40. *Experiments on the Synthesis of Aza-steroids. Part I.*

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Syntheses of 15 : 16-dihydro-11-aza*cyclo*penta[*a*]phenanthrene * and certain related substances have been achieved.

Certain alkaloids such as solanine, veratrine, and conessine which show interesting physiological properties have been shown to be steroid derivatives (Soltys and Wallenfels, *Ber.*, 1936, **69**, 811; Clemo, Morgan, and Raper, *J.*, 1936, 1299; Jacobs and Sato, *J. Biol. Chem.*, 1948, **175**, 57; Haworth *et al.*, *J.*, 1949, 831; 1951, 1371). Besides these natural products, many basic steroids have been synthesised for biological study (Antarci and Petrow, *J.*, 1951, 901; Marjori, Hutton, and Webb, *J.*, 1951, 2767; Dodgson and Haworth, *J.*, 1952, 67). All these, however, contain the basic group outside the *cyclo*penta[*a*]-phenanthrene ring; the only known steroids which contain the nitrogen in the ring are 4-aza-derivatives (Bolt, *Rec. Trav. chim.*, 1938, **57**, 905; U.S.P. 2,227,876) which have been synthesised from natural steroids. Cook and Thomson prepared 6-azachrysene, 1-azapyrene, and 3 : 4-benz-5-azaphenanthrene (*J.*, 1945, 395) for the study of their carcinogenic properties. Buu-Hoï also obtained interesting results for some polycyclic aza-compounds (*J.*, 1952, 2225). It was considered therefore that aza-steroids (compounds containing a nitrogen atom in different positions of the steroid skeleton) might possess interesting physiological properties and also assist in the elucidation of the structure of such phen-anthridine alkaloids as tazzetine, chelidonine, delphinine, and lycorine.

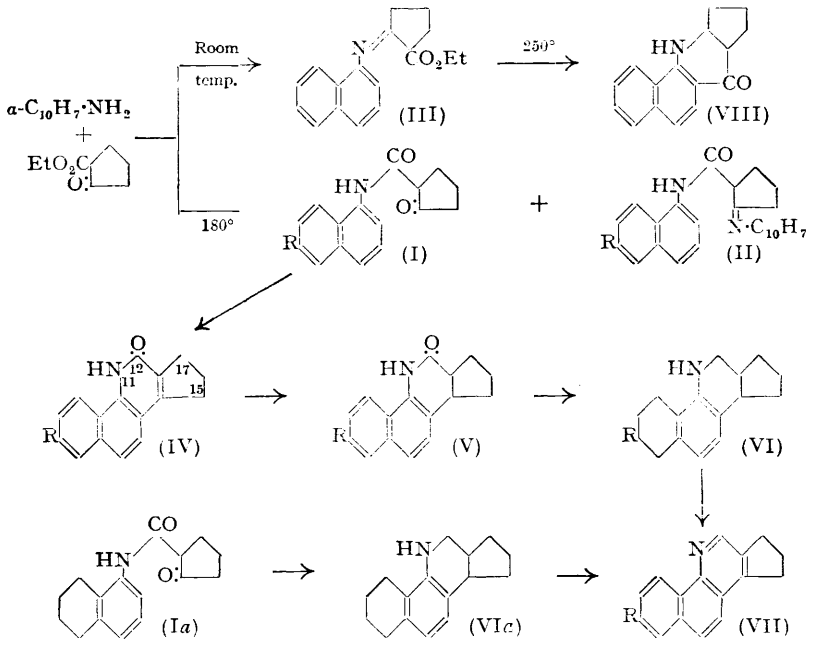
Our first syntheses started from α-naphthylamine which when heated with ethyl 2-keto*cyclo*pentanecarboxylate gave two products, (I and II; R = H). The naphthalide (I; R = H) gave a deep blue colour with ferric chloride and a crystalline 2 : 4-dinitro-phenylhydrazone. Ring closure of (I; R = H) by concentrated sulphuric acid yielded a high-melting solid (IV; R = H) which is insoluble in both dilute acid and alkali and is sparingly soluble in organic solvents. An alcoholic solution of (IV; R = H) gives a light brown colour with ferric chloride which is characteristic of the 2-pyridone and 2-quinolone systems, and, like the quinolone, (IV) can react in the 12-hydroxy-form. Catalytic reduction of this compound failed because of its sparing solubility, but sodium amalgam in boiling ethanol yielded a dihydro-product (V; R = H) which was reduced by sodium in boiling alcohol to a secondary base (VI; R = H). When (IV; R = H) was heated with phosphorus oxychloride, the 12-chloro-compound was obtained in moderate yield, but attempts to reduce this chloro-compound to a secondary base by sodium and alcohol gave 12-ethoxy-15 : 16-dihydro-11-aza*cyclo*penta[*a*]phenanthrene. Catalytic reduction of 12-chloro-15 : 16-dihydro-11-aza*cyclo*penta[*a*]phenanthrene with palladium–charcoal in acetic acid (*Org. Synth.*, **26**, 45) as well as with Adams's platinum oxide failed to give 15 : 16-dihydro-11-aza*cyclo*pent[*a*]phenanthrene. Mikailov's method (*J. Gen. Chem., U.S.S.R.*, 1936, **6**, 511) of reducing 2-chlorolepidine to lepidine also proved unsuccessful in this case, but a small quantity of (VI; R = H) was obtained when this chloro-compound was reduced with tin and alcoholic hydrochloric acid at 100°. Dehydrogenation of (VI; R = H) with selenium gave a crystalline base (VII; R = H) the melting point (130°) of which was very near to that of *cyclo*penta[*a*]phenanthrene (m. p. 134°) and which readily gave a methiodide. This, however, did not give the expected *pseudo*-base with the grouping $\mathrm{MeN}\text{–}\mathrm{CH}\cdot\mathrm{OH}$ on treatment with alkali, (VII; R = H) being recovered.

Attempts to introduce a keto-group into the 15- or the 17-position of (VII; R = H) by chromic acid or selenium dioxide failed.

At room temperature α-naphthylamine and ethyl 2-keto*cyclo*pentanecarboxylate gave a crystalline Schiff's base (III; R = H) which neither gave a colour with ferric chloride nor formed a 2 : 4-dinitrophenylhydrazone. Ring closure of this compound at 250° (Conrad and Limpach, *Ber.*, 1887, **20**, 944; 1931, **64**, 969) gave a high-melting, sparingly soluble substance (VIII; R = H) which resembled its isomer (IV; R = H).

* Ring Index names [steroid numbering except for (VIII)] are used in this paper.

When α-naphthylamine was replaced as starting material by 5 : 6 : 7 : 8-tetrahydro-1-naphthylamine, the reactions gave a series of reduced compounds up to the secondary base (VI*a*). This on selenium dehydrogenation gave a product identical with (VII; R = H). Although the secondary bases (VI) and (VI*a*) have similar ultra-violet spectra and analyses and give the same product on dehydrogenation, they had different melting points and the mixed melting point was depressed by 10°. We suggest that they are



cis- and *trans*-forms of 1 : 2 : 3 : 4 : 11 : 12 : 13 : 14 : 15 : 16-decahydro-11-aza*cyclo*penta[*a*]-phenanthrene. From the work of Skita (*Annalen*, 1923, **431**, 1) the higher-melting base (VI) which was also obtained by the reduction of the chloro-compound in acid solution may be considered the *cis*-form.

The same reactions were also carried out with 6-methoxy-1-naphthylamine and compounds up to the dihydro-product (V; R = OMe) obtained, but this could not be reduced to (VI; R = OMe).

An attempt was made to prepare (VI; R = H) with a 13-methyl group, but ethyl 2-keto-1-methyl*cyclo*pentanecarboxylate did not condense with α-naphthylamine. We also tried unsuccessfully to condense methylacrylonitrile and methyl methylacrylate with α-naphthylamine, although acrylonitrile gave good yields of condensation product. Bruson (*Org. Reactions*, Vol. V, p. 108) has also observed that methylacrylonitrile is much less reactive than acrylonitrile in the cyanoethylation of aromatic amines. Thus the introduction of the methyl group by direct synthesis does not seem possible. Other methods of introducing the 13-methyl group are being investigated.

The ultra-violet absorption spectra of 15 : 16-dihydro-11-aza*cyclo*penta[*a*]phenanthrene (VII) is similar to that of 15 : 16-dihydro*cyclo*penta[*a*]phenanthrene (Mayneord and Roe, *Proc. Roy. Soc.*, 1935, *A*, **152**, 299; Harper, Kon, and Ruzicka, *J.*, 1934, 124). It (Fig. 1) shows three main regions of absorption (250, 270—300, and 325—350 mμ). The maxima of the three absorption bands of (VII) are shifted to shorter wave-lengths, and the third band is more intense than that of its carbon analogue, in agreement with the findings of Badger, Pearce, and Petit (*J.*, 1951, 3199) for a series of aza-compounds. The ultra-violet spectra of (VI) and (VI*a*) (Fig. 2) have three absorption maxima (225, 250, and 295 mμ).

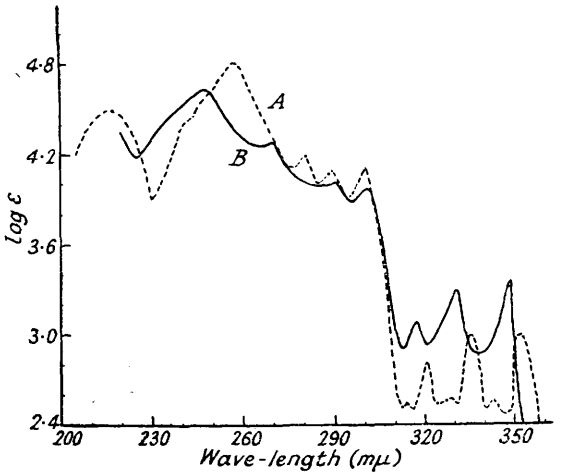
Experimental

M. p.s are uncorrected.

2-*Keto*cyclo*pentanecarboxy*-α-*naphthalide* (I; R = H).—α-Naphthylamine (14·3 g.) was added during 5 minutes to ethyl 2-keto*cyclo*pentanecarboxylate at 150°. The temperature was raised to 170—180° and the mixture refluxed for 3 minutes. The cooled product was extracted with methanol. On removal of methanol, the oily residue solidified when rubbed with light petroleum (b. p. 40—60°). The *naphthalide*, crystallised from light petroleum–ether, had m. p. 94—95° (15 g.) (Found : C, 75·8; H, 6·5. $C_{16}H_{15}O_2N$ requires C, 75·9; H, 6·0%). The 2 : 4-*dinitrophenylhydrazone* separated from alcohol as yellow crystals, m. p. 236—238° (Found : C, 60·9; H, 4·9. $C_{22}H_{21}O_6N_3$ requires C, 61·0; H, 4·4%).

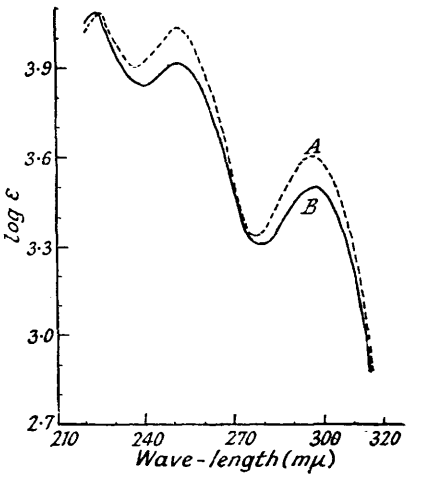
2-α-*Naphthylimino*cyclo*pentanecarboxy*-α-*naphthalide* (II; R = H).—The solid residue left after extraction with methanol from the above reaction mixture crystallised from ethanol in light yellow needles of the second *naphthalide*, m. p. 162° (4 g.) (Found : C, 82·7; H, 5·9; N, 8·0. $C_{26}H_{22}ON_2$ requires C, 82·5; H, 5·8; N, 7·5%). It gave neither a colour with ferric chloride, nor a crystalline 2 : 4-dinitrophenylhydrazone.

Fig. 1.



A, 15 : 16-*Dihydroxy*cyclo*penta*[a]*phenanthrene* (*Mayneord and Roe*, loc. cit.).
B, 15 : 16-*Dihydro*-11-*aza*cyclo*penta*[a]*phenanthrene*.
Both in ethanol.

Fig. 2.



A, (c–d)trans- *and*, *B*, cis-1 : 2 : 3 : 4 : 11 : 12 : 13 : 14 : 15 : 16-*Decahydro*-11-*aza*cyclo*penta*[a]*phenanthrene, in ethanol.*

Ethyl 2-α-*Naphthylimino*cyclo*pentanecarboxylate* (III; R = H).—A mixture of α-naphthylamine (14·3 g.) and ethyl 2-keto*cyclo*pentanecarboxylate (15·6 g.) was kept in a vacuum-desiccator ($CaCl_2$) for a fortnight, yielding a thick liquid, which on seeding and cooling in a refrigerator solidified. The *product* crystallised from methanol as needles, m. p. 73° (Found : C, 77·3; H, 7·1. $C_{18}H_{19}O_2N$ requires C, 76·9; H, 6·7%).

11 : 12 : 15 : 16-*Tetrahydro*-12-*keto*-11-*aza*cyclo*penta*[a]*phenanthrene* (IV; R = H).—2-Keto*cyclo*pentanecarboxy-α-naphthalide (15 g.) was added gradually to cooled concentrated sulphuric acid (25 ml.) with stirring. After the exothermic reaction subsided, the mixture was heated for 15 minutes on a steam-bath, and the deep brown viscous liquid obtained was slowly poured into cold water (1 l.). The precipitated solid *aza-ketone* was washed twice with alcohol and crystallised from 90% acetic acid as needles (11 g.) which sublimed above 250° (Found : C, 81·5; H, 5·7. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·5%).

11 : 12 : 13 : 14 : 15 : 16-*Hexahydro*-12-*keto*-11-*aza*cyclo*penta*[a]*phenanthrene* (V; R = H).—Carbon dioxide was passed into a suspension of (IV; R = H) (10 g.) in absolute alcohol (700 ml.), and sodium hydrogen carbonate (1 g.) then added. Sodium amalgam (700 g.; 4%) was added in portions during 6 hours, and stirring and heating were continued for another 4 hours. The thick pasty mass was filtered hot and the filtrate evaporated to dryness. The solid residue was extracted with benzene (250 ml.), the solvent removed, and the residue on crystallisation

from benzene gave a crystalline *product*, m. p. 180° (7·5 g.) (Found: C, 81·2; H, 6·7. $C_{16}H_{15}ON$ requires C, 81·5; H, 6·4%).

(c–d)cis-1 : 2 : 3 : 4 : 11 : 12 : 13 : 14 : 15 : 16-*Decahydro*-11-*aza*cyclo*penta*[a]*phenanthrene* (VI; R = H).—To a suspension of the previous compound (10 g.) in boiling ethanol (50 ml.), sodium (20 g.) was added, and a further 150 ml. of ethanol were added during the addition of sodium. The mixture, on cooling, solidified and was then dissolved in water. Alcohol was removed in steam. The residue was extracted with ether, the ethereal solution dried (Na_2SO_4), and the solvent removed. A residual thick brown oil solidified when rubbed with light petroleum (b. p. 40—60°). A solution of the crude product on methanol was decolorised with charcoal and filtered. Concentration and cooling yielded the *base*, m. p. 76—77° (Found: C, 84·8; H, 8·9; N, 6·5. $C_{16}H_{21}N$ requires C, 84·6; H, 9·2; N, 6·2%). The *picrate*, m. p. 185° (decomp.), separated from ethanol (Found: C, 58·1; H, 5·4; N, 11·8. $C_{16}H_{21}N,C_6H_3O_7N_3$ requires C, 58·0; H, 5·3; N, 12·3%), and the *benzoyl* derivative, m. p. 160°, from methanol (Found: C, 83·9; H, 7·6; N, 4·3. $C_{23}H_{25}ON$ requires C, 83·4; H, 7·6; N, 4·2%).

15 : 16-*Dihydro*-11-*aza*cyclo*penta*[a]*phenanthrene* (VII; R = H).—Compound (VI; R = H) (1 g.) and selenium (3 g.) were heated at 340—345° for 24 hours in a sealed tube. An ethereal extract of the product was set aside for 2 hours, most of the selenium being deposited. The filtrate therefrom was evaporated to dryness, and the residue dissolved in methanol (charcoal) and filtered. The clear filtrate was concentrated and cooled in ice-water, whereupon the *base*, m. p. 130°, separated (Found: C, 87·3; H, 6·4; N, 6·0. $C_{16}H_{13}N$ requires C, 87·6; H, 6·0; N, 6·4%). The *picrate*, m. p. 237—238°, separated from ethanol (Found: C, 58·9; H, 4·1; N, 12·8. $C_{16}H_{13}N,C_6H_3O_7N_3$ requires C, 59·0; H, 3·6; N, 12·5%). The *methiodide*, obtained by methyl iodide (2 mols.) in acetone at 100° for 24 hours, separated from methanol as yellow needles, m. p. 220° (Found: C, 56·5; H, 4·4. $C_{17}H_{16}NI$ requires C, 56·5; H, 4·4%). This (2 g.) was suspended in water (250 ml.), and 10% aqueous sodium hydroxide (50 ml.) was added gradually; the mixture was left for ½ hour and then extracted with ether, from which (VII) was recovered.

12-*Chloro*-15 : 16-*dihydro*-11-*aza*cyclo*penta*[a]*phenanthrene*.—Compound (IV; R = H) (11·75 g.) and freshly distilled phosphorus oxychloride (12 g.) were refluxed till the whole of the solid dissolved. The hot mixture was poured into ice and water, and set aside for 2 hours. The solid which separated was dissolved in concentrated hydrochloric acid (200 ml.), and the solution filtered. Dilution of the filtrate with water precipitated the hydrochloride, which was decomposed with excess of 30% sodium hydroxide solution. The *base* (4 g.) crystallised from a large volume of ethanol as plates, m. p. 195° (Found: C, 76·0; H, 5·0. $C_{16}H_{12}NCl$ requires C, 75·7; H, 4·7%).

12-*Ethoxy*-15 : 16-*dihydro*-11-*aza*cyclo*penta*[a]*phenanthrene*.—The above chloro-compound (2 g.) in boiling ethanol (200 ml.) was treated with sodium (5 g.). When all the sodium had dissolved, the ethanol was removed in steam and the residue extracted with ether. The extract was dried and evaporated. The *product* (0·8 g.), crystallised from methanol, had m. p. 125° (Found: C, 81·9; H, 6·9. $C_{18}H_{17}ON$ requires C, 82·1; H, 6·5%). 0·7 G. of starting material was recovered.

Reduction of the Chloro-compound.—This compound (1·5 g.), concentrated hydrochloric acid (10 ml.), ethanol (10 ml.), and tin (1·5 g.) were heated together for several hours on the steam-bath, a clear solution being obtained. Alcohol was distilled off. On cooling and dilution of the acid solution a gummy solid was obtained, which was decomposed with excess of 10% sodium hydroxide solution. The base was extracted with ether, the extract dried, and the solvent removed. The residue, crystallised from methanol, had m. p. 76° alone or mixed with (VI; R = H) (Found: C, 85·0; H, 8·8%).

7 : 7a : 9 : 10 : 10a : 11-*Hexahydro*-7-*keto*-11-*aza*cyclo*penta*[b]*phenanthrene* (VIII).—Compound (III; R = H) (14·0 g.) was added to paraffin (250 ml.) at 250° during 5 minutes. Stirring and heating were continued for another 5 minutes. On cooling to 100° the solution was filtered, and the dark brown solid was washed with benzene to remove the last traces of paraffin. The *product* (6·5 g.) separated from 80% acetic acid as colourless crystals which did not melt at 300° (Found: C, 81·7; H, 5·5. $C_{16}H_{13}ON$ requires C, 81·7; H, 5·6%). Its alcoholic solution produced a light reddish-brown colour with ferric chloride.

1 : 2 : 3 : 4 : 11 : 12 : 15 : 16-*Octahydro*-12-*keto*-11-*aza*cyclo*penta*[a]*phenanthrene* (as IV; R = H).—5 : 6 : 7 : 8-Tetrahydro-1-naphthylamine (14·7 g.) (Bamberger, *Ber.*, 1888, **21**, 1786) was condensed with ethyl 2-keto*cyclo*pentanecarboxylate (15·6 g.) as was α-naphthylamine. The *naphthalide* (10 g.) crystallised from ether–light petroleum (b. p. 40—60°) as needles, m. p. 77° (Found: C, 74·2; H, 7·6. $C_{16}H_{19}O_2N$ requires C, 74·7; H, 7·4%). It gave a deep blue

colour with ferric chloride. Ring closure by concentrated sulphuric acid gave a high-melting, sparingly soluble *product* (as IV; R = H), which crystallised from ethanol (Found: C, 80·8; H, 7·6. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·1%).

1 : 2 : 3 : 4 : 11 : 12 : 13 : 14 : 15 : 16-*Decahydro*-12-*keto*-11-*aza*cyclo*penta*[a]*phenanthrene* (as V; R = H).—The above product was reduced by sodium amalgam and boiling alcohol as was (as V; R = H). The *product*, m. p. 135°, crystallised from benzene or alcohol (Found: C, 79·9; H, 8·3. $C_{16}H_{19}ON$ requires C, 79·7; H, 7·9%).

(c–d)trans-1 : 2 : 3 : 4 : 11 : 12 : 13 : 14 : 15 : 16-*Decahydro*-11-*aza*cyclo*pent*[a]*phenanthrene* (VI*a*).—The previous compound was reduced by sodium and boiling alcohol as already described. The secondary *base* had m. p. 60° (from methanol) (Found: C, 84·4; H, 9·6; N, 6·3. $C_{16}H_{17}N$ requires C, 84·6; H, 9·3; N, 6·1%). The *picrate*, m. p. 180° (decomp.), crystallised from alcohol (Found: C, 57·8; H, 5·5. $C_{16}H_{21}N,C_6H_3O_7N_3$ requires C, 58·0; H, 5·3%), and the *benzoyl* derivative, m. p. 120°, from methanol (Found: C, 82·9; H, 7·9. $C_{23}H_{25}ON$ requires C, 83·4; H, 7·6%).

When (VI*a*) was dehydrogenated with selenium, (VII; R = H) (m. p. 129—130°) was produced.

11 : 12 : 15 : 16-*Tetrahydro*-12-*keto*-3-*methoxy*-11-*aza*cyclo*penta*[a]*phenanthrene* (IV; R = OMe).—6-Methoxy-1-naphthylamine (15·7 g.) (Bachman, Wild, and Cole, *J. Amer. Chem. Soc.*, 1940, **62**, 824) was condensed with ethyl 2-keto*cyclo*pentanecarboxylate at 180° as for α-naphthylamine. Ring closure of the crude product by concentrated sulphuric acid produced a high-melting *product* as needles (from 80% acetic acid), which did not melt up to 300° (Found: C, 77·5; H, 6·0. $C_{17}H_{15}O_2N$ requires C, 77·0; H, 5·7%).

11 : 12 : 13 : 14 : 15 : 16-*Hexahydro*-12-*keto*-3-*methoxy*-11-*aza*cyclo*penta*[a]*phenanthrene* (V; R = OMe).—Reduction of the above compound with sodium amalgam and boiling alcohol gave the *product*, m. p. 212° (from benzene) (Found: C, 76·7; H, 6·9. $C_{17}H_{17}O_2N$ requires C, 76·4; H, 6·4%). Reduction of this with (*a*) sodium and alcohol, (*b*) hydrogen in the presence of Adams's catalyst, or (*c*) lithium aluminium hydride in tetrahydrofuran proved unsuccessful and the original material in (*b*) and (*c*) was obtained unchanged, whereas a tar was obtained in (*a*).

N-2′-*Cyanoethylamino*-α-*naphthylamine*.—α-Naphthylamine (14·3 g.), acrylonitrile (7·5 g.), and glacial acetic acid (1 g.) were heated in a sealed tube for 16 hours at 120—125°. The *product* was distilled and the fraction, b. p. 154—155°/0·5 mm., a light yellow viscous mass, solidified overnight. Crystallised from methanol it had m. p. 71—72° (10 g.) (Found: C, 79·7; H, 6·3; N, 13·9. $C_{13}H_{12}N_2$ requires C, 80·0; H, 6·1; N, 14·3%). Hydrolysis with alcoholic potassium hydroxide on the steam bath produced the *carboxylic acid*, m. p. 145—146° (Found: C, 72·4; H, 6·4. $C_{13}H_{13}O_2N$ requires C, 72·5; H, 6·1%).

Methylacrylonitrile.—Methods of preparing this substance from acetone cyanohydrin have been described (Henry, *Chem. Zentr.*, 1898, **11**, 662; Buris, Jones, and Ritchie, *J.*, 1935, 716) but we did not find them convenient. We obtained better yields by dehydration of methylacrylamide (*Org. Synth.*, **29**, 61). Methylacrylamide (8·5 g.) and phosphoric oxide (7·0 g.) were heated in a distilling flask. A colourless liquid (5·0 g.), b. p. 85—95°, was collected, which was washed with sodium carbonate solution, dried (P_2O_5), and distilled. 4·0 g. of colourless liquid, b. p. 90—91°, were obtained. Henry (*loc. cit.*) recorded b. p. 90—92°.

KING'S COLLEGE, NEWCASTLE-ON-TYNE. [*Received, September 5th*, 1952.]