

***m*-Trifluoromethylbenzenediazonium Chloride and 2-Hydroxydibenzofuran.**—The diazonium solution from 2.62 g. (0.0163 mole) of *m*-trifluoromethylaniline was added slowly and with stirring to a cold solution of 3 g. (0.0163 mole) of 2-hydroxydibenzofuran in potassium hydroxide. The temperature was kept below 5° and stirring was continued for thirty minutes. The crude coupling product was filtered and then recrystallized from glacial acetic acid to give 2.7 g. (46.5%) of fine red needles of 1-(*m*-trifluoromethylphenylazo) - 2 - hydroxydibenzofuran [I] melting at 173–174°. From a second experiment starting with 5 g. of 2-hydroxydibenzofuran, the yield was 49.7%.



[I]

Anal. Calcd. for $C_{19}H_{11}O_2N_2F_3$: N, 7.86. Found: N, 7.94.

The structure of this compound, as well as that of the one which follows, is based on the knowledge that benzenediazonium chloride couples with 2-hydroxydibenzofuran in the 1-position to give 1-phenylazo-2-hydroxydibenzofuran.[4]

***m*-Trifluoromethylbenzenediazonium Chloride and 2,8-Dihydroxydibenzofuran.**—From a diazo coupling reaction involving 8 g. (0.04 mole) of 2,8-dihydroxydibenzofuran, 6.7 g. of potassium hydroxide in 200 cc. of water and 6.42 g. (0.04 mole) of *m*-trifluoromethylaniline, 10 cc. of concentrated hydrochloric acid and 2.72 g. of sodium nitrite, a deep reddish orange product separated immediately. This was filtered and extracted several times with 50 cc. portions of boiling 5% potassium hydroxide solution until acidification of a sample of the filtrate showed that no appreciable amount of material was being extracted. The combined, dark red extracts were acidified with hyd-

(4) Gilman and Van Ess, *ibid.*, **61**, 3146 (1939).