CCLXXXIII.—*The Synthesis of* n-*Propyl* n-*Amyl Ketone by Karrer and Co-workers.*

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THE first claim to have made *n*-propyl *n*-amyl ketone is that of Bouveault and Locquin (*Bull. Soc. chim.*, 1904, **31**, 1153), who, by treating the sodio-derivative of ethyl acetylcaproylacetate (acetyl-*n*-hexoylacetate) with ethyl iodide, obtained a 74% yield of ethyl ethylcaproylacetate. This on hydrolysis with concentrated sulphuric acid gave *n*-propyl *n*-amyl ketone, b. p. 75—76°/10 mm., which gave correct analytical results. The semicarbazone, m. p. 73—74°, was obtained in colourless laminæ (Found : N, 21·43. Calc. for $C_{10}H_{21}ON_3$: N, 21·11%).

Karrer and co-workers (*Helv. Chim. Acta*, 1928, **11**, 1062) reported having obtained this ketone as the key compound in the degradation of lupinine, and having synthesised it by condensing *n*-hexoyl chloride with zinc *n*-propyl iodide, although the yield from the condensation was only about 20% of the theoretical, and analyses of both the degradation and the synthetic ketone always gave a carbon value low by 2%. From each of the ketones a semicarbazone, m. p. 60—61°,* was obtained.

As an explanation of the discrepancy between the m. p.'s observed by Bouveault and Locquin and by themselves, Karrer and co-workers suggested that the ketone obtained by the former workers may have been *iso*propyl *n*-amyl ketone. They prepared an

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* Since writing the above, we have communicated our results to Professor Karrer, who has kindly sent us small specimens of his semicarbazones, made from the original degradation and synthetic ketones, which he now finds melt at 64—65°. The crystal habit of these specimens is somewhat different, and we find the mixed m. p. of his semicarbazone from the lupinine ketone with Bouveault's compound to be 64—72°. When Prof. Karrer's two specimens, however, and also Bouveault's compound, m. p. 73°, and the semicarbazone we obtained after potassium hydroxide treatment, m. p. 73°, but which would not analyse correctly, are recrystallised under similar conditions, all form practically indistinguishable irregular, biaxial, acicular prisms with extinction 40—44°. The semicarbazone from *iso*propyl *n*-amyl ketone under these conditions forms rather more plate-like prisms with extinction 40—44°. Our thanks are due to Mr. S. Tomkeieff for these observations.

authentic specimen of the semicarbazone of this ketone and found that it did, in fact, melt at 75°, but they do not appear to have taken a mixed m. p. of this with the compound made by Bouveault and Locquin.

We have repeated the synthetic work of Karrer and co-workers and that of Bouveault and Locquin and confirmed the latter. Further, we find the mixed m. p. of Karrer's *iso*propyl *n*-amyl ketone semicarbazone and the *n*-propyl *n*-amyl ketone semicarbazone of Bouveault and Locquin to be below 60°.

We also find that the *n*-propyl *n*-amyl ketone semicarbazone as prepared by Karrer melts at 72° after a few crystallisations from light petroleum (b. p. 40—60°), not raised by a further five recrystallisations. This product does not depress the m. p. of Bouveault and Locquin's compound, although it does not analyse correctly for a nonanone-semicarbazone (Found, by Schoeller: C, 55·5; H, 9·9; N, 25·4. Calc. for $C_{10}H_{21}ON_3$: C, 60·3; H, 10·6; N, 21·1%).

Karrer and co-workers explain the low carbon content of both their degradation and their synthetic ketone by the presence of a trace of water, but in view of the fact that the corresponding ketone of Bouveault and Locquin analyses correctly, it seemed to us that a more likely explanation in the case of Karrer's synthetic ketone might be the presence of ethyl *n*-hexoate (b. p. 166°) formed during the organo-zinc reaction in the presence of ethyl acetate. The correctness of this supposition was proved by refluxing some of the ketone with methyl-alcoholic potassium hydroxide, whereby potassium *n*-hexoate was formed, and identified by conversion to *n*-hexoamide, m. p. 101—102° (unchanged by admixture with an authentic specimen). The ketone thus purified gave no more potassium *n*-hexoate on a second treatment, the formation of the latter by the alkaline hydrolysis of the ketone being thus ruled out, and further, it analysed correctly (Found: C, 75·9, 76·4, 76·4; H, 12·8, 12·8, 13·0. Calc. for $C_9H_{18}O$: C, 76·0; H, 12·7%). The semicarbazone prepared from this purified ketone gave colourless plates, m. p. 65—66° after two crystallisations from light petroleum (b. p. 40—60°) (Found: C, 60·1; H, 10·4%). Recrystallisation, however, raises the m. p. finally to 73°, giving irregular laminæ which are not distinguishable from Bouveault and Locquin's compound under the microscope and do not depress its m. p.; but now the substance gives low carbon values (Found: C, 57·1, 57·4, 58·1; H, 10·1, 10·7, 10·7%). These values, which show the maximum variations, are selected from over a dozen determinations done here and also by Schoeller. That these results are not due to combustion difficulties is proved by the fact that Bouveault and Locquin's *n*-nonan-4-one-semicarbazone has been analysed without difficulty, both by ourselves (Found : C, 60·0; H, 10·9%), and also by Schoeller (Found : N, 21·8%).

So far we are unable to account for this anomaly, since an explanation based on the presence of some ethyl *n*-amyl ketone (Calc. for semicarbazone : C, 58·4; H, 10·3%) appears to be excluded by the fact that its semicarbazone has m. p. 117°.

It is necessary to bear in mind that semicarbazones should exist in two geometrically isomeric forms, for Mills and Bain (J., 1914, **105**, 64) resolved the semicarbazone of *cyclo*hexanone-4-carboxylic acid into optically active components. Moreover, the m. p.'s recorded for many ketone semicarbazones are very diverse.

We find, however, that the above-described anomalies shown by the semicarbazone of *n*-nonan-4-one do not appear in the case of the p-*nitrophenylhydrazone*, which, prepared from Karrer's *n*-nonan-4-one (whether or not this is purified by potassium hydroxide) separates from ligroin (b. p. 60—80°) in yellow, irregular plates, m. p. 84—85° (Found : C, 65·0; H, 8·7. $C_{15}H_{23}O_2N_3$ requires C, 65·0; H, 8·4%). An identical product is obtained from Bouveault's nonanone (Found : C, 64·8; H, 8·6%). The compound decomposes on keeping.

Like the normal ketone, *iso*propyl *n*-amyl ketone can be purified by treatment with methyl-alcoholic potassium hydroxide (Found : C, 76·4; H, 12·7%).

We conclude that the *n*-propyl *n*-amyl ketone semicarbazone of Bouveault and Locquin, m. p. 73—74°, is a pure compound and is correctly described, and that if *n*-propyl *n*-amyl ketone gives a pure semicarbazone, m. p. 60—61°, it is a form which we have been unable to obtain after repeated attempts. We consider it desirable that the *p*-nitrophenylhydrazone should be made from the ketone obtained from lupinine so as to clear up the present ambiguity underlying this important structural question.

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