

We have attempted the preparation of cyclobutylcarbinyl bromide by the reaction of phosphorus tribromide with the corresponding alcohol. The method of Bartleson, Burk and Lankelma² was chosen because it is less likely to lead to rearrangement³ than, for example, use of hydrogen bromide.⁴ Yields of bromide amounting to 72% were obtained. However, kinetic analysis showed the product to be a mixture of cyclopentyl bromide (56%) and, presumably, cyclobutylcarbinyl bromide (44%). The rates of solvolysis of the two bromides in 60% (by volume) aqueous ethanol at $75.0 \pm 0.5^\circ$ are $(12.2 \pm 0.6) \times 10^{-3} \text{ min.}^{-1}$ and $(1.00 \pm 0.11) \times 10^{-3} \text{ min.}^{-1}$, respectively.

Experimental

Reaction of Cyclobutylcarbinol with Phosphorus Tribromide.—The cyclobutylcarbinol was prepared in 76% yield by lithium aluminum hydride reduction⁵ of cyclobutanecarboxylic acid.⁶ A large test-tube containing 21.4 g. (0.25 mole) of cyclobutylcarbinol was cooled to -20° . Then 25.1 g. (0.093 mole) of phosphorus tribromide was added with stirring over a period of three hours during which the temperature was kept below -10° . After four more hours at -10° the vessel was cooled to -70° (Dry Ice-acetone), allowed to come to room temperature over a period of 36 hours and then let stand at room temperature for 10 days. The two layers were separated and the lower one extracted once with ether; the extract was added to the top layer. The combined mixture was treated with excess solid sodium bicarbonate, dried over magnesium sulfate and fractionated through a 35-theoretical plate column. The product (72% yield) had the following properties: b.p. $135\text{--}136^\circ$, d_{20}^{25} 1.366; n_D^{25} 1.4825; molar refraction, found 31.08, calcd. for cyclopentyl bromide 30.86, calcd. for cyclobutylcarbinyl bromide 31.34.

Anal. Calcd. for C_4H_9Br : Br, 53.7. Found: Br, 53.3.

Kinetic Analysis of Product.—The kinetics were measured by sealing 5-ml. aliquots of 60% aqueous ethanol solutions of the bromides in ampoules, which were placed in the constant temperature bath for prescribed periods, cooled, opened and titrated with sodium hydroxide. The rate constant for cyclopentyl bromide was determined on a pure sample; that for cyclobutylcarbinyl bromide was determined from the essentially linear portion of the conventional first-order kinetic plot near the end of the reaction involving the mixture of bromides from the above reaction. Extraction of the line to zero time provided a good estimate of the initial concentration of cyclobutylcarbinyl bromide: 45 versus 43% obtained by the method involving the integrated rate expressions for the two components as follows. Given

$$\ln(C_{p0}/C_p) = k_1 t \quad (1)$$

$$\ln(C_{b0}/C_b) = k_2 t \quad (2)$$

$$C_{p0} + C_{b0} = B_0 \quad (3)$$

$$C_p + C_b = B \quad (4)$$

where C_p , C_b and B refer to concentrations of cyclopentyl bromide, cyclobutylcarbinyl bromide and total bromide, respectively, the subscript zero refers to initial values, k_1 and k_2 are the first-order solvolysis rate constants. From (1) and (2) we get $C_{p0} = C_p e^{k_1 t}$ and $C_{b0} = C_b e^{k_2 t}$. Combining these with (3) and (4), eliminating C_p , C_{b0} and C_b leads to

$$C_{p0} = \frac{B_0}{B_0 e^{k_2 t} - e^{-k_1 t}} \quad (5)$$

In a typical experiment at times of 100 and 200 minutes, in-

(2) J. D. Bartleson, R. E. Burk and H. P. Lankelma, *THIS JOURNAL*, **68**, 2513 (1946).

(3) C. R. Noller and R. Adams, *ibid.*, **48**, 1080 (1926).

(4) S. S. Marnetkin and O. N. Morozova, *J. Russ. phys.-chem. Ges.*, **47**, 1607 (1915).

(5) "Organic Reactions," Vol. VI, R. Adams, Editor, John Wiley and Sons, Inc., New York, N. Y., p. 469.

(6) J. Cason and C. F. Allen, *J. Org. Chem.*, **14**, 1036 (1949).

ital cyclopentyl bromide percentages of 58 and 56 were obtained.

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Reaction of Ethylmagnesium Bromide with Alkyl Aryl Ketones

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The reaction of ethylmagnesium bromide with a group of alkyl aryl ketones has been recently reported.² Seventeen such ketones³ have been treated with ethylmagnesium bromide. The results are shown in Table I. As in the reaction with ethylmagnesium bromide² the para substituent of the aryl group has only a slight effect on the course of the reaction. As the alkyl group attached to the carbonyl becomes more highly branched, there is a general trend toward decreased enolization and increased reduction, culminating in almost quantitative reduction with the pivalophenone

TABLE I

ALKYL	4-R-PHENYL			KETONES AND		ETHYLMAGNESIUM		
	4-R	E ^a	R ^b	A ^c	Liquid ^d re- cov- ery, %	Analysis of tertiary alcohol Carbon, % Calcd. Found	Hydrogen, % Calcd. Found	
4-R-C ₆ H ₄ COCH ₃								
H	3	0	97	70	80.00	80.13	9.33	9.35
Me	4	1	95	80	80.49	80.60	9.76	9.86
Et	5	2	93	70	80.90	80.96	10.11	10.15
Isoprop	6	1	93	82	81.25	81.33	10.42	10.50
t-Bu	5	1	94	76	81.55	81.39	10.68	10.53
4-R-C ₆ H ₄ COC ₂ H ₅								
H	2	0	98	85	80.49	80.51	9.76	9.82
Me	3	1	96	70	80.90	80.92	10.11	10.22
Et	2	1	97	82	81.25	81.13	10.42	10.40
Isoprop	2	1	97	81	81.55	81.80	10.68	10.60
t-Bu	2	1	97	86	81.82	81.85	10.91	10.85
4-R-C ₆ H ₄ COCH(CH ₃) ₂								
H	0	2	98	86	80.90	81.13	10.11	10.23
Me	0	2	98	92	81.25	81.23	10.42	10.30
Et	0	3	97	86	81.55	81.80	10.68	10.60
Isoprop	0	4	96	81	81.82	82.09	10.91	10.85
t-Bu	0	3	97	81	82.05	81.97	11.11	11.15
Analysis of sec. alcohol ^e								
4-R-C ₆ H ₄ COC(CH ₃) ₃								
H	0	86	14 ^e	80	80.49	80.29	9.76	9.82
Me	0	87	13 ^e	79	80.90	80.68	10.11	10.09

^a % enolization based on gas analysis. ^b % reduction based on gas analysis. ^c % addition calculated by difference. ^d Grams of liquid collected in distillation $\times 100/g.$ calcd. from gas analysis. ^e Tertiary alcohol giving an acceptable analysis was not isolated.

(1) Taken from the Ph.D. Thesis of B. F. Landrum, Emory University, 1950.

(2) M. J. Craft, B. F. Landrum, E. C. Suratt and C. T. Lester, *THIS JOURNAL*, **73**, 4462 (1951).

(3) The preparation and properties of these 17 ketones are described in a previous publication, cf. R. T. Lagemann, B. F. Landrum, C. T. Lester, O. Milner and E. G. McLeroy, *ibid.*, **74**, 1602 (1952).

series. This is unusually large reduction for the ethyl Grignard reagent.⁴

Experimental

Preparation of Grignard Reagent.—A large supply of the reagent was prepared and diluted to a strength of 1.35 *M*. This was filtered and stored under nitrogen. Periodic checks on molarity were made.

Reaction of Ketones and Grignard Reagent.—A solution of 0.27 mole of ethylmagnesium bromide (200 ml.) was placed in a 3-neck flask equipped with dropping funnel, stirrer and ice-water condenser. The apparatus was previously flushed and filled with dry nitrogen. The solution was heated on a water-bath to reflux temperature and 0.25 mole of ketone in 125 ml. of dry ether was added. Reflux temperature and stirring was maintained during and for 30 minutes after addition. Any gas evolved was conveyed from the top of the condenser to the mouth of an inverted carboy filled with water. Samples were transferred from this to an Orsat apparatus and analyzed for unsaturated gas.⁵ Suitable corrections for volume of added liquid, water vapor, etc., were made. After 30 minutes of heating gas evolution had ceased. Water was then added through the dropping funnel until the stirrer was stopped by crystallization of magnesium salts. The gas evolved during this addition was collected in a separate reservoir. In all cases this gas corresponded quite closely (± 50 ml.) to the 0.02 mole excess of Grignard used. The saturated gas was taken as a measure of enolization; the unsaturated gas as a measure of reduction. Spot checks on these results indicated a reproducibility of ± 50 ml. ($\pm 1\%$).

Isolation of Liquid Products.—The clear ether solution resulting from the above procedure was decanted from the crystalline magnesium salts. The salts were triturated with dry ether and the two ether solutions combined in a Claisen flask and distilled without further treatment. No evidence of water was found in the subsequent distillation. After the ether was removed by distillation on a water-bath, the residue was distilled at reduced pressure. The pressure used was usually between 5 and 10 mm. Three-ml. fractions were taken. Fractions with the same refractive index and b.p. were combined and carbon and hydrogen analyses run. For the first 15 ketones, the index and b.p. were essentially constant after the first two fractions. For the last two ketones a constant boiling, constant index distillate was recovered in the first fractions. These crystallized to give secondary alcohol, m.p. 54–55°. The last two fractions collected in each case were discolored and gave unacceptable carbon and hydrogen values for tertiary alcohol.

(4) M. S. Kharasch and S. Weinhouse, *J. Org. Chem.*, **1**, 209 (1937), and H. S. Mosher and E. LaCombe, *This Journal*, **72**, 3994 (1950), contain most of the pertinent references related to reduction.

(5) F. C. Garrett, "Allen's Commercial Organic Analysis," Fourth Ed., Vol. III, Blakiston's Son and Co., Philadelphia, Penna., 1920, p. 4.

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Synthesis of 2-Methylaminofluorene-N-methyl-C¹⁴

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The synthesis of 2-methylaminofluorene-N-methyl-C¹⁴ was undertaken in a continuation of the study of derivatives of the carcinogen 2-aminofluorene.² Weisburger and Quinlin³ prepared 2-dimethylaminofluorene in 22% yield, but a synthesis of the secondary amine has not been reported in

(1) This investigation was supported by Research Grant C-1066 from the National Cancer Institute of the National Institutes of Health, Public Health Service. Presented before the Meeting in Miniature of the Florida Section, A.C.S., Jacksonville, May 3, 1952.

(2) H. P. Morris, C. S. Dubnik and J. M. Johnson, *J. Nat. Cancer Inst.*, **10**, 1201 (1950); F. E. Ray and M. F. Argus, *Cancer Research*, **11**, 783 (1951); *cf. ibid.*, p. 423.

(3) E. K. Weisburger and P. M. Quinlin, *This Journal*, **70**, 3964 (1948).

the literature. In our preparation of this latter compound it was desirable to design a method which would be applicable to the introduction of C¹⁴ in the methyl carbon in maximum yield. For isotopic dilution experiments the compound should be free from the dimethyl and unmethylated amines. For this purpose the sodium salt of 2-tosylaminofluorene (2-*p*-toluenesulfonamidofluorene) was treated with methyl iodide and the resulting compound was hydrolyzed with hydrochloric acid.

Experimental

2-Sodium Tosylaminofluorene.—Fifty-three grams (0.15 mole) of tosylaminofluorene, m.p. 161°,⁴ was dissolved with stirring and heating in 250 ml. of xylene dried over sodium hydride for 3 days. Sodium hydride, 4.2 g. (0.175 mole), was added and heating with stirring was continued for 15 minutes. The white sodium salt came out of solution. Excess sodium hydride was destroyed with 150 ml. of absolute ethanol and stirring. The precipitate became stiffer and whiter as the sodium ethylate reacted with more tosylaminofluorene until all the solvent was absorbed. The mixture was cooled, filtered with suction and washed with acetone until free of color. The yield of 2-sodium tosylaminofluorene was 55 g. or 98% of theoretical. This compound can be recrystallized from water containing a small amount of sodium hydroxide if necessary. The sodium salt should be freshly prepared for the next step.

2-Methyltosylaminofluorene.—2-Sodium tosylaminofluorene, 55 g. (0.15 mole), was dissolved in 800 ml. of 50% ethanol in a 2-liter flask and cooled. Ten ml. (0.16 mole) of methyl iodide was added and the flask was immediately connected to a long reflux condenser. The solution was warmed gently with occasional shaking for 1 hour and cooled. The white crystals of 2-methyltosylaminofluorene were collected with suction and dried. The yield was 48.4 g. (99.6%), m.p. 134–136°.

Anal. Calcd. for C₂₁H₁₉O₂NS: S, 9.73. Found: S, 9.54.

2-Methylaminofluorene.⁵—Seven-tenths gram of 2-methyltosylaminofluorene was placed in an 85-ml. Carius tube with 20 ml. of 50% hydrochloric acid. The tube was sealed and heated at 165° for 1 hour. It was found that placing the tube in a horizontal position and subjecting it to occasional agitation not only increased the yield but lowered the time necessary for hydrolysis. When cool, the tube was opened and the contents removed with warm water. The 2-methylaminofluorene hydrochloride was recrystallized once with charcoal from ethanol-water to remove a small amount of tar present.

Anal. Calcd. for C₁₄H₁₄NCl: Cl, 15.3. Found: Cl, 15.2.

The purified filtrate of the hydrochloride was converted to the free amine by cooling and neutralizing with 50% ammonium hydroxide. 2-Methylaminofluorene comes down as a white, flocculent precipitate which darkens on standing. It should be filtered with suction at once, washed several times with water, dried in a desiccator and stored in the dark; m.p. 73–75. Recrystallization from ethanol-water (charcoal) gave white plates, m.p. 76–77°. The yield was 0.34 g. (87%).

Anal. Calcd. for C₁₄H₁₃N: C, 86.16; H, 6.66; N, 7.17. Found: C, 86.41, 86.26; H, 6.30, 6.56; N (by difference), 7.29, 7.18.

2-Methylaminofluorene-N-methyl-C¹⁴.—One millimole, 0.1419 g. (specific activity 1 millicurie per millimole) of methyl-C¹⁴ iodide⁶ was treated in a vacuum line with two millimoles of 2-sodium tosylaminofluorene, 0.715 g., in acetone for 4 hours. Then the reaction was completed with

(4) N. Campbell, W. Anderson and J. Gilmore, *J. Chem. Soc.*, 446 (1940).

(5) NOTE ADDED IN PROOF.—Since this work was completed a synthesis of 2-methylaminofluorene has been published by F. Bielschowsky (*Brit. J. Cancer*, **6**, 89 (1952)) who treated the sodium derivative of 2-acetylaminofluorene with methyl iodide and obtained a compound of m.p. 74° in unspecified yield.

(6) Obtained from Tracerlab on allocation of the Atomic Energy Commission.