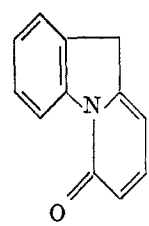
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

STUDIES ON α-PYRIDONES. ALKYLATION OF 2-CARBETHOXY-CYCLOHEXANONE WITH ETHYL 2-BROMOMETHYL-1,4,5,6-TETRAHYDRO-6-OXONICOTINATE AND ETHYL 2-BROMO-METHYL-6-CHLORONICOTINATE

FAUSTO RAMIREZ AND ALBERT P. PAUL[1]

Received September 3, 1953

This paper describes the synthesis of ethyl 2-(1′-carbethoxy-2′-oxocyclohexyl)methyl-1,4,5,6-tetrahydro-6-oxonicotinate (IV, Chart I) and of ethyl 2-(1′-carbethoxy-2′-oxocyclohexyl)methyl-6-chloronicotinate (XIII), prepared as potential intermediates in the synthesis of substituted α-pyridone derivatives of benzo[*b*]pyrrocoline (A).[2] The work of Robinson and Saxton (1) constitutes the only published exploration of this heterocyclic system.[3]

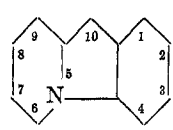


A

Ethyl 1,4,5,6-tetrahydro-2-methyl-6-oxonicotinate (I), prepared from ethyl (2-cyanoethyl)acetoacetate by the convenient procedure of Albertson (2), gave ethyl 2-bromomethyl-1,4,5,6-tetrahydro-6-oxonicotinate (II) on treatment with one equivalent of bromine. The structure of II[4] follows from its ultraviolet and infrared absorption spectra and is consistent with the susceptibility of the bromine to displacement by pyridine to form the pyridinium bromide III. The alkylation of the sodio salt of 2-carbethoxycyclohexanone with II proceeded smoothly in a mixture of benzene and dimethylformamide as solvent to yield

[1] From part of the Ph.D. Thesis of A. P. Paul. Presented at the W. E. Bachmann Memorial Session, Organic Chemistry Division, American Chemical Society, Chicago Meeting, September 8, 1953.

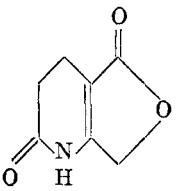
[2] Benzo[*b*]pyrrocoline, Ring Index No. 1647.



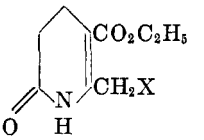
[3] Robinson and Saxton (ref. 1) have obtained 9,10-dialkyl- and 6,9,10-trialkyl-benzo[*b*]-pyrrocolines from the condensation of β-alkylindoles with levulinaldehyde (or 2-methylfuran) and acetonylacetone, respectively.

[4] Albertson (ref. 2) gave II as the likely but not proven structure of the monobromination product of I.

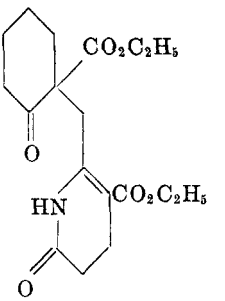
CHART I



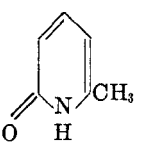
V



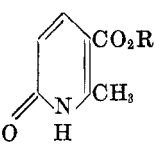
I, X = H
II, X = Br
III, X = $(NC_5H_5)^+Br^-$



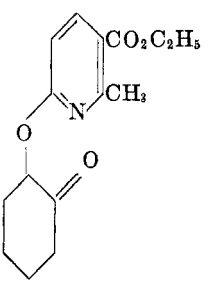
IV



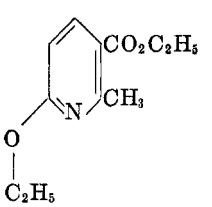
IX



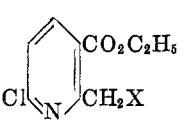
VI, R = C_2H_5
VII, R = H



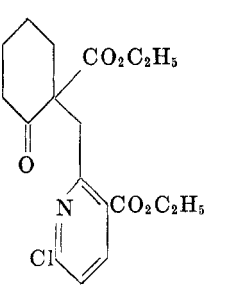
VIII



XIV



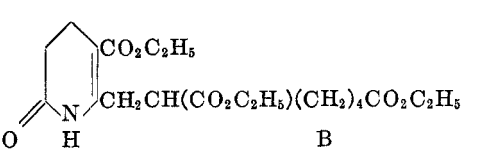
X, X = H
XI, X = Br
XII, X = $(NC_5H_5)^+Br^-$



XIII

IV.[5] IV exhibited bands at 3.00, 5.80, 5.85, 5.92, and 6.12 μ in the infrared as expected of the C-alkylated structure.

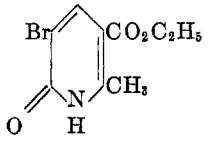
[5] Alkylation of 2-carbethoxycyclohexanone with II in ethanol solution containing 1.5 equivalents of sodium ethoxide gave a product, m.p. 92–93°, which on the basis of analysis and of chemical and spectral data is probably B, formed by fission of the cyclohexanone ring.



B

Ethyl 2-methyl-6-oxynicotinate (VI) was obtained in satisfactory yields by palladium-dehydrogenation of I. The structure of VI was proved by spectral data in the ultraviolet and in the infrared as well as by degradation to the known 2-methyl-6-oxypyridine (IX) as described in the Experimental section. The recently described (2) preparation of 2-methyl-6-oxynicotinic acid by pyrolysis of the bromoester II is in error (3). We have confirmed Albertson's (2) observations pertaining to the thermal decomposition of II but have assigned structure V, *i.e.*, the lactone of 2-hydroxymethyl-1,4,5,6-tetrahydro-6-oxo-nicotinic acid, to the resulting product, m.p. 259–260° of formula $C_7H_7NO_3$. The same substance V, whose structure is substantiated by chemical and spectral data furnished in the Experimental section, was obtained from the pyridinium bromide III on heating. The formation of V finds analogy[6] in the lactonization of γ,δ-unsaturated esters or acids by means of bromine studied by Arnold and co-workers (4a) and by Craig (4b, c).

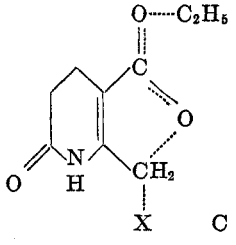
Treatment of VI with phosphorus oxychloride led to ethyl 2-methyl-6-chloronicotinate (X), from which the 2-pyridone structure can be easily regenerated upon acid hydrolysis. Thus a mixture of acetic acid and hydrochloric acid converted X into 2-methyl-6-oxynicotinic acid (VII). The side-chain bromination of X was effected by means of N-bromosuccinimide (5). The ethyl 2-bromomethyl-6-chloronicotinate (XI) thus formed can be conveniently characterized by means of the crystalline pyridinium bromide XII formed rapidly in the cold upon addition of pyridine. In agreement with previous observations (6) attempts to introduce halogen into the 2-methyl group of 2-methyl-6-oxypyridines failed. A crystalline product obtained on treatment of VI with bromine is formulated as ethyl 2-methyl-5-bromo-6-oxynicotinate (XV) in view of the unreactivity of the bromine in displacement reactions.



XV

Alkylation of the sodio salt of 2-carbethoxycyclohexanone with XI gave XIII in excellent yields. Comparisons of the ultraviolet absorption spectra of XIII and X leaves no doubt concerning the C-alkylated nature of the product formed.

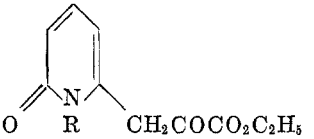
[6] As in the bromination of γ,δ-unsaturated esters (ref. 4) the pyrolysis of II results in the formation of ethyl bromide. The decomposition might proceed through a transition state of type C.



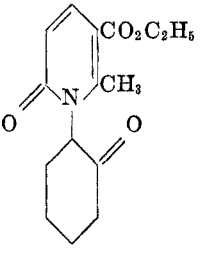
C

Furthermore, XIII gave a 2,4-dinitrophenylhydrazone and exhibited in the infrared bands at 6.30 and 6.40 μ (typical of the pyridine structure) as well as bands at 5.81 and 5.86 μ.[7]

The work of Adams and co-workers (6, 7) suggested an attractive route to α-pyridone derivatives of benzo[*b*]pyrrocoline. These authors condensed several 1-alkyl-2-methyl-6-pyridones with dimethyl oxalate and obtained ketoesters of type (D), thus demonstrating the suspected anionoid reactivity of the 2-methyl group of 2-methyl-6-pyridones. Accordingly, the alkylation of the alkaline salts of ethyl 2-methyl-6-oxynicotinate (VI) with 2-chlorocyclohexanone was investigated. The product isolated from this reaction in good yield was ethyl 2-methyl-6-(2′-oxocyclohexyloxy)nicotinate (VIII) instead of the desired N-alkylated product E. The structure of VIII follows from comparisons of its ultraviolet and infrared spectra with those of ethyl 2-methyl-6-ethoxynicotinate (XIV) prepared from the chloropyridine X. This example of O-alkylation is at variance with the general mode of behavior of 2-oxypyridines toward alkyl halides in alkaline medium, which is known to lead predominantly to N-alkylated products (8).[8]



D



E

The ultraviolet and infrared absorption spectra of several of the compounds described are of interest in connection with the lactam-lactim tautomerism of 2-oxypyridines. On the basis of ultraviolet absorption spectra (9) 2-oxypyridines are considered to exist, at least in solution, predominantly in the lactam (or 2-pyridone) form. The infrared spectra of the oxypyridines appear to confirm these views. The salient feature in these spectra is the strong band at 6.05 μ; no pyridine bands at 6.3 and 6.4 μ are observed. The ultraviolet absorption data are collected in Table I, which includes also some of the previously reported values. It is seen that the position of the longer wave length maximum of 2-oxypyridines (*ca.* 300 mμ) is not markedly affected by the presence of carbethoxy or carbamyl groups at position 5, while the shorter wave length maximum is affected considerably by such substitution.[9]

[7] The appearance of two rather than three bands in the carbonyl region is presumably the result of an accidental degeneracy; the presence of a keto group in XIII is substantiated by the formation of a 2,4-dinitrophenylhydrazone.

[8] Adams (ref. 7) has reported the N-alkylation of 2-pyridone with α-chloroacetaldehyde.

[9] Contrary to the statement of Specker and Gawrosch (ref. 10) the ultraviolet spectra of 2-oxypyridines was found to differ markedly in neutral and alkaline ethanolic solution. Thus one maximum at 290 mμ (23,000) is exhibited by VI in 95% ethanol containing 0.1 *N* aqueous sodium hydroxide.

TABLE I

SUMMARY OF ULTRAVIOLET ABSORPTION DATA

COMPOUND	λ'_{max}, mμ	ε	λ''_{max}, mμ	ε	λ'''_{max}, mμ	ε
IX[a]	228	7800	306	7200		
VI[a]	264	16500	300	5700		
VII[a]	261	13900	303	5730		
XV[a]	271	14400	307	8300	317	8600
2-Pyridone[b]	227	10000	297	9000		
1-Methyl-2-pyridone[b]	227	8000	300	—		
1-Methyl-5-carbamyl-2-pyridone[c]	260	—	300	—		
XIV[a]	248	12700	275	8700	283	shoulder
X[a]	231	11300	273	5800	280	4700
VIII[a]	248	14300	275	9500	283	shoulder
2-Ethoxypyridine[b]			270	8000		

[a] 90% ethanol as solvent. [b] Ref. 10; methanol as solvent. [c] Knox and Grossman, *J. Biol. Chem.*, **168**, 1363 (1947).

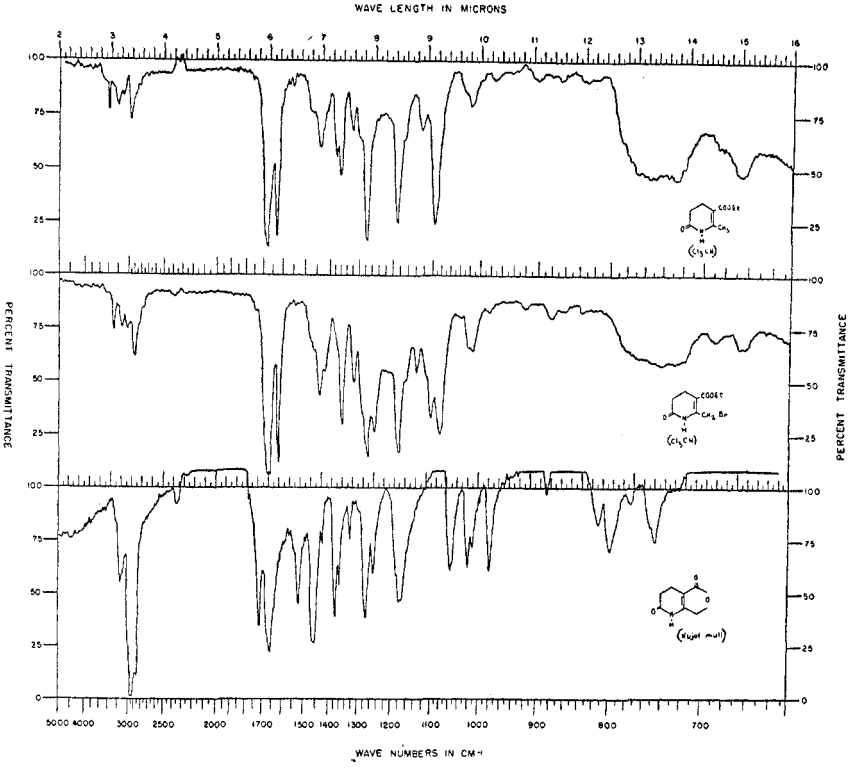


FIG. 1. INFRARED ABSORPTION SPECTRA. Upper curve: Ethyl 1,4,5,6-tetrahydro-2-methyl-6-oxonicotinate (I); Middle curve: Ethyl 2-bromomethyl-1,4,5,6-tetrahydro-6-oxonicotinate (II); Lower curve: the lactone of 2-hydroxymethyl-1,4,5,6-tetrahydro-6-oxonicotinic acid (V).

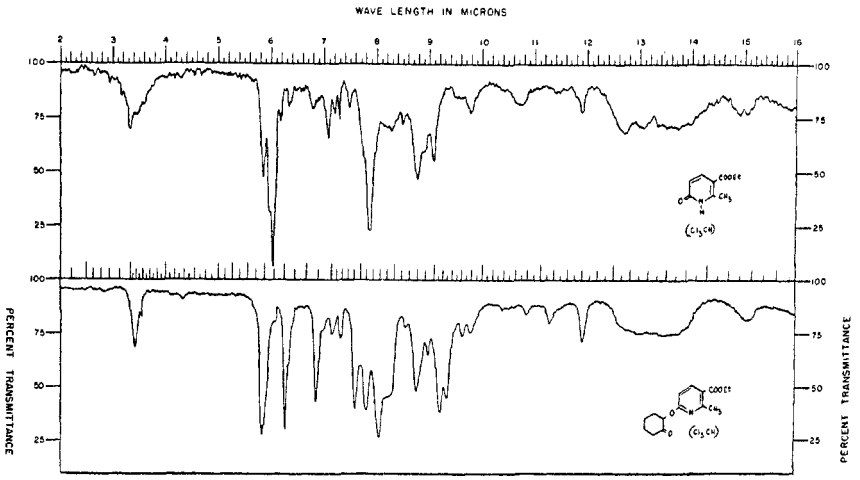


FIG. 2. INFRARED ABSORPTION SPECTRA. Upper curve: Ethyl 2-methyl-6-oxynicotinate (VI); Lower curve: Ethyl 2-methyl-6-(2'-oxocyclohexyloxy)nicotinate (VIII).

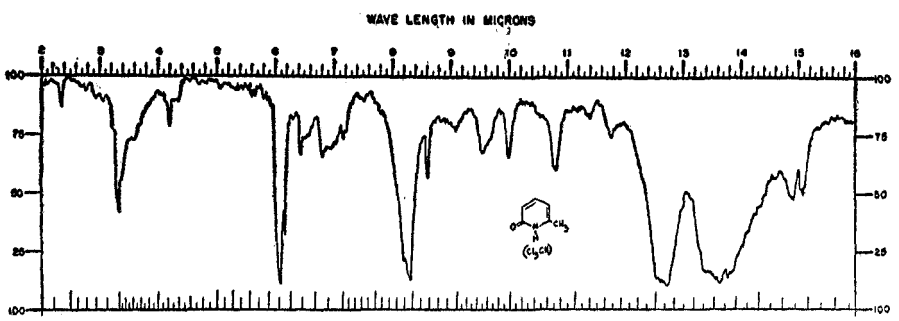


FIG. 3. INFRARED ABSORPTION SPECTRA of 2-Methyl-6-oxypyridine (IX).

EXPERIMENTAL

The microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill. and Schwarzkopf Microanalytical Laboratories, Woodside, New York. The ultraviolet absorption spectra were taken in 95% ethanol in a Cary Recording Spectrophotometer, Model 11. The infrared absorption spectra were determined in a Baird Associates Inc. Spectrophotometer (sodium chloride prism; 0.1 mm. cell thickness). The curves shown are tracings of the actual recordings, the curves being aligned at 3.40 μ. Melting points are uncorrected.

Ethyl 2-bromomethyl-1,4,5,6-tetrahydro-6-oxonicotinate (II). A solution of 52.0 g. of bromine in 190 ml. of anhydrous chloroform was added dropwise over a 70 minute-period to a stirred solution of 59.3 g. of ethyl 1,4,5,6-tetrahydro-2-methyl-6-oxonicotinate (I) (m.p. 156–157°; λ_{max}^{EtOH} 280 mμ, ϵ 21,200; bands at 2.95, 5.90, and 6.10 μ (chloroform) in 500 ml. of chloroform. After stirring for an additional 30 minutes the solvent was removed and the residue was recrystallized from methanol; yield of II: 60.3 g., m.p. 120–121°; λ_{max}^{EtOH} 289 mμ, ϵ 12,700; bands at 3.00, 5.90, and 6.10 μ (chloroform). Reported (2) m.p. 118–120°.

When a mixture of II (3.0 g.) and anhydrous pyridine (5 ml.) was warmed, an exothermic reaction occurred. After two minutes at its boiling point the solution was cooled and filtered. The resulting product was recrystallized from pyridine to yield 4.44 g. of the pyridinium

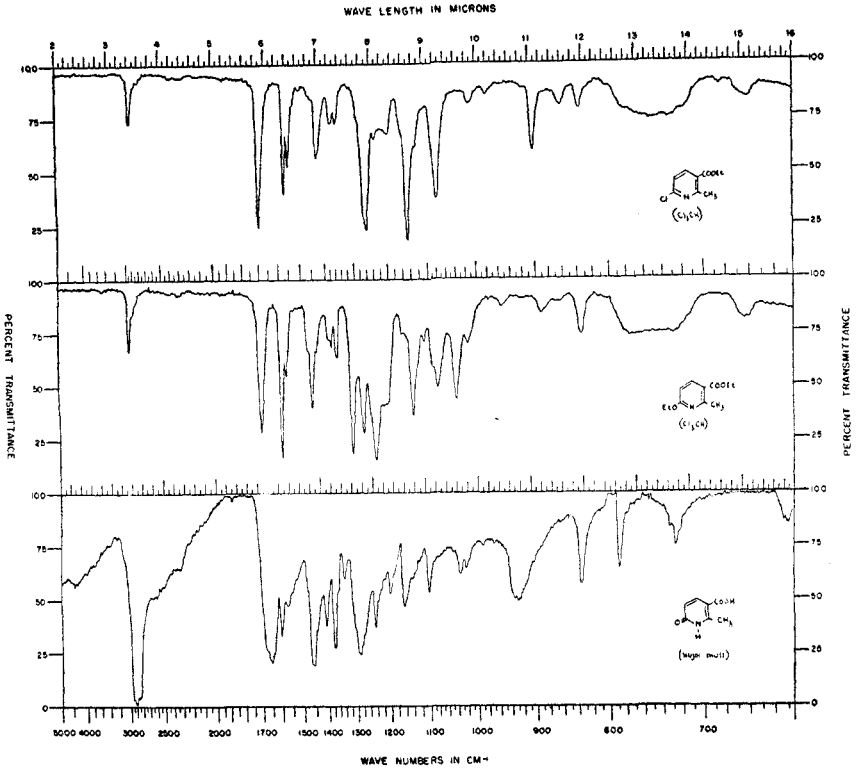


FIG. 4. INFRARED ABSORPTION SPECTRA. Upper curve: Ethyl 2-methyl-6-chloronicotinate (X); Middle curve: Ethyl 2-methyl-6-ethoxynicotinate (XIV); Lower curve: 2-Methyl-6-oxynicotinic acid (VII).

bromide III, m.p. 190–191° (gas evolution) which appeared to retain pyridine. After drying *in vacuo* over sulfuric acid and recrystallizing from ethanol the yield of III was 3.1 g., m.p. 181–182°; λ_{max}^{EtOH} 266 mμ, ε 13,100; 280 mμ, ε 11,600; bands at 5.90 and 6.10 μ (chloroform). This substance was soluble in water and gave an immediate precipitate with cold silver nitrate solution.

Anal. Calc'd for $C_{14}H_{17}BrN_2O_3$: C, 49.3; H, 5.0; N, 8.2; Br, 23.4.
Found: C, 49.7; H, 5.0; N, 8.0; Br, 23.8.

Ethyl 2-(1'-carbethoxy-2'-oxocyclohexyl)methyl-1,4,5,6-tetrahydro-6-oxonicotinate (IV). A solution of 5.95 g. of 2-carbethoxycyclohexanone in 40 ml. of anhydrous benzene was added dropwise (*ca.* one hour) to a stirred mixture of 0.91 g. of sodium hydride, 60 ml. of benzene, and 20 ml. of anhydrous dimethylformamide, kept at room temperature. The mixture was refluxed for one hour and then treated with 10.0 g. of ethyl 2-bromomethyl-1,4,5,6-tetrahydro-6-oxonicotinate (II), added in small portions.

The mixture was allowed to reflux overnight, poured into ice-water, and separated into two layers. The benzene layer was washed with water and combined with chloroform-extracts of the aqueous layer. Removal of the organic solvents left 11.68 g. of a thick oil from which 0.52 g. of 2-carbethoxycyclohexanone was removed upon distillation [b.p. 59° (0.5 mm.)]. The residue was molecularly distilled [bath temperature 100–120° (0.001 mm.)] to yield 6.53 g. of IV as a clear, slightly yellow, thick oil whose infrared spectrum was identical with that of the analytical sample. A two-stage molecular distillation gave the analytical sample: λ_{max}^{EtOH} 272 mμ, ε 16,500; bands at 3.00, 5.80, 5.85, 5.92, and 6.12 μ (chloroform).

Anal. Calc'd for $C_{18}H_{25}NO_6$: C, 61.5; H, 7.2; N, 3.9.
Found: C, 61.6; H, 7.2; N, 3.9.

The product forms a precipitate with 2,4-dinitrophenylhydrazine reagent.

Alkylation of 2-carbethoxycyclohexanone with II *in sodium ethoxide solution.* To a solution of sodium ethoxide prepared from 0.61 g. of sodium in 50 ml. of absolute ethanol was added 3.0 g. of 2-carbethoxycyclohexanone. The mixture was refluxed for 15 minutes, cooled to room temperature, and treated with stirring and under anhydrous conditions, with small portions of II (total of 4.6 g.). The bromo compound went into solution slowly. Removal of the solvent under reduced pressure, after stirring 14 hours at room temperature, left a gummy residue which crystallized upon addition of water (100 ml.). The yield of crude material was 4.0 g.; an infrared spectrum of the crude material was practically identical to that of the analytical sample (colorless plates) m.p. 93–94° (hexane); λ_{max}^{EtOH} 266 mμ, ε 20,000; in dilute carbon tetrachloride solution bands were observed at 5.80, 5.85, and 6.13 μ; in chloroform solution two of the carbonyl bands could not be resolved. This substance does not form a 2,4-dinitrophenylhydrazone and could be diethyl α-(3-carbethoxy-6-oxo-1,4,5,6-tetrahydro-2-pyridylmethyl)pimelate; it was not investigated further.

Anal. Calc'd for $C_{20}H_{31}NO_7$: C, 60.4; H, 7.9; N, 3.5; M.W. 397.
Found: C, 60.3; H, 7.7; N, 3.5; M.W. 394.

2-Hydroxymethyl-1,4,5,6-tetrahydro-6-oxonicotinic acid lactone (V). (a) Following the procedure described (2), 20 g. of II was heated for 30 minutes (bath temperature 130°), cooled and triturated with dilute ammonium hydroxide; yield: 11.7 g. of V, m.p. 252° (dec.). In this reaction ethyl bromide, b.p. 38°, was evolved. After one recrystallization from water (Norit) the yield was 7.7 g., m.p. 255–260° (dec.); λ_{max}^{EtOH} 270 mμ, ε 13,400; bands at 5.80 and 6.05 μ (broad; Nujol mull). A cleaner product (m.p. 260°) was obtained in 88% yield when xylene was used as a solvent (one-half hour at 130°). Reported for the pyrolysis product of II (and previously incorrectly labeled 2-methyl 6-oxynicotinic acid) m.p. 252° (2).

V was insoluble in 5% sodium bicarbonate; it slowly dissolved in 10% aqueous sodium hydroxide from which it was recovered (40%) upon acidification with 10% hydrochloric acid.

(b) When the pyridinium bromide III was kept at its melting point until gas evolution ceased, essentially complete conversion into the lactone V was observed.

Ethyl 2-methyl-6-oxynicotinate (VI). A well-stirred mixture of I (50 g.) and palladium (1.0 g.) was heated at 250–260° for four hours. During this treatment nitrogen introduced through the stirrer was bubbled through the melt. The hot mixture was poured into a mortar, allowed to solidify, and triturated with 120 ml. of 10% aqueous sodium hydroxide. Water (20 ml.) was added and the crystalline residue was filtered, washed with water, and dried to recover 11.0 g. of starting material (I). Acidification of the alkaline filtrate to *p*H 4–5 with concentrated hydrochloric acid gave the pyridone VI. Yield: 21.8 g., m.p. 207–209°, raised to 214–215° on recrystallization from benzene (colorless plates). λ_{max}^{EtOH} 264 mμ, ε 16,500; 300 mμ, ε 5,700. In 95% ethanol solution containing some 0.1 *N* sodium hydroxide: λ_{max} 290 mμ, ε 2,300. Bands at 5.82, 6.05 (very strong) and 6.18 μ (very weak); broad band in the 3.2–3.8 μ region (chloroform).

Anal. Calc'd for $C_9H_{11}NO_3$: C, 59.7; H, 6.1; N, 7.7.
Found: C, 59.8; H, 6.3; N, 7.8.

2-Methyl-6-oxynicotinic acid (VII). A mixture of 2.0 g. of VI, 2.5 g. of potassium hydroxide, and 50 ml. of ethanol was refluxed for 12 hours. The mixture was saturated with carbon dioxide (Dry Ice) and evaporated to dryness on a steam-bath. The residue was dissolved in water (50 ml.) and acidified to *p*H 4 with 10% hydrochloric acid. The precipitate after drying, amounted to 1.72 g., m.p. 286–288° (dec.). Short needles m.p. *ca.* 325° (dec.) were obtained after several recrystallizations from water. λ_{max}^{EtOH} 261 mμ, ε 13,900; 303 mμ, ε 5,700; bands at 5.9 and 6.1 μ (Nujol mull).

Anal. Calc'd for $C_7H_7NO_3$: C, 54.9; H, 4.6; N, 9.1.
Found: C, 55.0; H, 4.6; N, 8.8.

Decarboxylation of VII. A mixture of 2.0 g. of VII, 0.20 g. of copper-chromite catalyst, and 20 ml. of quinoline was heated at 300–315°. After one-half hour gas evolution ceased;

the solution was cooled and diluted with water. Hydrogen sulfide was bubbled through the mixture which was then filtered. The filtrate was concentrated to a small volume, made alkaline with potassium hydroxide, and extracted with ether. The alkaline layer was saturated with carbon dioxide and extracted with chloroform. Removal of the chloroform under reduced pressure left 1.0 g. of IX, m.p. 140–145°, raised to 159–160° after several recrystallizations from acetone-ethyl acetate and finally from *n*-heptane. This material did not depress the melting point of authentic 2-methyl-6-oxypyridine (m.p. 160–161°; λ_{max}^{EtOH} 228 mμ, ε 7,800; 306 mμ, ε 7,200; bands at 6.05 (strong), 6.15 (weak) and broad band in the 3.2–3.8 μ region) prepared, as described (6) from 2-methyl-6-aminopyridine.

Ethyl 2-methyl-6-chloronicotinate (X). The pyridone VI (4.0 g.) and phosphorus oxychloride (10.0 g.) were kept at 120–130° for four hours. The crystalline material obtained on pouring the mixture onto crushed ice melted at about 40° (3.7 g.). Sublimation under reduced pressure (18 mm.) gave X as colorless needles, m.p. 41–42°; λ_{max}^{EtOH} 231 mμ, ε 11,300; 273 mμ, ε 5,800; 280 mμ, ε 4,700; bands at 5.81, 6.30 and 6.40 μ (chloroform).

Anal. Calc'd for $C_9H_{10}ClNO_2$: C, 54.1; H, 5.0; N, 7.0; Cl, 17.8.
Found: C, 54.3; H, 5.2; N, 7.3; Cl, 18.1.

2-Methyl-6-oxynicotinic acid (VII) *from ethyl 2-methyl-6-chloronicotinate* (X). A mixture of 0.70 g. of X, 15 ml. of glacial acetic acid, and 8 ml. of concentrated hydrochloric acid was refluxed overnight. Removal of solvents under reduced pressure gave 0.44 g. of crystalline product shown to be VII by mixture-melting point and infrared spectrum.

Ethyl 2-bromomethyl-6-chloronicotinate (XI). A mixture of 4.0 g. of X, 3.5 g. of recrystallized N-bromosuccinimide, 25 mg. of recrystallized benzoyl peroxide, and 40 ml. of carbon tetrachloride (dried over phosphorus pentoxide and distilled) was illuminated with a 100-watt lamp and refluxed under anhydrous conditions for four hours. The crystalline solid (1.95 g. of succinimide) which resulted on cooling was filtered and the filtrate was evaporated under reduced pressure. The oil which remained gave an immediate precipitate with cold aqueous silver nitrate solution. Its infrared spectra showed bands at 5.81, 6.30 and 6.40 (weak) μ. It was rather unstable but could be distilled to give the following fractions: (a) 0.93 g. at 65–69° (0.2 mm.) (gave no precipitate with cold silver nitrate); (b) 0.18 g. at 70–94° (0.2 mm.); (c) 2.19 g. at 95–103° (0.2 mm.). Fractions (b) and (c) gave an immediate precipitate with cold aqueous silver nitrate. For identification purposes a good crystalline derivative of XI could be obtained on reaction with pyridine.

A solution of 0.75 g. of XI (fraction c) in 2 ml. of benzene gave an immediate crystalline precipitate upon addition of 2 ml. of pyridine. After two hours at room temperature the *pyridinium bromide XII* (0.94 g.) was filtered and recrystallized from ethanol, m.p. 219–220°, which did not improve on successive recrystallizations. λ_{max}^{EtOH} 233 mμ, ε 14,000; 263 mμ, ε 8,400; 268 mμ, ε 7,900; 278 mμ, ε 4,100. This spectrum is very similar to that of X except that the 273 mμ band of X appears to be displaced to 268 mμ in XII and a new band at 263 mμ is evident in XII.

Anal. Calc'd for $C_{14}H_{14}BrClN_2O_2$: C, 47.0; H, 4.0; N, 7.8; Br + Cl, 32.3.
Found: C, 47.1; H, 4.0; N, 7.6; Br + Cl, 32.2.

Ethyl 2-(1'-carbethoxy-2'-oxocyclohexyl)methyl-6-chloronicotinate (XIII). Ethyl 2-bromomethyl-6-chloronicotinate (XI) was prepared from 8.10 g. of X, 7.23 g. of N-bromosuccinimide, 100 ml. of carbon tetrachloride, and 0.15 g. of benzoyl peroxide as described above. The sodio salt of 2-carbethoxycyclohexanone was prepared from a suspension of 0.97 g. of sodium hydride in 60 ml. of benzene containing 20 ml. of anhydrous dimethylformamide and a solution of 6.21 g. of 2-carbethoxycyclohexanone in 40 ml. of benzene; the mixture was stirred during one hour.

A solution of the crude bromide (XI) in 75 ml. of benzene was added dropwise to the stirred mixture of the sodio salt of 2-carbethoxycyclohexanone, kept at room temperature (one-half hour). Stirring was continued at room temperature for an additional 15-hour period. The mixture was poured into ice-water containing 4 ml. of concentrated sulfuric acid and the resulting organic layer was collected and combined with ether-extracts of the aqueous layer. Removal of the organic solvents left an oily residue from which 1.39 g. of 2-carbethoxycyclohexanone (b.p. *ca.* 120° at 1.0 mm.) was removed upon distillation. The

residue (12.10 g.) was molecularly distilled [bath temperature 105° (0.001 mm.)]. The yield of XIII obtained as a clear thick oil was 10.23 g. The infrared spectrum of this material was identical with that of the analytical sample prepared by a two-stage molecular distillation [100° (0.001 mm.)]; λ_{max}^{EtOH} 232 mμ, ε 10,800; 273 mμ, ε 5,200; 279 mμ ε 4,200; bands at 5.81, 5.86, 6.30 and 6.40 μ (carbon tetrachloride).

Anal. Calc'd for $C_{18}H_{22}ClNO_5$: C, 58.7; H, 6.0; N, 3.8; Cl, 9.6.
Found: C, 58.5; H, 6.0; N, 4.0; Cl, 9.9.

The *2,4-dinitrophenylhydrazone of XIII*, prepared in the usual manner (11), was obtained as yellow needles, m.p. 125–126° from methanol.

Anal. Calc'd for $C_{24}H_{26}ClN_5O_8$: C, 52.6; H, 4.8; N, 12.3; Cl, 6.5.
Found: C, 53.1; H, 4.6; N, 12.3; Cl, 6.5.

Ethyl 2-methyl-6-ethoxynicotinate (XIV). To a solution of sodium ethoxide prepared from 0.35 g. of sodium in 50 ml. of absolute ethanol was added 2.4 g. of X. After 12 hours at its reflux temperature the solution was evaporated to dryness. The residue was treated with water and the mixture was extracted with chloroform. Distillation of the residue obtained on removal of the chloroform gave 0.98 g. of XIV as colorless oil, b.p. (2.5 mm.) 104–105°. The analytical sample, n_D^{26} 1.5039; λ_{max}^{EtOH} 248 mμ, ε 12,700; 275 mμ, ε 8,700; 283 mμ (shoulder); bands at 5.82, 6.28 and 6.38 (weak) μ, was obtained on redistillation (b.p. *ca.* 92° at 0.3 mm.).

Anal. Calc'd for $C_{11}H_{15}NO_3$: C, 63.1; H, 7.2; N, 6.7.
Found: C, 63.3; H, 7.2; N, 6.8.

Ethyl 2-methyl-6-(2'-oxo-cyclohexyloxy)nicotinate (VIII). (*a*) A stirred mixture of the sodio salt of the pyridone VI (prepared by evaporating to dryness a solution of 1.0 g. of VI in sodium ethoxide obtained from 0.13 g. of sodium in 50 ml. of absolute ethanol), 75 ml. of dry benzene, and 15 ml. of dimethylformamide, was treated at room temperature with a solution of 2-chlorocyclohexanone (0.73 g.) in 25 ml. of benzene, added over a one-half hour period. The mixture was refluxed for two hours, treated with water (100 ml.), and separated into two layers. The aqueous layer was extracted with benzene and chloroform. Removal of the organic solvents left a liquid which crystallized on cooling. One recrystallization from hexane gave 0.42 g. of VIII, m.p. 87–94°. The analytical sample was obtained as short colorless needles, m.p. 100–101° (hexane); λ_{max}^{EtOH} 248 mμ, ε 14,300; 275 mμ, ε 9,500; 283 mμ (shoulder); bands at 5.82, 5.85, 6.30, and 6.40 (weak) μ. VIII was soluble in 10% hydrochloric acid, insoluble in 10% aqueous sodium hydroxide, and gave an immediate precipitate with 2,4-dinitrophenylhydrazine reagent.

Anal. Calc'd for $C_{15}H_{19}NO_4$: C, 64.9; H, 6.9; N, 5.0.
Found: C, 64.7; H, 7.1; N, 4.8.

(*b*) VIII was the only product isolated when a warm mixture of 5 g. of VI, 1.74 g. of potassium hydroxide pellets, and 75 ml. of absolute ethanol was treated with a solution of 4.64 g. of 2-chlorocyclohexanone in 25 ml. of ethanol added drowpise over a 40-minute period. After refluxing for two hours, removing the ethanol, and extracting the residue with ether, 5.88 g. of oily crystals was obtained. Infrared spectra showed their identity with VIII. The yield was 2.66 g., m.p. 97–99° after one recrystallization from ethanol-water. The ether-insoluble residue of the previous extraction yielded 2.25 of starting material (VI) upon extraction with chloroform.

Ethyl 2-methyl-5-bromo-6-oxynicotinate (XV). To a stirred solution of VI (2.0 g.) in 50 ml. of chloroform was added dropwise a solution of 1.8 g. of bromine in 25 ml. of chloroform. After stirring for an additional hour the solvent was removed *in vacuo*. Crude yield: 3.08 g. of colorless crystals, m.p. 186–191°. Recrystallization from ethanol gave 1.4 g. of XV as needles, m.p. 216–220°. The analytical sample was obtained as needles, m.p. 226–227° from ethanol; λ_{max}^{EtOH} 271 mμ, ε 14,400; 307 mμ, ε 3,500; 317 mμ, ε 8,600 and 328 mμ, (inflection); lbands at 5.82, 6.05, and 6.20 μ and broad band in the 3.2–3.8 region.

Anal. Calc'd for $C_9H_{10}BrNO_3$: C, 41.6; H, 3.9; N, 5.4; Br, 30.7.
Found: C, 41.9; H, 4.2; N, 5.3; Br, 30.9.

This material gave no precipitate with hot silver nitrate solution and appeared not to react with pyridine.

SUMMARY

1. The synthesis of ethyl 2-(1′-carbethoxy-2′-oxocyclohexyl)methyl-1,4,5,6-tetrahydro-6-oxonicotinate (IV) and of ethyl 2-(1′-carbethoxy-2′-oxocyclohexyl)-methyl-6-chloronicotinate (XIII) is described. These intermediates are being used in attempts to prepare α-pyridone derivatives of benzo[*b*]pyrrocoline.

2. A recently described preparation of 2-methyl-6-oxynicotinic acid (VII) by pyrolysis of ethyl 2-bromomethyl-1,4,5,6-tetrahydro-6-oxonicotinate (II) was reinvestigated and found to be in error. The lactone of 2-hydroxymethyl-1,4,5,6-tetrahydro-6-oxonicotinic acid (IV) is given as the structure of the product of the thermal decomposition of II.

3. Alkylation of ethyl 2-methyl-6-oxynicotinate (VI) with 2-chlorocyclohexanone in alkaline medium was shown to yield the O-alkylated rather than the N-alkylated product.

4. The ultraviolet and infrared absorption spectra of several 2-oxypyridine derivatives are given and discussed.

NEW YORK 27, NEW YORK

REFERENCES

(1) (a) ROBINSON AND SAXTON, *J. Chem. Soc.*, 976 (1952); (b) ROBINSON AND SAXTON, *J. Chem. Soc.*, 3136 (1950).
(2) ALBERTSON, *J. Am. Chem. Soc.*, **74**, 3816 (1952).
(3) ALBERTSON, *J. Am. Chem. Soc.*, **74**, 6319 (1952).
(4) (a) ARNOLD, DE MOURA CAMPOS, AND LINDSAY, *J. Am. Chem. Soc.*, **75**, 1044 (1953). (b) CRAIG, *J. Am. Chem. Soc.*, **74**, 129 (1952). (c) CRAIG AND WITT, *J. Am. Chem. Soc.*, **72**, 4925 (1950).
(5) BUU-HOÏ, *Record Chem. Progr. (Kresge-Hooker Sci. Lib.)*, **13**, 30 (1952).
(6) ADAMS AND SCHRECKER, *J. Am. Chem. Soc.*, **71**, 1186 (1949).
(7) ADAMS AND JONES, *J. Am. Chem. Soc.*, **71**, 3826 (1949).
(8) *Cf.* MOSHER in ELDERFIELD, Editor, *Heterocyclic Compounds*, John Wiley and Sons, Inc., New York, 1950, Vol. I, p. 534.
(9) MOSHER, *Heterocyclic Compounds*, John Wiley and Sons, Inc., Vol. I, p. 435. See also TUCKER, JR. AND IRBIN, *J. Am. Chem. Soc.*, **73**, 1923 (1951) for a discussion of lactam-lactim tautomerism in 2-oxyquinolines.
(10) SPECKER AND GAWROSCH, *Ber.*, **75**, 1338 (1942).
(11) SHRINER AND FUSON, *Identification of Organic Compounds*, 3rd ed., John Wiley and Sons, New York, 1948, p. 171.