## 492. *Ring–Chain Tautomerism in the Acid Esters of Pyridine-2 : 3-dicarboxylic Acid.*

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Pyridine-2 : 3-dicarboxylic anhydride and methanol combine exothermally in equimolecular proportions at room temperature, to form a viscous compound which is probably a hemi-acetal. Within an hour at room temperature this changes spontaneously and completely into crystalline methyl 2-carboxypyridine-3-carboxylate which in turn changes to the isomeric methyl 3-carboxypyridine-2-carboxylate when its solutions are heated; conversely methyl 3-carboxypyridine-2-carboxylate is smoothly re-converted into methyl 2-carboxypyridine-3-carboxylate at 150°. The viscous compound is hygroscopic and forms a stable crystalline hydrate. Both the viscous compound and its crystalline hydrate with diazomethane readily give dimethyl pyridine-2 : 3-dicarboxylate.

(+)-*sec.*-Butyl 2-carboxypyridine-3-carboxylate, when heated in ethyl acetate, is converted into (+)-*sec.*-butyl 3-carboxypyridine-2-carboxylate without significant loss of molecular dissymmetry. (−)-*sec.*-Butyl 3-carboxypyridine-2-carboxylate is smoothly decarboxylated at 160° to optically pure (−)-*sec.*-butyl nicotinate.

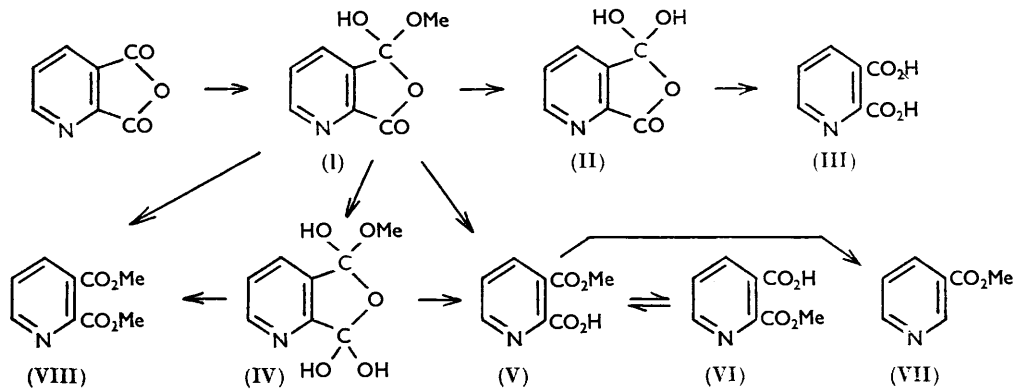
BY heating a mixture of pyridine-2 : 3-carboxylic anhydride and methanol for several hours, Kirpal [1] obtained a methyl carboxypyridinecarboxylate which, since it gave methyl nicotinate on decarboxylation, he believed to be methyl 2-carboxypyridine-3-carboxylate (V). Later he showed [2] that by the successive action of ammonia, hypobromite, and heat this compound gave 2-aminopyridine; accordingly he concluded that the compound was

[1] Kirpal, *Monatsh.*, 1899, **20**, 766.
[2] *Idem, ibid.*, 1900, **21**, 957.

the isomer, methyl 3-carboxypyridine-2-carboxylate (VI). Still later [3] he found that the reaction between pyridine-2 : 3-dicarboxylic anhydride and methanol afforded not only the 2-methyl ester but also, in much smaller proportion, the 3-methyl ester, the structure of which was similarly established by its conversion into 3-aminopyridine. Kirpal showed that this 3-methyl ester, like the 2-methyl ester, when heated above its melting point lost carbon dioxide and yielded methyl nicotinate (VII).

These results suggest that the first product of the combination of methanol and pyridine-2 : 3-dicarboxylic anhydride is the hemiacetal (I) which even at room temperature changes to methyl 2-carboxypyridine-3-carboxylate (V).

Recent work [5] on the ultraviolet absorption spectra of solutions of phthalic anhydrides in ethanol and non-hydroxylic solvents suggests the formation of intermediates of type (I) which isomerise gradually to alkyl hydrogen phthalates; *e.g.*, it is stated that a solution of




metahemipinic anhydride in ethanol gave results which " could be interpreted to mean that the monoester is formed almost instantaneously and, indeed, working up of our alcoholic solution after only a short time yields the ethyl hydrogen ester." In our hands metahemipinic anhydride did not display this great reactivity since after its solution in ethanol had been boiled for 2 hr. most of the anhydride crystallised unchanged from the cooled solution; when the heating was continued for 4 hr. the acid ester was obtained in excellent yield.

It appears that any intermediates of type (I) derived from metahemipinic anhydride and ethanol exist only in ethanolic solution.

More recently Chase and Hey [6] reinforced the arguments in favour of an intermediate cyclic structure by their detailed study of the reactions of the acid halides of the half esters of dibasic acids.

sec.-*Butyl Carboxypyridinecarboxylates.*—To gain more insight into the tautomerism of acid esters we examined the isomeric optically active *sec.*-butyl carboxypyridinecarboxylates. When pyridine-2 : 3-dicarboxylic anhydride and (±)-*sec.*-butyl alcohol are heated together both the 2- and the 3-ester are produced, the proportion of the former increasing as heating is continued. The 3-butyl ester when heated in ethyl acetate for an hour is almost completely converted into the 2-ester. The positions of the esterified groups have been assumed on the basis of their parallelism of behaviour with corresponding methyl esters.

These esters are readily resolved by fractional crystallisation of the brucine salts.

Heating the (+)-3-ester in ethyl acetatefor 2 hr. gives the 2-ester having $[\alpha]_D$ +20·8° in $CHCl_3$. Since the highest observed rotatory power of the 2-ester is $[\alpha]_D$ +22·2° this change involves little, if any, loss of molecular dissymmetry. Further, when the (−)-2-ester undergoes decarboxylation—which, by analogy with the methyl ester, must involve intermediate formation of the 3-ester—the resulting (−)-*sec.*-butyl nicotinate is almost optically pure.

Thus in these rearrangements migration of $OBu^s$ and not of $Bu^s$ is involved, as would be expected on general grounds. Support for the view that the reaction is completely

[5] Hirschberg, Lavie, and Bergman, *J.*, 1951, 1030.
[6] Chase and Hey, *J.*, 1952, 553.

intramolecular is afforded by the observation that heating methyl 2-carboxypyridine-3-carboxylate in *sec.*-butyl alcohol gives only methyl 3-carboxypyridine-2-carboxylate.

(+)-*sec.*-Butyl 2-carboxypyridine-3-carboxylate and (−)-*sec.*-butyl 3-carboxypyridine-2-carboxylate each yields a brucine salt of m. p. 186°. After the second of these has been kept at its m. p. for a short time, hydrochloric acid liberates *sec.*-butyl 2-carboxypyridine-3-carboxylate, m. p. 131°: thus the second brucine salt is converted into the first during melting.

During fractional crystallisation of the brucine salts of *sec.*-butyl 2-carboxypyridine-3-carboxylate from acetone one of the filtrates was concentrated *on the steam-bath* before decomposition with dilute acid; the liberated product was (−)-*sec.*-butyl 3-carboxypyridine-2-carboxylate: thus interconversion of the isomeric acid esters of pyridine-2 : 3-dicarboxylic acid occurs very readily.

## Experimental

2- *and* 3-*Methyl Carboxypyridinecarboxylate.*—(i) Pyridine-2 : 3-carboxylic anhydride (7·6 g.) and methanol (5 c.c.) were heated on the steam-bath for 40 min. The product (6·5 g.) was separated by one crystallisation from ethyl acetate into methyl 2-carboxypyridine-3-carboxylate (4·1 g., 45%), plates, m. p. 102—103°, and methyl 3-carboxypyridine-3-carboxylate (2·1 g., 23%), rhombs, m. p. 122—123°. After recrystallisation these esters had respectively m. p. 106° and 123° which are the values recorded by Kirpal.

(ii) The anhydride (3·6 g.) and methanol (2 c.c.) were heated under reflux for 10 min. and the excess of methanol removed *in vacuo*. The yields of the 3- (2·7 g., 62%) and the 2-methyl ester (0·9 g., 21%) indicate that the shorter reaction time had increased the ratio of two esters from 2 : 1 to 3 : 1. Kirpal, who used a reaction time of 4 hr., obtained the widely different ratio 1 : 10.

(iii) The anhydride (5·88 g.) and methanol (1·8 g.) were heated on the steam-bath for 2 hr. Crystallisation of the product from ethyl acetate yielded methyl 3-carboxypyridine-2-carboxylate (5·2 g., 73%), m. p. 122—123°; the filtrate slowly deposited the 3-methyl ester (1·2 g., 17%) which after crystallisation from benzene had m. p. 105—106°.

1 : 3-*Dihydro*-1-*hydroxy*-1-*methoxy*-3-*oxofurano*[3 : 4-b]*pyridine* (I).—Powdered pyridine-2 : 3-carboxylic anhydride (7·45 g.) was triturated with methanol (2 g., 1 : 2-mol.); within 5 min. a clear viscous liquid (I) resulted with rise of temperature to 48°.

*Structural experiments.* (i) Freshly prepared hemiacetal (I), shaken with 10 vols. of cold water, gave a clear solution which rapidly deposited pyridine-2 : 3-dicarboxylic acid quantitatively. (ii) Freshly prepared hemiacetal (I) was kept for 5—20 min. before being shaken with water: the resulting clear solution, on evaporation at low temperature, yielded methyl 2-carboxypyridine-3-carboxylate, m. p. 102—103°, almost quantitatively. (iii) After 20—30 min. the hemiacetal (I) began to solidify; the pressed solid, m. p. 100—125°, was separated by crystallisation from ethyl acetate into methyl 3-carboxypyridine-2-carboxylate, m. p. 122—123°, and methyl 2-carboxypyridine-3-carboxylate, m. p. 102—103°. (iv) After 30 min. at 60° the hemiacetal (I) was triturated with light petroleum: the product had m. p. 122—123°, showing that conversion into methyl 3-carboxypyridine-2-carboxylate was complete.

*The Hydrate,* 1 : 3-*Dihydro*-1 : 3 : 3-*trihydroxy*-1-*methoxyfurano*[3 : 4-b]*pyridine.*—Attempts to crystallise the hemiacetal (I) were unsuccessful, yet when a few drops of water were added to its concentrated ethereal solution crystals, m. p. 84°, of its hydrate separated. (ii) A few drops of water were added to freshly prepared heniacetal (I), from pyridine-2 : 3-carboxylic anhydride (7·45 g.) and methanol (2 c.c.), and the resultant clear liquid stirred: it set to a semisolid mass; this was washed with water (2 c.c.); the filtrate deposited a trace of pyridine-2 : 3-dicarboxylic acid. This washed solid, after rapid drying, weighed 6·2 g. and had m. p. 78—80° (incomplete). After 36 hr. it melted indefinitely at 84—102°. (iii) A portion (0·5 g.) of this freshly prepared material dissolved almost completely in cold ether and the solution deposited glassy rhombs (0·41 g.), m. p. 84°. (iv) Another portion (1 g.) was dissolved in water (6 c.c.) at 40° and the solution allowed to evaporate; there separated plates, m. p. 100—102° (0·9 g.), of methyl 2-carboxypyridine-3-carboxylate. The crystallised material (iii) behaves similarly. (v) Another portion (1 g.) in ethyl acetate (3 c.c.) was heated for an hour; the

cooled solution deposited methyl 3-carboxypyridine-2-carboxylate, rhombs, m. p. 118—120° (0·78 g.); the filtrate yielded the 3-methyl ester, plates, m. p. 100—101° (0·14 g.). (vi) Another portion, after an hour, was separated by extraction with cold ether into (*a*) an insoluble part (about 20%) of m. p. 102°, alone and when mixed with methyl 2-carboxypyridine-3-carboxylate, and (*b*) a soluble part (about 80%) which separated from the solution in glassy rhombs, m. p. 84° to a clear liquid which solidified on cooling and then had m. p. 102—104° alone and when mixed with methyl 2-carboxypyridine-3-carboxylate.

*The hydrate*, m. p. 84° (Found: C, 48·5; H, 4·7; N, 6·7. $C_8H_9O_5N$ requires C, 48·2; H, 4·5; N, 7·0%) (0·2909 g.), was titrated with 0·107N-sodium hydroxide with phenolphthalein as indicator; each addition of alkali gave a pink colour which disappeared after a few moments (total 13·8 c.c., whence $M$ = 197. $C_8H_9O_5N$ requires $M$, 199).

The monohydrate (0·5 g.) and methyl 2-carboxypyridine-3-carboxylate (0·5 g.) were separately heated for an hour with butan-2-ol (1 c.c.), and the resulting solutions warmed under reduced pressure to remove the butanol. In each case the product was pure methyl 3-carboxypyridine-2-carboxylate, m. p. 122—123°. Ethereal solutions of freshly prepared acetal (I) and its hydrate (IV) with diazomethane (excess) gave excellent yields of dimethyl pyridine-2 : 3-dicarboxylate, m. p. 54°.

(±)-sec.-*Butyl 3-Carboxypyridine-2- and 2-Carboxypyridine-3-carboxylate.*—A mixture of pyridine-2 : 3-dicarboxylic anhydride (30 g.) and *sec.*-butyl alcohol (20 c.c.), after an hour on the steam-bath, formed a clear solution from which needles began to separate: after an additional hour the product was almost wholly crystalline. The pressure was then reduced to remove the excess of alcohol and the residue was crystallised from hot ethyl acetate. The first crop (29·4 g.) consisted of the 2-*sec.*-butyl ester, plates, m. p. 149°: the filtrate next day yielded the 3-*sec.*-butyl ester (15 g.), needles, m. p. 129°. The 2-sec.-*butyl ester*, recrystallised from ethyl acetate, formed needles, m. p. 149—150° (Found: N, 6·1%; $M$, by titration, 222. $C_{11}H_{13}O_4N$ requires N, 6·3%; $M$, 223). The 3-sec.-*butyl ester*, recrystallised from acetone, formed needles, m. p. 129—130° (Found: N, 6·2%; $M$, 222).

(+)- *and* (−)-sec.-*Butyl 3-Carboxypyridine-2-carboxylate.*—Brucine (49·5 g.) dissolved readily in a warm solution of the (±)-2-butyl ester (28 g.) in acetone (100 c.c.); the solution soon crystallised. Filtration yielded a brucine salt (m. p. 184°; 65 g.; crop A): this was heated for 2 hr. under reflux with acetone (200 c.c.), and the suspension cooled and filtered to give crop B (45·5 g.). This, in turn, was heated under reflux with acetone (100 c.c.) for an hour, cooled, and filtered, to give crop C (36·5 g.), needles, m. p. 186°. Crop C was triturated with acetone (40 c.c.), and the suspension mixed slowly with 0·5N-sulphuric acid (116 c.c.) and shaken. The resulting brucine sulphate was removed and washed with hot acetone (20 c.c.). The aqueous acetone filtrate was slowly evaporated on a current of air, (+)-*sec.*-butyl 3-carboxypyridine-2-carboxylate (10·5 g.) separating as needles, m. p. 150—151°, $[\alpha]_D$ +22·2° (*l* 1; *c* 3·361 in $CHCl_3$).

The combined filtrates containing the more soluble fraction of the brucine salt were concentrated and mixed with 0·5N-sulphuric acid (116 c.c.) and treated as described above. The liberated (−)-*sec.*-butyl 3-carboxypyridine-2-carboxylate (10·2 g.) formed needles, m. p. 150—151°, $[\alpha]_D$ −21·1° (*l* 1; *c* 3·134 in $CHCl_3$).

(+)- *and* (−)-sec.-*Butyl 2-Carboxypyridine-3-carboxylate.*—A clear solution of the (±)-3-butyl ester (21 g.) and brucine (37 g.) in warm acetone (100 c.c.) soon deposited crystals of the brucine salt. This (crop A; 46 g.) was removed, washed with acetone, and dissolved in warm chloroform (20 c.c.). Dilution with acetone (40 c.c.) yielded crop B (34 g.). Repetition of the process yielded crop C (28·7 g.) as needles, m. p. 186°. Crop C (25 g.), triturated with acetone (70 c.c.) and 0·5N-sulphuric acid (81 c.c.) and treated as described above, yielded (+)-*sec.*-butyl 2-carboxypyridine-3-carboxylate (6·8 g.) which separated from acetone in needles, m. p. 130—131°, $[\alpha]_D$ +10·9° (*l* 1; *c* 4·60 in $CHCl_3$). The more soluble fraction of the brucine salt contained in the filtrates, which it is essential to concentrate *without heating*, after decomposition as described above, yielded (−)-*sec.*-butyl 2-carboxypyridine-3-carboxylate (7·1 g.) which separated from acetone in needles, m. p. 130—131°, $[\alpha]_D$ −8·6° (*l* 1; *c* 3·86 in $CHCl_3$).

When the filtrates containing the brucine salt were concentrated on the steam-bath before decomposition, the product was the more stable (−)-*sec.*-butyl 3-carboxypyridine-2-carboxylate, m. p. 150—151°, $[\alpha]_D$ −12° in $CHCl_3$.

The brucine salt (1 g.) of *sec.*-butyl 3-carboxypyridine-2-carboxylate was heated at 190° until completely molten, cooled, and decomposed with hydrochloric acid. Crystallisation of

the liberated product from cold acetone yielded *sec.*-butyl 2-carboxypyridine-3-carboxylate (0·15 g.), m. p. and mixed m. p. 130—131°.

*Conversion of* (+)-sec.-*Butyl 2-Carboxypyridine-3-carboxylate into* (+)-sec.-*Butyl 3-Carboxypyridine-2-carboxylate.*—A solution of the (+)-3-ester (1 g.) in ethyl acetate (5 c.c.) was heated under reflux for 2 hr.; after cooling, it gave the (+)-2-ester (0·5 g.) which, after recrystallisation, had m. p. 150—151°, $[\alpha]_D$ +20·8° (*l* 1; *c* 4·850 in $CHCl_3$).

The (±)-3-ester (1 g.) was converted after 1 hr. into the (±)-2-ester (0·48 g.); the unchanged (±)-3-ester (0·39 g.) isolated from the filtrate was heated under reflux for 2 hr. in ethyl acetate; this solution deposited the (±)-2-ester (0·15 g.), needles, m. p. and mixed m. p. 149—150°.

Conversion of (±)-butyl 3-carboxypyridine-2-carboxylate into (±)-*sec.*-butyl 2-carboxypyridine-3-carboxylate occurred at 155—160° in 0·5 hr.; the molten product set to a crystalline mass, m. p. and mixed m. p. 129—130°.

*Decarboxylations.*—(−)-*sec.*-Butyl 3-carboxypyridine-2-carboxylate, $[\alpha]_D$ −21·1° (5 g.), and a little copper powder were heated at 180—185° under reduced pressure. After an hour, when reaction ceased, the residual liquid was dissolved in ether and washed with sodium carbonate solution. The resultant (−)-*sec.*-butyl nicotinate (2·1 g.) had b. p. 86—87°/0·8 mm., $n_D^{20}$ 1·4913, $[\alpha]_D$ −21·8° (*l* 1; *c* 3·990 in $CHCl_3$).

The corresponding (±)-ester similarly yielded (±)-sec.-*butyl nicotinate*, b. p. 86—87°/0·8 mm., $n_D^{20}$ 1·4912 (Found: N, 7·7. $C_{10}H_{13}O_2N$ requires N, 7·3%).

(±)-*sec.*-Butyl nicotinate, prepared in excellent yield from nicotinoyl chloride, (±)-butan-2-ol and pyridine, had b. p. 92°/2 mm., $n_D^{20}$ 1·4913 (Found: N, 7·8%). When the (±)butanol was replaced by (+)-butan-2-ol, $\alpha_D^{20}$ +4·17° (*l* 0·5), the resulting (−)-*sec.*-butyl nicotinate, $n_D^{20}$ 1·4914, had $[\alpha]_D^{20}$ −16·9 (*l* 1; *c* 4·98 in $CHCl_3$). Since the (+)-butan-2-ol had only 74·7% of its maximum rotation, optically pure (−)-*sec.*-butyl nicotinate will probably show $[\alpha]_D^{20}$ −22·6°. (+)-Butan-2-ol, $\alpha_D$ +3·01° (*l* 0·5), gave butyl nicotinate, $[\alpha]_D$ −12·1°, which suggests that the rotation of optically pure *sec.*-butyl nicotinate will be $[\alpha]_D^{20}$ −21·8°.

(+)-*sec.*-Butyl 2-carboxypyridine-3-carboxylate and a little copper powder at 160—165° gave butyl nicotinate, $n_D^{20}$ 1·4912, $[\alpha]_D$ +21·9° (*l* 1; *c* 4·64 in $CHCl_3$). The (±)-3-ester yielded (±)-*sec.*-butyl nicotinate, $n_D^{20}$ 1·4913.

*Ethyl Hydrogen Metahemipinate.*—A solution of metahemipinic anhydride (0·5 g.) in absolute ethanol (2 c.c.) was evaporated at room temperature after 4 hr.; the residue was unchanged anhydride. Presence of acetone did not alter the result. The anhydride (0·5 g.), when heated in absolute ethanol (3 c.c.) under reflux for 2 hr., gave unchanged anhydride but after 4 hr. yielded ethyl hydrogen metahemipinate (0·4 g.), m. p. 125—127°: after one recrystallisation, this had m. p. 129° (Rossin [7] gives m. p. 127°). Addition of pyridine brings about the reaction within 2 hr.

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[7] Rossin, *Monatsh.*, 1891, **12**, 489.