CXLIII.—ortho- *and* meta-*Derivatives of Simple Alkyl Phenyl Ketones.*

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In connexion with a part of an extended investigation of certain types of organic arsenical compound it has been necessary to review our knowledge of derivatives of aceto-, propio-, and *n*-butyrophenones required as starting materials. In certain cases, the published methods of preparation were not suitable for our purpose and, in others, the compounds as described were apparently not pure. This preliminary investigation was, of necessity, somewhat prolonged and entailed the preparation of derivatives not hitherto described.

The first compounds required were the *o*- and *m*-amino-derivatives of the above ketones and their preparation was carried out in the same way in all cases. Each of these ketones, on nitration, yields a mixture of the *o*- and *m*-nitro-compounds, from which the *m*-compound is easily separated and obtained pure, leaving an uncrystallisable oil (crude *o*-nitro-ketone) which is chiefly the *o*-compound containing some of the *m*-isomeride. The pure *m*-nitro-ketone is reduced to the corresponding *amino*-compound, which can be easily obtained in a state of purity. The crude *o*-nitro-ketone on reduction yields a mixture of the *o*- and the *m*-amino-ketone. From this mixture, the *o*-amino-ketone is separated by steam distillation; in every case, the *m*-isomeride is much less volatile in steam than the *o*-compound, which can thus be readily obtained pure.

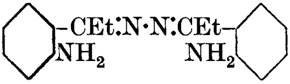
o-Aminoacetophenone has now been obtained as a pale yellow, crystalline solid, m. p. 20°. m-*Bromoacetophenone* has m. p. 7—8°; it yields 3 : ω-*dibromoacetophenone* on direct bromination and 5-*bromo*-2-*nitroacetophenone* on nitration.

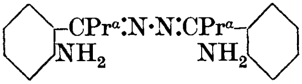
m-Aminopropiophenone does not yield a semicarbazone under the same conditions as the *o*-compound. The reaction between *o*-aminopropiophenone and semicarbazide hydrochloride, under the conditions described in the experimental portion, besides giving the semicarbazone, yields another product which is mentioned below. *o*-Bromopropiophenone, when brominated in acetic acid solution, yields 2 : α-*dibromopropiophenone*.

n-Butyrophenone (*n*-propyl phenyl ketone), prepared from *n*-butyryl chloride by the Friedel–Crafts reaction, has m. p. 13° (compare Morgan and Hickinbottom, J., 1921, **119**, 1882). *o*-Bromobutyrophenone on bromination yields first 2 : α-*dibromobutyrophenone* and then 2 : α : α-*tribromobutyrophenone*. Analysis of the latter compound and of 4 : α-*dibromobutyrophenone*—prepared from bromobenzene and α-bromobutyryl chloride by the Friedel–Crafts reaction—indicated the great tendency of these compounds to lose hydrogen bromide. 4-*Chloro*-α-*bromobutyrophenone* was, however, isolated in the crystalline state from chlorobenzene and α-bromobutyryl chloride by the Friedel–Crafts reaction. Like *m*-aminopropiophenone, *m*-aminobutyrophenone does not yield a semicarbazone under the usual conditions. The reaction between *o*-aminobutyrophenone and semicarbazide hydrochloride is discussed below.

With the exceptions noted above, there is little difficulty in isolating the semicarbazones of many of the compounds described and these may prove useful for identification purposes. The reactions, however, between *o*-aminopropiophenone and semicarbazide and between the latter compound and *o*-amino-*n*-butyrophenone need special comment. In isolating the semicarbazone of *o*-aminopropiophenone, it was noticed that the crude substance was contaminated with a bright yellow substance the quantity of which was increased when the reaction was prolonged and especially when the mixture was heated. A yellow substance only was obtained when *o*-amino-*n*-butyrophenone was treated with semicarbazide hydrochloride under the usual conditions, and the yield, again, of this product was increased when the reaction mixture was heated. The two yellow substances resembled each other very closely, both crystallising in yellow needles; that obtained from *o*-aminopropiophenone had m. p. 130° and that from *o*-amino-*n*-butyrophenone had m. p. 135°, this being obtained the more easily. The latter compound had the empirical formula $C_{10}H_{13}N_2$ and the molecular weight determination by the method of Rast indicated that this was half the molecular formula. It soon became evident that the two compounds were ketazines, that from *o*-aminopropiophenone being *ethyl-*o*-aminophenylketazine* (I) and that from *o*-amino-*n*-butyrophenone being n-*propyl*-o-*aminophenylketazine* (II).

(I.)





(II.)

The ease of formation of these substances seems unusual, ketazines being generally formed either by the action of hydrazine on ketones or by heating the semicarbazones to a moderately high temperature (Scholtz, *Ber.*, 1896, **29**, 610; Borsche, *Ber.*, 1901, **34**, 4301; Bruining, *Rec. trav. chim.*, 1922, **41**, [ii], 655), ammonia and hydrazodicarbonimide being formed during the decomposition. An attempt to prepare substance (I) by heating *o*-aminopropiophenonesemicarbazone above its melting point was unsuccessful, although the formation of a yellow material and evolution of ammonia were noticed. An attempt to prepare methyl-*o*-aminophenylketazine by the action of semicarbazide hydrochloride on *o*-aminoacetophenone in a similar manner to that described above led only to the isolation of the semicarbazone.

EXPERIMENTAL.

The nitration of acetophenone has been extensively studied by Morgan and Moss (*J. Soc. Chem. Ind.*, 1923, 461T). For the present work, acetophenone in lots of 30 c.c. was run slowly into stirred nitric acid (*d* 1·50), 140 c.c. being used each time and the temperature kept below 0°. After ½ hour, the product was poured on ice, and the crystalline *m*-nitroacetophenone separated by filtration. From the filtrate, made alkaline with sodium carbonate and hydroxide, the crude *o*-nitroacetophenone (containing some of the *m*-isomeride) was extracted with ether, the extract was washed with water and dried with calcium chloride, and the ether evaporated. To this crude *o*-nitroacetophenone was added the oily residue resulting from the evaporation of the alcoholic mother-liquor from the recrystallisation of the *m*-nitroacetophenone.

The pure *m*-nitroacetophenone was reduced under substantially the same conditions as described by Morgan and Moss. After recrystallisation from alcohol, *m*-aminoacetophenone was obtained in pale yellow plates, m. p. 98—99° (Morgan and Moss give 92—93°).

m-*Aminoacetophenonesemicarbazone* crystallises from water in colourless prisms, m. p. 196° (decomp.) (Found : N, 29·3. $C_9H_{12}ON_4$ requires N, 29·2%), and m-p-*toluenesulphonamidoacetophenone* from alcohol in colourless needles, m. p. 130° (Found : N, 4·9. $C_{15}H_{15}O_3NS$ requires N, 4·85%).

The crude *o*-nitroacetophenone was reduced with tin and hydrochloric acid as described by Morgan and Moss. The resulting mixture was made strongly alkaline with sodium hydroxide and submitted to steam distillation. The *o*-aminoacetophenone in the distillate was extracted with ether, dried with calcium chloride, and recovered; it had b. p. 130·5°/14 mm., 124°/10 mm., m. p. 20° (compare Morgan and Moss, *loc. cit.*). The pure ketone is almost colourless.

o-*Aminoacetophenonesemicarbazone* crystallises from alcohol in colourless plates, m. p. 290° (decomp.) (Found : N, 29·8. $C_9H_{12}ON_4$ requires N, 29·2%). The p-*toluenesulphonyl* derivative crystallises from alcohol in colourless hexagonal plates, m. p. 148° (Found : N, 4·9. $C_{15}H_{15}O_3NS$ requires N, 4·85%).

From 180 g. of acetophenone were obtained 40 g. of pure *o*-aminoacetophenone and 65 g. of pure *m*-aminoacetophenone.

To obtain *o*-bromoacetophenone (compare Meisenheimer, Zimmermann, and Kummer, *Annalen*, 1926, **446**, 205), *o*-aminoacetophenone (40 g.) was dissolved in hydrobromic acid (36%, 122 c.c.) and water (120 c.c.) and diazotised with a solution of sodium nitrite (21·2 g.) in water (36 c.c.) below 0°. The diazotised solution was treated with a solution in hydrobromic acid (*d* 1·49, 100 c.c.) of cuprous bromide made by reducing copper sulphate crystals (54·2 g.) in water (180 c.c.), mixed with potassium bromide (27·2 g.) dissolved in water (63 c.c.), with sulphur dioxide. After heating for some time on the water-bath, the *o*-bromoacetophenone was removed by steam distillation, extracted from the distillate with ether, washed successively with dilute sodium hydroxide solution, dilute hydrochloric acid, and water, dried with calcium chloride, and recovered. On distillation under reduced pressure it was obtained as a pale yellow liquid , b. p. 112°/10 mm., which did not solidify above — 16°. Yield, 80%.

o-*Bromoacetophenonesemicarbazone* crystallised from alcohol in colourless prisms, m. p. 177° (Found : N, 16·7. $C_9H_{10}ON_3Br$ requires N, 16·4%).

m-*Bromoacetophenone*, obtained from *m*-aminoacetophenone as *o*-bromoacetophenone from *o*-aminoacetophenone, is a pale yellow oil, b. p. 127·5°/14 mm. and 131°/16 mm., which solidifies to an almost colourless, crystalline solid, m. p. 7—8°. Yield, 54% (Found : Br, 40·5. C_8H_7OBr requires Br, 40·15%). On oxidation with sodium hypobromite it was converted into *m*-bromobenzoic acid, m. p. 155°.

m-*Bromoacetophenonesemicarbazone* crystallised from alcohol in colourless needles, m. p. 232—233° (decomp.) (Found: N, 16·3. $C_9H_{10}ON_3Br$ requires N, 16·4%).

5-*Bromo-2-nitroacetophenone* was obtained by adding *m*-bromoacetophenone (10 g.) to well-stirred nitric acid (*d* 1·50, 70 c.c.) below 0° and pouring the mixture on ice; the solid produced crystallised from alcohol (charcoal) in almost colourless needles, m. p. 98° (Found: N, 5·8. $C_8H_6O_3NBr$ requires N, 5·7%). It gave 5-bromo-2-nitrobenzoic acid, m. p. 138—140°, on oxidation with sodium hypobromite.

3 : ω-*Dibromoacetophenone.*—*m*-Bromoacetophenone (12·2 g.), dissolved in acetic acid (50 c.c.), was treated with bromine (3·08 c.c., 1 mol.). On heating on the water-bath, hydrogen bromide was evolved and the liquid became colourless. It was then poured into water and the 3 : ω-*dibromoacetophenone* was extracted with ether, washed with dilute sodium hydroxide solution and then with water, dried with calcium chloride, recovered, and distilled under reduced pressure, some unchanged material distilling first. The dibromo-ketone, obtained in 40% yield, had b. p. 172—174°/14 mm., solidified on cooling, and crystallised from ligroin (b. p. 60—80°) in long colourless needles, m. p. 51° (Found: Br, 57·1. $C_8H_6OBr_2$ requires Br, 57·5%). By oxidation with sodium hypobromite it was converted into *m*-bromobenzoic acid, m. p. 154°.

3 : ω-*Dibromoacetophenonesemicarbazone* crystallises in clusters of flattened needles, m. p. 163—164° (decomp.) (Found: N, 13·05. $C_9H_9ON_3Br_2$ requires N, 12·55%).

The Nitration of Propiophenone.—This was carried out exactly similarly to that of acetophenone and the products were also worked up similarly. The *m*-nitropropiophenone crystallises in pale yellow needles, m. p. 98—100°, and on oxidation with potassium permanganate is converted into *m*-nitrobenzoic acid (compare, however, Comanducci and Pescitelli, *Gazzetta*, 1906, **36**, ii, 787).

The reduction of *m*-nitropropiophenone was carried out with iron turnings and acetic acid, and the product worked up in the usual manner. m-*Aminopropiophenone* was obtained as a pale yellow oil, b. p. 168—169°/15 mm., which solidified to a yellow solid, m. p. 42° (Found: C, 73·3; H, 7·5. $C_9H_{11}ON$ requires C, 72·5; H, 7·4%). The yield is variable and may be as high as 60%; in some cases a large quantity of a resinous mass remained after the first distillation.

m-p-*Toluenesulphonamidopropiophenone* crystallised from alcohol in colourless needles, m. p. 97° (Found: N, 4·7. $C_{16}H_{17}O_3NS$ requires N, 4·6%).

The reduction of the crude *o*-nitropropiophenone with tin and hydrochloric acid was carried out in the same manner as for the crude *o*-nitroacetophenone. The *o*-aminopropiophenone was isolated by steam distillation and crystallised from the distillate in pale yellow plates, m. p. 46° (compare Auwers and Düesberg, *Ber.*, 1920, **53**, 1208). From 290 g. of propiophenone were obtained in a state of purity 35 g. of *o*-aminopropiophenone and 73 g. of *m*-aminopropiophenone.

o-*Aminopropiophenonesemicarbazone*, when prepared in the usual manner *in the cold*, crystallises from alcohol in colourless prisms, m. p. 190° (decomp.) (Found : N, 27·3. $C_{10}H_{14}ON_4$ requires N, 27·2%). When the solution of the reacting substances is heated, the semicarbazone obtained is mixed with the ketazine (see below). o-p-*Toluenesulphonamidopropiophenone* crystallises from alcohol in colourless prisms; it does not appear to have a definite melting point, softening at about 125° and then decomposing over a considerable range (Found : N, 4·6. $C_{16}H_{17}O_3NS$ requires N, 4·6%).

o-*Bromopropiophenone*, prepared from *o*-aminopropiophenone in the same way as the bromoacetophenones from the corresponding amino-compounds, was obtained as a pale yellow oil, b. p. 125°/12 mm., which does not solidify above − 16°; yield, 75% (Found : Br, 37·3. C_9H_9OBr requires Br, 37·5%). o-*Bromopropiophenonesemicarbazone* crystallises from alcohol in colourless plates, m. p. 182° (Found : N, 15·7. $C_{10}H_{12}ON_3Br$ requires N, 15·55%).

On bromination of *o*-bromopropiophenone in acetic acid under similar conditions to those described above, what was probably o : *α-dibromopropiophenone* was formed. This was obtained as a pale yellow liquid, b. p. 154—155°/12 mm., which solidified and crystallised in flat prisms with pyramidal ends, m. p. 38—39°; yield, 75% (Found : Br, 54·0. $C_9H_8OBr_2$ requires Br, 54·7%). It gave, on oxidation with potassium permanganate, *o*-bromobenzoic acid, m. p. 147°.

m-*Bromopropiophenone*, prepared in the usual manner from *m*-aminopropiophenone, is a yellow liquid, b. p. 143°/18 mm., which sets to a pale yellow solid, m. p. 36°; yield, 52% (Found : Br, 36·7. C_9H_9OBr requires Br, 37·5%). m-*Bromopropiophenonesemicarbazone* crystallises from alcohol in colourless needles, m. p. 180° (Found : N, 15·6. $C_{10}H_{12}ON_3Br$ requires N, 15·55%).

n-Butyrophenone was obtained in 66% yield by the action of *n*-butyryl chloride on benzene in the presence of aluminium chloride. It has m. p. 13°. It was nitrated in the manner above described for the analogous compounds (compare Morgan and Hickinbottom, J., 1921, **119**, 1882) and the products were worked up in the usual manner. *m*-Nitro-*n*-butyrophenone had m. p. 62—63° when recrystallised from alcohol (almost colourless plates) and was obtained in 42% yield. m-*Nitro*-n-*butyrophenonesemicarbazone* crystallised from alcohol in pale yellow needles, m. p. 166—167° (Found : N, 22·8. $C_{11}H_{14}O_3N_4$ requires N, 22·4%). The constituents of the crude *o*-nitro-*n*-butyrophenone could not be separated by fractional distillation under reduced pressure.

Pure *m*-nitro-*n*-butyrophenone was reduced with iron turnings and acetic acid in the manner already described, and the reaction product worked up in the usual manner. *m*-Amino-*n*-butyrophenone is a pale yellow liquid, b. p. 179—180°/16 mm., which sets to a yellow solid, m. p. 27—28°. m-p-*Toluenesulphonamido*-n-*butyrophenone* crystallises from somewhat diluted alcohol in colourless needles, m. p. 70° (Found : N, 4·3. $C_{17}H_{19}O_3NS$ requires N, 4·4%).

The crude *o*-nitro-*n*-butyrophenone was reduced with tin and hydrochloric acid and the reduction product was worked up in a similar manner to that employed for the crude *o*-nitroacetophenone, the *o*-amino-*n*-butyrophenone, unlike the corresponding *m*-compound, being volatile in steam. o-*Amino*-n-*butyrophenone* crystallises from alcohol in colourless plates, m. p. 45° ; it has b. p. 153°/16 mm. (Found : N, 8·9. $C_{10}H_{13}ON$ requires N, 8·6%). From 375 g. of *n*-butyrophenone were obtained 55 g. of pure *o*-amino-*n*-butyrophenone and 85 g. of pure *m*-amino-*n*-butyrophenone.

o-p-*Toluenesulphonamido*-n-*butyrophenone* crystallises from alcohol in colourless rhombic plates, m. p. 110° (Found : N, 4·35. $C_{17}H_{19}O_3NS$ requires N, 4·4%).

o-*Bromo*-n-*butyrophenone*, prepared from the *o*-amino-compound in the usual way, is a very pale yellow oil, b. p. 143°/16 mm., which does not solidify above − 16°. The yield is 68% (Found : Br, 34·5. $C_{10}H_{11}OBr$ requires Br, 35·2%).

o-*Bromo*-n-*butyrophenonesemicarbazone* crystallises from alcohol in colourless needles, m. p. 172° (Found : N, 15·15. $C_{11}H_{14}ON_3Br$ requires N, 15·45%).

What is presumably o : *α-dibromo*-n-*butyrophenone* was obtained by the bromination of *o*-bromo-*n*-butyrophenone in acetic acid solution with bromine (1 mol.). It is a pale yellow oil, b. p. 172°/16 mm., which darkens in the air. It does not solidify above − 16° (Found : Br, 51·4. $C_{10}H_{10}OBr_2$ requires Br, 52·2%). When oxidised with potassium permanganate it is converted into *o*-bromobenzoic acid, m. p. 148°.

When *o*-bromo-*n*-butyrophenone was brominated with bromine (3 mols.), some of the latter remained unabsorbed and was evaporated. The product was poured into water, extracted with ether, and the ether evaporated. The solid residue was crystallised by allowing its solution in alcohol to evaporate slowly and was obtained in colourless plates, m. p. 27—28° (Found : Br, 61·3. $C_{10}H_9OBr_3$ requires Br, 62·3%). The substance, probably o : α : α-*tribromo*-n-*butyrophenone*, was not readily oxidised by the ordinary methods.

m-*Bromo*-n-*butyrophenone*, obtained from *m*-amino-*n*-butyrophenone, is a pale yellow liquid, b. p. 152°/20 mm. It solidifies to an almost colourless solid, m. p. 9—10°; yield, 41% (Found : Br, 34·2. $C_{10}H_{11}OBr$ requires Br, 35·2%). Its *semicarbazone* crystallises from alcohol in colourless prisms, m. p. 158° (Found : N, 15·4. $C_{11}H_{14}ON_3Br$ requires N, 15·45%).

p-*Chloro*-α-*bromo*-n-*butyrophenone* was obtained by treating α-bromobutyryl chloride (46·4 g.) with chlorobenzene (84·4 g.) in the presence of aluminium chloride (36 g.) and carbon disulphide (46 c.c.). After the vigorous reaction had ceased, the mixture was boiled for 2 hours, poured into water, and extracted with ether and the extract was evaporated after being washed and dried. The product was distilled and had b. p. 162°/14 mm.; yield, 66%. It crystallised from alcohol in colourless rectangular plates, m. p. 43° (Found : 0·3928 g. gave 0·4960 g. of mixed silver halides. $C_{10}H_{10}OClBr$ requires 0·4974 g.). On oxidation with potassium permanganate, *p*-chlorobenzoic acid, m. p. 236°, was obtained.

On attempting to prepare *p* : α-dibromo-*n*-butyrophenone by the same method, an almost colourless liquid having b. p. 180°/15 mm. and containing 47·1% of bromine ($C_{10}H_{10}OBr_2$ requires Br, 52·2%) was obtained in a yield of 79%. The substance obtained in 58% yield by the bromination of *m*-bromo-*n*-butyrophenone was a yellow oil, b. p. 180°/18 mm. (Found : Br, 49·9%).

Both of these substances darken rapidly on standing and the low bromine content is due to partial decomposition with elimination of hydrogen bromide from the side chain.

n-*Propyl*-o-*aminophenylketazine* (II).—A mixture of *o*-amino-*n*-butyrophenone (3·4 g.), alcohol (22 c.c.), semicarbazide hydrochloride (2·7 g.), sodium acetate (6 g.), and water (22 c.c.) was kept for several days; yellow needles then separated. The substance, which was formed more rapidly when the mixture was heated on the water-bath, crystallised from alcohol, in which it was readily soluble, in yellow needles, m. p. 135° (Found : C, 74·6; H, 8·0; N, 17·4; *M*, 328. $C_{20}H_{26}N_4$ requires C, 74·5; H, 8·1; N, 17·4%; *M*, 322).

The compound is insoluble in water and dissolves to a colourless solution in dilute hydrochloric acid, from which, on being made alkaline, an oil, probably *o*-amino-*n*-butyrophenone, is precipitated.

Ethyl-o-*aminophenylketazine* (I).—A mixture of *o*-aminopropiophenone (3·3 g.), semicarbazide hydrochloride (2·7 g.), sodium acetate (6 g.), alcohol (22·5 c.c.), and water (22·5 c.c.) was boiled for several days; the yellow ketazine then separated together with some colourless semicarbazone. The mixture of solids was boiled with a little alcohol to dissolve the more soluble ketazine, and the solution filtered. The ketazine which crystallised from the filtrate was pure after one further crystallisation from alcohol, forming yellow needles, m. p. 130° (Found: C, 73·8; H, 7·8; N, 18·8. $C_{18}H_{22}N_4$ requires C, 73·5; H, 7·5; N, 19·05%). Like compound (II), it dissolves to a colourless solution in hydrochloric acid; when this solution is made alkaline, an oil, probably *o*-aminopropiophenone, is precipitated.

On heating *o*-aminopropiophenonesemicarbazone for 2 hours at 230—240°, a yellow resinous material was produced, ammonia having been evolved. It was not possible to separate any of the expected ketazine from the solid product.

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