1025. *Some Derivatives of 9-Azabicyclo[3,3,1]nonane.*

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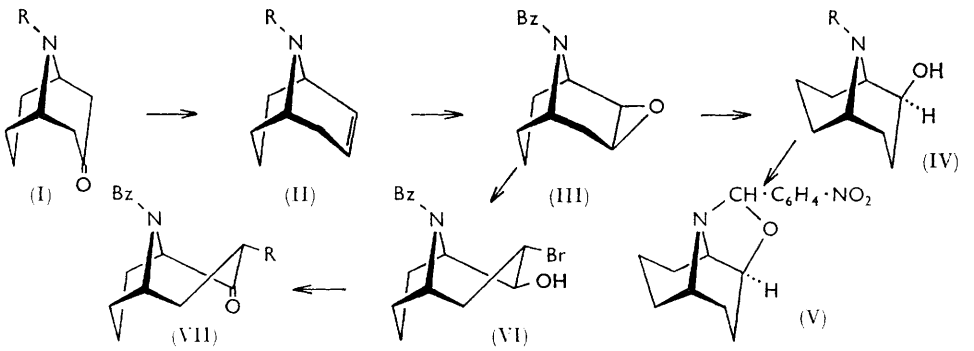
9-Benzoyl-9-azabicyclo[3,3,1]nonan-2-one (VII; R = H) has been synthesised by two routes; the first involves the transposition of the carbonyl function of 9-benzoylnor-ψ-pelletierine (I; R = Bz), while the second entails the use of methyl 6-methyl-2-picolinate as starting material. Conversion of this ketone into 9-benzoyl-1,2,3,4-tetrahydro-1,3-propano-β-carboline (X; R = H_2), and the identification of the latter with material obtained by another route, is described.

The synthesis of derivatives of 1,2,3,4-tetrahydro-1,3-propan-β-carboline has recently been described [1] and their use as intermediates for the elaboration of certain indole alkaloids is currently being investigated. An obvious alternative route to compounds having this ring system consists in the application of the Fischer indole synthesis to the appropriate bicyclic ketone. In order to explore this possibility, and at the same time provide compounds suitable for model studies in connection with the work mentioned, we undertook the preparation of the bicyclic ketone (VII; R = H).

Nor-ψ-pelletierine (I; R = H), available by a modified Robinson–Schöpf synthesis,[2] was reduced with sodium borohydride, and the crude mixture of alcohols was dehydrated to 9-azabicyclo[3,3,1]non-2-ene (granatenine) (II; R = H), isolated and purified as the



carbamate. Trifluoroperacetic acid [3] smoothly converted the *N*-benzoyl olefin (II; R = Bz) into the epoxide (III), which, although apparently resistant to reduction with lithium aluminium hydride, was reduced by lithium and ethylamine to 2β-hydroxy-9-azabicyclo[3,3,1]nonane (IV; R = H), characterised as the *N*-benzoyl derivative. The configuration of this base, and therefore of the epoxide, was demonstrated by the formation of the oxazolidine (V) by condensation with *p*-nitrobenzaldehyde.[4]

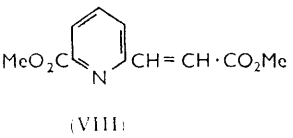
Treatment of (III) with hydrogen bromide gave the 2β-hydroxy-3α-bromo-derivative, *i.e.*, the configuration to be expected from normal epoxide ring opening leading to diaxial substitution in the chair conformation.[5,*] Mild alkali quantitatively reconverted this

* The preferred conformation of this compound would seem likely to be as shown in (VI) because of the serious interactions involving axial substituents at C-3 and C-7 in the twin-chair conformation of saturated bicyclo[3,3,1]nonanes.[6] Moreover, it being assumed that the geometry of the product is partially established in the transition state for acid-catalysed ring opening of epoxides,[5] it is possible that the above reaction is an example of the usually less favoured mode of cleavage, *i.e.*, that leading to diequatorial substitution, in this case involving a ring in the boat conformation.

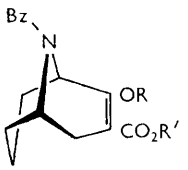
[1] Hobson, Raines, and Whiteoak, *J.*, 1963, 3495.
[2] Alder, Betzing, Kuth, and Dortmann, *Annalen*, 1959, **620**, 73.
[3] Emmons and Pagano, *J. Amer. Chem. Soc.*, 1955, **77**, 89.
[4] Hardegger and Ott, *Helv. Chim. Acta*, 1953, **36**, 1186.
[5] Parker and Isaacs, *Chem. Rev.*, 1959, **59**, 737.
[6] Eliel, " Stereochemistry of Carbon Compounds," McGraw-Hill, New York, 1962, p. 296.

bromohydrin (VI) into the epoxide (III). Oxidation with chromic acid, under conditions not normally causing epimerisation,[7] gave the α-bromo-ketone (VII; R = Br), the infrared spectrum of which showed a carbonyl band at 1740 cm.$^{-1}$, *i.e.*, 19 cm.$^{-1}$ higher than that of the parent ketone, indicating an equatorial bromine atom.[8] Debromination was accomplished smoothly with zinc and acetic acid, giving the ketone (VII; R = H), isomeric with *N*-benzoylnor-ψ-pelletierine (I; R = Bz).

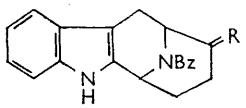
A second route to this compound, following established procedures,[9] was also studied, but proved to be less satisfactory. Methyl 6-methyl-2-picolinate was converted into methyl β-(6-methoxycarbonyl-2-pyridyl) acrylate (VIII), and thence, after reduction, benzoylation, and Dieckmann cyclisation, into the bicyclic β-keto-ester (IX; R = H, R′ = Me). Like the more complex analogues already encountered [1] this compound possessed markedly enolic properties, having an infrared spectrum which showed exclusively the conjugated chelate type of absorption in the carbonyl region.[10,11] The ultraviolet spectrum given by a solution in 95% ethanol, displayed a broad maximum centred at



(VIII)



(IX)



(X)

251 mμ (ε 12,400), a somewhat shorter wavelength than the range, 255—268 mμ, recently observed for a series of alicyclic β-keto-esters.[11] The already high intensity of this band was not significantly enhanced by changing the solvent to cyclohexane. Since the latter normally favours a greater predominance of the enol tautomer than does ethanol,[11] it is clear that the compound is virtually completely enolic in both these solvents. In this case, it seems reasonable to ascribe this property to the relief of non-bonded interactions associated with the hydrogen atoms attached to C-3 and C-4 in the keto-form.

In accord with previous experience,[1] the most reliable and efficient route for the conversion of this compound into the ketone (VII; R = H) was *via* the *O*-methyl ether (IX; R = R′ = Me), obtained with diazomethane. Hydrolysis of this compound with mild alkali, followed by hydrolysis and decarboxylation of the resulting acid (IX; R = Me, R′ = H) with mineral acid, furnished the ketone (VII; R = H) obtained previously.

Cyclisation of the corresponding phenylhydrazone readily gave 9-benzoyl-1,2,3,4-tetrahydro-1,3-propano-β-carboline (X; R = H_2), and comparison of this product with material obtained by reduction of the ketone (X; R = O) satisfactorily confirmed their identity.

Experimental

9-Azabicyclo[3,3,1]non-2-ene (II; R = H).—A solution of nor-ψ-pelletierine [2] (20 g.) and sodium borohydride (4 g.) in ethanol (200 ml.) was refluxed for 4 hr. Removal of the solvent, followed by dilution with water and isolation with ether, gave an oil, which was heated with acetic acid (15 ml.) and concentrated sulphuric acid (35 ml.) at 160° for 6 hr. The cooled mixture was diluted with water, basified with 40% sodium hydroxide solution, and extracted with ether continuously for 24 hr. Saturation of the extract with carbon dioxide precipitated the olefin as the hydrated *carbamate* (12·5 g.) (Found: C, 66·0; H, 9·0; N, 9·2. $C_{17}H_{26}N_2O_2,H_2O$ requires C, 66·2; H, 9·15; N, 9·1%).

[7] *E.g.*, *inter alia*, Fajkos and Sorm, *Coll. Czech. Chem. Comm.*, 1959, **24**, 3115.
[8] Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828.
[9] Tullock and McElvain, *J. Amer. Chem. Soc.*, 1939, **61**, 961; Nikitskaya and Rubtsov, *Zhur. obshchei Khim.*, 1957, **27**, 3133.
[10] Leonard, Gutowsky, Middleton, and Petersen, *J. Amer. Chem. Soc.*, 1952, **74**, 4070.
[11] Rhoads, Gilbert, Decora, Garland, Spangler, and Urbigkit, *Tetrahedron*, 1963, **19**, 1625.

Addition of picric acid to an ethanolic solution of this compound gave 9-*azabicyclo*[3,3,1]*non*-2-*ene picrate*, crystallising from ethanol as yellow plates, m. p. 234° (Found: C, 47·4; H, 4·5; N, 15·8. $C_{14}H_{16}N_4O_7$ requires C, 47·7; H, 4·6; N, 15·9%).

The 9-*benzoyl derivative* (II; R = Bz), prepared by treatment of the carbamate with benzoyl chloride and sodium hydroxide solution, crystallised from light petroleum (b. p. 60—80°) as needles, m. p. 76°, $\nu_{max.}$ (in CS_2) 1640 cm.$^{-1}$ (Found: C, 79·4; H, 7·5; N, 5·9. $C_{15}H_{17}NO$ requires C, 79·3; H, 7·5; N, 6·2%).

9-*Benzoyl*-2β,3β-*epoxy*-9-*azabicyclo*[3,3,1]*nonane* (III).—A solution of trifluoroperacetic acid, prepared [3] by the addition of trifluoroacetic anhydride (16·8 g.) to a cooled solution of 80% hydrogen peroxide (2·6 g.) in dichloromethane (20 ml.), was added slowly to a cooled stirred solution of the *N*-benzoyl-olefin (10 g.) in dichloromethane (50 ml.) containing anhydrous sodium carbonate (20 g.). Stirring was continued for 2 hr. at room temperature, and the filtered solution was evaporated. The residue, which solidified under light petroleum (b. p. 40—60°), was recrystallised from cyclohexane giving the *epoxide* (III) (7·8 g.) as needles, m. p. 137°, $\nu_{max.}$ (in CCl_4) 1650 and 968 cm.$^{-1}$ (Found: C, 74·1; H, 7·0; N, 5·9. $C_{15}H_{17}NO_2$ requires C, 74·05; H, 7·0; N, 5·8%). The compound was recovered after being refluxed with excess of lithium aluminium hydride in ether or tetrahydrofuran solution for 6 hr.

2β-*Hydroxy*-9-*azabicyclo*[3,3,1]*nonane* (IV; R = H).—Lithium (0·5 g.), in small pieces, was added to a stirred solution of the epoxide (1 g.) in anhydrous ethylamine (40 ml.) chilled to 0°. After 1 hr., water (15 ml.) was added, the ethylamine was removed by distillation, and the product, a pale brown oil (0·5 g.), $\nu_{max.}$ (in CCl_4) 3340 cm.$^{-1}$, was isolated with ether.

Treatment of this product with excess of benzoyl chloride and 4N-sodium hydroxide solution gave 9-*benzoyl*-2β-*hydroxy*-9-*azabicyclo*[3,3,1]*nonane* (IV; R = Bz), obtained from light petroleum as plates, m. p. 119°, $\nu_{max.}$ (in CCl_4) 3450 and 1645 cm.$^{-1}$ (Found: C, 73·6; H, 7·4; N, 5·9. $C_{15}H_{19}NO_2$ requires C, 73·4; H, 7·8; N, 5·7%).

Slow distillation of benzene (100 ml.) from a mixture of the oily alcohol (100 mg.) and *p*-nitrobenzaldehyde (100 mg.) gave the *oxazolidine* (V), crystallising from light petroleum (b. p. 60—80°) as fawn needles, m. p. 115° (140 mg.), $\nu_{max.}$ (in Nujol) 1530 and 1350 cm.$^{-1}$ (Found: C, 65·6; H, 6·6; N, 10·5. $C_{15}H_{18}N_2O_3$ requires C, 65·7; H, 6·6; N, 10·2%).

9-*Benzoyl*-3α-*bromo*-2β-*hydroxy*-9-*azabicyclo*[3,3,1]*nonane* (VI).—A solution of hydrogen bromide in acetic acid (10 ml. of 48%) was added to a cooled solution of 9-benzoyl-2β,3β-epoxy-9-azabicyclo[3,3,1]nonane (7·8 g.) in acetic acid (20 ml.). After 4 hr. at room temperature the mixture was diluted with ice–water and shaken with ether, and the extract washed free from acid with aqueous sodium hydrogen carbonate. Evaporation of the solvent gave the *bromohydrin* (VI) (6·5 g.), obtained from ethyl acetate as prisms, m. p. 161°; $\nu_{max.}$ (in $CHCl_3$) 3610, 3400—3200, and 1635 cm.$^{-1}$ (Found: C, 55·8; H, 5·6; N, 4·6. $C_{15}H_{18}BrNO_2$ requires C, 55·6; H, 5·6; N, 4·3%).

A solution of the bromohydrin (0·1 g.) in dioxan (3 ml.) and 2N-sodium hydroxide (0·5 ml.) was kept at room temperature for 24 hr. Dilution with water and isolation with ether gave the epoxide (70 mg.), m. p. 137°, identical (mixed m. p. and infrared spectrum) with the starting material.

9-*Benzoyl*-3-*bromo*-9-*azabicyclo*[3,3,1]*nonan*-2-*one* (VII; R = Br).—A solution of chromium trioxide (1·2 g.) in 90% acetic acid (10 ml.) was slowly added to a stirred solution of the bromohydrin (6 g.) in acetic acid (30 ml.) kept at 10°. After 2 hr., dilution with water and isolation with ether gave the α-*bromo-ketone* (VII; R = Br) (4·1 g.) obtained from ethyl acetate as prisms, m. p. 144°, $\nu_{max.}$ (in Nujol) 1740 and 1618 cm.$^{-1}$ (Found: C, 56·2; H, 5·0; N, 4·2. $C_{15}H_{16}BrNO_2$ requires C, 55·9; H, 5·0; N, 4·35%).

Condensation of Chloral with Methyl 6-*Methyl*-2-*picolinate*.—A mixture of freshly prepared chloral (50 g.) and methyl 6-methyl-2-picolinate (45 g.) was heated at 100° for 100 hr. Unchanged starting materials were removed at 150° *in vacuo*, and the cooled reaction mixture was extracted with ether. Evaporation of the solvent gave a brown crystalline product, which, after several recrystallisations from ether gave *methyl* 6-(2-*hydroxy*-2-*trichloromethyl*)*ethyl*-2-*picolinate* (35 g.), m. p. 115° (Found: C, 40·1; H, 3·4; N, 4·1. $C_{10}H_{10}Cl_3NO_3$ requires C, 40·2; H, 3·4; N, 4·7%).

Methyl β-(6-*Methoxycarbonyl*-2-*pyridyl*)*acrylate*.—A solution of potassium hydroxide (40 g.) in ethanol (200 ml.) was added with cooling and shaking to a solution of the above ester (30 g.) in ethanol (200 ml.). The mixture was allowed to attain room temperature, at which it was kept until the vigorous reaction had subsided, whereupon it was refluxed for 2 hr. After

evaporation of the filtered solution, the residue was taken up in dry methanol (200 ml.) and saturated at 0° with dry hydrogen chloride. After 24 hr., evaporation *in vacuo* and isolation with ether gave a crude pasty product (15 g.) which was used directly for the following reductions. Purification of a specimen by recrystallisation from ether yielded leaflets, m. p. 107—109°, of the unsaturated *ester* (VIII); $\nu_{max.}$ (in $CHCl_3$) 1745, 1725, 1650, and 1600 cm.$^{-1}$ (Found: C, 60·0; H, 5·1; N, 6·4. $C_{11}H_{11}NO_4$ requires C, 59·7; H, 5·0; N, 6·3%).

Methyl β-(6-*Methoxycarbonyl*-2-*pyridyl*)*propionate*.—A solution of the crude unsaturated ester (1 g.) in methanol (20 ml.) was hydrogenated over Adams catalyst (50 mg.) until the initial rapid absorption ceased. The *dicarboxylic ester* crystallised from ether as needles, m. p. 53—54° (0·6 g.), $\nu_{max.}$ (in $CHCl_3$) 1745 and 1600 cm.$^{-1}$ (Found: C, 59·3; H, 5·8; N, 5·8. $C_{11}H_{13}NO_4$ requires C, 59·2; H, 5·9; N, 6·3%).

9-*Benzoyl*-3-*methoxycarbonyl*-9-*azabicyclo*[3,3,1]*nonan*-2-*one*.—A solution of the crude unsaturated ester (VIII) (5 g.) in methanol (80 ml.) and 5N-hydrochloric acid (10 ml.) was shaken with freshly prepared Adams catalyst (200 mg.) under hydrogen (5 atm.) for 6 hr. Evaporation of the filtered solution, treatment of the residue with aqueous sodium carbonate, and isolation with chloroform gave a pale brown gum (4·6 g.), $\nu_{max.}$ (liquid film) 3420 and 1745 cm.)[1], which showed no tendency to crystallise. Benzoylation, with an excess of benzoyl chloride in pyridine solution, gave, after chromatography on alumina, a glass (4·5 g.), $\nu_{max.}$ (liquid film) 1745 and 1645 cm.$^{-1}$, also non-crystalline. A solution of the latter (4 g.) in anhydrous tetrahydrofuran (50 ml.) containing 2 drops of ethanol was added to a suspension of sodium hydride (5 g. of a 50% oil dispersion) in anhydrous tetrahydrofuran (20 ml.), stirred under nitrogen. After 36 hr. at room temperature the mixture was refluxed for 4 hr., cooled, and diluted with ether containing methanol (5 ml.). Addition of ice and 4N-hydrochloric acid was followed by extraction with ether, the extract being washed with aqueous sodium hydrogen carbonate, dried, and evaporated Crystallisation of the residue from ether gave the β-*keto-ester* (2·9 g.) as prisms, m. p. 124—126°, $\nu_{max.}$ (in Nujol) 1675 and 1630 cm.$^{-1}$, $\lambda_{max.}$ (in 95% EtOH) 251 mμ (ε 12,400), $\lambda_{max.}$ (in cyclohexane) 250 mμ (ε 12,900) (Found: C, 68·1; H, 6·4; N, 4·9. $C_{17}H_{19}NO_4$ requires C, 67·8; H, 6·4; N, 4·7%).

The *enol ether* (IX; R = R′ = Me), obtained by treatment of the β-keto-ester with ethereal diazomethane at room temperature for 36 hr., crystallised from ether as cubes, m. p. 111—113°, $\nu_{max.}$ (in $CHCl_3$) 1720 and 1640 cm.$^{-1}$ (Found: C, 68·6; H, 6·7; N, 4·6. $C_{18}H_{21}NO_4$ requires C, 68·6; H, 6·7; N, 4·4%).

9-*Benzoyl*-9-*azabicyclo*[3,3,1]*nonan*-2-*one* (VII; R = H).—(*a*) Zinc dust (1 g.) was added in small portions to a stirred solution of the α-bromo-ketone (VII; R = Br) (3 g.) in acetic acid (15 ml.) maintained at 70°. After 4 hr., the filtered solution was diluted with water, and the product was isolated with ether. Recrystallisation from ethyl acetate yielded the *ketone* (VII; R = H) as prisms (1·9 g.), m. p. 95°, $\nu_{max.}$ (in Nujol) 1721 and 1632 cm.$^{-1}$ (Found: C, 74·3; H, 7·1; N, 5·6. $C_{15}H_{17}NO_2$ requires C, 74·05; H, 7·0; N, 5·8%).

(*b*) A solution of the enol ether (IX; R = R′ = Me) (350 mg.) in ethanol (5 ml.) and 4N-sodium hydroxide (5 ml.) was heated on a steam-bath for 15 min. Neutralisation with dilute hydrochloric acid and isolation with ether gave the αβ-unsaturated β-*methoxy-acid* (IX; R = Me, R′ = H) (300 mg.), crystallising from ether as prisms, m. p. 110° (Found: C, 67·7; H, 6·4; N, 4·5. $C_{17}H_{19}NO_4$ requires C, 67·8; H, 6·6; N, 4·7%).

A solution of the acid (250 mg.) in acetic acid (10 ml.) and concentrated hydrochloric acid (10 ml.) was refluxed for 1 hr. The cooled solution was neutralised with aqueous sodium hydroxide, and the product (180 mg.) was isolated with ether. Recrystallisation from ether gave the ketone (VII; R = H), m. p. 95°, identical (mixed m. p., infrared spectra) with the compound obtained above.

2-*Benzoyl*-1,2,3,4-*tetrahydro*-1,3-*propano*-β-*carboline* (X; R = H_2).—(*a*) A solution of hydrazine hydrate (0·1 ml.) and 2-benzoyl-1,2,3,4-tetrahydro-10-oxo-1,3-propan-β-carboline (X; R = O) [1] (100 mg.) in ethylene glycol (2 ml.) was refluxed for 10 min., potassium hydroxide (0·1 g.) was added, and the mixture was heated at 185° for 3 hr. Dilution with water and isolation with dichloromethane gave 2-*benzoyl*-1,2,3,4-*tetrahydro*-1,3-*propano*-β-*carboline* (X; R = H_2), obtained from ethyl acetate as plates (45 mg.), m. p. 226°; $\nu_{max.}$ (in CCl_4) 3460, 3280, 1630, and 1610 cm.$^{-1}$; $\lambda_{max.}$ (in 95% EtOH) 226, 278, and 290 mμ (ε 48,000, 8100, and 6600) (Found: C, 79·9; H, 6·3; N, 8·6. $C_{21}H_{20}N_2O$ requires C, 79·7; H, 6·4; N, 8·85%).

(*b*) A solution of the ketone (X; R = O) (200 mg.) and boron trifluoride etherate (0·3 ml.) in ethane-1,2-dithiol (0·3 ml.) was kept for 16 hr. The crude product was isolated in the usual way,

and added to a suspension of Raney nickel (1 g.) in ethanol (10 ml.). After refluxing for 3 hr., evaporation of the filtered solution, followed by crystallisation from ethyl acetate, gave the compound (120 mg.), m. p. 226°, obtained above.

(*c*) To a solution of 9-benzoyl-9-azabicyclo[3,3,1]nonan-2-one (VII; R = H) (700 mg.) and phenylhydrazine (350 mg.) in acetic acid (10 ml.) was added 40% sulphuric acid (40 ml.). After 24 hr., the mixture was worked up in the usual way, giving material (480 mg.) identical (mixed m. p., infrared and ultraviolet spectra) with that obtained by the above methods.

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