66. *Halogenated Ketones. Part I. The Bromination of Acetone and Methyl Ethyl Ketone.*

By J. R. Catch, D. F. Elliott, D. H. Hey, and E. R. H. Jones.

Acetone and methyl ethyl ketone have been monobrominated in aqueous solution in the presence of potassium chlorate. By careful fractionation the pure isomeric monobromo-compounds from methyl ethyl ketone have been isolated and characterised and their structures rigidly proved by comparison with synthetic materials prepared by alternative routes. By treatment with aniline under mild conditions the bromo-ketones have been converted into crystalline anilino-ketones which, on boiling with aniline, yield alkylindoles.

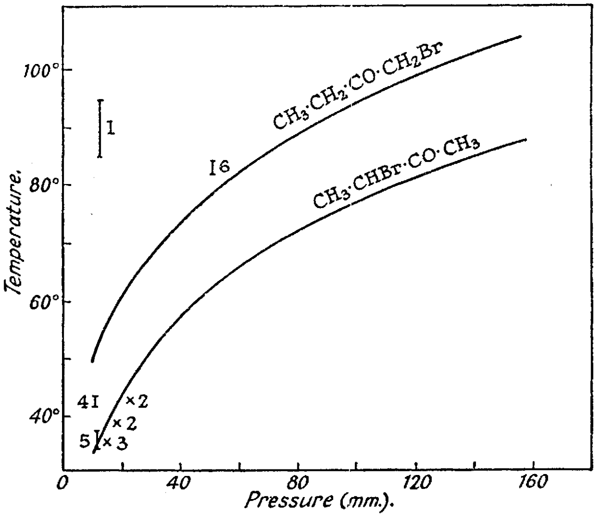
Various methods have been employed for the bromination of aliphatic ketones. Direct treatment with bromine (Sokolowsky, *Ber.*, 1876, **9**, 1687; Emmerling and Wagner, *Annalen*, 1880, **204**, 29; van Reymenant, *Bull. Acad. roy. Belg.*, 1900, 724) gives very impure materials since the liberated hydrogen bromide tends to promote the formation of condensation products. This difficulty is minimised by brominating in the presence of calcium carbonate (Scholl and Matthaiopoulos, *Ber.*, 1896, **29**, 1555; Cherbuliez and Hegar, *Helv. Chim. Acta*, 1932, **15**, 191) or by the use of acetic acid as solvent (Nef, *Annalen*, 1904, **335**, 259; Levene, *Org. Synth.*, 1930, **10**, 12). The most convenient and economical method is undoubtedly that described by Norris (*J. Ind. Eng. Chem.*, 1919, **11**, 828) as having been used in Germany for the manufacture of bromoacetone and brominated methyl ethyl ketone, consisting of bromination in aqueous solution in the presence of potassium chlorate.

$$6CH_3{\cdot}CO{\cdot}CH_3 + 3Br_2 + KClO_3 = 6CH_3{\cdot}CO{\cdot}CH_2Br + KCl + 3H_2O$$

Bromination of acetone under these conditions gave a product which, after fractionation, yielded pure bromoacetone as a colourless liquid with b. p. 63·5—64°/50 mm., $n_{\mathrm{D}}^{15^\circ}$ 1·4697. The freezing point of this material was found to be $-$ 36·5° $\pm$ 0·5°, the highest previously recorded having been $-$ 54° (Anon., *Gasschutz und Luftschutz*, 1932, **2**, 264; Stoltzenberg, "Chemische Fabrik," Hamburg, 1930). The latter value probably refers to the crude bromination product, which we found to have a freezing point of $-$ 52° to $-$ 50°. The stability of bromoacetone is notably dependent upon its purity. In the absence of any stabiliser, the crude product appears to keep much better than purified material, but the position is reversed when a trace of magnesium oxide is present. Samples of the crude product were sealed up, both with and without magnesium oxide, both in air and in nitrogen, and were stored in the dark at the ordinary temperature for fifteen months. They had all completely resinified after this time. On the other hand, specimens of the pure bromo-ketone kept over a trace of magnesium oxide, without other precautions, have remained water-white even after six years. It may be noted that the stabilisation of bromo-ketones by the addition of 0·1% or more water is claimed (Commercial Solvents Corp., U.S.P. 2,229,625).

Several studies of the bromination of methyl ethyl ketone have been made in the past, but, as will be seen below and from the figure, it is unlikely that any of the previous workers obtained both of the isomeric monobromo-compounds in a completely pure state. van Reymenant (*loc. cit.*) treated the ketone directly with bromine, de Montmollin and Matile (*Helv. Chim. Acta*, 1924, **7**, 106) claimed to have prepared bromomethyl ethyl ketone by oxidation of bromomethylethylcarbinol, and Cherbuliez and Hegar (*loc. cit.*) brominated the ketone in the presence of water and calcium carbonate. The failure of these workers to obtain the pure isomers is not surprising as their separation is difficult unless efficient fractionating columns are used. With a 25 cm. Widmer column several systematic fractionations, taking about a week to complete, were necessary in order to resolve the mixture of isomers, but with a twenty-plate (CCl_4–C_6H_6) column packed with single-turn glass helices, an almost complete separation of the pure bromo-ketones could be effected in a few hours. Distillation at atmospheric pressure results in considerable decomposition, at water pump pressure the boiling points of the isomers are inconveniently low, and it was found most convenient to operate at 150 mm., using an electrically controlled manostat.

Vapour-pressure curves of bromomethyl ethyl and methyl 1-bromoethyl ketones.



Boiling points quoted by previous workers.

$CH_3{\cdot}CH_2{\cdot}CO{\cdot}CH_2Br$:

(1) *Cherbuliez and Hegar*, loc. cit. (2) *Mohler and Pólya*, Helv. Chim. Acta, 1936, **19**, 1222. (3) *Mohler*, ibid., 1938, **21**, 67. (4) *de Montmollin and Matile*, loc. cit. (6) *Specimen prepared from propionyl bromide and diazomethane* (*Part III*).

$CH_3{\cdot}CHBr{\cdot}CO{\cdot}CH_3$:

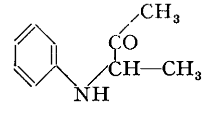
(5) *Cherbuliez and Hegar*, loc. cit.

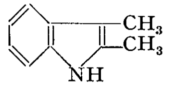
The vapour-pressure curves of the two isomers, which incidentally afford convincing evidence of their individuality, are given in the figure, together with the boiling points reported by previous workers and also that of a sample of bromomethyl ethyl ketone prepared by an alternative route (Part III, this vol., p. 278).

Chemical evidence of the correctness of the structures assigned to these two bromo-ketones has been adduced by treatment with potassium benzoate in alcohol. The resulting keto-benzoates gave crystalline *semicarbazones*, identical with those obtained from substances synthesised by alternative methods.

By treatment with aniline in dilute ethereal solution at the ordinary temperature (the bromomethyl isomer reacts more readily) the bromo-ketones are converted into *methyl* 1-*anilinoethyl ketone* (I), m. p. 54—55°, and *anilinomethyl ethyl ketone* (III), m. p. 81°. These well-crystallised products are useful for characterisation purposes, but the replacement reactions have to be carried out with care as the anilino-ketones readily cyclise to indoles and tarry by-products are often formed. When methyl 1-anilinoethyl ketone (I) is boiled with aniline and aniline hydrobromide for a few minutes, it is converted into 2 : 3-dimethylindole (II), a reaction previously effected by the single-stage treatment of the halogenated ketone with aniline (Vladesco, *Bull. Soc. chim.*, 1891, **6**, 826; Richard, *Compt. rend.*, 1907, **145**, 131).

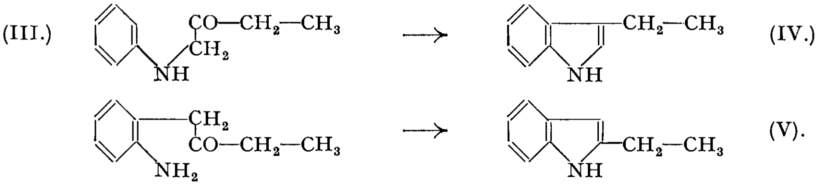
(I.)





(II.)

The question of the mechanism of this type of indole synthesis has been the subject of considerable discussion (*inter alia*, Julian, Meyer, Magnani, and Cole, *J. Amer. Chem. Soc.*, 1945, **67**, 1203; Crowther, Mann, and Purdie, *J.*, 1943, 58; Janetzky, Verkade, and Lieste, *Rec. Trav. chim.*, 1946, **65**, 193 and earlier papers), but in the case cited above no ambiguity can possibly arise. With anilinomethyl ethyl ketone (III) on the other hand, the alternative mechanisms could lead to either 3- or 2-ethylindoles (IV and V respectively), *e.g.* :



Although there is much confusion in the literature in the description of these two substances there is little doubt that the compound (m. p. 46°; *picrate*, m. p. 124°) obtained by treating the anilino-ketone (III) with aniline and aniline hydrobromide is 2-ethylindole. For this isomer m. p.s of 43° and 35° are recorded, but no picrate has hitherto been prepared. The most reliable values for 3-ethylindole would appear to be m. p. 37° [picrate, m. p. 121° (143—144°)] (cf. Robinson and Cornforth, *J.*, 1942, 680).

EXPERIMENTAL.

Bromination of Methyl Ethyl Ketone.—Commercial methyl ethyl ketone was kept overnight over about one-tenth of its weight of anhydrous calcium chloride and then filtered and fractionally distilled. The fraction, b. p. 78·5—80·5°, was collected. Bromine (1600 g.) was added dropwise to a mechanically stirred mixture of the ketone (1240 g.), water (2500 c.c.), and potassium chlorate (300 g.). The temperature of the mixture was at first raised to 50° to initiate the reaction which subsequently proceeded smoothly at 35—40°. After the addition was complete the mixture was allowed to stand for an hour, and the heavy layer of crude material was separated off, shaken with magnesium oxide and water, and dried ($CaCl_2$). The crude product (2250 g.) was practically colourless and remained so in a stoppered bottle left on the bench for 2 months. It could not be fractionally distilled at atmospheric pressure without undergoing considerable decomposition. A portion of this material was roughly distilled to remove small quantities of unchanged ketone and dibromo-ketone, and 425 g. of the isomeric mixture were carefully fractionated as follows. The column contained a packed section, 140 × 1·4 cm., of single-turn 5 mm. diameter glass helices (Fenske), insulated with a 5 cm. thick lagging of magnesia–asbestos. (When tested with carbon tetrachloride–benzene, this column had a theoretical plate value of about 20.) It was fitted with a total condensation partial take-off head, which was operated at a reflux ratio of about 6 : 1. The pressure was controlled at 150 ± 0·5 mm. by an electrically operated manostat. The following fractions were collected (total 409 g.) during an operating period of five hours: (i) b. p. 70—86·5°/150 mm. (7 g.); (ii) b. p. 86·5—87°/150 mm. (245 g.); (iii) b. p. 87—88°/150 mm. (37 g.); (iv) b. p. 88—96°/150 mm. (5 g.); (v) b. p. 96—103°/150 mm. (7 g.); (vi)

b. p. 103—104·5°/150 mm. (10 g.); (vii) b. p. 104·5—105°/150 mm. (98 g.). All the fractions were collected in receivers containing a little magnesium oxide; by this means they did not become discoloured, and samples kept during a period of six years in contact with magnesium oxide have remained practically colourless.

Fractions (ii) and (iii) consisted of methyl 1-bromoethyl ketone, $n_{D}^{20^\circ}$ 1·4571. The vapour-pressure figures in the accompanying table were obtained by distillation at various pressures, controlled by a manostat.

Fractions (vi) and (vii) consisted of *bromomethyl ethyl ketone*, $n_{D}^{20^\circ}$ 1·4670 (Found: Br, 52·7. C_4H_7OBr requires Br, 53·0%).

Vapour Pressures of Methyl 1-*Bromoethyl and Bromomethyl Ethyl Ketones.*

Pressure (mm.)	10	20	30	40	50	70	90	110	140	150	760 *
$CH_3 \cdot CHBr \cdot CO \cdot CH_3$ (b. p.)	33°	44°	52°	57·5°	—	70°	75·5°	80°	86·5°	87°	136°
$CH_2Br \cdot CO \cdot CH_2 \cdot CH_3$ (b. p.)	49°	61°	69°	74·5°	79°	87°	92·5°	98°	103·5°	105°	154—5°

* B. p.s. can be measured at 760 mm. if only small quantities are distilled.

Benzoate of Acetylmethylcarbinol (*Benzoate of Acetoin*).—(*a*) Methyl 1-bromoethyl ketone (15·1 g.) and potassium benzoate (16·1 g.) in alcohol (50 c.c.) were heated under reflux for 30 minutes. The alcohol was distilled off, finally under reduced pressure; the benzoyl derivative (15 g.), isolated by means of ether, had b. p. 136—137°/8 mm., $n_{D}^{19^\circ}$ 1·5082. The *semicarbazone* crystallised from alcohol in plates, m. p. 149° (Found: C, 57·6; H, 6·0; N, 17·1. $C_{12}H_{15}O_3N_3$ requires C, 57·8; H, 6·0; N, 16·85%).

(*b*) To a mixture of granulated zinc (100 g.) and sulphuric acid (560 g.; 10%) on the steam-bath, diacetyl (40 g.) was added during 20 minutes with frequent agitation. After a further 15 minutes' heating the product was isolated by continuous ether extraction yielding acetoin (19·3 g.), b. p. 140—142°. Benzoylation was carried out in pyridine with benzoyl chloride, and the product gave the semicarbazone, m. p. 149°, undepressed on admixture with the derivative described under (*a*).

Methyl 1-*Anilinoethyl Ketone.*—A mixture of methyl 1-bromoethyl ketone (6·0 g.) and aniline (5 c.c.) was set aside at 20° for 20 hours. The product, isolated with ether, solidified in a vacuum and after crystallisation from light petroleum (b. p. 60—80°) gave *methyl* 1-*anilinoethyl ketone* (2·5 g.) in blunt needles, m. p. 54—55°. The base is soluble in dilute hydrochloric acid and insoluble in alkalis (Found: N, 8·7. $C_{10}H_{13}ON$ requires N, 8·6%). The *semicarbazone* was obtained from alcohol as a crystalline powder, m. p. 190° (Found: C, 60·4; H, 7·0. $C_{11}H_{16}ON_4$ requires C, 60·0; H, 7·3%).

2 : 3-*Dimethylindole.*—Methyl 1-anilinoethyl ketone (0·25 g.) was heated under reflux with aniline (2 c.c.) containing aniline hydrobromide (0·5 g.) for 15 minutes. On the mixture being poured into dilute hydrochloric acid a crystalline precipitate was obtained, which on crystallisation from light petroleum (b. p. 60—80°) gave 2 : 3-dimethylindole in almost theoretical yield as plates, m. p. 104—105° (*lit.* m. p. 106°).

Benzoate of Propionylcarbinol.—(*a*) Prepared by the method described above from bromomethyl ethyl ketone (7·6 g.), potassium benzoate (8 g.), and alcohol (25 c.c.), the *benzoyl* derivative (7·9 g.) had b. p. 150—152°/8 mm., $n_{D}^{14^\circ}$ 1·5162 (Found: C, 69·0; H, 6·5. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·3%). The *semicarbazone* formed flat needles, m. p. 147°, from alcohol and gave a considerable depression in m. p. on admixture with the isomeric semicarbazone, m. p. 149°, described above (Found: C, 57·6; H, 6·2; N, 16·9. $C_{12}H_{15}O_3N_3$ requires C, 57·8; H, 6·0; N, 16·85%).

(*b*) The bromo-ketone prepared by the method described in Part III (*loc. cit.*) was converted into a benzoyl derivative and a semicarbazone identical with those described above.

Anilinomethyl Ethyl Ketone.—To a solution of bromomethyl ethyl ketone (6·05 g.) in ether (10 c.c.) a solution of aniline (5 c.c.) was added with shaking. Aniline hydrobromide began to separate after 5—10 minutes, and after 4 hours the product was isolated with ether. Crystallisation from light petroleum (b. p. 40—60°) yielded *anilinomethyl ethyl ketone* (2 g.) as plates, m. p. 81° (Found: C, 74·3; H, 8·0; N, 8·8. $C_{10}H_{13}ON$ requires C, 73·6; H, 8·0; N, 8·6%). The *semicarbazone* formed clusters of needles from alcohol, m. p. 154° (Found: C, 60·6; H, 7·1. $C_{11}H_{16}ON_4$ requires C, 60·0; H, 7·3%).

2-*Ethylindole.*—Anilinomethyl ethyl ketone (0·45 g.) was heated under reflux with aniline (2 c.c.) and aniline hydrobromide (0·5 g.) for 15 minutes. The product, isolated with ether after the mixture had been poured into dilute hydrochloric acid, had b. p. 150°/14 mm., 105°/0·5 mm. The distillate (almost quantitative yield) solidified on cooling, and after recrystallisation from light petroleum (b. p. 40—60°) formed large plates of 2-ethylindole, m. p. 46° (Verley and Beduwe, *Bull. Soc. chim.*, 1925, **37**, 189, give m. p. 43°; I.C.I. Ltd., Piggott and Rodd, B.P. 330,332 give m. p. 35°). When mixed with an authentic specimen of 3-ethylindole (m. p. 37°), kindly provided by Sir Robert Robinson, P.R.S., a liquid resulted. The *picrate* separated from aqueous alcohol in orange-red needles, m. p. 124°, depressed to 105—108° on admixture with a specimen (m. p. 121—122°) of the picrate of 3-ethylindole (Found: N, 14·7. $C_{16}H_{14}O_7N_4$ requires N, 14·95%).

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