Campbell and Sherman. For an increase of 10° in the temperature range of 100° to 130°, the rate of heat destruction of vitamin B in solutions such as here studied is increased only 1.3–1.4-fold, as compared with a 2-fold increase in most chemical reactions.

In the work here presented there was no indication of an increased temperature coefficient of heat destruction at temperatures around 120°. We find no evidence of any departure from the orderly course of a chemical reaction under the accelerating influence of heat but with a less than average temperature coefficient.

In this respect the heat destruction of the vitamin is in marked contrast with the heat coagulation of typical proteins and with the heat destruction of such typical enzymes as have been investigated.

As previously suggested in the case of vitamin C, the low temperature coefficient of the heat destruction of vitamin B may perhaps be due to the reaction being one which involves two phases of a heterogeneous system, the vitamin being in combination with or adsorbed upon colloidal material rather than in true solution in the hot water by which it is destroyed.

NEW YORK, N. Y.

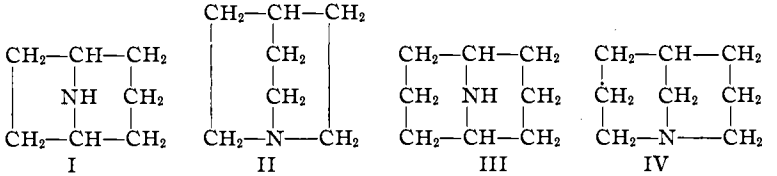
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

SYNTHESIS OF A NEW BICYCLIC NITROGEN RING. ISOGRANATANINE DERIVATIVES. PREPARATION OF AN ISOMER OF HOMOCOCAINE

BY S. M. McELVAIN[1] WITH ROGER ADAMS

RECEIVED AUGUST 9, 1923

Molecules containing bicyclic rings of an aliphatic character with a nitrogen atom in common occur in many of the natural alkaloids. Of these the most important are dihydro-nortropidine (I), quinuclidine (II), and granatanine (III), the basic nuclei of cocaine, quinine and pseudopelletierine respectively. The method described in this communication has been developed for the preparation of derivatives of a nucleus isomeric with granatanine, to which has been given the name isogranatanine (IV); a new ring resembling quinuclidine fairly closely.

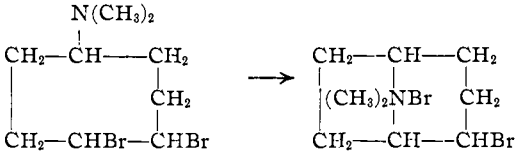


I II III IV

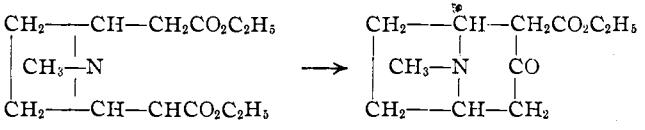
[1] This communication is an abstract of a thesis submitted by S. M. McElvain in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.

A nomenclature for the derivatives of this ring exactly analogous to that given granatanine compounds[2] has been adopted.

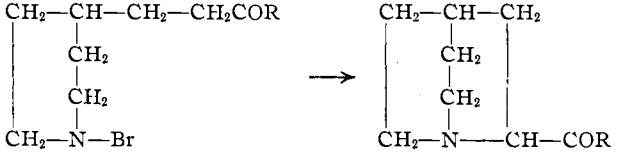
The syntheses of compounds containing rings of this character are very limited in number. Willstätter[3] has prepared dihydro-nortropidine compounds in two ways, the first represented by the formation of bromotropane methyl ammonium bromide by heating δ-4-dimethylamino-cycloheptene bromide,



and the second by the formation of ethyl tropinone-carboxylate[4] by an internal aceto-acetic ester condensation from pyrrolidine diacetic ester.



A study of quinine has led to a third method for the preparation of a bicyclic ring. This is illustrated by the formation of quininone[5] by the action of alkali on N-bromoquinicine. In this reaction a 4-(β-keto-ethyl)piperidine, upon treatment with sodium hypobromite and alkali, gives first a 4-(β-keto-ethyl)piperidine-N-bromide which then loses hydrogen bromide to give a bicyclic ring, the hydrogen of the hydrogen bromide coming from the carbon atom adjacent to the ketone group.



Still another method has appeared, but it is doubtful whether it can be applied as generally as those methods illustrated by the examples just given. Robinson[6] has prepared tropinone in 42% yields by the action of succinaldehyde, methyl amine and calcium acetone-dicarboxylate.

The method employed for the preparation of isogranatanine derivatives has involved an internal aceto-acetic ester condensation. Ethyl β-(3-

[2] Meyer and Jacobson, "Lehrbuch der organischen chemie," Walter De Gruyter and Co., **1920,** vol. 2, sec. III, p. 1077.

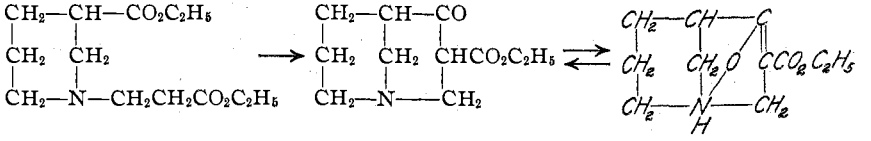
[3] Willstätter, *Ber.*, **34,** 129 (1901).

[4] Willstätter and Bommer, *Ann.*, **422,** 15 (1921).

[5] Rabe and Kindler, *Ber.*, **51,** 466 (1918).

[6] Robinson, *J. Chem. Soc.*, **111,** 762 (1917).

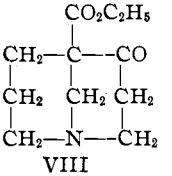
carbo-ethoxy-piperidino)propionate has been converted by means of sodium in xylene into ethyl isogranatonine-carboxylate.



V VI VII

With this substance available it is obvious that, by employing well-known reactions, isogranatanine and numerous other derivatives can be produced.

The general properties of ethyl isogranatonine-carboxylate are of interest. The free base is a colorless liquid, the hydrochloride a white solid. Both Ruzicka[7] and Willstätter[8] have studied amino β-ketonic esters of an analogous type and the latter has mentioned that they were thick oils which could not be purified because of the fact that even on standing in the cold they showed a tendency toward isomerization with the formation of a crystalline inner salt. This ketonic ester also is a thick oil which on standing in the cold gradually crystallizes. It has been found, however, that the ester can be purified if the proper conditions are used and it is probable that in a similar way the compounds made by these previous investigators could also be purified. The bath must be heated to considerably above the boiling point of the ester before the distilling flask containing it is immersed in the bath. In this way 60% of the original keto ester distils as a clear, colorless liquid while about 40% isomerizes or decomposes and remains behind in the flask. The distilled product is apparently perfectly stable and has been kept for several months without showing the slightest tendency to crystallize. The crystalline isomerization product can be readily obtained by dissolving the crude keto ester in ether and allowing the solution to stand; white crystals gradually deposit which have the solubility in organic solvents not of a base but of an ammonium compound. Undoubtedly an inner salt formation has taken place, as represented by Formula VII. The keto ester gives a characteristic coloration with ferric chloride, thus making it possible to distinguish it from its isomer, VIII, none of which, however, could be isolated from the reaction mixture.



VIII

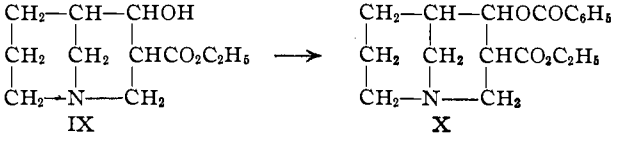
[7] Ruzicka and others, *Helvetica Chim. Acta*, **3**, 817 (1920); **5**, 717 (1922).

[8] Ref. 4, p. 30.

The yields in this synthesis were low, as has also been true in all syntheses of similar types of compounds previously described. This is unquestionably due to the fact that the condensation may take place in several ways, especially with the formation of several types of dimolecular compounds. Moreover, unlike the compounds used for analogous internal condensations, which are symmetrical, the starting material in this reaction is unsymmetrical in nature. In spite of the low yields, a study of the ethyl isogranatonine carboxylate and its derivatives was rendered possible because of the ease with which the starting material, ethyl β-(3-carbo-ethoxy-piperidino)propionate, could be made in quantity. This latter substance (V) is produced from nicotinic acid (pyridine-3-carboxylic acid) which is readily formed by the oxidation of nicotine with nitric acid. Since nicotine is now a cheap commercial product, nicotinic acid is an easily available substance for the organic chemist. By means of a platinum oxide catalyst described recently,[9] nicotinic acid hydrochloride may be readily reduced in comparatively large quantities to nipecotic acid hydrochloride, the hexahydro derivative. This reduced product is esterified to ethyl nipecotate and the latter condensed in the usual way with ethyl β-chloropropionate to give ethyl β-(3-carbo-ethoxy-piperidino) propionate.

The ethyl nipecotate was also condensed with ethyl chloro-acetate to give ethyl (3-carbo-ethoxy-piperidino)acetate. This latter substance did not condense with sodium to give a bicyclic ring.

The particular isogranatanine derivative of which a study has been made is the hydrochloride of ethyl benzoyl-isogranatoline-carboxylate (X) formed by the benzoylation of the hydrochloride of the alcohol, ethyl isogranatoline-carboxylate (IX), obtained by the reduction of the hydrochloride of ethyl isogranatonine-carboxylate (VI). This benzoyl derivative is very closely related to cocaine in structure.

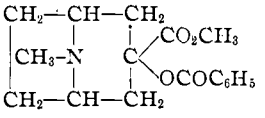


IX X

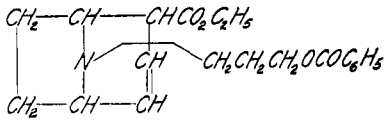
During the past 25 years the importance of cocaine has led to a thorough study of synthetic substitutes. The important members of this latter class which have been discovered do not contain an alicyclic ring and are comparatively simple compounds. A study of substances more closely related to cocaine has been neglected on account of the difficulty of preparation and of the purely theoretical value of such information. It has been shown that slight changes in the structure of the cocaine molecule

[9] Voorhees and Adams, THIS JOURNAL, **44**, 1397 (1922). Carothers and Adams, *ibid.*, **45**, 1071 (1923). Adams and Shriner, *ibid.*, **45**, 2171 (1923).

modify the therapeutic effect materially. This can be seen by a comparison of cocaine with α-cocaine[10] (XI) and eccaine[11] (XII).

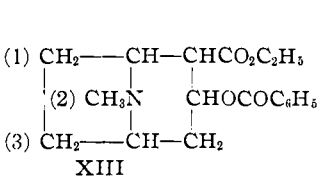


XI

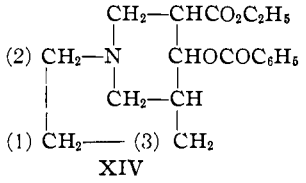


XII

α-Cocaine has no anesthetic action, whereas eccaine is a more powerful anesthetic than cocaine and is considerably less toxic. In the production of these two latter substances, basic changes in the bicyclic nucleus of cocaine have not been effected; the groups attached to the nucleus have merely been rearranged and changed. Until now, no attempt to find the effect of changes in the nature of the bicyclic ring has been made. In ethyl benzoyl-isogranatoline-carboxylate the ring containing the groupings essential to anesthesia in the bicyclic ring is left intact and the second ring is changed. The similarity between homococaine (XIII) and ethyl benzoyl-isogranatoline-carboxylate (X), and the change that has been effected, may be seen by writing the formula of the latter in a slightly different form (XIV).



XIII



XIV

The carbon atoms numbered 1, 2 and 3 in homococaine are still present in the new compound, but are attached in a slightly different manner.

The pharmacological action of ethyl benzoyl-isogranatoline-carboxylate hydrochloride was kindly tested by Mr. Carl Nielsen of the Abbott Laboratories, Chicago, Illinois. It was found that if a 1% solution was injected intravenously into rabbits at the rate of 1 cc. in 18 seconds, the average toxicity was about twice that of cocaine hydrochloride. By a similar procedure, by injecting subcutaneously, the toxicity appeared to be about five times that of cocaine hydrochloride.

A 2% solution was applied to a rabbit's cornea. This, however, did not produce complete anesthesia. Moreover, the solution appeared to be distinctly more irritating than a similar solution of cocaine hydrochloride though it was only very faintly acid in reaction. There was no sign of dilation of the pupil, as is noticed with cocaine hydrochloride.

In regard to the formation of ethyl benzoyl-isogranatoline-carboxylate, it may be mentioned that the ethyl isogranatoline-carboxylate hydro-

[10] Willstätter, *Ber.*, **29**, 2216 (1896).

[11] Von Braun, *Ber.*, **51**, 235 (1918).

chloride was formed by the catalytic reduction of the keto ester hydrochloride by means of platinum oxide as a catalyst. Willstätter[12] found that the reduction of an analogous keto ester was accomplished conveniently by means of sodium amalgam but the yields were very low. The results in this investigation showed that sodium amalgam could also be used but not only was the yield low, but two stereoisomers were formed simultaneously. No such complication occurred in the catalytic reduction; it required, however, a long period of time and a large amount of platinum. The product formed in this latter way was the same as one of the two isomers obtained by the sodium amalgam reduction. Benzoylation of the ethyl isogranatoline-carboxylate could not be accomplished by means of benzoic anhydride in toluene.[12] It was effected by the action of benzoyl chloride upon the hydrochloride of the ethyl isogranatoline-carboxylate at a moderately high temperature.

Experimental Part[13]

Nicotinic Acid Nitrate (Pyridine-3-carboxylic Acid Nitrate).—In a 5-liter round-bottom flask was placed 4 kg. of c. p. concd. nitric acid (d., 1.42). To this was added in 25cc. portions 210 g. of 95% nicotine. The addition was made carefully in order to prevent local heating and consequent loss of material. After each addition of nicotine the flask was shaken in order to insure a homogeneous solution. The addition of the nicotine caused the temperature of the liquid to rise somewhat but not sufficiently to cause evolution of oxides of nitrogen. The flask was then placed on a steam cone under a hood. As the liquid became warmed a vigorous reaction set in and sufficient heat was evolved to cause the liquid to boil. The boiling ceased after about 1 hour, but the flask was allowed to stand on the steam cone for 10 hours, during which time there was a more or less continuous evolution of oxides of nitrogen.

The contents of the flask were then poured into an evaporating dish and evaporated to dryness on the steam cone. The purification which follows was best carried out with the product of two such runs as described above.

The nicotinic acid nitrate from two runs, after evaporation of most of the liquid, was transferred to a 1.5-liter beaker, 400 cc. of distilled water was added, and the mixture heated until complete solution resulted. As this solution cooled, the nicotinic acid nitrate separated as yellowish crystals. It contained one molecule of water of crystallization and melted at 190–192°. By recrystallization from water with bone black, it could be obtained almost white. The yield was 430–460 g. No more of the nitrate could be obtained from the filtrate.

Nicotinic acid salts have been prepared by a number of methods of which only three are practical for making them in any quantity. Fischer[14] prepared 3-cyanopyridine by the fusion of the corresponding sulfonic acid with sodium cyanide and then hydrolyzed this compound to nicotinic acid. The second method is by the decomposition of quinolinic acid.[15] The third is by the oxidation of nicotine with nitric acid,[16] with potassium per-

[12] Ref. 4, p. 32.

[13] All melting points and boiling points herein given are corrected.

[14] Fischer, *Ber.*, **15,** 63 (1882).

[15] "Organic Chemical Reagents," University of Illinois Press, **1922,** IV, p. 39.

[16] (a) Weidel, *Ann.*, **165,** 331 (1873). (b) Pictet, *Chem. Zentr.*, **1898,** 1, 677.

manganate,[17] and with chromic acid.[18] Since nicotine is a commercial product[19] sold at a comparatively low cost, this latter method is by far the best process. The details given above allow for its production on a comparatively large scale with cheap reagents.

Nicotinic Acid Hydrochloride.—The nicotinic acid nitrate, which did not necessarily have to be dried, was placed in a 3-liter flask and 1000 cc. of concd. hydrochloric acid (d., 1.2) was added. This mixture was heated on a steam cone as long as gas evolution continued (6–8 hours). The flask was then connected to a condenser and the liquid removed under diminshed pressure (17–100 mm.). The dry salt thus obtained was covered with 500 cc. more of concd. hydrochloric acid (d., 1.2) and heated on a steam cone for about 5 hours longer. This was also distilled off in a vacuum and the dry salt remaining transferred to a 2-liter beaker and dissolved in 400 cc. of distilled water. Heating nearly to the boiling point was necessary to effect solution. The solution was diluted to about 4 times its original volume with 95% alcohol, placed in an ice-bath and stirred vigorously in order to form fine crystals. The precipitated hydrochloride was filtered and air-dried. It was white or cream colored and weighed 245 to 250 g. The filtrate was evaporated to dryness and the residue dissolved in the smallest possible amount of boiling water, diluted with alcohol and precipitated as described above. The precipitate was usually a light straw color and weighed 65 to 70 g. From the filtrate of this crystallization 10 to 15 g. of the hydrochloride was recovered. The total yield from two runs was 315 to 325 g. (80–83% yield); m. p., 273–274°. The material could be obtained pure and white by one recrystallization from water with bone black.

Nicotinic acid hydrochloride[16,17] has previously always been prepared from nicotinic acid by neutralization with hydrochloric acid, a procedure much more tedious than the one just described.

Nicotinic Acid.—This was best prepared by dissolving 160 g. of the hydrochloride in 300 cc. of water and adding slowly a solution of 53 g. of anhydrous sodium carbonate in 150 cc. of water. Free nicotinic acid precipitated out and was filtered off. By concentrating the filtrate and allowing it to crystallize, more of the acid was obtained. Nicotinic acid was best recrystallized from hot water. The yield in this preparation was from 117 to 120 g. (95–98%); m. p., 230–232°.

Nicotinic acid has previously been made from the silver salt by precipitation with hydrogen sulfide[16a] or from the copper salt by a similar procedure.[16b] There is no difficulty in obtaining it directly from the salts by the action of sodium carbonate; in fact, it could undoubtedly be prepared from the nitrate instead of the hydrochloride. The reason why a method from the nitrate was not used was that the nitrate varies in composition as regards water of crystallization, thus complicating the calculation for the exact amount of alkali needed. The hydrochloride has no water of crystallization.

Ethyl Nicotinate.—A mixture of 50 g. of nicotinic acid, or 65 g. of nicotinic acid hydrochloride, with 200 g. of thionyl chloride was refluxed until complete solution took place (2 hours). The excess thionyl chloride was recovered by distillation from a steam cone and the last traces removed in a vacuum. The flask, containing the crystalline residue of the acid chloride hydrochloride, was again fitted with a reflux condenser and 100 cc. of absolute alcohol was added through the condenser. After refluxing this mixture for 1 hour the excess alcohol was removed under diminished pressure. The remaining crystals were covered with 150 cc. of benzene and 20% sodium carbonate solution

[17] Laiblin, *Ber.*, **10,** 2136 (1877); *Ann.*, **196,** 135 (1879).

[18] Huber, *Ann.*, **141,** 271 (1867); *Ber.*, **3,** 849 (1870).

[19] The nicotine used in this investigation was purchased from the Hall Tobacco Company, St. Louis, Missouri. It was 95% pure but by one fractionation could readily be obtained practically 100% pure. The commercial material, however, was perfectly satisfactory for the oxidation with nitric acid.

was added until the aqueous layer was alkaline (about 135 cc.). The benzene layer was separated, the benzene removed, and the ethyl nicotinate distilled under diminished pressure; b. p., 103–105° (5 mm.); yield, 52–55 g., or 85–90%.

The esters of nicotinic acid have been prepared previously by the action of nicotinic acid,[20] alcohol and hydrogen chloride, or nicotinic acid, alcohol and sulfuric acid.[21] It is mentioned in a paper on the preparation of acid chlorides of pyridine-carboxylic acids that the esters may be made by the action of alcohols on these compounds[22] but no experimental details are given. This last procedure was found to be by far the most satisfactory for giving consistent results.

Nipecotic Acid Hydrochloride.—To a solution of 50 g. of nicotinic acid hydrochloride in 125 cc. of water was added 1 g. of platinum oxide catalyst, made from C. P. chloroplatinic acid[23] of commerce and the mixture was reduced under 1.5 atmospheres' pressure. The reduction was complete in 24 hours when one reactivation was made about 10 hours after the hydrogenation was started. The same catalyst was used over again, but it was advisable to add 0.25 g. of fresh platinum oxide with each subsequent reduction of 50 g. portions of nicotinic acid hydrochloride. In this way it was possible to reduce 300 g. of nicotinic acid hydrochloride with 2.25 g. of catalyst in approximately 6 days, when one reactivation with air[24] was made about 10 hours after the beginning of each reduction. After the catalyst was filtered off, the water was removed under diminished pressure. The yield was quantitative. After one recrystallization from alcohol the product melted at 240–242°.

The melting points which have previously been found by Ladenberg[25] and Freudenberg[26] are, respectively, 239–240° and 240–241°. These agree with the melting point obtained in this research, showing unquestionably that Hess[27] did not use nicotinic acid in his investigation.

Nipecotic acid hydrochloride has been previously prepared by the reduction of nicotinic acid with sodium and alcohol,[25] by the reduction of quinolinic acid with sodium and amyl alcohol[28] and by the catalytic reduction with platinum black.[26] The platinum oxide catalyst has proved to be much more active than any of those previously used and is to be recommended when large amounts of this product are desired.

Ethyl Nipecotate.—The aqueous solution of nipecotic acid hydrochloride representing the reduction of three 50 g. portions of nicotinic acid hydrochloride, was placed in a 3-liter flask and the water removed completely under diminished pressure. The dry residue was covered with 1200 cc. of a 5–6% solution of hydrogen chloride in absolute alcohol. The solution thus obtained was refluxed for 12 hours. The alcohol was then removed in a vacuum until 500–600 cc. of solution remained, the solution cooled to 0–5°, and 200 cc. of ether added. The liquid was transferred to a 2-liter separatory funnel and shaken vigorously with 150 cc. of 30% sodium hydroxide solution. The aqueous

[20] Engler, *Ber.*, **27**, 1784 (1894). Pollak, *Monatsh.*, **16**, 46 (1895).

[21] Camps, *Arch. Pharm.*, **240**, 354 (1902).

[22] Meyer, *Monatsh.*, **22**, 113 (1901).

[23] The chloroplatinic acid was the C. P. grade purchased from the Mallinckrodt Chemical Company, St. Louis, Mo.

[24] It is probable that if oxygen under pressure had been used for reactivation of the platinum catalyst, the time necessary for the reduction would have been reduced considerably. This work was completed before it was found that oxygen under pressure was very much more efficient than air in the reactivation.

[25] Ladenberg, *Ber.*, **25**, 2768 (1892).

[26] Freudenberg, *Ber.*, **51**, 1668 (1918).

[27] Hess and Liebbrandt, *Ber.*, **50**, 385 (1917).

[28] Besthorn, *Ber.*, **28**, 3151 (1895).

alkaline layer was withdrawn, and extracted twice more with 200cc. portions of ether. The ether was removed from the combined ether extracts, thus leaving an alcoholic solution of the ester from which the alcohol was best removed under diminished pressure. The remaining ester was distilled under diminished pressure. The yield was 103–110 g. (70–75%) of product boiling at 102–104° (7 mm.). The ester was a colorless water-soluble liquid; d_{20}^{20}, 1.0121; n_D^{19}, 1.4592.

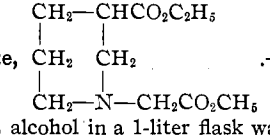
Analyses. Subs., 0.6421, 0.7116: 41.68 cc., 45.87 cc. of 0.0969 *N* HCl. Calc. for $C_8H_{15}O_2N$: N, 8.92. Found: 8.80, 8.75.

Ethyl Nipecotate Hydrochloride.—The hydrochloride was prepared by the addition of hydrogen chloride to an ether solution of the free base. The ether was poured off and the precipitate dissolved in as small a quantity of hot 95% alcohol as possible. To this solution ether was added until a faint cloudiness appeared, and the solution was then placed in an ice-bath. Ethyl nipecotate hydrochloride crystallized from the solution in needles which melted at 110–111°. This hydrochloride was stable to alkali carbonates.

Analyses. Subs., 0.1840, 0.2065: AgCl, 0.1358, 0.1525. Calc. for $C_8H_{16}O_2NCl$: Cl, 18.35. Found: 18.25, 18.26.

Ethyl nipecotate was also prepared by the catalytic reduction of ethyl nicotinate hydrochloride in alcoholic solution and by the reduction of ethyl nicotinate in alcohol containing 2 molecules of acetic acid. The yields were not nearly so satisfactory as in the above procedure.

Ethyl (3-Carbo-ethoxy-piperidino)acetate,

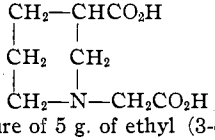


.—A solution of 100 g. of ethyl nipecotate in 500 cc. of 95% alcohol in a 1-liter flask was treated with 80 g. of ethyl chloro-acetate. The solution on shaking became warm. To this was added 80 g. of finely powdered silver oxide and the mixture shaken at frequent intervals until a test portion of the supernatant liquid, after acidification with nitric acid, gave no appreciable test for chloride with silver nitrate. This required from 6 to 8 hours. The contents of the flask were then heated to boiling on a steam cone in order to coagulate the silver chloride precipitate. This precipitate was filtered off by suction and washed once with 100 cc. of warm alcohol, while stirred in a beaker. The alcohol from the combined filtrates was removed under diminished pressure and the remaining ester distilled. It boiled at 147–149° (5 mm.); d_{20}^{20}, 1.0684; n_D^{18}, 1.4607; yield 120–125 g., or 80–83%. It was colorless when freshly distilled but on standing slowly acquired a pale yellow tinge. It was insoluble in water, and solutions of its mineral acid salts were decomposed by alkali carbonates.

Analyses. Subs., 1.1630, 1.2830: 48.85, 52.80 cc. of 0.0969 *N* HCl. Calc. for $C_{12}H_{21}O_4N$: N, 5.76. Found: 5.71, 5.60.

Attempts were made to condense this ester into a bicyclic system by the use of sodium ethylate in benzene, and sodium in toluene, xylene and cymene. However, the ring formation could not be effected with any of these reagents and it was possible to recover from 60–80% of the unchanged diester from each attempted condensation.

(3-Carboxy-piperidino)acetic Acid,



FROM ETHYL (3-CARBO-ETHOXY-PIPERIDINO)ACETATE.—A mixture of 5 g. of ethyl (3-carbo-ethoxy piperidino)-acetate, 10 g. of barium hydroxide and 250 cc. of water was refluxed for 2 hours in a 500cc. flask. The excess barium was removed from the hot solution by carbon dioxide and

filtration. To the filtrate was added dil. sulfuric acid until the remaining barium was just completely precipitated. This precipitate was filtered and to the resulting filtrate 10 g. of copper oxide powder was added. After the mixture had been refluxed for 1 hour and filtered, a deep blue solution of the copper salt of the acid was obtained. This solution was concentrated to a volume of about 25 cc. and allowed to cool. The copper salt of the acid crystallized in deep blue crystals. These were dissolved in 100 cc. of hot water and the copper was precipitated by hydrogen sulfide. The precipitated sulfide was removed by filtration and the filtrate evaporated to dryness on a steam cone. The residue after recrystallization from an alcohol-ether mixture formed white crystals and melted at 268–270° (with decomp.); yield, 2.5 g., or 65%.

FROM NIPECOTIC ACID HYDROCHLORIDE.—A mixture of 10 g. of nipecotic acid hydrochloride, 7 g. of chloro-acetic acid and 13 g. of sodium hydroxide was dissolved in 250 cc. of water and the solution stirred for 3 hours. Hydrochloric acid was then added until the reaction was acid to congo red and the solution evaporated to dryness under diminished pressure. The residue was treated with 200 cc. of hot 95% alcohol and the sodium chloride remaining was removed by filtration. From the filtrate the alcohol was removed under diminished pressure, leaving a yellowish amorphous residue. From this residue, the dibasic acid was isolated through the copper salt as described above; yield, 3.5–4.5 g., or 31–40%. This acid was identical with the one obtained by the hydrolysis of ethyl (3-carbo-ethoxy-piperidino)acetate.

Analyses. Subs., 0.7432, 0.6918: 40.35, 36.85 cc. of 0.0969 *N* HCl. Calc. for $C_8H_{13}O_4N$: N, 7.48. Found: 7.35, 7.22.

Ethyl (3-Carbo-ethoxy-piperidino)propionate (V). FROM ETHYL NIPECOTATE.—A solution of 100 g. of ethyl nipecotate in 500 cc. of 95% alcohol was mixed with 90 g. of ethyl chloropropionate in a 1-liter round-bottom flask. The remainder of the procedure was exactly the same as that described for the preparation of the ethyl (3-carbo-ethoxy-piperidino)acetate. The product was a colorless, water-insoluble oil, boiling at 159–161° (5 mm.); d_{20}^{20}, 1.0452; n_D^{18}, 1.4605; yield, 126–135 g., or 78–83%. As in the case of its lower homolog, aqueous solutions of its mineral acid salts were decomposed by alkali carbonates.

Analyses. Subs., 0.9790, 1.1891: 38.05, 46.93 cc. of 0.0969 *N* HCl. Calc. for $C_{13}H_{23}O_4N$: N, 5.45. Found: 5.29, 5.36.

FROM NIPECOTIC ACID HYDROCHLORIDE.—A mixture of 50 g. of nipecotic acid hydrochloride, 50 g. of β-chloropropionic acid and 65 g. of sodium hydroxide in 500 cc. of water was stirred for 3 hours at room temperature. After this time hydrochloric acid was added until the reaction was acid to congo red. The water was then removed from the solution under diminished pressure and the resultant salt residue treated with 500 cc. of hot 95% alcohol. The solution was filtered from the sodium chloride, placed in a 1-liter flask and evaporated to complete dryness under diminished pressure. The residue was esterified and the ester recovered by the same method as that described for the preparation of ethyl nipecotate from nipecotic acid hydrochloride; yield, 20–28 g., or 25–35%; b. p., 157–162° (5 mm.).

Ethyl Isogranatonine-carboxylate Hydrochloride (VI).—A mixture of 10 g. of freshly cut sodium and 100 cc. of xylene was placed in a 500cc. flask fitted with a ground-glass reflux condenser. The sodium was finely powdered by first heating it in the xylene to boiling and then stoppering the flask and shaking vigorously. To the xylene-sodium mixture was then added 100 g. of ethyl-β-(3-carbo-ethoxy-piperidino)propionate and the mixture heated in an oil-bath. When the liquid inside the flask reached a temperature of about 130° a vigorous reaction set in with the liberation of sufficient heat to cause the xylene to boil for 15–20 minutes. The temperature of the oil-bath was maintained between 140–150° for about 45 minutes after the primary reaction had ceased. This was

necessary in order to obtain maximum yields. The end of the reaction was shown by an excessive foaming of the contents of the flask. The flask was then cooled, whereupon the contents turned to a semi-solid mass. This product was then mixed with 150–200 cc. of ice water, and the xylene layer separated. The aqueous layer was extracted with 150 cc. of ether and this extract added to the xylene layer. This ether-xylene solution will be referred to later.

The aqueous solution obtained above was dark red in color. It was kept at a temperature of 0–5° and acidified with hydrochloric acid until acid to congo red. Upon acidification the color of the solution changed from a dark red to a light yellow. To the cold acid solution, potassium carbonate was added until it was distinctly alkaline, and the resulting alkaline solution was extracted with 150cc. portions of ether until test portions of the ether, when shaken with a dil. acidified aqueous solution of ferric chloride, caused no pronounced reddish purple coloration of the aqueous layer. The ether extracts (usually four) were concentrated to a volume of about 100 cc. and dry hydrogen chloride was passed in. The hydrochloride of the keto ester precipitated usually in an amorphous form.

The amorphous keto ester hydrochloride was crystallized by the following procedure. The material from the ether precipitation was dissolved in 15 cc. of warm absolute alcohol. To this solution dry ether was added until a faint cloudiness appeared, at which point the solution was cooled to about —12°. By scratching the sides of the container with a stirring rod, crystallization was started. Ethyl isogranatonine-carboxylate hydrochloride crystallized as white microscopic crystals which melted at 187–189°. It was extremely soluble in water, 95% alcohol and absolute alcohol. Only a trace of it added to a dil. ferric chloride solution gave a deep reddish-purple coloration. The yield of recrystallized material from the above run was 5.5–6.5 g. or 6–7%. From 1 to 1.5 g. of uncrystallizable material remained in the mother liquors.

Analyses. Subs., 0.1035, 0.1465: AgCl, 0.0590, 0.0850. Calc. for $C_{11}H_{18}O_3NCl$: Cl, 14.34. Found: 14.12, 14.34.

Internal condensations of this diester were attempted also with sodium ethylate in benzene and sodium in toluene and cymene. At the temperatures obtained with benzene and toluene the ester was left practically unchanged. Sodium in cymene, however, did completely condense the ester, but the products were of high molecular weight and it was not possible to isolate any of the cyclic keto ester by the procedure used in isolating it from the sodium-xylene condensation.

Ethyl Isogranatonine-carboxylate (VI).—A mixture of 4 g. of ethyl isogranatonine-carboxylate hydrochloride and 10 cc. of saturated potassium carbonate solution was shaken and then extracted twice with 20cc. portions of ether. The ether layer was separated and the ether then distilled. The remaining ester was placed in a small distilling system and the system evacuated to a pressure of 8 mm. The distilling flask was then immersed directly in an oil-bath at a temperature of 150–160°. The keto ester distilled at 137–139° (8 mm.); d_{20}^{20}, 1.1381; n_D^{18}, 1.5070; yield, 2.2 g., or 60%. It was a thick, colorless oil, insoluble in water, soluble in acid and alkali, and gave a pronounced coloration with acidified ferric chloride solution. The remainder of the ester was left in the distilling flask, probably partly as an inner salt (VII).

Analyses. Subs., 0.7185, 0.6905: 34.60, 33.40 cc. of 0.0969 *N* HCl. Calc. for $C_{11}H_{17}O_3N$: N, 6.63. Found: 6.55, 6.57.

When the crude ethyl isogranatonine-carboxylate obtained as described above by the evaporation of the ether was redissolved in ether and allowed to stand, white hygroscopic crystals separated in 12 to 24 hours. These were insoluble in ether. By acidifying with hydrochloric acid and repeating the process described above the oily isomer was again obtained.

An attempt was made to prove the presence of the isomeric ketonic ester (VIII) in the xylene-ether layer. This layer from condensations representing 400 g. of ethyl β-(3-carbo-ethoxy-piperidino)propionate was extracted with hydrochloric acid. The hydrochloric acid layer was made alkaline with potassium carbonate and extracted with ether. After evaporation of the ether 15 g. of an oil was obtained. This was refluxed with 150 cc. of 20% hydrochloric acid for 4 hours in order to hydrolyze it to the corresponding amino ketone. No product, however, was obtained.

Ethyl Isogranatoline-carboxylate Hydrochloride (IX). REDUCTION WITH SODIUM AMALGAM.—A solution of 5 g. of ethyl isogranatonine-carboxylate hydrochloride in 1 liter of 5% hydrochloric acid was placed in a 20cm. evaporating dish. Sodium amalgam (3%) was added in small pieces at a rate sufficient to maintain a vigorous evolution of gas. At the same time the temperature of the solution was kept below 20° by an external ice-bath and the reaction of the solution was kept acid to congo red by the addition of 50cc. portions of concd. hydrochloric acid when the solution appeared alkaline to the indicator. About 1500 g. of 3% sodium amalgam, added during 5 hours, was required to complete the reduction, the end of which was shown by a negative ferric chloride test. When this point was reached the mercury was separated and the aqueous layer filtered. The colorless aqueous solution was evaporated to dryness under diminished pressure and the resulting salt residue treated with two successive 300cc. portions of hot 95% alcohol. The resulting alcoholic solution, after removal of the sodium chloride, was evaporated to complete dryness under diminished pressure. The straw-colored, amorphous residue was covered with 500 cc. of 5–6% alcoholic hydrochloric acid and esterified by refluxing for 12 hours. The alcoholic hydrochloric acid was removed under diminished pressure and the residue was treated with 25 cc. of saturated potassium carbonate solution, then extracted with ether. The ether extract was concentrated to a volume of 100 cc. and dry hydrogen chloride was passed in. The hydrochloride of the base precipitated as a brown amorphous mass.

This amorphous material was crystallized as was the ethyl isogranatonine-carboxylate hydrochloride. The first crystallization yielded a light brown material which after three crystallizations appeared as practically colorless, microscopic crystals which melted at 199–201° (Isomer A); yield, 0.35 g., or 7%.

Analyses. Subs., 0.0810, 0.0800: AgCl, 0.0465, 0.0454. Calc. for $C_{11}H_{20}O_3NCl$: Cl, 14.23. Found: 14.20, 14.05.

From the mother liquors of the crystallization described it was impossible to obtain any more crystalline material, so they were combined, evaporated and the free base was liberated into ether by means of a saturated potassium carbonate solution. The ether was removed from the extract and the remaining oil subjected to distillation at 5 mm. pressure. It was dissolved in dry ether and the hydrochloride prepared and crystallized. After one crystallization the product melted at 199–201°. A mixed melting point with the crystals (Isomer A) obtained as described above was 170–175°. This product was Isomer B and the yield was 0.450 g., or 9%. There remained in the mother liquors of B 0.6 g. of uncrystallizable material.

Analyses. Subs., 0.1047, 0.1022: AgCl, 0.0589, 0.0581. Calc. for $C_{11}H_{20}O_3NCl$: Cl, 14.23. Found: 13.95, 14.10.

CATALYTIC REDUCTION.—A solution of 4 g. of ethyl isogranatonine-carboxylate hydrochloride in 50 cc. of absolute alcohol was shaken with hydrogen at 4 atmospheres' pressure in the presence of 2 g. of platinum oxide catalyst. Every 12 hours the catalyst was shaken with air and at 24-hour intervals 0.5 g. of fresh catalyst was added. The reduction was complete, as shown by a negative ferric chloride test, in 85 hours. The platinum was filtered off and the solution evaporated to dryness under diminished pressure.

The residue on recrystallization gave 2.5 g. (62.5%) of a product which was identical with Isomer B from the sodium amalgam reduction.

Ethyl Benzoyl-isogranatoline-carboxylate Hydrochloride (X). BENZOYL CHLORIDE BENZOYLATION.—In a 100cc. flask fitted with a ground-glass reflux condenser was placed 3 g. of ethyl isogranatoline-carboxylate hydrochloride (Isomer B) and 10 cc. of freshly distilled benzoyl chloride. The flask was then heated in an oil-bath to 140–160°. At this temperature a vigorous evolution of hydrogen chloride took place and in 20 minutes the reaction was complete. The resulting solution was cooled and diluted with 75 cc. of ether. The hydrochloride of the benzoyl derivative precipitated as a light brown, amorphous mass. The ether solution was poured off and the precipitate dissolved in 20 cc. of warm absolute alcohol. This solution was heated with 0.1 g. of bone black and filtered. From the filtrate the hydrochloride of the benzoyl derivative was obtained in pure white crystals by a method analogous to that described for ethyl isogranatonine-carboxylate hydrochloride; yield, 3.4 g., or 80%.

Analyses. Subs., 0.1044, 0.1058: AgCl, 0.0415, 0.0429. Subs., 0.4760: 13.51 cc. of 0.0951 *N* HCl. Subs., 0.2030: CO_2, 0.4523; H_2O, 0.1280. Calc. for $C_{18}H_{24}O_4NCl$: C, 61.07; H, 6.84; N, 3.96; Cl, 10.03. Found: C, 60.77; H, 7.00; N, 3.78; Cl, 9.84, 10.03.

An attempt was made to obtain this benzoylation product by the action of benzoic anhydride in toluene upon ethyl isogranatoline-carboxylate, obtained from the hydrochloride by the action of saturated potassium carbonate. No benzoylation product was obtained.

Summary

1. A method for the preparation of a derivative of a new bicyclic nucleus containing a nitrogen atom common to both rings has been developed. The new nucleus has been called isogranatanine because it is isomeric with granatanine.

2. The particular derivative especially investigated was ethyl benzoyl-isogranatoline-carboxylate, prepared by reduction of the ethyl isogranatonine-carboxylate and subsequent benzoylation.

3. The ethyl benzoyl-isogranatoline-carboxylate hydrochloride is isomeric with homococaine hydrochloride, and is a local anesthetic. It is considerably more toxic and less anesthetic than cocaine. Its 2% solution is irritating to a rabbit's cornea and does not cause dilation.

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