quantitative except that the filtrates from the crystallizations were not reworked. [d] Melting points are uncorrected. [e] Tested by the method of Magnus [*Arch. ges. Physiol.* (*Pflügers*), **102**, 123 (1904); **103**, 515 (1904)] against acetylcholine chloride spasm. The results are expressed as a fraction of the activity of atropine sulfate. [f] In this preparation the intermediate acid chloride was not isolated. The yield is based on the acid. [g] $d^{25}{}_4$ 1.0650. [h] Phenyl-Δ^2-cyclopentenylacetyl chloride [Horclois, *Chemie and Industrie*, Special No. 357–363 (April, 1934)] was obtained in crystalline, form; freezing point about 11°. [i] The intermediate acid chloride is reported in second paper of this series [THIS JOURNAL, **71**, 3988 (1949)]. [j] $d^{25}{}_4$ 1.0756. [k] The intermediate acid chloride was reported by Moffett, Hart and Neil, in press [l] Hydrochlorides were analyzed for chlorine, acid citrates for nitrogen. [m] Acid citrate salt.

The intermediate pyrrolidylalkanols have been reported recently from this Laboratory,[2] and the intermediate acids are in general those found to give the most active antispasmodics when esterified with pyrrolidylethanol.[1]

It will be noted that these esters contain one or more asymmetric carbon atoms, but no attempt was made to separate either diastereoisomers or optically active forms.

Preliminary pharmacological assays have been carried out by Dr. Milton J. Vander Brook of our Department of Pharmacology and the results are indicated in Table I. It appears that substitution of a methyl group on the carbon atom next to the nitrogen has little effect on the antispasmodic activity, whereas substitution of a methyl group on the carbon atom adjacent to the oxygen greatly decreases the activity.

Experimental

Pyrrolidyl-alkyl Esters.—To a solution of 0.05 mole of the appropriate acid chloride in 10 ml. of dry benzene was added a solution of 0.06 mole of the pyrrolidylalkanol in 15 ml. of dry benzene. After the initial reaction had subsided the mixture was refluxed on a steam-bath for one-half to four hours. The longer times of refluxing were used when the initial reaction appeared sluggish. The reaction mixture was diluted with ice water, acidified with hydrochloric acid, and extracted twice with ether. The aqueous solution was made basic with cold sodium hydroxide solution, and the oil which separated was taken up in ether. The ether solution of the free base was washed twice with water and dried over anhydrous sodium sulfate. After removal of the ether the product was distilled from a Claisen flask giving a nearly colorless liquid with the properties listed in Table I.

Salts of the Pyrrolidylalkyl Esters.—Hydrogen chloride gas was bubbled into an absolute ether solution of the free base until the solution tested strongly acidic. In most cases the hydrochlorides crystallized either immediately or on standing and scratching. In a few cases crystallization was obtained by removing the solvent *in vacuo* and scratching the oily residue. The crude crystals were recrystallized from the solvents indicated in Table I. When the hydrochlorides proved very difficult to crystallize the acid citrates were prepared by adding a slight molar excess of citric acid in a minimum amount of hot absolute ethyl alcohol to a solution of the free base in ethyl acetate. The acid citrates separated on standing and needed no further purification. The properties of all these salts are listed in Table I.

Phenylcyclopentylacetyl Chloride.—A solution of 102.1 g. (0.5 mole) of phenylcyclopentylacetic acid[1] and 75 ml. of thionyl chloride in 75 ml. of dry benzene was warmed on a steam-bath for one-half hour and allowed to stand overnight. After removal of the solvent, the acid chloride was distilled through a short column (packed with glass helices) giving 101 g. (90.8%) of a light yellow liquid, b. p. 145° (12 mm.), $n^{25}{}_D$ 1.5312.

Anal. Calcd. for $C_{13}H_{15}ClO$: Cl, 15.92. Found: Cl, 15.34.

Summary

1. Twenty-four new pyrrolidylethyl esters of disubstituted acetic acids are described in which methyl groups are substituted on the ethyl link.

2. Preliminary pharmacological assays indicate that some of these compounds have high antispasmodic activity.

KALAMAZOO, MICHIGAN RECEIVED JUNE 18, 1949

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(2) Moffett, *J. Org. Chem.*, **14**, 862 (1949).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND PURDUE RESEARCH FOUNDATION, PURDUE UNIVERSITY]

Bromination of Trifluoromethylbenzenes

BY E. T. MCBEE, R. A. SANFORD(1) AND P. J. GRAHAM

A study of the bromination of trifluoromethyl and bis-(trifluoromethyl) derivatives of benzene and chlorobenzene was conducted to produce intermediates for use in the synthesis of fluorine-containing styrenes. The catalytic bromination of trifluoromethylbenzene[2] in the presence of iron at 60° gave a low yield of bromo-(trifluoromethyl)-benzene since a substantial proportion of the trifluoromethylbenzene was converted to benzoic acid. A search for other halogen carriers, applicable in brominations, led to the use of antimony(V) chloride. Although the activity of this halogen carrier diminished rapidly because of its reduction to antimony(III) salts, continuous introduction of chlorine into the reaction mixture maintained a sufficient concentration of antimony(V) chloride for satisfactory bromination. The application of this technique proved particularly advantageous since the yield of bromo-(trifluoromethyl)-benzene, for example, was greater than that expected from the stoichiometric relationship: $C_6H_5CF_3 + Br_2 \rightarrow C_6H_4(CF_3)Br + HBr$. In some instances, as high as 94% of the bromine added was converted to the desired organic bromo compound. Bromine chloride, which is known to be a powerful brominating

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(1) Abstracted from doctoral theses of R. A. Sanford and P. J. Graham. Presented before the Division of Organic Chemistry at the 113th meeting of the American Chemical Society, Chicago, Illinois.

(2) J. H. Simons and E. O. Ramler, THIS JOURNAL, **65**, 389 (1943).

Table I

Physical Properties

	Yield,	Conv.,	M. p.,	B. p.					Analyses, % Bromine		Chlorine		Fluorine	
	%	%	°C.	°C.	Mm.	$n^{25}D$	d^t_4	t, °C.	Calcd.	Found	Calcd.	Found	Calcd.	Found
$\text{5-Br-2-ClC}_6\text{H}_3\text{CF}_3$	86	26	−21.9 to −20.5	197–198	740	1.505	1.752	25	30.8	31.1	13.7	13.8	21.9	21.9
$\text{4-Br-3-ClC}_6\text{H}_3\text{CF}_3$	90	42	−25.0 to −22.8	193–194	740	1.500	1.748	25	30.8	30.0	13.7	13.3	21.9	21.4
$\text{2-Br-5-ClC}_6\text{H}_3\text{CF}_3$			17.8 to 19.3	195–196	740	1.504	1.751	25	30.8	30.4	13.7	13.5	21.9	21.5
$\text{3-Br-4-ClC}_6\text{H}_3\text{CF}_3$	74	31	−22.5 to −21.9	191–192	740	1.496	1.743	25	30.8	30.4	13.7	13.5	21.9	21.5
$\text{5-Br-2,4-Cl}_2\text{-C}_6\text{H}_2\text{CF}_3$	74	25	8.0 to 9.4	224–225	740	1.525	1.845	25	27.2	26.8	24.2	23.8	19.4	19.0
$\text{5-Br-3,4-Cl}_2\text{-C}_6\text{H}_2\text{CF}_3$	94	24	−24.0 to −20.8	220–221	740	1.519	1.836	25	27.2	26.9	24.2	23.9	19.4	18.9
$\text{2-Br-1,4-(CF}_3)_2\text{C}_6\text{H}_3$	67	44	4.5 to 5.0	161.8	751	1.431	1.741	23	26.9	27.2	..	..	38.9	38.9
$\text{2,5-Br}_2\text{-1,4-(CF}_3)_2\text{C}_6\text{H}_2$	18	12	72.0 to 72.5	112.0	40	...	...	..	43.0	42.5	..	..	30.6	29.9
$\text{5-Br-1,3-(CF}_3)_2\text{C}_6\text{H}_3$	90	70	−16.0 to −15.5	151.3	750	1.425	1.715	23	26.9	27.0	..	..	38.9	40.1
$\text{4-Br-1,2-(CF}_3)_2\text{C}_6\text{H}_3$	87	66	−48.0 to −47.0	87.0	40	1.440	1.759	23	26.9	27.1	..	..	38.9	38.3
$\text{5-Br-2-Cl-1,4-(CF}_3)_2\text{C}_6\text{H}_2$	83	68	45.0 to 45.3	189.5	750	...	...	..	24.4	25.1	10.8	11.1	34.8	36.0
$\text{5-Br-2-Cl-1,3-(CF}_3)_2\text{C}_6\text{H}_2$	91	82	20.5 to 20.9	192.1	748	1.460	1.815	26	24.4	24.1	10.8	10.7	34.8	34.8
$\text{1-Br-2-Cl-3,5-(CF}_3)_2\text{C}_6\text{H}_2$	55	45	−11.5 to −11.0	186.5	745	1.455	1.825	23	24.4	24.4	10.8	10.8	34.8	34.7
$\text{2-Br-3,4-Cl}_2\text{-1,5-(CF}_3)_2\text{C}_6\text{H}$	21	8	40.0 to 40.5[a]	84.5	10	1.465	1.707	23	22.1	21.8	19.6	19.4	31.5	..

[a] Crystallized only after long standing.

agent,[3] may have been the active agent in these brominations. It is theoretically possible to obtain complete utilization of the bromine if the reaction follows the stoichiometric equation: $RH + BrCl \rightarrow RBr + HCl$.

Various chloro-(trifluoromethyl)-benzenes were brominated at 20° under atmospheric pressure to give high yields of the corresponding bromochloro-(trifluoromethyl)-benzenes. Bromination of the bis-(trifluoromethyl)-benzenes and chloro-bis-(trifluoromethyl)-benzenes proved to be more difficult and it was necessary to conduct these latter brominations at temperatures ranging from 125–200° under autogenous pressures. The bromo and bromochloro derivatives of trifluoromethyl- and bis-(trifluoromethyl)-benzenes were isolated by rectification and their identities were established by hydrolysis to the corresponding bromo- and bromochlorobenzoic or phthalic acids. The yields and conversions, observed in these brominations, are reported in Table I, along with the physical properties of the new bromo compounds.

The orientation of the bromine substituent conformed with predicted results. When the position meta to a trifluoromethyl group and either para or ortho to chlorine was open, the bromine substituted in that position. In all instances where the directive influence of a trifluoromethyl group opposed that of chlorine, the influence of the chlorine overshadowed that of the trifluoromethyl group. When it was possible for the bromine to enter either para or ortho to chlorine, it generally substituted para, often with the exclusion of detectable ortho substitution.

Acknowledgment.—The authors are indebted to Ethyl Corporation and Westinghouse Electric Company for finanical support which made this investigation possible.

Experimental

Trifluoromethylbenzene was obtained from Hooker Electrochemical Company and used without further purification. Other trifluoromethyl derivatives of benzene and chlorobenzene were prepared by procedures described previously.[4]

4-Chloro-(trifluoromethyl)-benzene was brominated at atmospheric pressure in a Pyrex tube 120 cm. in length and 52 mm. in diameter fitted with cooling coils, a gas dispersion disc, a thermocouple well, and a reflux condenser. Sixty grams of antimony(V) chloride was placed in the reactor and a solution containing 52 g. (0.325 mole) of bromine in 361 g. (2.0 moles) of 4-chloro-(trifluoromethyl)-benzene was added slowly. An immediate and vigorous reaction began and external cooling was necessary to maintain the reaction temperature at 20°. When the initial reaction had subsided, chlorine was introduced at a rate of about one mole per hour. During the introduction of chlorine, bromination proceeded smoothly and the color of the reaction mixture changed gradually from deep red to light orange, at which time the reaction was considered complete and the mixture was poured into water and steam distilled. The organic layer of the steam distillate was separated and dried. Rectification through a column packed with glass helices gave 209 g. (1.16 moles) of 4-chloro-(trifluoromethyl)-benzene and 162 g. (0.623 mole) of 3-bromo-4-chloro-(trifluoromethyl)-benzene. A 96% utilization of the bromine was realized in the form of 3-bromo-4-chloro-(trifluoromethyl)-benzene which was obtained in a 31.1% conversion and 74.2% yield. This technique was also used for the bromination of (trifluoromethyl)-benzene, 2-chloro-(trifluoromethyl)-benzene, 3-chloro-(trifluoromethyl)-benzene, 2,4-dichloro-(trifluoromethyl)-benzene and 3,4-dichloro-(trifluoromethyl)-benzene.

1,4-Bis-(trifluoromethyl)-benzene (214 g., 1 mole), 50 g. of antimony(V) chloride and 80 g. (0.5 mole) of bromine were mixed in a one-liter from autoclave fitted with a pressure gage, a safety disc and a valve. The autoclave was then charged with chlorine to a pressure of 11 atmospheres (chlorine cylinder pressure). The reaction mixture was heated to 125°, agitated at that temperature under an autogenous pressure of approximately 28 atmospheres for eight hours, and then cooled to room temperature. The pressure was slowly released and the exciting gases were bubbled through an alkaline solution. The autoclave was opened and the contents poured onto cracked ice. After the unreacted bromine had been neutralized with sodium bicarbonate, the mixture was steam distilled and the organic layer separated and dried. The organic layer was rectified at atmospheric pressure through a column packed with glass helices to obtain 73 g. (0.34 mole) of unreacted 1,4-bis-(trifluoromethyl)-benzene. Further rectification under reduced pressure gave

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(3) A. E. Remick, "Electronic Interpretation of Organic Chemistry," J. Wiley and Sons, Inc., New York, N. Y., 1943, p. 129.

(4) E. T. McBee, *et al.*, This Journal, **69**, 947 (1947); L. C. Holt, and H. W. Daudt (to du Pont) U. S. Patent 2,174,513, Oct. 3, 1939; E. T. McBee, *et al.*, *Ind. Eng. Chem.*, **39**, 298–301 (1947); and O. Scherer, W. Schumaker and F. Muller (to General Aniline Works, Inc.), U. S. Patent 2,121,330, June 21, 1938.

129 g. (0.44 mole) of 2-bromo-1,4-bis-(trifluoromethyl)-benzene and 44.5 g. (0.12 mole) of 2,5-dibromo-1,4-bis-(trifluoromethyl)-benzene representing conversions of 44 and 12%, and yields of 67 and 18%, respectively. In other experiments, it was found that at a reaction temperature of 100° bromination occurred very slowly. At temperatures above 125°, however, the conversion to the dibromide increased with a corresponding decrease in the conversion to the monobromide.

The technique described above for the bromination of 1,4-bis-(trifluoromethyl)-benzene was used in the bromination of 1,3-bis-(trifluoromethyl)-benzene, 1,2-bis-(trifluoromethyl)-benzene, 2-chloro-1,4-bis-(trifluoromethyl)-benzene, 2-chloro-1,3-bis-(trifluoromethyl)-benzene, 4-chloro-1,3-bis-(trifluoromethyl)-benzene and 1,2-dichloro-3,4-bis-(trifluoromethyl)-benzene.

Summary

A procedure for the bromination of trifluoromethyl and bis-(trifluoromethyl) derivatives of benzene and chlorobenzene is described which comprises the simultaneous use of bromine and chlorine in the presence of the halogen carrier, antimony(V) chloride. Physical properties of the new compounds are reported.

LAFAYETTE, INDIANA RECEIVED NOVEMBER 12, 1949

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

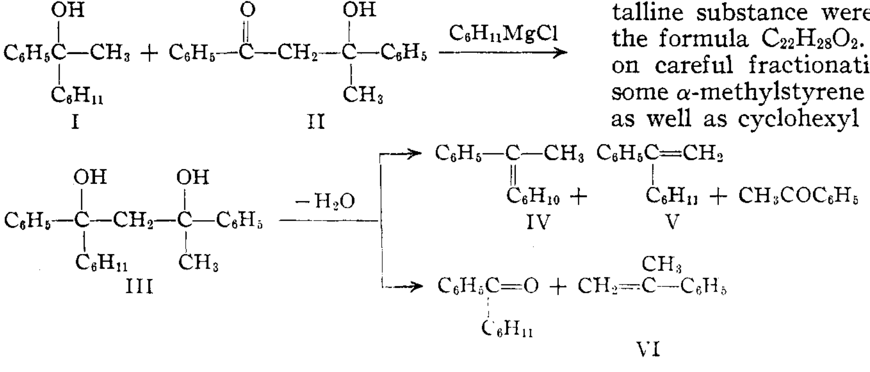
The Dehydration of Cyclohexylmethylphenylcarbinol and Related Tertiary Alcohols[1]

BY JAMES ENGLISH, JR., CHARLES A. RUSSELL AND F. V. BRUTCHER, JR.

Cyclohexylmethylphenylcarbinol has been prepared by Venus-Danilova and Bol'shukhin[2] and by Sabatier and Mailhe.[3] The former reported the product of the reaction between acetophenone and cyclohexylmagnesium halide as a liquid while the latter reported a liquid having a "stereoisomeric" solid form melting at 100–111°.

When this synthesis was repeated, the product was found to be a mixture of a liquid alcohol and a solid product, m. p. 119.5°, presumably the compound of Sabatier and Mailhe.

Dehydration with potassium bisulfate or anhydrous oxalic acid of either the crude reaction product or the crystalline substance gave a poor yield of a mixture of 1-cyclohexylid*ine*thylbenzene (IV) and α-cyclohexylstyrene (V) together with about 30% of cyclohexyl phenyl ketone. Ozonolysis of the hydrocarbon mixture showed that it was composed of approximately 90% α-cyclohexylstyrene and 10% 1-cyclohexylid*ine*thylbenzene.



$$C_6H_5COCH_3 + C_6H_{11}MgCl \longrightarrow$$

$$\underset{\text{I}}{C_6H_5\overset{OH}{\underset{C_6H_{11}}{C}}-CH_3} + \underset{\text{II}}{C_6H_5-\overset{O}{\overset{\|}{C}}-CH_2-\overset{OH}{\underset{CH_3}{C}}-C_6H_5} \xrightarrow{C_6H_{11}MgCl}$$

$$\underset{\text{III}}{C_6H_5-\overset{OH}{\underset{C_6H_{11}}{C}}-CH_2-\overset{OH}{\underset{CH_3}{C}}-C_6H_5} \xrightarrow{-H_2O} \underset{\text{IV}}{C_6H_5-\underset{C_6H_{10}}{\overset{}{C}}\!=\!\!-CH_3} + \underset{\text{V}}{C_6H_5\underset{C_6H_{11}}{C}=CH_2} + CH_3COC_6H_5$$

$$\longrightarrow \underset{C_6H_{11}}{C_6H_5C}=O + \underset{\text{VI}}{CH_2=\overset{CH_3}{C}-C_6H_5}$$

When cyclohexylmethylphenylcarbinol was prepared from cyclohexyl phenyl ketone and methylmagnesium iodide the product was a homogeneous liquid which, on dehydration, yielded only the mixture of hydrocarbons (IV and V). No evidence for the presence of cyclohexyl phenyl ketone could be obtained. This result, coupled with the absence of any methane, which might have been expected from a thermal cracking of cyclohexylmethylphenylcarbinol[4] or any one-carbon oxidation products from possible oxidation[5] of α-cyclohexylstyrene led to the suspicion that the crystalline product of Sabatier and Mailhe was not cyclohexylmethylphenylcarbinol.

The analysis and molecular weight of this crystalline substance were found to agree best with the formula $C_{22}H_{28}O_2$. Its dehydration products on careful fractionation were found to include some α-methylstyrene and a trace of acetophenone as well as cyclohexyl phenyl ketone and the hydrocarbon mixture (IV and V) mentioned above. It appears that this substance is in fact 1,3-diphenyl-1-cyclohexyl-1,3-butanediol (III) and that it was produced as a result of the condensation of acetophenone with itself followed by reaction with cyclohexylmagnesium chloride as shown in the equations.

Although Grignard reagents are known[6,7] to lead to condensation reactions, we are not aware of a previous reaction in which the condensation product in turn has been shown to react with the Grignard reagent. The cleavage of II as shown might be predicted by analogy with the work of Grignard[8]

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[1] This paper is taken in part from the thesis presented by Charles A. Russell to the Graduate School of Yale University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Venus-Danilova and Bol'shukhin, *J. Gen. Chem.* (USSR), **12**, 73 (1942).

[3] Sabatier and Mailhe, *Ann. chim. phys.*, [8] **10**, 538 (1907).

[4] Grignard and Escourrou, *Compt. rend.*, **176**, 1860 (1923); **182**, 299 (1926).

[5] Tiffeneau, *Ann. chim. phys.*, [8] **10**, 539 (1907).

[6] Shine and Turner, *Nature*, **158**, 170 (1946).

[7] V. Grignard, *Bull. soc. chim.*, [4] **39**, 1285; Tuot, *Compt. rend.*, **206**, 1019 (1938).

[8] Grignard and Chambret, *Compt. rend.*, **182**, 299 (1926).