o-bromobenzotrifluoride does not appear to react with lithium metal using the conventional procedure and yet it undergoes halogen–metal interconversion in high yields. This parallels the observations made on m-bromotrifluoromethylbenzene.[4]

### Experimental

**o-Bromobenzotrifluoride.**—To a solution of n-butyllithium prepared from 278 g. (3 moles) of n-butyl chloride and 43 g. (6.2 g. atoms) of lithium in 1 l. of dry ether, was added 438 g. (3 moles) of trifluoromethylbenzene. This mixture was refluxed for 12 hours after the spontaneous evolution of butane had ceased. Bromine vapor was then carried into the reaction flask by a stream of nitrogen until approximately 400 g. had been added. The reaction mixture was poured into 1 l. of water with thorough mixing. The organic layer was washed with dilute sodium hydroxide, a sodium thiosulfate solution, and then with water. The resulting material was steam distilled to remove a rather large amount of tar. The organic layer from this operation was dried and fractionated giving 134 g. (30% recovery) of trifluoromethylbenzene, b.p. 100–101°, and after a relatively small intermediate fraction, 129 g. (28% yield) of o-bromobenzotrifluoride, b.p. 167–168°, $n^{25}\text{D}$ 1.4806.

To 6.75 g. (0.03 mole) of the o-bromotrifluoromethylbenzene thus prepared was added 66 ml. of an ether solution containing 0.03 mole of n-butyllithium at such a rate as to allow gentle reflux. The mixture was stirred for an additional 30 minutes and then carbonated with Dry Ice. Working up in the usual manner gave 4.73 g. (83%) of material, melting at 106–108°. Recrystallization from petroleum ether gave 4 g. (70%) of o-trifluoromethylbenzoic acid, m.p. 108–109.5°.

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[4] H. Gilman and L. Woods, THIS JOURNAL, **66**, 1981 (1944).

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## Preparation of Pure Secondary Bromides

BY JAMES CASON AND ROBERT H. MILLS

It has long been realized that conversion of a secondary alcohol to the corresponding bromide is likely to be accompanied by rearrangement of the intermediate carbonium ion to yield an isomeric secondary bromide. In this connection, the s-amyl bromides have been studied carefully[1,2] for there are only two possible isomers. Lauer and Stodola[3] have made a careful study of the analysis of mixtures of the isomeric s-amyl bromides, and have concluded that analysis based on the index of refraction is quite unreliable but that the binary melting point diagram of the anilides may be used for reliable analysis of mixtures of the bromides. These investigators prepared 2-bromo- and 3-bromopentane by the methods judged to be most reliable for furnishing the pure bromides, but there has actually been no evidence that these "best" samples are entirely homogeneous isomers.

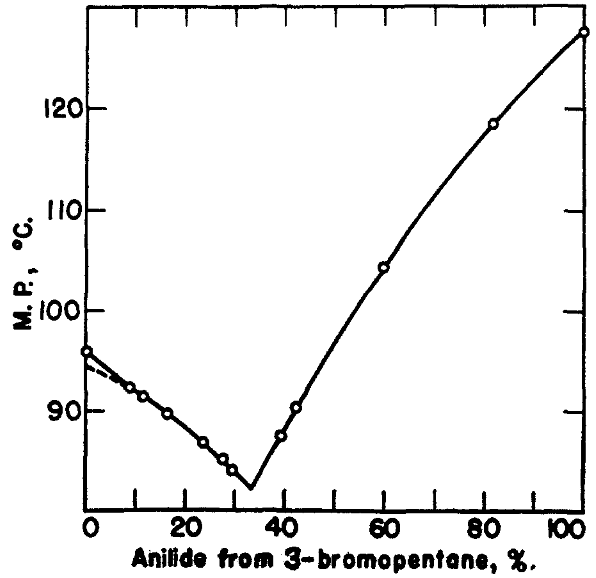

Fig. 1.—Binary melting point diagram of mixtures of the anilides prepared by reaction of 2-pentyl- and 3-pentylmagnesium bromide with phenyl isocyanate.

Evidence has been presented[4] that the reaction of bromine with the silver salt of a carboxylic acid, to give an alkyl halide, proceeds by way of a free radical mechanism. If this is the case, since free radicals are much less prone to rearrangement than carbonium ions, the reaction of bromine with the silver salt of an α-alkylalkanoic acid should lead to an isomerically pure s-alkyl halide. In the present investigation, this reaction has been carried out with silver 2-methylpentanoate and silver 2-ethylbutanoate to give, respectively, 2- and 3-bromopentane. The anilides obtained from these compounds proved to melt significantly higher than the best samples obtained by Stodola and Lauer,[3] who prepared the bromides from the alcohols with hydrogen bromide. Also, a direct comparison has been made with a sample of the bromide prepared by reaction of phosphorus tribromide with synthetic 2-pentanol, according to the procedure[5] considered best. The anilide from this bromide exhibited a melting point in agreement with the value reported by Stodola and Lauer, thus below the melting point of a sample prepared from bromide obtained *via* the silver salt reaction. It thus appears that a pure secondary bromide cannot be obtained from the corresponding alcohol in instances where isomeric secondary bromides are structurally possible.

Since analysis of mixtures of the s-amyl bromides is often desirable,[3] a binary melting point diagram has been constructed by use of mixtures of the pure anilides prepared from the s-amyl bromides obtained from the silver salt reactions. From this diagram (Fig. 1), it is indicated that the best sample of 2-bromopentane obtained previously[3] was of about 92% purity, and the best sample of 3-bromopentane was of about 87% purity. The right side of this curve (anilide from 3-bromopentane crystallizing) has a form normally characteristic of such diagrams, but the left side (anilide from 2-bromopentane crystallizing) does not. A characteristic curve (terminal portion dotted) may be drawn through all points except the upper one, and it is felt that the actual curve bends up at this point on account of association in the concentrated solution of a molecular compound of the *d*- and *l*-forms of the anilide. In another instance[6] in which the optical

[1] Sherrill, Otto and Pickett, THIS JOURNAL, **51**, 3027 (1929).

[2] Sherrill, Baldwin and Hass, *ibid.*, **51**, 3036 (1929).

[3] Lauer and Stodola, *ibid.*, **56**, 1215 (1934).

[4] Arnold and Morgan, *ibid.*, **70**, 4248 (1948); Dauben and Tilles, *ibid.*, **72**, 3185 (1950); Smith and Hull, *ibid.*, **72**, 3309 (1950).

[5] Hsueh and Marvel, *ibid.*, **50**, 855 (1928).

[6] Cason and Winans, *J. Org. Chem.*, **15**, 157 (1950).

isomers were available, curves of this form were actually obtained. A similar behavior was first observed and discussed by Weitkamp.[7]

### Experimental[8]

**2-Methylpentanoic Acid.**—Diethyl methyl-*n*-propylmalonate was prepared by alkylation, in the usual way,[9] of diethyl methylmalonate (prepared from ethyl oxalpropionate). The average yield was 83%, b.p. 108–112° (16 mm.), $n^{22}_{\text{D}}$ 1.4210. The diester was saponified with alcoholic potassium hydroxide, alcohol was distilled, and the acidified residue was extracted with ether. The crude malonic acid (m.p. 99–103°) was decarboxylated at 175°, to give 90% yield of 2-methylpentanoic acid, b.p. 95–96° (14 mm.), $n^{24}_{\text{D}}$ 1.4128. Hommelen[10] has reported b.p. 192–193.6°, $n^{20}_{\text{D}}$ 1.4136.

**2-Ethylbutanoic acid**, b.p. 113.4–113.6° (40 mm.), was obtained in a pure state by fractionation of the commercial acid through a three-foot packed column.

**2-Bromopentane.**—(A) The silver salt and bromine reaction was carried out as described for preparation of tridecyl bromide[11] except that acid was removed as the sodium salt rather than the barium salt. The carbon tetrachloride solvent was flash-distilled through a three-foot packed column, keeping the mole fraction of bromide in the pot below 0.2 until all solution had been added. After an intermediate fraction, the 2-bromopentane was collected in 55–65% yield at 117.0–117.8°, $n^{24}_{\text{D}}$ 1.4389. Stodola and Lauer[3] reported b.p. 116.4–117.4°, $n^{20}_{\text{D}}$ 1.4414.

This reaction was also carried out in methylene dichloride, in order to avoid the tedious separation from carbon tetrachloride, but this method proved even more troublesome on account of formation of small amounts of bromodichloromethane. From a 1-mole run there was obtained 2.4 g. of material of b.p. 90.4–92°, which after redistillation had $n^{20}_{\text{D}}$ 1.4911 (reported[12] for bromodichloromethane, b.p. 90.2°, $n^{20}_{\text{D}}$ 1.4985).

(B) Synthetic 2-pentanol[13] was converted to the bromide by the method of Hsueh and Marvel[5] except that the final heating period was omitted; yield 82%, b.p. 117–117.4°, $n^{20}_{\text{D}}$ 1.4413, $n^{24}_{\text{D}}$ 1.4392.

**3-Bromopentane,** prepared from silver 2-ethylbutanoate by the method described for the 2-isomer, was obtained in 76% yield, b.p. 118.1–118.9°, $n^{20}_{\text{D}}$ 1.4452. Lauer and Stodola[3] reported b.p. 117.4–118.4°, $n^{20}_{\text{D}}$ 1.4443.

**Anilides from the** bromopentanes were prepared by the method of Lauer and Stodola[3] except that the Grignard reaction with freshly distilled phenyl isocyanate was carried out in a three-necked test-tube fitted with mercury sealed stirrer, dropping funnel and reflux condenser. Crystallization of the anilides from aqueous methanol was as previously described except that the final addition of water was omitted.

**The anilide from 2-bromopentane from the silver salt reaction,** after a single crystallization, melted at 95.9–96.2°, and the best sample obtained (three crystallizations) melted at 96.0–96.4°.

**The anilide from 2-bromopentane prepared from 2-pentanol,** after a single crystallization, melted at 92.5–93.0°, and after three crystallizations, the m.p. was 94.7–95.6°. The best value previously reported[3] was 94.3°.

**The anilide from 3-bromopentane,** after a single crystallization, melted at 127.2–127.7° (best previous value[3] 125°). This anilide is polymorphic, for on removing the capillary from the m.p.-bath until crystallization sets in then immediately returning it to the bath, the substance rapidly remelts completely at temperatures down to 123.8°. Below this temperature, reversion to the original form occurred, with re-m.p. 127.4°. With the larger sample used for the binary melting point diagram, no difficulty with the lower-melting polymorph was encountered.

**The binary melting point diagram** was determined by the method described in detail by Cason and Winans.[6]

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RECEIVED JULY 5, 1950

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[7] Weitkamp, THIS JOURNAL, **67**, 447 (1945).

[8] All melting points are corrected; all boiling points are uncorrected. All distillations, unless otherwise specified, were through a half-meter Vigreux type column with heated jacket and partial-reflux head.

[9] Adams and Kamm, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 250.

[10] Hommelen, *Bull. soc. chim. Belg.*, **42**, 243 (1933).

[11] Cason and Winans, *J. Org. Chem.*, **15**, 142 (1950).

[12] Timmermans and Martin, *J. chim. phys.*, **23**, 766 (1926).

[13] Cason and Coad, THIS JOURNAL, **72**, 4695 (1950).

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## Molecular Compounds of Aminoazo Dyes and Bile Acids I[1]

BY G. CILENTO

This paper describes the first results of an investigation of the coördinating affinity of aminoazo dyes for biologically important compounds. Related to this research was a recent note[2] in which the preparation of *p*-aminoazobenzenecholeic acid and of its N-dimethyl derivative was reported. Interest in this subject was induced by the present views on chemical carcinogenesis.

It is a well founded hypothesis that a common feature to carcinogenic molecules is the presence of at least one region which has a high electron density and an increased ability for addition reactions.[3] Actually there is an increasing amount of evidence which suggests that the carcinogen forms, in a first step—as it may be expected on the basis of its peculiar properties—an addition complex with some tissue constituent.[3] The results of the investigation, herein reported, of the coördinating ability of *p*-aminoazobenzene and *p*-dimethylaminoazobenzene, "butter yellow," for cholesterol, desoxycholic and cholic acids are in agreement with the views mentioned above.

*p*-Aminoazobenzene is a border line molecule with slight, if any, carcinogenic power, whereas the dimethyl derivative is very active when orally administered in inducing hepatomas in rats. Desoxycholic acid is known easily to form molecular compounds, the so-called choleic acids, with organic derivatives. This property, however, is rarely found in cholesterol or cholic acid.[4]

The research consisted of working out the solid-liquid equilibrium diagram between the azo dye and the sterid. Application was also made of ultraviolet and visible light spectrophotometry.

It has been found that neither of the two azo dyes form mixed crystals or molecular compounds with cholesterol. The eutectic point lies at 48% (by weight) *p*-aminoazobenzene, 108.5° in one case and at 60% (by weight) *p*-dimethylaminoazobenzene, 105.5° in the other case.

Figures 1 and 2 illustrate the phase diagrams involving desoxycholic acid. As it was expected, in both cases a maximum occurs in the liquid curve which indicates molecular addition. However, due to the flat shape of these maxima, it was impossible to decide if four or six molecules of the bile acid were associated with one molecule of the azo dye, nor could additional information be obtained from the

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[1] From a paper presented at the Second Meeting of the Sociedade Brasileira Para o Progresso da Ciência, Curitiba, November, 1950.

[2] G. Cilento, THIS JOURNAL, **72**, 4272 (1950).

[3] For a survey see P. Daudel and R. Daudel, *Biol. méd.* (*Paris*), **39**, 201 (1950).

[4] Harry Sobotka, "The Chemistry of the Sterids," The William and Wilkins Company, Baltimore, Md., 1938, p. 122.