

## 67. Halogenated Ketones. Part II. The Bromination of Methyl Propyl and Methyl isoPropyl Ketone.

By J. R. CATCH, D. H. HEY, E. R. H. JONES, and WALTER WILSON.

Bromination of methyl propyl ketone in an aqueous medium in the presence of potassium chlorate gave the two expected monobromo-ketones, whereas the *isopropyl* ketone yielded a single product, none of the bromomethyl *isopropyl* ketone being detectable. Bromomethyl propyl ketone readily gave an anilino-derivative, but this could not be cyclised to an alkyl indole; the isomeric 1-bromopropyl ketone, on the other hand, was smoothly converted into a methylethylindole on being heated with aniline and its hydrobromide.

APPLICATION of the bromination method described in the preceding paper to methyl propyl ketone gave a mixture of the two isomeric bromo-ketones, *bromomethyl propyl* and *methyl 1-bromopropyl ketone*, which were separated by fractional distillation.\* The bromination of methyl *isopropyl* ketone has been studied previously by Favorski (*J. pr. Chem.*, 1913, **88**, 658) and by Aston and Greenberg (*J. Amer. Chem. Soc.*, 1940, **62**, 2590, 3135), and methyl 1-bromo*isopropyl* ketone was isolated and characterised, but in neither case was any deliberate attempt made to determine whether any of the isomeric bromo-ketone was produced. The bromination product from this ketone has now been carefully fractionated, and no trace of the bromomethyl *isopropyl* ketone, the properties of which were known as a result of an independent synthesis described in Part III (next paper), could be detected.

The structure of methyl bromopropyl ketone was proved by oxidation with nitric acid,  $\alpha$ -bromobutyric acid being obtained in good yield. The bromopropyl ketone was also characterised by interaction with thiourea, a reaction which provides useful confirmation of its structure since the 2-amino-4-methyl-5-ethylthiazole so formed is quite different from the known 2-amino-4-*n*-propylthiazole which would be obtained from the isomeric ketone.

The isomeric bromomethyl ketone smoothly gave *anilinomethyl propyl ketone* on treatment with aniline (identical with the product prepared from the bromo-ketone prepared by the alternative method detailed in Part III), but a few attempts to convert this into either 2- or 3-propylindole by boiling it with aniline in the presence of aniline hydrobromide were unsuccessful. The bromopropyl isomer reacted much more sluggishly with aniline, and the anilino-ketone could not be isolated. Heating with aniline and its hydrobromide, however, converted the bromopropyl ketone into 3-methyl-2-ethylindole, identical with the product obtained by the Fischer reaction from diethyl ketone.

If the structure assigned to the product of the Fischer synthesis is correct [this is by no means certain since it has been shown that alkyl group migrations in the indole series can be brought about by heating with zinc chloride (Crowther, Mann, and Purdie, *J.*, 1943, 58; Verkade and Janetzky, *Rec. Trav. chim.*, 1943, **62**, 763)], the conversion of the methyl bromopropyl ketone into the indole could be regarded as proceeding by a simple cyclisation reaction, in marked contrast to the formation of 2-ethylindole from bromomethyl ethyl ketone (Part I, preceding paper) which apparently proceeds by a different mechanism.

At the time the above work was carried out (1940—42) the main objectives were the preparation and characterisation of the bromo-ketones, and it was not possible to study further examples and to investigate the formation of indoles in greater detail. Sufficient indications have been obtained, however, to show that the further development of this field is not only highly desirable but that it offers distinct possibilities of throwing light on reaction mechanisms at present still obscure, since less complications might be expected to arise from the use of alkyl instead of aryl halogeno-ketones.

### EXPERIMENTAL.

*Bromination of Methyl n-Propyl Ketone.*—Commercial methyl *n*-propyl ketone was dried overnight ( $\text{CaCl}_2$ , filtered, and fractionated. The fraction, b. p. 100.5—102°,  $n_D^{20}$  1.3880, was collected. Bromine (320 g.) was added dropwise to a stirred mixture of the ketone (309 g.), water (240 c.c.), and potassium chlorate (55.2 g.), the reaction vessel being illuminated throughout by a 60-watt lamp. The reaction was initiated by warming to 55—60°, and once started, it was allowed to proceed at 40—45°. The bromine addition was complete in about 6 hours; the mixture was kept overnight after which the heavy oil was separated, shaken with water and magnesium oxide, and dried ( $\text{CaCl}_2$ ). The crude dry product (544 g.), which was practically colourless, was then fractionally distilled. A well-lagged column packed with short lengths of glass tubing was used; the length of the packed portion was about 35 cm. An

\* Borrow, Holland, and Kenyon (*J.*, 1946, 1086) describe the bromination of methyl propyl ketone, but their product ( $n_D^{20}$  1.4629) was probably a mixture of the two isomers.

electrically controlled manostat maintained the pressure at 50 mm. throughout the distillation. Each fraction was collected in a receiver containing a little powdered magnesium oxide. After 6 distillations the following fractions were obtained from 694 g. of crude material: (i) b. p. 70°/50 mm. (14.5 g.); (ii) b. p. 70—76°/50 mm. (5.0 g.); (iii) b. p. 76—78°/50 mm. (93.6 g.); (iv) b. p. 78—80°/50 mm. (173.2 g.); (v) b. p. 80—82°/50 mm. (47.7 g.); (vi) b. p. 82—84°/50 mm. (17.5 g.); (vii) b. p. 84—88°/50 mm. (15.7 g.); (viii) b. p. 88—90°/50 mm. (34.2 g.); (ix) b. p. 90—92°/50 mm. (56.4 g.); (x) b. p. 92—94°/50 mm. (101.7 g.); (xi) b. p. 94—100°/50 mm. (6.3 g.); (xii) b. p. 100°/50 mm. (19.5 g.). Unfortunately the column described in the preceding paper was not available when the above fractionation was carried out; a better separation of the isomers would undoubtedly have been obtained.

Redistillation of fractions (iii), (iv), and (v) (total, 315 g.) gave *methyl 1-bromo-n-propyl ketone*, b. p. 78.0—78.5°/50 mm.,  $n_D^{25}$  1.4563 (Found: Br, 48.5, 48.5.  $C_6H_9OBr$  requires Br, 48.5%). Fractions (viii), (ix), and (x) (total, 192 g.) gave *bromomethyl n-propyl ketone*, b. p. 92.0—92.5°/50 mm.,  $n_D^{25}$  1.4620 (Found: Br, 48.8%).

*a-Bromobutyric Acid from Methyl 1-Bromo-n-propyl Ketone.*—The bromo-ketone (16.5 g.) was dropped into a mixture of concentrated nitric acid (80 g.) and water (15 c.c.), heated on the steam-bath. After 1 hour the mixture was poured into water, and isolation with ether gave *a-bromobutyric acid* (10 g.), b. p. 118—120°/25 mm.,  $n_D^{20}$  1.4700 (Michael, *Ber.*, 1901, **34**, 4043 gives b. p. 105—107°/12 mm.). Treatment of the acid chloride with ammonia gave the amide, which crystallised from benzene in needles, m. p. 110° (lit., 112°, 108°, 110—112°).

*Anilinomethyl n-Propyl Ketone.*—Solutions of bromomethyl *n*-propyl ketone (8.3 g.) and aniline (9.3 g.) in dry ether were mixed; after 2 days at 20° the odour of bromo-ketone had almost disappeared. The precipitated aniline hydrobromide was filtered off, and, on evaporation of the ether under reduced pressure, the residue crystallised. The crystals were washed with small quantities of cold methyl alcohol, and crystallisation from the same solvent gave *anilinomethyl n-propyl ketone* (6 g.) as plates, m. p. 63—64° (Found: C, 74.6; H, 8.5.  $C_{11}H_{15}ON$  requires C, 74.55; H, 8.55%). The anilino-ketone is soluble in dilute hydrochloric acid, from which it is reprecipitated by alkalis.

*3-Methyl-2-ethylindole.*—A mixture of methyl 1-bromopropyl ketone (10 g.), freshly distilled aniline (25 c.c.), and aniline hydrobromide (5 g.) was kept at 20° for 1 hour and then refluxed gently for a further hour. The resulting liquid was cooled and poured into a large excess of hydrochloric acid. The crystalline precipitate was washed with dilute ammonia, dried, and distilled, yielding 3-methyl-2-ethylindole (5.5 g.), m. p. 60—62°, b. p. 178°/34 mm., 169—170°/24 mm. The slightly brown product was further purified by steam distillation and then crystallised three times from light petroleum (b. p. 40—60°), in the absence of air, giving the indole in colourless glistening plates, m. p. 65—66° (Found: C, 82.9; H, 8.2. Calc. for  $C_{11}H_{13}N$ : C, 82.95; H, 8.25%) (Plancher, *Gazzetta*, 1898, **28**, 388, gives m. p. 66°; b. p. 185°/35 mm.). It formed a picrate in methyl alcoholic solution, which, when recrystallised from benzene—light petroleum (b. p. 60—80°) formed brownish-purple needles and had m. p. 150—151° (Plancher, *loc. cit.*, gives m. p. 151°). The m. p. of the indole and of its picrate were not depressed on admixture with authentic specimens prepared by the Fischer reaction from diethyl ketone.

*2-Amino-4-methyl-5-ethylthiazole.*—A mixture of methyl 1-bromo-*n*-propyl ketone (16.5 g.), thiourea (7.6 g.), alcohol (5 c.c.), and water (5 c.c.) was heated for 3 hours on the steam-bath and then evaporated to dryness under reduced pressure. The base was liberated from the crystalline hydrobromide with alkali, and isolation with ether gave the *aminothiazole* (12 g.), b. p. 147—149°/19 mm., 110°/0.6 mm.,  $n_D^{20}$  1.5625 (Found: C, 50.7; H, 6.9.  $C_6H_{10}N_2S$  requires C, 50.65; H, 7.1%). The *picrate*, formed in methyl alcohol, crystallised from acetone in yellow needles, m. p. 239° (decomp.) (Found: C, 38.6; H, 3.7.  $C_{12}H_{13}O_7N_5S$  requires C, 38.8; H, 3.5%).

*Bromination of Methyl isoPropyl Ketone* (cf. Favorski, *loc. cit.*; Aston and Greenberg, *loc. cit.*).—The ketone (171 g.) prepared according to Whitmore, Evers, and Rothrock, *Org. Synth.*, Coll. Vol. II, 408) was brominated as described above for the normal ketone. The crude product (278 g.) was fractionated through a column containing a 40 × 1.4 cm. section packed with single-turn glass helices, and working at a reflux ratio of 10:1 and 150 mm. the following fractions were collected: (i) b. p. 79° (6.6 g.); (ii) b. p. 79—83° (7.6 g.); (iii) b. p. 83—84° (115.5 g.); (iv) b. p. 84—86° (10.1 g.); (v) b. p. 86—91° (5.2 g.); (vi) b. p. 91—94° (4.6 g.); (vii) b. p. 94—104° (5.8 g.); (viii) b. p. > 100°/35 mm. (18.7 g.) (probably dibromide). Fraction (iii), which had  $n_D^{16}$  1.4590, was pure methyl 1-bromo-*isopropyl* ketone (Found: Br, 48.4. Calc. for  $C_6H_9OBr$ : Br, 48.5%). No evidence could be obtained of the presence of any appreciable amount of bromomethyl *isopropyl* ketone, which has b. p. 86°/50 mm.,  $n_D^{14.5}$  1.4467 (Part III; following paper).

*Tetrabromopentan-2-one.*—Bromine (170 g.) was gradually added to methyl propyl ketone (24 g.) with cooling and at such a rate that hydrogen bromide was smoothly and rapidly evolved. After standing overnight the product was heated on a steam-bath for 1 hour and poured into water, and the excess of bromine was removed by passing in sulphur dioxide. The solid product was separated from oil by filtration, and crystallisation from light petroleum (b. p. 40—60°) gave *tetrabromopentan-2-one* (80 g.) as glistening plates, m. p. 57—58° (Found: Br, 80.3.  $C_5H_8OBr_4$  requires Br, 79.6%).