[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA]

AZABICYCLOALKANES. 2-AZABICYCLO[3·3·1]NONANE[1,2]

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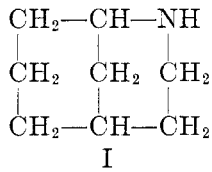
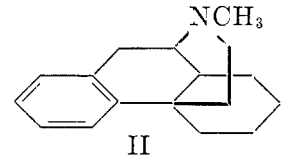
Although a large number of compounds bearing certain structural relationships to morphine have been synthesized and tested for analgesic activity (1) no study has yet been made of derivatives of the simple bicyclic N-bridge system (I) postulated for the Gulland and Robinson morphine formula (2). Recently Grewe (1b, 3) has synthesized an analgesically active compound (II) containing the entire morphine skeleton with the exception of the oxygen bridge, and Schnider and Grüssner (4), using Grewe's method, have made the 3-hydroxy



I



II

derivative. Horning (5) has prepared a tetralin-piperidine structure with a bicyclic N-bridge and phenolic hydroxyls corresponding to those in positions 3 and 4 of morphine. Barltrop (6) has made two quaternary salts containing the fused system.

Attempted syntheses of the unsubstituted (I) itself have not proved fruitful (7)[4] and it was felt that if convenient methods of synthesis could be developed for the simple azabicyclononanes, further work of a similar nature with slightly more complex structures might lead to pharmacologically interesting derivatives.

The fact that Ferber and Bruckner (8) were able to prepare 2-azabicyclo-[2·2·2]octane by copper chromite reduction of the lactam of *cis*-4-aminocyclohexanecarboxylic acid suggested that the unsubstituted 2-azabicyclo[3·3·1]nonane (I) could be synthesized in an analogous fashion by lactamization of *cis*-3-aminocyclohexaneacetic acid and subsequent catalytic reduction of the resulting lactam. When *m*-nitrobenzaldehyde was treated with benzoyl chloride and sodium cyanide according to the procedure of Francis and Davis (9) *m*-nitro-O-benzoylmandelonitrile (III) was obtained in good yield. Alcoholic hydrogen chloride converted the nitrile into the ester (IV) which was hydrogenated in

[1] Presented before the Division of Organic Chemistry, American Chemical Society, Chicago, Illinois, April 22, 1948.

[2] Robinson and Barltrop have suggested the trivial name "morphan" for this ring system (6).

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[4] Protiva and Sorm, *Collection Czechoslov. Chem. Communs.*, **13**, 428 (1948); *Chem. Abstr.*, **43**, 1730 (1949), started the preparation of this lactam by way of cyclohexanone-3-acetic acid→oxime→amino acid but did not proceed further after receiving the preliminary report (footnote 1) of this work; M. Protiva, private communication.

ethanol over Raney nickel and sodium carbonate at 120° to give the ethyl ester of *m*-aminophenylacetic acid in an over-all yield from *m*-nitrobenzaldehyde of 69% for the three-step process. If sodium hydroxide, sodium bicarbonate, or N,N′-diethylcyclohexylamine were used in place of the sodium carbonate to react with the benzoic acid produced by the hydrogenolysis the reaction was slow and incomplete even at 150°.[5]

Previously mandelic nitriles, acids, esters, and O-acyl nitriles and esters have been reduced over platinum or palladium (11) and ethyl mandelate has been reduced over Raney nickel (12).

Three different methods were used for the preparation of the lactam (VI) of *cis*-3-aminocyclohexaneacetic acid. The first method followed the procedure used by others (8, 13) for the reduction of an amino acid containing an aromatic amino group to its corresponding hexahydro derivative. The hydrochloride of ethyl *m*-aminophenylacetate was hydrogenated over platinum at 60–70° in ethanol to give a mixture of the *cis* and *trans* hexahydro esters (V) in the ratio of about 3:7. By heating this mixture at 200° in ethanol the *cis* ester was converted into the lactam (VI) and a majority of the *trans* ester was recovered unchanged.

The second method of preparation made use of the hydrogenation of the sodium salt of *m*-aminophenylacetic acid over Raney nickel at 200° in a *tert*-butyl alcohol-water mixture. The reduction was unsatisfactory when carried out in either the alcohol or water alone. Heating the amino acids so obtained at 250° gave the desired lactam in a yield which indicated a *cis-trans* ratio of 5:1. The free *m*-nitrophenylacetic acid reduced under the same conditions gave a 20% yield of the lactam (VI). The ethyl ester gave only unchanged starting material and tar.

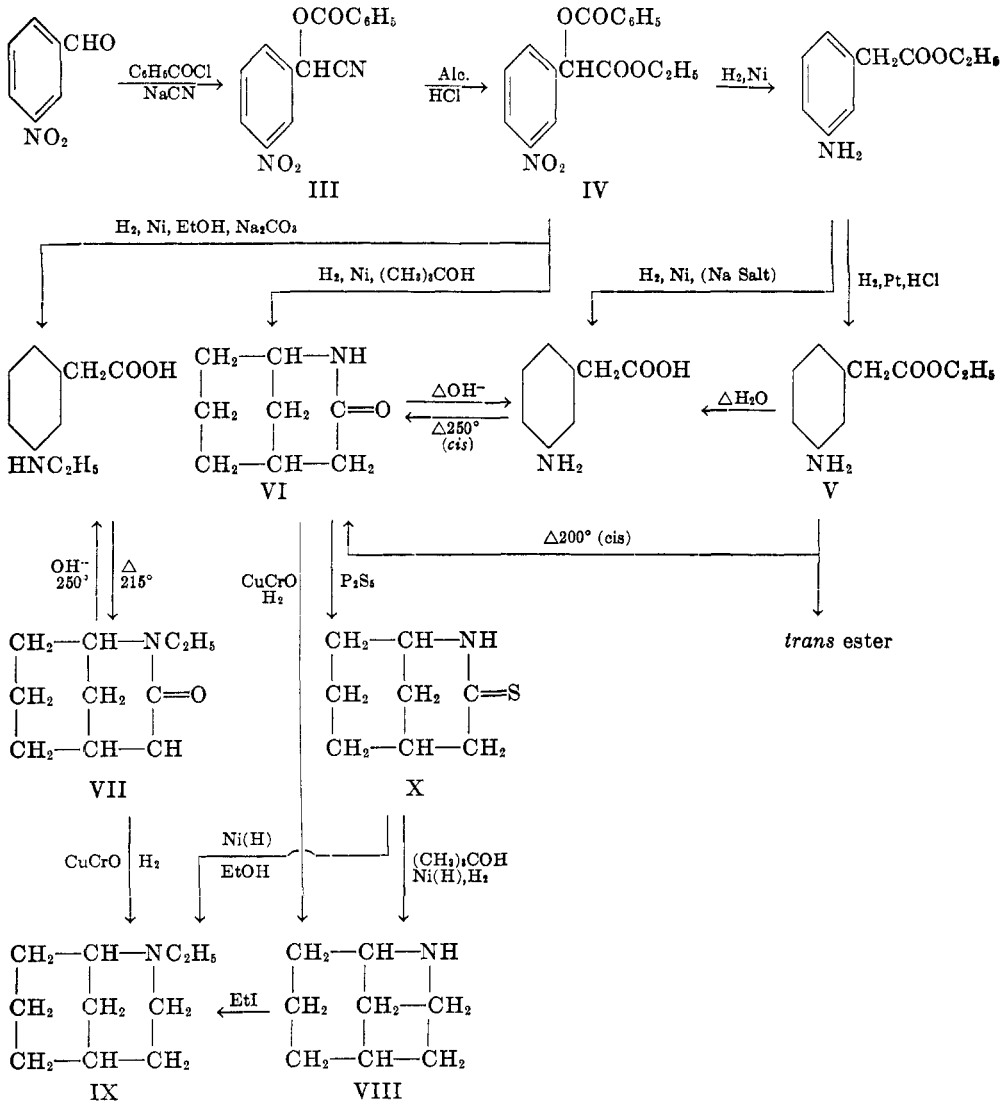
The third and most useful method for the synthesis of the lactam was the direct hydrogenation over Raney nickel of the ethyl ester of *m*-nitro-O-benzoylmandelic acid (IV) in *tert*-butyl alcohol at 200°. After a number of runs under a variety of conditions the optimum yields obtainable were 32–36%. When *m*-nitro-O-benzoylmandelic acid was hydrogenated as the sodium salt under the same conditions the yield of lactam was less than 10%. When one or two equivalents of sodium bicarbonate or sodium carbonate were added in the reduction of the ester (IV) the yields were 10–20% and *m*-nitromandelic acid alone gave only a 10% yield. The rate of hydrogen uptake seemed to indicate that the O-benzoyl group was removed more rapidly and at a lower temperature than the free hydroxyl and that the hydrogenolysis occurred more satisfactorily with the ester than with the free acid or its sodium salt.

tert-Butyl alcohol was chosen as the solvent for these hydrogenations when it was found that it could be used directly without special purification, that it did not alkylate the amino group (14), and that it was apparently stable over Raney nickel up to 220°. It has been used over copper chromite up to 260°.[6]

[5] The apparently increased activity of Raney nickel in the presence of sodium carbonate has been noted in other cases (10).

[6] The maximum useable temperatures were not determined.

Ethyl *m*-nitro-O-benzoylmandelate (IV) hydrogenated over Raney nickel in ethanol at 180° gave a mixture of the two lactams (VI) and VII) and the ethyl ester of N,N′-diethyl-3-aminocyclohexaneacetic acid. However, when two moles



of sodium carbonate were added so that the hydrogenation proceeded first (120°) to ethyl *m*-aminophenylacetate and then through the sodium salt, the principal product was N-ethyl-*cis*-3-aminocyclohexaneacetic acid which was heated at 215° and lactamized to (VII) in an over-all yield of 27–32%.

The two lactams (VI) and (VII) were hydrogenated to their respective amines

(VIII) and (IX) over copper chromite in *tert*-butyl alcohol. The 2-azabicyclo[3·3·1]nonane (VIII) was apparently unstable over copper chromite under the conditions necessary for hydrogenation since the yield was 30% with 16% recovery of starting lactam after three hours at 220° and 20% with no recovery after six hours. The same decrease of yield with increased time of contact was also observed at 200° and 250°. The N-ethyl lactam (VII), on the other hand, required a temperature of 250° for any appreciable reduction and the resulting amine (IX) was more stable and was obtainable in higher yield. For comparison 2-ethyl-2-azabicyclo[3·3·1]nonane (IX) was also made by the reaction of (VIII) with ethyl iodide.

As a variation the lactam (VI) was converted into the thiolactam (X) by means of phosphorus pentasulfide. In order to convert thiolactams to cyclic amines Ruzicka (15) used an electrolytic method;[7] however, it has been found that this reduction could also be accomplished by refluxing the thiolactam with Raney nickel in an alcohol solvent. Although a number of different types of compounds have been desulfurized in this fashion (16) the procedure has not been applied previously to thiolactams.

When the thiolactam was refluxed with Raney nickel in absolute ethanol the product was the N-ethyl derivative (IX).[8] The alkylation of amines by alcohols has been studied extensively at 150–200° (17) but apparently the method has not been used at lower temperatures; although it has been observed that aniline was alkylated by ethanol during the reduction of nitrobenzene under similar conditions (18). A sample of the secondary amine (VIII) was alkylated to (IX) under hydrogen, thus demonstrating that the process is actually one of direct alkylation rather than the possible reductive alkylation via the acetaldehyde which may be generated by refluxing the ethanol solution open to the air or in contact with a hydrogen acceptor such as the aldimine form —CH=N— (19).

The secondary amine (VIII) was obtained in 64% yield by heating the thiolactam with Raney nickel in *tert*-butyl alcohol under a positive pressure of hydrogen. Refluxing the thiolactam with the catalyst in *tert*-butyl alcohol gave incomplete reduction and a mixture of products similar to that which was obtained with the less active nickel in ethanol.[8]

The two lactams showed differences in the ease with which they could be hydrolyzed. Sixty per cent of the lactam (VI) was recovered after refluxing with 10% sodium hydroxide for twenty-four hours and 80% was unchanged after twenty-four hours with concentrated hydrochloric acid at 160° in a sealed tube. It was finally hydrolyzed to the extent of at least 90% after six hours at 210° in 1 *N* sodium hydroxide. The N-ethyl lactam (VII) at 220° for twelve hours in 1 *N* sodium hydroxide gave 65% unreacted starting material. Even after fifteen hours at 250° in 2 *N* sodium hydroxide 27% was recovered unchanged.

The azabicycloalkanes described in this work have been tested for possible

[7] Ruzicka (23) has recently applied $LiAlH_4$ to lactam reduction and obtained 60–95% yields of the polymethylene imines.

[8] In early experiments a less active catalyst than that described by Adkins and Pavlic (20) was used. The results have not been clarified as yet since the products seemed to be a mixture of (IX) and the aldimine —CH=N— or its trimer.

analgesic activity under the direction of Dr. Nathan B. Eddy, National Institutes of Health, Bethesda, Maryland. The lactams (VI) and (VII) exhibit definite analgesic activity, which appears quickly and is brief. Both are convulsant. The amines (VIII) and (IX) were toxic and inactive.

EXPERIMENTAL

All melting points are corrected. Microanalyses were performed by C. W. Koch and V. H. Tashinian.

m-Nitro-O-benzoylmandelonitrile (III). To a well-stirred suspension of 302 g. (2 moles) of *m*-nitrobenzaldehyde (Eastman) in 400 ml. of water in a 4-liter beaker cooled to 0–5° in an ice-bath there was added, in one portion, 245 ml. (2.05 moles) of benzoyl chloride. After a few seconds for mixing, a solution of 118 g. (2.2 moles) of 95% sodium cyanide in 250 ml. of water was added all at once. Within a few seconds the temperature rose to 80° and then dropped to 50–60° at which time crystallization set in. The solid was filtered, washed with water, and air dried. One crystallization from ethanol gave 495 g. (88%) of product; m.p. 98–101°. A sample recrystallized from alcohol formed colorless leaflets; m.p. 99.5–101°.

Anal. Calc'd for $C_{17}H_{16}N_2O_6$: C, 63.81, H, 3.57; N, 9.92.

Found: C, 64.05; H, 3.75; N, 9.95.

Ethyl m-nitro-O-benzoylmandelate (IV). To a solution of 200 g. of dry hydrogen chloride in 1200 ml. of absolute ethanol there was added 564 g. (2.0 moles) of the nitrile (III). The solution was heated to refluxing and there was added 50 ml. of water in several portions with swirling. The mixture was refluxed for thirty minutes and was filtered hot. The ester crystallized from the filtrate and was thoroughly washed with water and air dried to give 562 g., m.p. 76–79°; a second crop was recrystallized from ethanol to give 32 g., m.p. 75–79° (yield 90%). A sample was recrystallized from absolute ethanol; small prisms, m.p. 78.5–80.0°.

Anal. Calc'd for $C_{10}H_{13}NO_2$: C, 62.00; H, 4.59; N, 4.25.

Found: C, 61.90; H, 4.48; N, 4.56.

Ethyl m-aminophenylacetate. A suspension of 165 g. (0.5 mole) of the mandelic ester (IV), 53 g. of sodium carbonate (0.5 mole), and 25 g. of Raney nickel (20)[9, 10] in 300 ml. of absolute

[9] The method of preparation of the nickel seemed to have no discernable effect on the yield, and catalyst which had stood for six months was no less effective than the fresh material.

[10] During the course of this work some rather interesting observations were made concerning the effects exerted by the stainless steel liners sometimes used for catalytic hydrogenations. The optimum conditions for the three different Raney nickel hydrogenations starting with the ester (VI) had been worked out with several score reactions on a 0.05-mole scale in bomb sizes of 180 to 300 ml. capacities without a liner. When the reactions were scaled up to the 0.5-mole size larger bombs with stainless steel liners were used. The results, at first attributed simply to the increased size of the run, varied from 10% less yield than expected down to nothing at all. Furthermore, the nature of the products had changed. A majority of the hexahydrobenzoic acid, obtained as a by-product in the preparation of the lactam (IV), was isolated as the ethyl ester without the liner (the final solution was alkaline); but it was obtained as the free acid when the liner was used. Due to the large ratios of catalyst to reactants the reductions of the nitro group were extremely rapid. Without the liner, and regardless of the size of the run, there was only a twenty to thirty degree temperature rise (at 60–70°) and no more than a few hundred pounds pressure increase, if at all. However, with the liner in use these effects were very erratic, perhaps due to the insulating effect of the space between the liner and bomb. The temperature rose rapidly as much as 50–130° and on one occasion with 0.5 mole of the nitro-ester there was a sudden momentary pressure increase of 2000 lbs. Had this been a larger quantity of material a considerable strain might have been placed on the equipment. Without the liners, and using quantities of the ester (IV) up to 0.7 mole, the products and yields agreed very well with those obtained on the 0.05 mole scale.

ethanol was heated and shaken under 150–200 atm. of hydrogen. The reduction of the nitro group was exothermic between 60° and 100° and over a period of fifty minutes between 120° and 130° the fourth mole of hydrogen was absorbed. The filtered solution was distilled to a small volume, dissolved in benzene, washed with water and 5% sodium bicarbonate, and dried over magnesium sulfate. Distillation of the product gave a slight forerun of 1.5 g. which was followed by 78 g. (87%) of ethyl *m*-aminophenylacetate; b.p. 138–140° (3–4 mm.); n_D^{21} 1.5435.

Anal. Calc'd for $C_{10}H_{13}NO_2$: C, 67.00; H, 7.31; N, 7.82.
Found: C, 66.84; H, 7.37; N, 7.99.

The *hydrochloride* was obtained as fine leaflets from ethanol–ether; m.p. 129–131°.

Anal. Calc'd for $C_{10}H_{14}ClNO_2$: C, 55.67; H, 6.54; Cl, 16.44; N, 6.49.
Found: C, 55.82; H, 6.59; Cl, 16.13; N, 6.83.

m-Aminophenylacetic acid. A mixture of 17.9 g. (0.1 mole) of the ethyl ester of *m*-aminophenylacetic acid and 20 ml. of 6.0 *N* sodium hydroxide was refluxed for thirty minutes. The alcohol was boiled off and 20 ml. of 6.0 *N* hydrochloric acid was added; yield, 14.5 g., m.p. 146–148° [literature (21); 148–149°].

Ethyl 3-aminocyclohexaneacetate (V). To a solution of 4 g. of dry hydrogen chloride in 150 ml. of absolute ethanol was added 17.9 g. (0.1 mole) of ethyl *m*-aminophenylacetate and 1.3 g. of Adams platinum oxide catalyst (American Platinum Works). After two hours of shaking at 60–65° and 30–40 lbs. hydrogen pressure the hydrogen uptake had ceased at the calculated amount. The catalyst was filtered, the alcohol was distilled to a small volume, and the residue was taken up in ether and water. Evaporation of the ether left 0.7 g. of ethyl hexahydrobenzoate. The aqueous solution was basified over chloroform with 20 ml. of 6.0 *N* sodium hydroxide. The chloroform extracts were dried and distilled to give 11.8 g. (64%) of the hexahydro ester boiling at 110° (6 mm.) and 4.2 g. of a fraction with a b.p. of 195–200° (6 mm.).

Lactam of cis-3-aminocyclohexaneacetic acid (VI). *A. Via platinum reduction.* The 11.8 g. of the *cis* and *trans* esters was dissolved in 45 ml. of absolute ethanol and heated at 200° for an hour and a half. After distillation 2.1 g. of the lactam (VI) was obtained by crystallization from ether; m.p. 156–164°. Including 0.3 g. recovered after the distillation of the filtrate the yield amounted to 27%. Several recrystallizations of a sample from ether gave clear colorless prisms; m.p. 163.5–165.5°.

Anal. Calc'd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06.
Found: C, 69.28; H, 9.53; N, 10.33.

After the lactam had been removed the residue was fractionated and gave 7.3 g. (62%) of *ethyl trans-3-aminocyclohexaneacetate*; b.p. 110° (6 mm.), n_D^{23} 1.4650. When a sample of this ester was again heated in ethanol for three hours at 210° no lactam was obtained; thus the ratio of *cis* to *trans* must have been about 3:7.

Anal. Calc'd for $C_{10}H_{19}NO_2$: C, 64.80; H, 10.31; N, 7.56.
Found: C, 64.69; H, 10.28; N, 7.79.

A solution (clear at room temperature, cloudy when warmed) of 3.0 g. of the *trans* ester in 10 ml. of water was refluxed for twenty-four hours. The residue after evaporation of the water was triturated with alcohol to give 2.1 g. (82%) of *trans-3-aminocyclohexaneacetic* acid, m.p. 258–260° dec. A sample was sublimed and recrystallized from water–alcohol to give clusters of tiny needles, m.p. 266–267° dec. (sealed tube).

Anal. Calc'd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91.
Found: C, 61.29; H, 9.73; N, 8.92.

When the mixture of *cis* and *trans* esters has hydrolyzed in the same manner and a 1.0-g. sample of the resulting amino acids was heated at 260° for half an hour in a N_2 atmosphere there was obtained 0.25 g. (28%) of the lactam (VI). The *trans* acid polymerized and gave no lactam under the same conditions.

One and three tenths grams of the *trans* ester after treatment with benzoyl chloride followed by a room temperature saponification gave 1.5 g. of the *benzoate of trans-3-aminocyclohexaneacetic acid*, m.p. 151–156°. Three crystallizations from acetone gave tiny clusters

of fine needles which, when heated slowly, started to melt at 156–157° then resolidified and finally melted at 183–185°.

Anal. Calc'd for $C_{15}H_{19}NO_3$; C, 68.93; H, 7.33; N, 5.36.
Found: C, 68.93; H, 7.46; N, 5.41.

cis-3-Aminocyclohexaneacetic acid. A solution of 2.0 g. of the lactam (VI) in 20 ml. of 1.0 *N* sodium hydroxide was heated at 200° for six hours. After the addition of 20 ml. of 1.0 *N* hydrochloric acid the water was evaporated under a current of air on the steam-bath. The residue was sublimed at 220° (6 mm.) and was then extracted with boiling ether (0.5 g. of lactam was recovered) to leave 1.5 g. of the amino acid. Recrystallization from alcohol-water gave fine needles, m.p. 272–273° dec. (sealed tube). A mixture with the *trans* acid melted at 251–255° with decomposition.

Anal. Calc'd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91.
Found: C, 61.04; H, 9.36; N, 9.26.

One-half gram of the *cis* amino acid heated in a N_2 atmosphere for thirty minutes at 260° gave 0.40 g. (90%) of the lactam (VI).

A 0.47-g. sample of the amino acid gave 0.56 g. of the *benzoate* of *cis-3-aminocyclohexaneacetic acid*, m.p. 185–190°. After recrystallization from acetone fine hair-like needles were obtained which started melting at 185–187° leaving a little solid; if the capillary was then removed from the bath momentarily the sample recrystallized and subsequently melted at 191–192°.

Anal. Calc'd for $C_{15}H_{19}NO_3$: C, 68.93; H, 7.33; N, 5.36.
Found: C, 68.82; H, 7.19; N, 5.53.

A mixture with the *trans* benzoate sintered at 147° and melted at 149–155°.

B. From m-aminophenylacetic acid via Raney nickel reduction. To a solution of 15.1 g. (0.1 mole) of *m*-aminophenylacetic acid in 16.7 ml. of 6.0 *N* sodium hydroxide there was added 12 g. of Raney nickel and 45 ml. of *tert*-butyl alcohol (Eastman). Two and a half moles of hydrogen were absorbed after an hour and a half at 200° and 300 atm. The product was washed out with water and after filtration and washing of the catalyst the solution was distilled to a small volume and 16.5 ml. of 6.0 *N* hydrochloric acid was added. A small amount of insoluble material was removed, the water was evaporated, and the residue was sublimed at 210° (3–5 mm.). A total of 10.5 g. of sublimate was collected, extracted with boiling benzene, and triturated with absolute ethanol to leave 5.4 g. of amino acid; m.p. 240–250° (dec.). From the benzene extracts there was recovered 2.2 g. of the lactam (VI), m.p. 155–162° alone and when mixed with the lactam from *A*.

A 1.0-g. sample of the amino acid heated at 260° for thirty minutes gave 0.60 g. of the lactam. Assuming that the lactam obtained from the benzene solution originated during the sublimation, the total yield of amino acid from this reduction was 50% and the ratio of the *cis* to *trans* isomers must have been approximately 5:1.

C. From ethyl m-nitro-O-benzoylmandelate (III) *via Raney nickel reduction.* A suspension of 165 g. (0.5 mole) of ethyl *m*-nitro-O-benzoylmandelate and 85 g. of Raney nickel in 325 ml. of *tert*-butyl alcohol was shaken and heated up to 200° over a one-hour period during which 4–5 mole-equivalents of hydrogen were consumed.[10] A total of 10–11 mole-equivalents of hydrogen were taken up after 3–5 hours at 200°. Distillation of the product gave 45 g. of ethyl hexahydrobenzoate; b.p. 85–90° (50 mm.) and 50–55 g. (the last half solidified) of material boiling over the range 110–170° (3–5 mm.). This distillate was dissolved in water and ether; the ether was extracted with water and the combined aqueous solutions were acidified to *p*H 2 with 2–3 ml. of 6 *N* hydrochloric acid. The acidic solution was washed with ether and the ether was discarded; then 4–5 ml. of 6 *N* sodium hydroxide was added, the solution was extracted with ether and the ether was again discarded. The aqueous solution was distilled to a small volume and adjusted to *p*H 7–8 (Universal paper). The residue was evaporated dry and sublimed at 3–5 mm. and 140–150°. The 25–28 g. of sublimate was crystallized from acetone–ether to give a total of 22–25 g. (32–36%) of the lactam (VI), m.p. 163.5–165.5° alone and when mixed with lactam from *A*.

Lactam of N-ethyl-cis-3-aminocyclohexaneacetic acid (VII). A suspension of 165 g. (0.5

mole) of the ester (IV), 85 g. of Raney nickel, and 133 g. of sodium carbonate in 300 ml. of absolute ethanol was shaken and heated up to 180° over a one-hour period under 300 atm. of hydrogen.[10] Within two and a half hours at 180° 11–12 mole-equivalents of hydrogen had been consumed. The products were washed out of the bomb with water, filtered, concentrated, and hydrochloric acid (417 ml. of 6.0 *N*) was added in portions. After removing the hexahydrobenzoic acid and further concentrating the solution, alcohol was added to remove most of the sodium chloride. Distillation of the water and alcohol left the amino acid which was lactamized by heating under reflux at 215° (50–60 mm.). The product was distilled directly from the reaction flask with a bath temperature of 200–240° (50 mm.); finally the pressure was reduced to 3–5 mm. and everything distilling up to 150° was collected. The combined distillates (30–35 g.) were dissolved in water and ether. The ether solution was washed twice with water and the combined aqueous solutions were refluxed a few minutes with 5% sodium hydroxide, cooled, and extracted several times with chloroform. The chloroform was washed with 5% hydrochloric acid, the acid solution was washed with chloroform, and the combined chloroform solutions were washed again with 5% sodium hydroxide, dried over potassium carbonate, and distilled to give 23–27 g. (27–32%) of the N-ethyl lactam (VII), b.p. 122–123° (5–6 mm.), n_D^{23} 1.5020.

Anal. Calc'd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38.
Found: C, 71.27; H, 10.18; N, 8.68.

After several unsuccessful hydrolyses under milder conditions 3.34 g. (0.02 mole) of the N-ethyl lactam was dissolved in 30 ml. of 2.0 *N* sodium hydroxide and heated in a steel autoclave at 250° for fifteen hours. To the cooled solution was added 10 ml. of 6.0 *N* hydrochloric acid and the unreacted lactam was then recovered by chloroform extraction. Distillation gave 0.91 g. (27%) of unreacted material; n_D^{21} 1.5020. The aqueous solution was evaporated dry at room temperature in a stream of air and the residue was sublimed at 220° (6 mm.) to give 2.4 g. (65%) of *N-ethyl-cis-3-aminocyclohexaneacetic acid*. A sample of the amino acid crystallized from acetone-alcohol-water in fine needles; m.p. 239–240° dec. (sealed tube).

Anal. Calc'd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56.
Found: C, 64.78; H, 10.37; N, 7.77.

An 0.85-g. sample of the acid heated at 240° for thirty minutes gave 0.67 g. (87%) of the lactam, n_D^{22} 1.5025.

2-Azabicyclo[3.3.1]nonane (VIII). *A. By copper chromite reduction.* The lactam of *cis*-3-aminocyclohexylacetic acid (VI) (2.8 g.) was hydrogenated at 200–210° and 300 atm. for five hours in 45 ml. of *tert*-butyl alcohol with 9 g. of copper chromite (22). After allowing for the amount of hydrogen taken up by the copper chromite (as determined in a blank run) the absorption of hydrogen was 70–80% of theory. The product was washed out of the bomb with ethanol, filtered, and titrated to *p*H 6. After evaporation of the solvent on the steam-bath the residue was sublimed at 160° (3 mm.) and gave 0.3 g. of unreacted amide. The material which sublimed at 220° was crystallized from alcohol-acetone to give 1.5 g. (46%) of the *hydrochloride* of *2-azabicyclo[3.3.1]nonane*; m.p. 280–295°. A sample was sublimed and recrystallized as sugary prisms or fine needles; m.p. 300–302° dec. (sealed tube).

Anal. Calc'd for $C_8H_{16}ClN$: C, 59.42; H, 9.98; Cl, 21.93; N, 8.66.
Found: C, 59.62; H, 9.90; Cl, 21.80; N, 8.60.

The *free base* (VIII) obtained by basification of an aqueous solution of the hydrochloride and ether extraction, was purified by sublimation at 75–80° (50 mm.) to give a camphoraceous solid, m.p. 135–137° (with partial melting and resolidification at 120–130°).

The *phenylthiourea* derivative crystallized as fine needles from ethanol, m.p. 125–127°.

Anal. Calc'd for $C_{15}H_{20}N_2S$: C, 69.19; H, 7.74; N, 10.76; S, 12.31.
Found: C, 69.05; H, 7.76; N, 10.58; S, 12.13.

B. From the thiolactam (X). A suspension of 7.0 g. (0.05 mole) of the lactam (VI) with 13.3 g. of phosphorus pentasulfide in 50 ml. of xylene was stirred vigorously and heated at 125–130° for an hour in an oil-bath. The cooled solution was stirred with 100 ml. of 25% sodium hydroxide for half an hour at room temperature and the insoluble thiolactam was filtered, washed with water, and air dried. After sublimation at 200° (6 mm.) and crystalliza-

tion from ethanol there was obtained 6.0 g. (77%) of the thiolactam (X), m.p. 187–196°. Recrystallization of a sample from ethanol gave prisms and leaflets; m.p. 196–198° (sealed tube).

Anal. Calc'd for $C_8H_{13}NS$: C, 61.90; H, 8.44; N, 9.03; S, 20.62.
Found: C, 62.17; H, 8.47; N, 9.21; S, 20.82.

Three grams of the thiolactam (X) in 50 ml. of *tert*-butyl alcohol was heated and shaken with 18 g. of Raney nickel for four hours at 80–85° under 40 lbs. of hydrogen. After removal of the nickel, titration (to *p*H 6) of the filtered solution with 1.0 *N* hydrochloric acid indicated a 70–80% conversion of the thiolactam into basic material. The acidic solution was evaporated dry and sublimed. Crystallization of the sublimate from alcohol-acetone gave 2.0 g. (64%) of fine needles, m.p. 292–298° alone and when mixed with a sample from *A*.

2-Ethyl-2-azabicyclo[3.3.1]nonane (IX). *A. By copper chromite reduction.* A solution of 3.34 g. of the N-ethyl lactam (VII) in 45 ml. of *tert*-butyl alcohol was heated and shaken with 10 g. of copper chromite at 250° under 300 atm. of hydrogen until the theoretical amount of hydrogen had been taken up (two hours). Titration of the filtrate after removal of the catalyst indicated the presence of about 85% of the nitrogen as a free base. The solution was evaporated dry and sublimation gave 3.1 g. (82%) of the *hydrochloride* of *2-ethyl-2-azabicyclo-[3.3.1]nonane*. Crystallization from benzene gave small clusters of tiny needles, m.p. 142–144°. The compound was extremely hygroscopic and could not be exposed to the air for more than a few seconds without liquefaction. For analysis a sample was sublimed in the presence of P_2O_5.

Anal. Calc'd for $C_{10}H_{20}ClN$: C, 63.30; H, 10.63; Cl, 18.69; N, 7.38.
Found: C, 62.92; H, 10.39; Cl, 18.58; N, 7.98.

A sample of the *free base* (IX) was obtained as an oil by basification of the hydrochloride, n_D^{22} 1.488.

B. From VIII. (a) A mixture of 1.25 g. of 2-azabicyclo [3.3.1] nonane and 1.56 g. of ethyl iodide in 5 ml. of benzene was allowed to stand several hours and was then basified. The hydrochloride was sublimed (1.40 g.) and after crystallization from benzene there was obtained 1.1 g., m.p. 139–144° alone and when mixed with a sample prepared as in part *A*.

(b) One half gram of the free base (VIII) was added to 4 g. of Raney nickel in 50 ml. of absolute ethanol and the mixture was shaken for four hours under 30 lbs. of hydrogen at 80°. Sublimation and crystallization of the hydrochloride from benzene gave 0.43 g. (60%), m.p. 142–144° alone and when mixed with a sample from *A*.

C. From the thiolactam (X). A solution of 4.0 g. of the thiolactam in 100 ml. of absolute ethanol, protected with a soda-lime tube, was refluxed for three hours with 25 g. of Raney nickel. Titration of the filtered solution indicated 87% conversion of the thiolactam to free amine. The solvent was removed and the residue was sublimed to give 4.2 g. of the hygroscopic hydrochloride of the amine (IX). Crystallization from benzene gave 3.7 g. (76%) of tiny needles, m.p. 142–144° alone and when mixed with a sample from part *A*.

SUMMARY

1. A procedure has been developed for the preparation of the ethyl ester of *m*-aminophenylacetic acid in a three-step process from *m*-nitrobenzaldehyde.

2. Catalytic hydrogenation of ethyl *m*-aminophenylacetic acid over platinum in alcoholic hydrogen chloride to the corresponding hexahydro derivative gave a *cis-trans* ratio of 3:7. Over Raney nickel in *tert*-butyl alcohol–water at 200° the sodium salt gave a *cis-trans* ratio of 5:1. In ethanol with Raney nickel the ethyl ester gave N-ethyl-3-aminocyclohexaneacetic acid.

3. Raney nickel in *tert*-butyl alcohol under hydrogen has been used for the reduction of a thiolactam to the corresponding cyclic amine. In refluxing ethanol the N-ethyl amine was obtained.

4. The synthesis of 2-azabicyclo[3·3·1]nonane and several of its derivatives has been described.

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