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# THE SYNTHESIS AND RESOLUTION OF (±)-TROPAN-2-ONE

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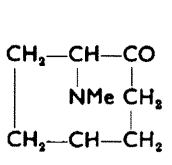
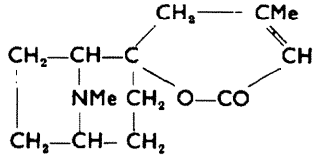
**Abstract**—Two routes to the synthesis of (±)-tropan-2-one, and its resolution into optically active forms, are described. The base $C_8H_{13}NO$, obtained by degradation of dioscorine, is not identical with tropan-2-one, and the alkaloid is therefore not derived from tropane.

RECENT studies[1,2] on the constitution of dioscorine suggested that the alkaloid was derived from tropane, and this was apparently confirmed by the degradation[2] of the alkaloid to a base $C_8H_{13}NO$, reported[3] to be identical with (+)-tropan-2-one (I), synthesized from (−)-cocaine.[4] This degradation led to the formulation of dioscorine as II.[1,3]



I



II

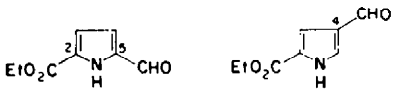
Tropan-2-one is an obvious starting point in a synthesis of II, and we describe here two routes to the synthesis of the racemic keto-base, and its resolution into optically active forms.

The formylation of 2-ethoxycarbonylpyrrole with phosphoryl chloride and dimethylformamide[5] afforded two isomeric aldehydic products, m. pp. 75° and 107°, which were separated by fractional distillation *in vacuo*. The former agreed in properties and m.p. with 2-ethoxycarbonyl-5-formylpyrrole (III), previously prepared by Siedel and Winkler[6] by the oxidation of 2-ethoxycarbonyl-5-methylpyrrole, and by Reichstein[7] by the Gattermann–Hoesch reaction with 2-ethoxycarbonylpyrrole. We therefore place the formyl group at position 5 in this product, and regard the isomeric compound, m.p. 107°, as 2-ethoxycarbonyl-4-formylpyrrole (IV); support for both these structural assignments is to be found in the sequel.

Condensation of III with ethyl hydrogen malonate[8] afforded ethyl β-(2-ethoxycarbonylpyrrol-5-yl)acrylate (V), which was reduced catalytically stepwise to the

[1] J. B. Jones and A. R. Pinder, *Chem. & Ind.* 1000 (1958); *J. Chem. Soc.* 615 (1959), and earlier papers there cited.
[2] G. Büchi, D. E. Ayer and D. M. White, XVI*th Internat. Congr. Pure Appl. Chem.* Paris, July (1957).
[3] D. E. Ayer, G. Büchi, P. Reynolds-Warnhoff and D. M. White, *J. Amer. Chem. Soc.* **80**, 6146 (1958).
[4] M. R. Bell and S. Archer, *J. Amer. Chem. Soc.* **80**, 6147 (1958); **82**, 4642 (1960).
[5] Cf. *Org. Synth.* **36**, 74 (1956).
[6] W. Siedel and F. Winkler, *Liebigs Ann.* **554**, 162 (1943).
[7] T. Reichstein, *Helv. Chim. Acta* **13**, 349 (1930).
[8] Cf. H. Moureu, P. Chovin and L. Petit, *Bull. Soc. Chim. Fr.* 203 (1951).

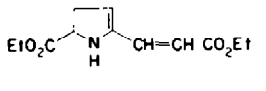
diester (VI) and the pyrrolidine diester (VII, R = H), as a mixture of *cis*- and *trans*-forms. N-Methylation yielded the tertiary base (VII, R = Me), which smoothly underwent a Dieckmann cyclization to 3-ethoxycarbonyltropan-2-one (VIII). Acid hydrolysis then gave (±)-tropan-2-one (I). The structure of the final product was proved by its reduction to tropane, and by the identity of its infra-red absorption curve with that of a specimen of (+)-tropan-2-one, kindly provided by Dr. S. Archer.[4] The aldehyde group in III is therefore correctly placed at position 5.



III



IV



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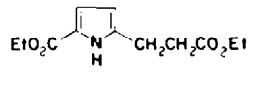

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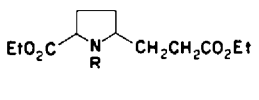
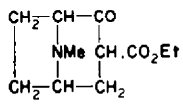
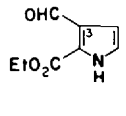


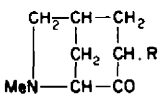
VII



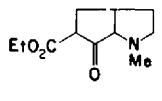
VIII



IX



X



XI

When the aldehyde m.p. 107° was subjected to a similar sequence of transformations, the penultimate product was a β-ketoester whose physical (e.g. infra-red spectrum) and chemical properties indicated that it was highly enolized. Of the two possible structures, IV and IX, for this aldehyde, the former would lead to the oxoazabicyclo[3,2,1]octane ester (X, R = $CO_2Et$) and the latter to the oxoazabicyclo [3,3,0]octane ester (XI). It would be anticipated that of these two structures, (X, R = $CO_2Et$), being derived from 2-ethoxycarbonylcyclohexanone, would be highly enolized, whereas XI, a derivative of 2-ethoxycarbonylcyclopentanone, would have a low enol content.[9] The β-ketoester is therefore assigned structure (X, R = $CO_2Et$), and the aldehyde m.p. 107° is 2-ethoxycarbonyl-4-formylpyrrole (IV). There are also theoretical and steric grounds for rejecting the structure IX for the aldehyde. Hydrolysis and decarboxylation of the β-ketoester yielded 6-methyl-4-oxo-6-azabicyclo[3,2,1]-octane (X, R = H).

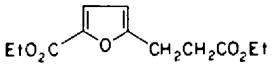
A second route to tropan-2-one began with ethyl 2-furoate, which on chloromethylation,[10] reaction with ethyl sodioacetoacetate, hydrolysis,[11] and esterification, afforded the diester (XII). This on hydrogenation gave the corresponding tetrahydrofuran (XIII), as a mixture of *cis* and *trans* isomers, which was cleaved by hydrogen bromide and phosphorus tribromide to diethyl 2,5-dibromosuberate (XIV). Reaction

[9] N. J. Leonard, H. S. Gutowsky, W. J. Middleton and E. M. Petersen, *J. Amer. Chem. Soc.* **74**, 4070 (1952); P. B. Russell, *Chem. & Ind.* 326 (1956).

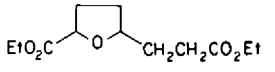
[10] A. E. Stubbs, *Syntheses of Heterocyclic Compounds* (Edited by A. L. Mndzhoian) Vol. 1 p. 29. Consultants Bureau Inc., New York (1959).

[11] Cf. ref. 10, Vol. 2, p. 37.

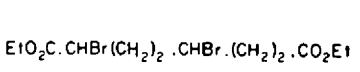
of the latter with methylamine afforded the pyrrolidine diester (VII, R = Me), convertible into (±)-tropan-2-one as already described. A Dieckmann cyclization on the tetrahydrofuran diester (XIII) furnished 3-ethoxycarbonyl-2-oxo-8-oxabicyclo[3,2,1]-octane (XV, R = $CO_2Et$), which on hydrolysis and decarboxylation gave the tropan-2-one analogue (XV, R = H). This on treatment with hydrogen bromide followed by phosphorus tribromide gave 2,5-dibromocycloheptanone (XVI), which reacted with methylamine to yield (±)-tropan-2-one.



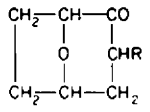

XII



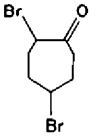

XIII



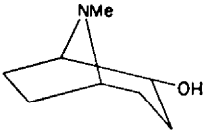

XIV




XV




XVI




XVII

(±)-Tropan-2-one was resolved into optically active forms by fractional crystallization of the D-bromocamphor-π-sulphonate from water. The first fraction proved to be the salt of the (−)-base, and on basification yielded (−)-tropan-2-one. The mother liquor yielded on basification a base rich in the (+)-enantiomer; this was further resolved with di-*p*-toluoyl-D-tartaric acid into the (+)- and (±)-bases. The former proved to be identical in all respects with a specimen of (+)-tropan-2-one, kindly provided by Dr. S. Archer.[4] Our (+)-, (−)-, and (±)-bases, and Dr. Archer's (+)-base, had identical infra-red spectra in solution. A direct comparison of this spectrum with that of the $C_8H_{13}NO$ keto-base obtained by degradation of dioscorine[1,3] showed that this base and (+)-tropan-2-one were quite different. Further, in contrast to observations in another laboratory,[3] we have found that the reduction of the $C_8H_{13}NO$ base yields a base $C_8H_{15}N$ which is isomeric with, but different from, tropane, and we wish here to correct our earlier statement[12] to the contrary, which was based on unreliable criteria of identity. In addition, we have confirmed Bell and Archer's observation[4] that tropan-2-one methiodide is stable to mild base, whereas it has been reported,[2] and we have confirmed, that the $C_8H_{13}NO$ base methiodide undergoes facile Hofmann degradation under these conditions. We conclude that dioscorine is not related to tropane, and that formula II for the alkaloid must be rejected. In a forthcoming paper we hope to discuss the constitution of the $C_8H_{13}NO$ keto-base.[13]

The reduction of (±)-tropan-2-one with lithium aluminium hydride gave (±)-tropan-2α-ol (XVII), the hydroxyl group being assigned the α-configuration because the product differs from (±)-tropan-3β-ol, obtained by the reduction of 2β,3β-epoxytropane,[3,12] and on infra-red grounds. Bell and Archer[4] have reported that a similar reduction of (+)-tropan-2-one affords mainly the 2α epimer, with a trace of the 2β.

[12] W. A. M. Davies, J. B. Jones and A. R. Pinder, *J. Chem. Soc.* 3504 (1960).
[13] For a preliminary account see W. A. M. Davies, I. G. Morris and A. R. Pinder, *Chem. & Ind.* 1410 (1961).

## EXPERIMENTAL

*Formylation of 2-ethoxycarbonylpyrrole*[5]

2-Ethoxycarbonylpyrrole was obtained by the reaction of pyrrolylmagnesium bromide with ethyl chloroformate at −50°,[14] it was separated from 1-ethoxycarbonylpyrrole, formed simultaneously, by fractional distillation, and crystallized from light petroleum (b.p. 40–60°) in needles, m.p. 40–42° (lit[14] m.p. 41–42°). Dimethylformamide (40 g) was mixed gradually with phosphoryl chloride (84·5 g) during 15 min at 10–20°. Ethylene dichloride (125 cc) was added, and the solution cooled to 5° during the gradual addition (1 hr), with stirring, of 2-ethoxycarbonylpyrrole (69·5 g) in ethylene dichloride (125 cc). The solution was then refluxed for 15 min, cooled to 20°, and treated with a solution of sodium acetate trihydrate (375 g) in water (500 cc). After 15 minutes' reflux, the organic layer was separated and the aqueous layer thoroughly extracted with ether. The combined extracts were washed with aqueous sodium hydrogen carbonate until neutral, dried and concentrated. The dark red residue (82 g) was distilled fractionally through a 20 cm Vigreux column. The first fraction, b.p. 82–86°/0·05 mm (42·6 g) was 2-ethoxycarbonyl-5-formylpyrrole (III), which solidified and crystallized from light petroleum (b.p. 60–80°) in needles, m.p. 75° (lit 72·5–73·5°,[7] 74–75° [6]) (Found: C, 57·9; H, 5·5; N, 8·2. Calc. for $C_8H_9NO_3$: C, 57·5; H, 5·4; N, 8·4%). The second fraction, *2-ethoxycarbonyl-4-formylpyrrole* (IV), b.p. 126–127°/0·05 mm (15·9 g), separated from the same solvent in needles, m.p. 106–107° (Found: C, 57·6; H, 5·5; N, 8·4%).

*Ethyl β-(2-ethoxycarbonylpyrrol-5-yl) acrylate* (V)

2-Ethoxycarbonyl-5-formylpyrrole (20 g), ethyl hydrogen malonate (15·8 g),[8] pyridine (100 cc), and piperidine (2 cc) were heated on the water-bath for 20 hr. The cooled solution was poured into ice-cold dil hydrochloric acid, and the solid liberated collected and washed with water. Ethyl β-(2-ethoxycarbonylpyrrol-5-yl)acrylate (18·3 g) crystallized from light petroleum (b.p. 60–80°) in needles, m.p. 129° (Found: C, 60·7; H, 6·4; N, 5·7. $C_{12}H_{15}NO_4$ requires: C, 60·7; H, 6·4; N, 5·9%), bands at 3330 (NH), 1700 and 1670 (αβ-unsaturated and aryl ester C=O), 1626 (conjugated C=C), and 1200 $cm^{-1}$ (ester C—O) (in $CCl_4$).

When the condensation was effected at room temp during 5 days, the intermediate *5-β-carboxy-β-ethoxycarbonylvinyl-2-ethoxycarbonylpyrrole* was isolated (80% yield). It separated from ethanol-light petroleum (b.p. 60–80°) in pale cream needles, m.p. 167–168° (decomp). (Found: C, 55·6; H, 5·4; N, 5·1. $C_{13}H_{15}NO_6$ requires: C, 55·5; H, 5·4; N, 5·0%), and dissolved in sodium carbonate solution with effervescence.

*Ethyl β-(2-ethoxycarbonylpyrrol-5-yl)propionate* (VI)

A suspension of the acrylic ester (V; 10 g) in ethanol (50 cc) was shaken in hydrogen at room temp and press with Raney nickel for 40 min (uptake $H_2$). Evaporation of the filtered solution afforded ethyl β-(2-ethoxycarbonylpyrrol-5-yl)propionate as a syrup, b.p. 130–132°/0·15 mm, which crystallized gradually, and which separated from light petroleum (b.p. 40–60°) in needles, m.p. 52–54° (9·5 g). (Found: C, 60·05; H, 7·2; N, 5,8. $C_{12}H_{17}NO_4$ requires: C, 60·2; H, 7·2; N, 5·85%), bands at 1739 (saturated ester C=O), 1701 and 1678 sh $cm^{-1}$ (aryl ester C=O) (in $CCl_4$).

*Ethyl β-(2-ethoxycarbonylpyrrolidin-5-yl)propionate* (VII, R = H)

The foregoing diester (6·0 g) in glacial acetic acid (18 cc) was shaken in hydrogen at room temp and press with pre-reduced 5% rhodium-on-alumina catalyst for 5 hr (uptake $2H_2$). The solution was filtered, diluted with water, and basified at 0° with potassium carbonate. Continuous ether extraction afforded the pyrrolidine diester (VII, R = H) as a basic liquid, b.p. 104–105°/0·1 mm (5·9 g). (Found: C, 59·1; H, 8·7; N, 5·9. $C_{12}H_{21}NO_4$ requires: C, 59·2; H, 8·7; N, 5·8%), bands at 3448 (NH), 1727 (saturated ester C—O), and 1180 $am^{-1}$ (ester C—O; liquid film). It formed an oily nitrosamine, picrate, and methiodide, in harmony with the expectation that the product is a mixture of *cis* and *trans* isomers.

Methylation of the ester (24·3 g) with formic acid (11·7 g of 98–100%) and formaldehyde (8·3 cc of 40%)[15] at room temp for 4 hr, and then on the water-bath for 1 hr, gave, after basification and ether extraction, *ethyl β-(2-ethoxycarbonyl-1-methylpyrrolidin-5-yl)propionate* (VII, R = Me), b.p. 98°/0·1 mm (21·3 g) (Found: C, 60·7; H, 8·9; N, 5·45. $C_{13}H_{23}NO_4$ requires: C, 60·7; H, 9·0; N, 5·45%), band at 1736 $cm^{-1}$ (saturated ester C=O) no NH band (in $CCl_4$). The picrate was oily, but the *methiodide* crystallized partially, and separated from ethanol–ether in needles, m.p. 86–87°. (Found: C, 42·2; H, 7·0; N, 3·6. $C_{14}H_{26}INO_4$ requires: C, 42·1; H, 6·6; N, 3·5%).

[14] F. K. Signaigo and H. Adkins, *J. Amer. Chem. Soc.* **58**, 1122 (1936).
[15] Cf. H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, *J. Amer. Chem. Soc.* **55**, 4571 (1933).

*3-Ethoxycarbonyltropan-2-one* (VIII)

The above N-methylpyrrolidine diester (16·2 g) in dry benzene (40 cc) was mixed with alcohol-free sodium ethoxide (from 3 g sodium), and the mixture heated so that the benzene–ethanol azeotrope distilled over gradually. Benzene was added from time to time and the distillation continued for 2 hr after the distillation temperature reached the b.p. of pure benzene. The orange solution was cooled and treated with water, and the layers separated. The organic layer was extracted thrice with 4N hydrochloric acid and the combined aqueous layers basified with potassium carbonate at 0°. 3-Ethoxycarbonyltropan-2-one, isolated by continuous ether extraction, distilled at 110–111°/0·7 mm (11·9 g). (Found: C, 62·5; H, 8·1; N, 6·6. $C_{11}H_{17}NO_3$ requires: C, 62·5; H, 8·1; N, 6·6%). The infra-red absorption was of the conjugate chelate type, with bands at 3650–3030 (wide, bonded OH), 1754 (non-enolized ester C=O), 1724 (non-enolized ketone C=O), 1667 (chelated enolized β-keto-ester C=O), and 1621 $cm^{-1}$ (conjugated C=C; liquid film). The product gave a deep red colouration with ferric chloride. The *picrate* separated from water in yellow elongated prisms, m.p. 147–150° (decomp). (Found: C, 46·0; H, 4·9; N, 12·8. $C_{17}H_{20}N_4O_{10}$ requires: C, 46·35; H, 4·6; N, 12·7%). The *methiodide* crystallized from ethanol–ether in clusters of small prisms, m.p. 178–180° (decomp). (Found: C, 40·8; H, 5·7; N, 3·6. $C_{12}H_{20}INO_3$ requires: C, 40·8; H, 5·7; N, 4·0%).

*(±)-Tropan-2-one* (I)

A solution of the foregoing keto-ester (11·5 g) in 50% hydrochloric acid (100 cc) was refluxed for 3 hr, cooled, basified with potassium carbonate at 0°, and subjected to continuous ether extraction. Evaporation of the dried extract afforded (±)-tropan-2-one, b.p. 99–99·5°/11 mm (7·4 g). (Found: C, 68·2; H, 9·4; N, 10·1. $C_8H_{13}NO$ requires: C, 69·0; H, 9·4; N, 10·1%), bands at 1723 (in $CCl_4$) and 1726 $cm^{-1}$ (in hexane; ketonic C=O). The spectrum was identical with that of a specimen of (+)-tropan-2-one kindly provided by Dr. S. Archer.[8] The *picrate* crystallized from a small volume of benzene–ethanol in yellow prisms, m.p. 235° (decomp). (Found: C, 45·9; H, 4·5; N, 15·4. $C_{14}H_{16}N_4O_8$ requires: C, 45·65; H, 4·4; N, 15·2%). The *methiodide* separated from a little water in parallelepipeds, m.p. 307–308° (decomp). (Found: C, 38·5; H, 5·8; N, 5·1. $C_9H_{16}INO$ requires: C, 38·4; H, 5·7; N, 5·0%), band at 1727 $cm^{-1}$ (ketonic C=O; in Nujol).

The methiodide was stable to sodium hydrogen carbonate at room temp for an indefinite period (cf.[4]).

*6-Methyl-4-oxo-6-azabicyclo*[3,2,1]*octane* (X, R = H)

Condensation of 2-ethoxycarbonyl-4-formylpyrrole (IV) with ethyl hydrogen malonate, exactly as described above for the 5-formyl isomer, afforded *ethyl β-(2-ethoxycarbonylpyrrol-4-yl)acrylate* (cf. V) in 90% yield; it crystallized from light petroleum (b.p. 60–80°) in needles, m.p. 106·5–107°. (Found: C, 60·8; H, 6·35; N, 6·1. $C_{12}H_{15}NO_4$ requires: C, 60·7; H, 6·4; N, 5·9%), bands at 1701 and 1688 sh (αβ-unsaturated and aryl ester C=O), and 1634 $cm^{-1}$ (conjugated C=C) in $CCl_4$. Hydrogenation in the presence of Raney nickel gave *ethyl β-(2-ethoxycarbonylpyrrol-4-yl)propionate* (cf. VI), b.p. 128–130°/0·05 mm (95%). (Found: C, 60·6; H, 7·0; N, 5·9. $C_{12}H_{17}NO_4$ requires: C, 60·2; H, 7·2; N, 5·85%), bands at 1733 (saturated ester C=O), 1700 and 1688 sh $cm^{-1}$ (aryl ester C=O; in $CCl_4$). Further reduction using rhodium-on-alumina catalyst gave, as a mixture of isomers, *ethyl β-(2-ethoxycarbonylpyrrolidin-4-yl)propionate* (cf. VII, R = H), b.p. 101–102°/0.05 mm. (Found: C, 59·4; H, 8·5; N, 5·8. $C_{12}H_{21}NO_4$ requires; C, 59·3; H, 8·7; N, 5·8%), bands at 3470 (NH) and 1733 $cm^{-1}$ (saturated ester C=O; liquid film). N-Methylation with formaldehyde and formic acid yielded *2-ethoxycarbonyl-4-(β-ethoxycarbonylethyl)-1-methylpyrrolidine* (cf. VII, R = Me), b.p. 98°/0·05 mm (75%). (Found: C, 60·3; H, 9·1; N, 5·54. $C_{13}H_{23}NO_4$ requires: C, 60·7; H, 9·0; N, 5·45%), band at 1738 $cm^{-1}$ (saturated ester C=O), no NH band (liquid film). Dieckmann cyclization of the foregoing diester, by the procedure outlined above, afforded *3-ethoxycarbonyl-6-methyl-4-oxo-6-azabicyclo*[3,2,1]*octane* (X, R = $CO_2Et$), b.p. 118–119°/$_2$ mm. (Found: C, 62·1; H, 7·9; N, 6·5. $C_{11}H_{17}NO_3$ requires: C, 62·5; H, 8·1; N, 6·6%); typical conjugate chelate spectrum, bands at 3850–3030 (wide, bonded OH), 1742 w (non-enolized β-ketoester C=O), 1661 (wide, chelated C=O), and 1613 $cm^{-1}$ (conjugated C=C; liquid film). The product gave a deep red ferric colour and formed a *picrate*, which crystallized from water in yellow needles, m.p. 205–206° (decomp). (Found: N, 12·6. $C_{17}H_{20}N_4O_{10}$ requires: N, 12·7%). Hydrolysis and decarboxylation of the β-ketoester with boiling 30% hydrochloric acid furnished 6-methyl-4-oxo-6-azabicyclo[3,2,1]octane (X, R = H), b.p. 106·5–107°/15 mm. (Found: C, 69·0; H, 9·1. $C_8H_{13}NO$ requires: C, 69·0; H, 9·4%), carbonyl band at 1718 $cm^{-1}$ (in $CCl_4$). The *picrate* separated from isopropanol in clusters of yellow prisms, m.p. 214–215° (decomp, with previous shrinking). (Found: C, 45·8; H, 4·3; N, 15·2. $C_{14}H_{16}N_4O_8$ requires: C, 45·65; H, 4·4; N, 15·2%).

*Reduction of (±)-tropan-2-one*

(a) The ketone (0·37 g) in 2N hydrochloric acid (20 cc) was shaken in hydrogen at room temp and press with pre-reduced Adams platinic oxide catalyst for 2½ hr (uptake $2H_2$). The solution was filtered,

basified with potassium hydroxide, and extracted continuously with ether. Evaporation of the dried ($K_2CO_3$) extract via a Vigreux column afforded tropane, b.p. 98–99°/100 mm (0·25 g), identical (infra-red comparison) with an authentic specimen prepared by a similar reduction of either tropinone or tropidine. The picrate separated from aqueous methanol in large, yellow needles, m.p. 292–292·5° (decomp) (lit[16] m.p. 284–285°).

(b) (±)-Tropan-2-one (0·70 g) in dry ether (5 cc) was added during 10 min, with swirling, to lithium aluminium hydride (0·20 g) in dry ether (10 cc). After 1 hr at room temp the mixture was refluxed for ½ hr, then cooled and decomposed with the minimum amount of ice-water in the presence of "Celite". Evaporation of the dried, ethereal decantate afforded an oil, b.p. 130° (bath)/11 mm (0·63 g), which was treated with methanolic picric acid. (±)-Tropan-2α-ol picrate (1·46 g), which separated, crystallized from methanol in sheaves of long, yellow needles, m.p. 269·5–270·5° (decomp, rapid heating). (Found: C, 45·75; H, 4·9; N, 15·1. $C_{14}H_{18}N_4O_8$ requires: C, 45·4; H, 4·9; N, 15·1%). The picrate was suspended in ether and basified with cold 50% aqueous potassium hydroxide. Decantation of the ether, followed by drying (KOH) and evaporation, yielded (±)-*tropan-2α-ol* (XVII), b.p. 114–115°/6 mm, in quantitative yield. The product crystallized on cooling and triturating with ether, and separated from ether–light petroleum (b.p. 40–60°) in elongated prisms, m.p. 38–41°. (Found: C, 67·5; H, 10·95; N, 9·7. $C_8H_{15}NO$ requires: C, 68·0; H, 10·7; N, 9·9%), bands at 3125–3225 (broad, bonded OH; liquid film) and 3590 $cm^{-1}$ (free OH, increasing in intensity on dilution) (in $CCl_4$).

*2-Ethoxycarbonyl-5-β-ethoxycarbonylethylfuran* (XII)

Ethyl 2-furoate was chloromethylated[10] and the product condensed with ethyl acetoacetate.[11] Hydrolysis of the resulting β-ketoester afforded 2-carboxy-5-β-carboxyethylfuran;[11] this acid (26·4 g), dry ethanol (110 cc), and conc sulphuric acid (2·7 cc) were refluxed on the water-bath for 6 hr. Most of the ethanol was distilled off, and the residue diluted with water and extracted with ether. The ether was washed with sodium hydrogen carbonate and water, and dried. Evaporation yielded the diester, b.p. 120–124°/0·5 mm (28·7 g). (Found: C, 60·4; H, 6·6. $C_{13}H_{16}O_5$ requires: C, 60·1; H, 6·7%), bands at 1724 (saturated ester C=O) and 1706 $cm^{-1}$ (aromatic ester C=O; liquid film).

*2-Ethoxycarbonyl-5-β-ethoxycarbonylethyltetrahydrofuran* (XIII)

The foregoing diester (5·0 g) in ethanol (10 cc) was shaken in hydrogen at room temp and press with 10% rhodium-on-carbon catalyst for 3 hr (uptake $2H_2$). The mixture was filtered and concentrated, yielding the tetrahydrofuran diester, b.p. 113–114°/0·25 mm (5·0 g). (Found: C, 59·4; H, 8·4. $C_{17}H_{30}O_5$ requires: C, 59·1; H, 8·3%), bands at 1730 (saturated ester C=O) and 1092 $cm^{-1}$ (cyclic ether; liquid film).

*Diethyl 2,5-dibromosuberate* (XIV)

The above tetrahydrofuran diester (5·0 g) in absolute ethanol (40 cc) was saturated with dry hydrogen bromide at 0°. After 15 hr the solution was poured into water and extracted with ether. The extract was washed with sodium hydrogen carbonate, dried and concentrated, and the residue heated on the water-bath for 1 hr with phosphorus tribromide (2·5 g). After a further 24 hr at room temp the product was taken up in ether-methylene dichloride (1:1). The solution was neutralized with sodium hydrogen carbonate, dried, and evaporated, leaving diethyl 2,5-dibromosuberate, b.p. 132–133°/0·05 mm (4·2 g). (Found: C, 37·0; H, 4·8; Br, 40·6. $C_{12}H_{20}Br_2O_4$ requires: C, 37·2; H, 5·0; Br, 41·2%), bands at 1786 (α-bromoester C=O) and 1739 $cm^{-1}$ (saturated ester C=O liquid film).

When the ester (1·0 g) was mixed with a 20% solution of methylamine in benzene (1·2 g), kept overnight, and then heated at 60° for 4 hr, it yielded, after treatment with ether, filtration, and evaporation, ethyl β-(2-ethoxycarbonyl-1-methylpyrrolidin-5-yl) propionate (VII, R = Me), b.p. 98°/0·1 mm (0·3 g), identical (infra red comparison) with the product obtained by synthesis from pyrrole above (p. 408).

*3-Ethoxycarbonyl-2-oxo-8-oxabicyclo*[3,2,1]*octane* (XV, R = $CO_2Et$)

Dieckmann cyclization of the tetrahydrofuran diester (XIII; 2·4 g) in dry benzene (75 cc) by means of sodium ethoxide (from 0·5 g sodium), using the azeotropic distillation technique, yielded the above β-keto-ester, b.p. 91–94°/0·3 mm, which crystallized in rectangular plates, m.p. 37°. (Found: C, 60·9 H, 7·3. $C_{10}H_{14}O_4$ requires: C, 60·6; H, 7·1%), conjugate chelate infra-red spectrum with wide bands in the 3000 and 1650 $cm^{-1}$ regions (liquid film). The product gave a deep purple colour with alcoholic ferric chloride and formed a *copper complex*, which crystallized from 2-ethoxyethyl acetate in green

[16] W. L. Archer, C. J. Cavallito and A. P. Gray, *J. Amer. Chem. Soc.* **78**, 1227 (1956).

microcrystals, m.p. 232–233°. (Found: C, 52·9; H, 6·0. $C_{20}H_{36}CuO_6$ requires: C, 52·5; H, 5·7%).

*2-Oxo-8-oxabicyclo*[3,2,1]*octane* (XV, R = H)

The foregoing ketoester (10 g) and a mixture of water, acetic acid, and conc sulphuric acid (40 cc, 8:8:1) were boiled under reflux for 2½ hr. *2-Oxo-8-oxabicyclo*[3,2,1]*octane*, isolated by dilution, neutralization (NaOH), and continuous ether extraction, distilled at 89°/13 mm (6·0 g). (Found: C, 66·6; H, 8·2. $C_7H_{10}O_2$ requires: C, 66·7; H, 7·9%), band at 1724 $cm^{-1}$ (six-membered ring C=O) (liquid film). The *2,4-dinitrophenylhydrazone* separated from benzene–ethanol in bright yellow needles, m.p. 207°. (Found: C, 51·5; H, 4·5; N, 18·5. $C_{13}H_{14}N_4O_6$ requires: C, 51·0; H, 4·6; N, 18·3%).

(±)-*Tropan-2-one* (I)

A solution of the foregoing 2-oxo-8-oxabicyclo[3,2,1]octane (2·0 g) in absolute ethanol (16 cc) was saturated with dry hydrogen bromide at 0°. After being kept overnight at room temp the solution was poured into ice-water and the oil taken up in ether. The extract was freed from acid with sodium hydrogen carbonate, dried and concentrated. *2-Bromocycloheptan-5-ol-1-one*, which remained, distilled at 85–87°/0·05 mm (1·57 g). (Found: C, 40·9; H, 5·4; Br, 38·6. $C_7H_{11}BrO_2$ requires: C, 40·6; H, 5·4; Br, 38·6%), bands at 3509 (alcoholic OH) and 1724 $cm^{-1}$ (saturated C=O; liquid film). This bromohydrin (1·57 g) was kept at room temp with phosphorus tribromide for 48 hr. The dark semi-solid mass was leached with ether–chloroform, and the extract evaporated, affording *2,5-dibromocycloheptanone* (XVI), b.p. 98–100°/0·05 mm (0·7 g), which was unstable and could not be analysed satisfactorily; band at 1706 $cm^{-1}$ (saturated ketone C=O; in $CCl_4$). The crude dibromide (0·6 g) was mixed, with cooling, with a saturated solution (1·0 g) of methylamine in dry benzene. After 24 hr at room temp, followed by 3 hr at 60–70°, the red solution was mixed with ether, and the ethereal solution filtered and evaporated. The residual (±)-tropan-2-one distilled at 82°/9 mm (0·08 g) and was identical (infra-red comparison) with the product described above (p. 409).

*Resolution of* (±)-*tropan-2-one*

(a) The D-(+)-tartrate of the base, obtained by mixing equivalent amounts of the base and the acid in ethanol or water, followed by evaporation, was a gum which could not be induced to crystallize.

(b) The base (400 mg) and D-camphor-10-sulphonic acid (668 mg) were dissolved in ethanol (1·5 cc). After 4 days at room temp in an open flask the crystals which had separated were collected, washed with cold ethanol and dried. The *D-camphor-10-sulphonate* of (±)-tropan-2-one had m.p. 237–240° (decomp, with previous softening), $[\alpha]_D^{20}$ + 10° (*c*, 1·0 in water). (Found: C, 56·2; H, 7·9; N, 3·8. $C_{18}H_{29}NO_5S$ requires: C, 58·2; H, 7·9; N, 3·8%). Concentration of the mother liquor gave a second fraction of the same salt.

(c) (±)-Tropan-2-one (0·50 g) and di-*p*-toluoyl-D-tartaric acid (1·39 g) were dissolved in methanol (15 cc), and the solution seeded with a crystal obtained by allowing a few drops of the solution to evaporate on a watch-glass. Fine needles of (±)-tropan-2-one hydrogen di-*p*-toluoyl-D-tartrate, which gradually separated during 2 days, were collected and dried *in vacuo* (0.03 g), m.p. 161–163° (decomp), $[\alpha]_D^{19}$ −94° (*c*, 1·81 in ethanol). (Found: C, 62·1; H, 6·0; N, 2·5. $C_{28}H_{31}NO_9 \cdot CH_3OH$ requires: C, 62·5; H, 6·3; N, 2·5%). Two further crops obtained by concentration of the filtrate proved to be the same product.

(d) An aqueous solution of D-bromocamphor-π-sulphonic acid was prepared[17] from the ammonium salt (10·0 g), and concentrated *in vacuo* to ca. 40 cc. (±)-Tropan-2-one (4·23 g) was added, the solution warmed, seeded with a crystal obtained from a small-scale experiment, and kept at room temp overnight. The crystals (6·43 g) were collected and recrystallized twice from water, from which (−)-*tropan-2-one D-bromocamphor-π-sulphonate* (3·20 g) separated in elongated rectangular prisms of its dihydrate, m.p. 115–135° (decomp), $[\alpha]_D^{21}$ +57·5° (*c*, 2·5 in water). (Found: C, 44·4; H, 6·6; N, 2·9. $C_{18}H_{28}BrNO_6S \cdot 2H_2O$ requires: C, 44·45; H, 6·6; N, 2·9%). The anhydrous salt had m.p. 190–193° (decomp). The salt was dissolved in water, basified ($K_2CO_3$) and extracted continuously with ether. Evaporation of the extract yielded (−)-tropan-2-one, b.p. 103–104°/13 mm (0·89 g), $[\alpha]_D^{23}$ −23·3° (*c*, 1·93 in water). The base crystallized when kept at 0°, m.p. 27–29°. (Found: C, 68·9; H, 9·0; N, 10·1. $C_8H_{13}NO$ requires: C, 69·0; H, 9·4; N, 10·1%). The infra-red spectra of the product, that of (±)-tropan-2-one (see above), and that of (+)-tropan-2-one (kindly supplied by Dr. S. Archer[4]) (all in $CCl_4$) were identical. Basification of the filtrates afforded a base rich in the (+)-isomer, having $[\alpha]_D^{23}$ +10·7° (*c*, 2·16 in water). This base (1·86 g) and di-*p*-toluoyl-D-tartaric acid (5·20 g) were dissolved in methanol (30 cc) and the solution kept for 24 hr. The *salt* of the (+)-isomer, which separated, was collected; it had m.p. 171–172° (decomp). (Found: C, 62·3; H, 6·5; N, 2·4. $C_{28}H_{31}NO_9 \cdot CH_3OH$ requires: C, 62·5; H, 6·3; N, 2·5%). Bell and Archer give m.p. (of solvent-free salt) 163° (decomp). Basification of the salt with potassium carbonate, followed by ether extraction,

[17] W. H. Perkin and R. Robinson, *J. Chem. Soc.* **99**, 788 (1911).

gave (+)-tropan-2-one (0·51 g), b.p. 101°/13·5 mm. It crystallized on cooling to 0°, m.p. 27–28°, $[\alpha]_D^{20}$ +23·8° (*c*, 1·81 in water) [Bell and Archer[4] give m.p. ca. 27° and $[\alpha]_D^{25}$ +23·2° (*c*, 1·6 in water)]. The base was identical with a specimen of (+)-tropan-2-one kindly supplied by Dr. S. Archer[4] (mixed m.p. and infra-red comparison). The methiodide had m.p. 330° (decomp) [lit[4] m.p. 332° (decomp)], and was stable to sodium hydrogen carbonate at room temp (cf.[4]).

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