48 hours. The product was isolated in the same manner as II and purified by reprecipitating from sodium hydroxide solution with concd. hydrochloric acid; yield 0.8 g. (31%), m.p. 253°.

Anal. Calcd. for $C_{14}H_{15}N_5O_2$: N, 24.56. Found: N, 24.65.

Acknowledgments.—The author is grateful to the American Cyanamid Company for a sample of dicyandiamide, the Carbide and Carbon Chemicals Company for a sample of pentanedione-2,4, to Dr. C. K. Banks and Mr. Robert E. Cox for helpful suggestions during the course of this research and to Dr. W. F. Cantrell for aid in the testing of the compounds reported.

LOUISVILLE, KY.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS UNIVERSITY]

The Synthesis of the 3,9-Diazabicyclo[3.3.1]nonane Ring System[1]

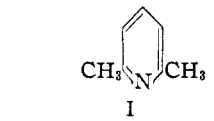
BY RODERICK A. BARNES AND HENRY M. FALES[2]

RECEIVED SEPTEMBER 12, 1952

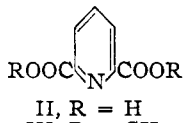
Dimethyl scopolinate has been prepared from 2,6-lutidine by oxidation to dipicolinic acid followed by esterification, catalytic reduction and methylation. The reaction of dimethyl scopolinate with benzylamine produced the bicyclic imide which was converted by lithium aluminum hydride to 3-benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonane.

The most widely used method for synthesizing bicyclic amines related to the tropane alkaloids has been the procedure developed by Robinson and co-workers.[3] The most difficult aspect of this procedure is usually the preparation of the required dialdehyde.

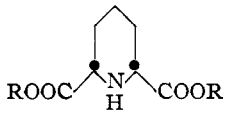
The present investigation was undertaken to see if a practical method could be worked out for converting the readily available 2,6-lutidine (I) to a bicyclic system. Several attempts were made to transform the two methyl groups into substituents which would be capable of further elaboration toward the desired bicyclic system. The only transformation which was satisfactory from the standpoint of yield was oxidation to dipicolinic acid (II).



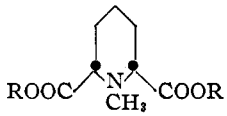
I



II, R = H
III, R = CH_3



IV, R = H
V, R = CH_3

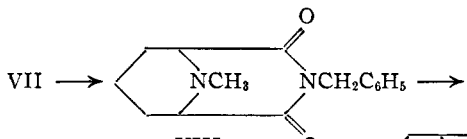


VI, R = H
VII, R = CH_3

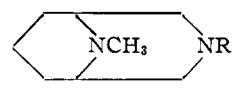
Acid II, either as its potassium salt or its ester (III), was readily hydrogenated by Raney nickel to yield the corresponding piperidine (IV or V). In order to prove that the hydrogenation had taken place to yield the *cis* isomer, IV was converted to scopolinic acid (VI). Since VI was originally obtained by oxidation of dihydroscopoline[4] it must have the *cis* structure.

Our sample of dimethyl scopolinate (VII) formed a methiodide which differed in melting point from that previously reported.[5] This discrepancy was resolved when an attempted acyloin condensation with VII failed. The recovered ester was found to produce a methiodide which did agree with the literature value. However, saponification of the recovered ester did not yield scopolinic acid but its stereoisomer, isoscopolinic acid which is the previously unreported *trans*-acid. From this it was concluded that the alkaline conditions during the attempted acyloin condensation caused isomerization of the *cis*-ester to the *trans*-ester. It was later observed that even on standing ester VII was gradually isomerized; the tertiary nitrogen is apparently a strong enough base to cause some enolization. This accounts for the fact that the methiodide reported by Schmidt was actually a derivative of isoscopolinic acid even though it had been prepared from scopolinic acid.

When either stereoisomer of VII was heated with benzylamine the bicyclic imide (VIII) was formed in 60% yield along with small amounts of the diamide. The reduction of VIII with lithium



VIII



IX, R = $CH_2C_6H_5$
X, R = H

aluminum hydride proceeded very smoothly (86% yield) to form the oxygen-free base IX.[6] The benzyl group could be removed by hydrogenolysis in alcoholic hydrochloric acid solution to yield X which was isolated as the dihydrochloride.

It was found that IX formed only a monomethiodide and a monopicrate while X formed a dipicrate and a dihydrochloride. An examination of models of these two bases suggested that this difference between the two bases is due to steric

(1) Presented at the 122nd Meeting of the A.C.S., Atlantic City, N. J., September 15, 1952.

(2) Abstracted from a thesis presented by H. M. Fales to the Graduate Faculty for the Ph.D. degree, September, 1952.

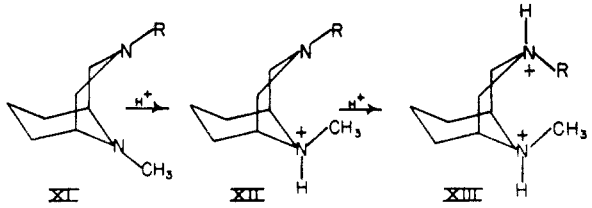
(3) B. K. Blount and R. Robinson, *J. Chem. Soc.*, 2485 (1932), have prepared the only previously reported example of the 3,9-diazabicyclo[3.3.1]nonane ring system; *N*-methylaztropinone was obtained in 7.5% yield.

(4) E. Schmidt, *Arch. Pharm.*, **247**, 79 (1909).

(5) E. Schmidt, *ibid.*, **253**, 499 (1915).

(6) A 5-mg. sample of this compound caused immediate depressor action when administered by vein to an anesthetized cat. The authors wish to thank Dr. E. Rohrmann and the Eli Lilly Company for making this test.

factors. The most likely configuration for the bases is represented by XI. When monosalt



XI XII XIII

(XII) is being formed it makes no difference whether R is a hydrogen or benzyl group. However, the formation of the dibasic salt (XIII) requires that the methyl group and the group R be so close together that a stable compound results only when R is a hydrogen atom.[7]

Experimental[8]

Dimethyl Dipicolinate (III).—Dipicolinic acid hydrate (100 g.) prepared by permanganate oxidation of 2,6-lutidine[9] was refluxed for 48 hours with purified thionyl chloride (300 ml.). The excess thionyl chloride was distilled, the residue was taken up in carbon tetrachloride and treated with methanol (55 ml.) keeping the temperature at 50–60°. The crude ester which precipitated on cooling was purified by vacuum distillation, b.p. 155–160° (0.5 mm.). There was obtained 95.7 g. (*ca.* 95%) of III which melted at 124–125°.[10]

Anal. Calcd. for $C_9H_9O_4N$: C, 55.38; H, 4.65. Found: C, 55.31; H, 4.64.

Dimethyl 2,6-Piperidinedicarboxylate (V).—A solution of dimethyl 2,6-dipicolinate (93 g.) in dioxane (250 ml.) was hydrogenated for 30 minutes at 150° and 3000 lb. using Raney nickel (15 g.). The catalyst was filtered and the solvent removed to leave a residue (nearly quant.) which melted at 92°. Recrystallization from chloroform produced pure ester V which melted very sharply at 93°.

Anal. Calcd. for $C_9H_{15}O_4N$: C, 53.71; H, 7.51; N, 6.96. Found: C, 53.68; H, 7.66; N, 6.86.

Dimethyl Scopolinate (VII). A.—Methyl iodide (70.6 g.) was added in one portion to a suspension of moist silver oxide (prepared from 100 g. of silver nitrate) in methanol (250 g.) containing dimethyl 2,6-piperidinedicarboxylate (100 g.). Some cooling was necessary to prevent loss of methyl iodide. After the mixture was stirred for one hour at room temperature the precipitate was removed by filtration and the solvent distilled. Distillation of the residual oil yielded 62.2 g. (58%) of colorless product which boiled at 71–76° (0.14 mm.), $n^{25}D$ 1.4659.

Anal. Calcd. for $C_{10}H_{17}O_4N$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.89; H, 7.93; N, 6.55.

This ester was also prepared by reductive alkylation with formaldehyde in 85% yield.[11]

The methiodide of this ester was prepared by allowing it to stand at room temperature for 12 hours. Recrystallization from ethanol–ethyl acetate produced square plates which melted with decomposition at 145–152°.

Anal. Calcd. for $C_{11}H_{20}O_4NI$: C, 36.98; H, 5.64. Found: C, 36.68; H, 5.53.

B.—Scopolinic acid (m.p. 225°) was prepared by catalytic reduction with Raney nickel of potassium dipicolinate followed by methylation with formaldehyde.[12] The reaction of scopolinic acid with diazomethane in moist ether produced the dimethyl ester. This ester formed a methiodide which melted at 145–152° (dec.) alone or when mixed with the sample prepared in part A.

Dimethyl Isocopolinate.—Sodium (1.4 g.) was added to a solution of ester VII (3 g.) in xylene (50 ml.) and the mixture refluxed for 25 hours. Methanol and water were added to decompose the sodium. The xylene layer was separated and the aqueous layer extracted with ether. The combined organic layer concentrated and the residue vacuum distilled. The product boiled at 85° (0.20 mm.), $n^{25}D$ 1.4665. The methiodide was prepared as for ester VII. It melted at 175–180°[13] after repeated recrystallization from ethanol.

Anal. Calcd. for $C_{11}H_{20}O_4NI$: C, 36.98; H, 5.64. Found: C, 37.02; H, 5.67.

A sample of dimethyl scopolinate which was allowed to stand for several months also formed only a methiodide melting at 175–180°. There were only minor differences in the infrared absorption curves of dimethyl scopolinate and dimethyl isoscopolinate; absorption bands at 2.85 and 10.50 μ were more intense for dimethyl scopolinate.

Isoscopolinic Acid.—Dimethyl isoscopolinate (0.5 g.) was saponified at room temperature with 3 *N* barium hydroxide. An exact equivalent of sulfuric acid was added, the barium sulfate filtered and the filtrate concentrated. The crude acid was purified by several recrystallizations from aqueous ethanol; the m.p. was 263° with decomposition beginning at 253°.

Anal. Calcd. for $C_8H_{13}O_4N$: C, 51.33; H, 7.00. Found: C, 51.39; H, 6.86.

A mixture of this acid with scopolinic acid melted from 225–250° with decomposition.

N-Benzylscopolinimide (VIII).—A mixture of benzylamine (16 g.) and either dimethyl scopolinate or dimethyl isoscopolinate (13 g.) was refluxed gently for 48 hours. Then the methanol and excess benzylamine were distilled; about 10 g. of distillate was collected. The residue was boiled for a few minutes with ligroin and then the hot ligroin solution was decanted. The imide crystallized when the solution was chilled. Further heating of the residual ligroin-insoluble material followed by extraction again with hot ligroin produced a further quantity of imide. The imide was purified by recrystallization from ligroin. There was obtained 10 g. (60%) of product which melted at 113–118°. The analytical sample was further purified by sublimation, m.p. 116–118°.

Anal. Calcd. for $C_{15}H_{18}O_2N_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.58; H, 6.91; N, 10.70.

The ligroin-insoluble residue was dissolved in hot ethanol and treated with decolorizing charcoal. After several further recrystallizations from ethanol a pure sample was obtained which melted sharply at 200°. This is believed to be N,N′-dibenzylisoscopolindiamide.

Anal. Calcd. for $C_{22}H_{27}O_2N_3$: C, 72.30; H, 7.45. Found: C, 72.63; H, 7.62.

3-Benzyl-9-methyl-3,9-diazabicyclo[3.3.1]nonane (IX).—N-Benzylscopolinimide (7.6 g.) was added to a slurry of lithium aluminum hydride (2.4 g.) in anhydrous ether (300 ml.). The suspension was stirred for 72 hours and then treated with ethanol to destroy the excess hydride and 20% sodium hydroxide to dissolve the salts. The ether layer was separated and the aqueous layer extracted with additional ether. The ether solution containing the product was dried and concentrated. The residue was purified by evaporative distillation at 115° (0.33 mm.). There was obtained 5.8 g. (86%) of product IX, $n^{20}D$ 1.5447.

Anal. Calcd. for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63. Found: C, 78.23; H, 9.55.

The monomethiodide melted at 248–250° (dec.) after recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{25}N_2I$: C, 51.61; H, 6.77. Found: C, 52.14; H, 7.00.

(7) Experiments are in progress to convert IX and X to a tricyclic system by linking the nitrogen atoms with a two carbon bridge.

(8) Analyses by W. Manser, Zurich, Switzerland, and J. F. Alicino, Metuchen, New Jersey. All melting points were determined using the Kofler hot-stage.

(9) G. Black, E. Depp and B. B. Corson, *J. Org. Chem.*, **14**, 17 (1949).

(10) H. Meyer, *Monatsh.*, **24**, 205 (1903), reported a melting point of 121° for ester III which was prepared by a different procedure.

(11) R. F. Feldkamp, J. A. Faust and A. J. Cushman, THIS JOURNAL, **74**, 3331 (1952).

(12) This was essentially the procedure used by K. Hess and F. Wissing, *Ber.*, 48, 1907 (1915), except that they employed colloidal platinum for reduction of the free acid.

(13) E. Schmidt, ref. 5, reported a melting point of 175–176° for the methiodide which was incorrectly stated to be dimethyl scopolinate. **R. Willstätter, *ibid.*, 35, 2068 (1903), prepared a methiodide, m.p. 167–168°, from an ester which we believe was a mixture of dimethyl scopolinate and dimethyl isoscopolinate from its method of preparation.**

The monopicrate formed immediately in ethanol and after recrystallization from this solvent melted at 204–208°.

Anal. Calcd. for $C_{21}H_{25}O_7N_5$: C, 54.90; H. 5.49. Found: C, 55.20; H, 5.46.

9-Methyl-3,9-diazabicyclo[3.3.1]nonane Dihydrochloride.—A solution of IX (4.7 g.) in ethanol (200 ml.) was acidified with hydrochloric acid and shaken with hydrogen (30 lb.) in the presence of 5% palladium-on-charcoal (1 g.). The hydrogenolysis product was completely absorbed on the surface of the catalyst and could be washed off only with several portions of boiling water. The aqueous solution was evaporated to a sufficiently small volume to cause crystallization of the product, yield 3.3 g. (70%). Further recrystallization followed by sublimation produced a sample which sublimed unchanged on the hot-stage beginning at 260°.

Anal. Calcd. for $C_8H_{18}N_2Cl_2$: C, 45.08; H, 8.51. Found: C, 45.09; H, 8.53.

A portion of the hydrochloride was treated with sodium hydroxide and steam distilled. An aqueous solution of picric acid was added to the distillate. A dark yellow extremely insoluble picrate separated. This substance could be recrystallized only from a large amount of hot 80% acetic acid, m.p. 239–242° (dec.).

Anal. Calcd. for $C_{20}H_{22}O_{14}N_8$: C, 40.14; H, 3.17. Found: C, 40.82; H, 3.68.

NEW BRUNSWICK, N. J.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

On the Structure of Pyrrolidinetriones and Oxazolidinediones

BY GLENN S. SKINNER AND CHARLES B. MILLER, JR.

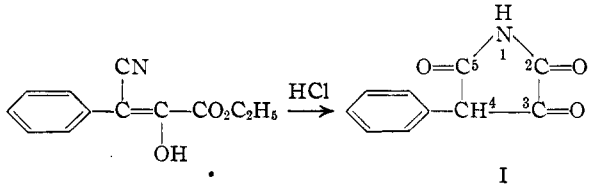
RECEIVED AUGUST 4, 1952

The condensation of ethyl oxalate with phenylacetamide yields 4-phenylpyrrolidinetrione identical with the product obtained by cyclization of ethyl β-cyano-α-hydroxycinnamate. Oxalyl chloride yields the isomeric oxazolidinedione. These isomers are further distinguished by their behavior toward alcohol, aniline and urea. The "pyrrolidinetriones" from oxalyl chloride (*vide infra*) are oxazolidinediones.

A series of compounds[1] made by the action of oxalyl chloride[2] on derivatives of acetamide has been reported. The assignment of the pyrrolidinetrione (I) structure[3] was accepted and no structural evidence was given beyond the infrared absorption studies which seemed to substantiate the structure previously assigned. Our studies of structure have not been completed but in view of interruptions and the seriousness of the question it is desirable to report the progress which shows them to be oxazolidinediones.

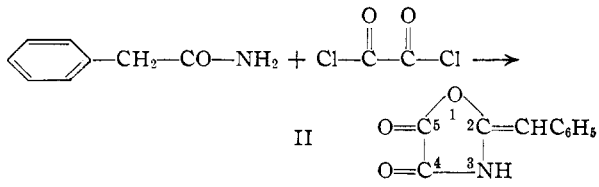
The above structure was questioned by Stolle and Luther[4] because the product from oxalyl chloride and acetanilide reacted with water to give acetic acid and oxanilic acid. It also failed to give a deep green color with dilute ferric chloride solution. Their assignment of the oxazolidinedione structure was supported by Spielman[5] especially on account of the cleavage of the ring by alcohol to the oxamic ester. Sheehan and Corey[6] have converted an oxazolidinedione through ring cleavage and condensation in an alkaline medium to an isomeric compound which was assigned the pyrrolidinetrione structure. These investigators conclude that the infrared data of the compounds from oxalyl chloride agree better with the oxazolidinedione structure.

While these arguments are very compelling and the initial error in not considering the possible oxazolidinedione structure is freely acknowledged, it is also true that the formation of isomers having different reaction characteristics is not absolute proof of the structure of either. We have therefore sought to compare the two isomers to a compound prepared in such manner that its ring structure has not been questioned. Such a reference pyrrolidinetrione (I) is provided by the reaction[7]



I

The compound (m.p. 217°) prepared by condensation of ethyl oxalate and phenylacetamide with the aid of sodium ethoxide in toluene was found to be identical with the pyrrolidinetrione (I). The product (II) from oxalyl chloride and phenylacetamide was obtained as brilliant yellow scales (dec. p. 166–167°) when crystallized from tetrahydrofuran.



II

The compound (I) when refluxed in absolute alcohol for 51 hours was recovered unchanged. The compound II after refluxing in absolute alcohol for 13.5 hours gave an almost colorless solution from which phenylacetamide (m.p. 156–157°) was isolated. With a trace of pyridine in alcohol (II) gave phenylacetyloxamic ester, m.p. 72–73°.

The compound (I) yielded a stable salt with aniline while (II) readily suffered aminolysis at room temperature to give N-phenyl-N′-phenylacetyloxamide. The aniline salt of (I) was dehydrated to 4-phenyl-3-phenyliminopyrrolidine-2,5-dione by heating at 185°.

(1) G. S. Skinner and J. F. Perkins, THIS JOURNAL, **72**, 5569 (1950).
(2) T. Figee, *Rec. trav. chim.*, **34**, 289 (1915).
(3) *Beilstein*, Vol. 4, p. 21 (436).
(4) R. Stolle and M. Luther, *Ber.*, **53**, 314 (1920).
(5) M. A. Spielman in "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 239.
(6) J. C. Sheehan and E. J. Corey, THIS JOURNAL, **74**, 360 (1952).
(7) V. Harlay, *C. A.*, **31**, 6226[1] (1937); *J. pharm. chim.*, **26**, 537 (1936).