ture for an arbitrary period ranging from one to three days. If treatment of the aqueous acidic solution of the product with excess sodium hydroxide resulted in the precipitation of a solid free base, it was separated by filtration and recrystallized from an appropriate solvent (usually a Skellysolve or other hydrocarbon solvent). If, on the other hand, an oil was formed, it was taken up in ether and dried. If removal of the ether still did not yield a solid residue it was taken up in more dry ether and converted to the hydrochloride. The solvents used most frequently for recrystallizations of these hydrochlorides were isopropyl alcohol–acetone, ethyl acetate and the solvent pairs, methanol–ether and ethanol–ether. Two basic amides (see table) of 2-phenylbutanoic acid were purified by distillation *in vacuo*. The diethylaminoethylamide of allyl diphenylacetic acid was isolated as the acid oxalate, and the corresponding dimethylaminoisopropylamide by distillation.

Reaction of 2,2-Diphenyl-3-chloropropanoyl Chloride with N,N′-Dimethylethylenediamine.—The reaction carried out as described above gave, in addition to a 55% yield of the desired amide, a 28% yield of an acid-insoluble product which proved to be the bis-amide formed by reaction of the acid chloride with both secondary amino groups. Recrystallization from 70% acetic acid gave colorless leaflets, m. p. 210–211°.

Anal. Calcd. for $C_{34}H_{34}Cl_2N_2O_2$: C, 71.19; H, 5.97; N, 4.88. Found: C, 71.71; H, 6.11; N, 4.77.

Similar treatment of 2,2-diphenyl-3-chloropropanoyl chloride with ethylenediamine resulted in exclusive formation of the bis-amide in a nearly quantitative yield. It formed colorless needles from 60% acetic acid, m. p. 190–191°.

Anal. Calcd. for $C_{32}H_{30}Cl_2N_2O_2$: C, 70.45; H, 5.54; N, 5.13. Found: C, 70.41; H, 5.62; N, 5.12.

Summary

The synthesis of a number of basic esters and amides of carboxylic acids of type, $(C_6H_5)_2$-$RCCOOH$, where R = CH_3, C_2H_5, $CH_2{=}CHCH_2$, $ClCH_2$ and $BrCH_2$, and of the acid, $C_6H_5CH(C_2H_5)COOH$, is reported. The results of tests for analgesic activity in these compounds are summarized.

NORTH CHICAGO, ILLINOIS RECEIVED NOVEMBER 21, 1949

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

The Nitrogen Compounds in Petroleum Distillates. XXVII. Isolation and Identification of 2,3-Dimethyl-6-isopropyl-pyridine from California Petroleum

BY H. L. LOCHTE, A. D. BARTON,[1,2] STILES M. ROBERTS[3] AND J. R. BAILEY[4]

The bases used in the present study were recovered from the hydrochlorides found in the chloroform layers after the "cumulative" extraction[5] of an aqueous solution of the hydrochlorides of petroleum bases boiling in the range 175–235°. When these bases were subjected to a procedure which involved fractionation by sulfurous acid, fractional distillation and fractional methiodide formation, the methiodide of a $C_{10}H_{15}N$ base was isolated and analyzed. The base was liberated by thermal decomposition of the purified methiodide and again subjected to fractional distillation.

The structure of the base was established through the following reactions: (1) Oxidation of the base by permanganate yielded 2,5-pyridinedicarboxylic acid under conditions such that it probably was formed by decarboxylation of 2,3,6-pyridinetricarboxylic acid produced originally since this is the only pyridinetricarboxylic acid which yields 2,5-pyridinedicarboxylic acid on decarboxylation; oxalic acid was also isolated, thus confirming the presence of two adjacent unsubstituted positions in the pyridine nucleus. (2) Condensation with phthalic anhydride yielded a phthalone which indicated the presence of a methyl group in one of the alpha positions. (3) On ozonolysis the base yielded isobutyramide; this indicated the presence of an isopropyl group in the other alpha position, since the carbon and nitrogen atoms of the carboxamide group must have come from the alpha carbon and nitrogen atom of the pyridine ring.[6] (4) To determine the relative positions of the three substituents, the α-methyl group was removed by condensation with benzaldehyde followed by ozonolysis of the 2-stilbazone derivative formed to give the corresponding 2-pyridinecarboxylic acid which was then decarboxylated. When the resulting demethylated base was oxidized with permanganate, 2,5-pyridinedicarboxylic acid was formed, thus showing that the demethylated base was 3-methyl-6-isopropylpyridine and that the base isolated from petroleum was 2,3-dimethyl-6-isopropylpyridine.

Isolation of the $C_{10}H_{15}N$ Base.—The material for this investigation consisted of 750 ml. of bases boiling in the range 192–230° which had been isolated[7] from the hydrochlorides in the chloroform layers after the extraction of an aqueous solution of the hydrochlorides of petroleum bases[8] boiling in the range 170–235°. The material was

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(1) Abstracted from theses submitted by Stiles M. Roberts (1939) and A. D. Barton (1949) in partial fulfillment of requirements for the degree of Doctor of Philosophy.

(2) du Pont Fellow, 1947–1948; McArdle Memorial Laboratory, Medical School, University of Wisconsin, Madison, Wis.

(3) Central Research Laboratory, General Aniline and Film Corporation, Easton, Penna.

(4) Isolation and preliminary study of this base was carried out by Stiles M. Roberts before the death of Professor Bailey.

(5) This method of fractionating petroleum bases was developed in this Laboratory by Perrin and Bailey, THIS JOURNAL, **55**, 4136 (1933).

(6) Shive, Roberts, Mahan and Bailey, *ibid.*, **64**, 909 (1942); Lochte, Crouch and Thomas, *ibid.*, **64**, 2753 (1942); Shive, Ballweber and Ackermann, *ibid.*, **68**, 2144 (1946).

(7) Meadows, Ph.D. Dissertation, University of Texas, 1937.

(8) These bases comprised part of a large quantity of bases which were generously donated to this Laboratory by the Union Oil Company of California.

dissolved in aqueous sulfurous acid and aerated at 100° for ten hours. The bases liberated during this period were dried over solid potassium hydroxide and distilled through an efficient fractionating column. The first 150 ml. of distillate boiled between 198 and 205° and showed n^{25}_{D} 1.4932; this material was then dissolved in 150 ml. of purified hydrocarbon oil boiling between 195 and 200°, 75 ml. of methyl iodide was added and the mixture was heated under reflux for ten hours. The oily addition product which separated was removed and the solution was heated for an additional twenty-four hours. The basic material which remained was heated in sealed tubes with methyl iodide in hydrocarbon oil at 100° for seventy-two hours. The crystalline addition product which formed during this time was washed with acetone and found to melt at 160–165°; after repeated recrystallization from absolute alcohol the melting point became constant at 180–181°.[9]

Anal. Calcd. for $C_{10}H_{15}NCH_3I$: N, 4.80; I, 43.60. Found: N, 4.74; I, 43.53.

In order to liberate the base, the methiodide was heated to a temperature slightly above its melting point and the methyl iodide was removed *in vacuo*. The residue distilled at 197.4–197.8° (747 mm.); d^{20}_{4} 0.9036; n^{20}_{D} 1.4952; n^{25}_{D} 1.4932; MR_{D} calcd. 47.75, found 47.71.

Anal. Calcd. for $C_{10}H_{15}N$: C, 80.46; H, 10.13. Found: C, 80.48; H, 10.26.

The **picrate** was prepared in aqueous sulfurous acid solution and recrystallized from dilute ethyl alcohol; m. p. 99–100°.

Anal. Calcd. for $C_{16}H_{18}O_7N_4$: C, 50.77; H, 4.80; N, 14.81. Found: C, 50.47; H, 4.89; N, 14.67.

The **phthalone** was prepared by heating a sample of the base with a slight excess of phthalic anhydride in a sealed tube at 210° for eight hours. The crude product was dissolved in glacial acetic acid and the solution poured onto chipped ice. The material which separated was recrystallized from ethyl alcohol yielding needles melting at 132°.

Anal. Calcd. for $C_{18}H_{17}O_2N$: C, 77.38; H, 6.14. Found: C, 77.19; H, 6.28.

Permanganate Oxidation of the $C_{10}H_{15}N$ Base.—Five grams of the base was oxidized in aqueous potassium permanganate solution and the acids formed were precipitated as the silver salts which were then dissolved in concentrated aqueous ammonia solution and reprecipitated in three fractions by the addition of dilute nitric acid, following the procedure described by Lochte, Crouch and Thomas.[6] The first fraction of salts was suspended in warm water and the mixture treated with hydrogen sulfide and filtered. Upon evaporation to dryness the filtrate yielded 431 mg. of air-dried solid which contained a considerable amount of oxalic acid. The residue was extracted with two 0.5-ml. portions of absolute alcohol and the alcoholic solutions were evaporated to dryness. The residue dried over phosphorus pentoxide weighed 154 mg. This material was maintained at 120–130° in a sublimation apparatus; after seven hours the residue had attained a constant weight of 74 mg. while 53 mg. of a sublimate consisting mainly of oxalic acid had been collected. The loss was thus 27 mg. The production of 74 mg. of a pyridinedicarboxylic acid by decarboxylation of a pyridinetricarboxylic acid involves the liberation of 20 mg. of carbon dioxide. A small part of the sublimate was not readily soluble in water.

After recrystallization from water, the sublimate was shown to be oxalic acid by its melting point, its titration curve and its equivalent weight. Identity was confirmed by a mixed melting point with an authentic sample.

The residue which did not sublime was no longer soluble in absolute alcohol; it was recrystallized twice from water and dried *in vacuo* over phosphorus pentoxide; m. p. and mixed m. p. with an authentic sample of 2,5-pyridinedicarboxylic acid[10] 258° with effervescence. Its titration curve was typical of a pyridinedicarboxylic acid. It produced a red color in ferrous sulfate solution.

Anal. Calcd. for $C_7H_5NO_4$: N, 8.39; equiv. wt., 83.6. Found: N, 8.45; equiv. wt. by titration, 85.4.

Isolation of Isobutyramide.—A stream of oxygen containing approximately 8% ozone was passed through a solution of 4.0 g. of the $C_{10}H_{15}N$ base in 30 ml. of carbon tetrachloride in an ice-bath for twenty-four hours. The carbon tetrachloride layer was separated and shaken at room temperature with 2 ml. of 50% potassium hydroxide solution. During the course of ten minutes, 76 mg. of glistening white platelets formed; after two recrystallizations from water they melted at 128–129°. A mixed melting point with an authentic sample of isobutyramide showed no depression.

Anal. Calcd. for C_4H_9NO: N, 16.01. Found: N, 16.22.

Conversion of the $C_{10}H_{15}N$ Base to the 2-Stilbazole Derivative.—Five grams of the $C_{10}H_{15}N$ base, 3.5 g. of benzaldehyde and 9 g. of acetic anhydride were mixed and heated under reflux at 150–155° for forty hours as described by Shaw and Wagstaffe.[11] On fractional distillation the reaction mixture yielded 4.3 g. (54%) of 6-isopropyl-3-methyl-2-stilbazole which distilled at 179–180° (2 mm.) and was characterized by d^{20}_{4} 1.020; n^{20}_{D} 1.6015. The **picrate** was prepared in ethanol solution and recrystallized from 50% ethanol; m. p. 162–163°.

Anal. Calcd. for $C_{23}H_{22}N_4O_7$: N, 12.01. Found: N, 12.16.

Oxidation of the 2-Stilbazole Derivative to the Corresponding 2-Pyridinecarboxylic Acid.—A stream of oxygen containing approximately 5% ozone was passed at 3 l. per hour through 50 ml. of carbon tetrachloride containing 4.1 g. of the stilbazole derivative; the mixture was maintained at 0°. Ozonization was stopped when the odor of ozone became evident in the effluent gas. A solution of 2 g. of sodium hydroxide and 10 ml. of 30% hydrogen peroxide in 20 ml. of water was added and the carbon tetrachloride was distilled off. The solution remaining was heated on a steam-cone for half an hour, cooled, and extracted with ether. The aqueous layer was then acidified to a *p*H of 2.0 and extracted with ether to remove the benzoic acid produced. The aqueous solution was then adjusted to a *p*H of 6.5 and the acid converted to the copper salt which was obtained after washing with water, and drying *in vacuo* over phosphorus pentoxide in a yield of 1.5 g. (40%); m. p. 256–257°.

Anal. Calcd. for $Cu(C_{10}H_{12}NO_2)_2 \cdot 1H_2O$: N, 6.40. Found: N, 6.54.

The acid was liberated in water by means of hydrogen sulfide; the mixture was filtered and the filtrate concentrated under reduced pressure. Even after prolonged drying *in vacuo* over phosphorus pentoxide, 6-isopropyl-3-methyl-2-pyridinecarboxylic acid proved to be a colorless, viscous, hygroscopic liquid which did not crystallize even at −35°. In ferrous sulfate solution it produced a yellow color characteristic of 2-pyridinecarboxylic acid derivatives.

Decarboxylation of the 2-Pyridinecarboxylic Acid.—The 2-pyridinecarboxylic acid derivative (1.2 g.) was heated in a small distilling flask. Decarboxylation was appreciable at 150° and at 180° there was a vigorous evolution of carbon dioxide. When distilled, the residue yielded 515 mg. (56%) of 2-isopropyl-5-methylpyridine which distilled at 181–183° (742 mm.).

The **picrate**, recrystallized from ethanol, melted at 113–114°.

Anal. Calcd. for $C_{15}H_{16}N_4O_7$: N, 15.38. Found: N, 15.29.

Oxidation of the $C_9H_{13}N$ Base.—The $C_9H_{13}N$ base (490 mg.) was suspended in water and the mixture was stirred and heated on a steam-cone while a 2% potassium permanganate solution was added in small portions. After two days of this procedure approximately 6 moles of po-

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[9] Melting points corrected.

[10] Prepared by permanganate oxidation of 5-ethyl-2-methylpyridine.

[11] Shaw and Wagstaffe, *J. Chem. Soc.*, 79 (1933).

tassium permanganate per mole of the base had been consumed. The excess permanganate was decolorized with formic acid and the mixture heated to 75° and filtered. The acid was precipitated as the copper salt and liberated in hot water by means of hydrogen sulfide. The copper sulfide was filtered off and the filtrate yielded 32 mg. (5.4%) of white crystals which melted at 258° after recrystallization from water. A mixed melting point with an authentic sample of 2,5-pyridinedicarboxylic acid showed no depression.

Anal. Calcd. for $C_7H_5NO_4$: N, 8.39. Found: N, 8.50.

Experimental

A $C_{10}H_{15}N$ base has been isolated from California petroleum. By a series of degradation reactions it has been shown to be 2,3-dimethyl-6-isopropylpyridine.

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[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC AND PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF BUDAPEST, HUNGARY]

On Disalicylideneacetone and Analogs

BY PETER T. MORA[1] AND TIBOR SZÉKI

It is well known that *o*-hydroxy aromatic aldehydes will condense with acetone and other ketones to form compounds structurally related to the anthocyanidins and to the dicoumarins. It was suggested[2,3,4] that the mechanism of the condensation involves, in the case of equimolar proportions of acetone and salicylaldehyde, an unsaturated intermediate, *viz.*, *o*-hydroxystyryl methyl ketone. The condensation of salicylaldehyde and various homologs with some ketones in alkaline solution has now been studied in detail. This work is part of a program to study the anticoagulant and antibacterial activity of compounds of related structure.

Salicylaldehyde (2 moles) reacts with 1 mole of acetone and certain other ketones in the presence of sodium hydroxide furnishing the disodium salt of disalicylideneacetone (I, X = Na, X′ = Na).[5,6,7] Under acidic conditions or when the above disodium salt is subsequently treated with dilute acids, colored substituted benzopyrylium salts (II) are formed and these have been isolated as the chloride,[2,7,8] sulfate[7] and perchlorate.[8] Treatment of the disodium salt (I, X = Na, X′ = Na) with carbon dioxide resulted in the elimination of the sodium as sodium carbonate and a phenolic compound was obtained which was assumed formerly to have the structure I (X = H, X′ = H), *i.e.*, 2,2′-dihydroxydistyryl ketone. Dehydration of this compound or of the benzopyrylium salts (II) derived from it, yielded the same diphenospiropyran (IV)[7,9] the structure of which is known. Whilst the literature[5,7,10,11] describes the free phenolic disalicylideneacetone as 2,2′-dihydroxydistyryl ketone (I, X = H, X′ = H) there is some evidence in analogous cases[3,8,10] that ring closure to a 2-chromenol of the type III structure can occur, the resulting compound being a monophenol. The same or a similar substance is formed also by neutralization of the corresponding benzopyrylium derivatives (II).

Methylation of this free phenolic disalicylideneacetone with methyl iodide resulted in the formation of a dimethyl ether (I, X = CH_3, X′ = CH_3), *i.e.*, the ring, if present, had been opened. Similarly, attempts to acetylate, benzoylate or to form an oxime from the initial phenolic substance resulted in the "open" form, giving a diacetate and a dibenzoate (I, X = Ac, X′ = Ac; X = Bz, X′ = Bz) and an oxime.

On the other hand, methylation with diazomethane produced a sirupy monomethyl ether which when treated with sodium hydroxide, yielded a crystalline monosodium salt (I, X = Na, X′ = CH_3). Also, the initial monomethyl ether could be converted into crystalline monobenzoyl and mono-*p*-nitrobenzoyl derivatives.

This result shows that there is some difference in the reactivity of the two hydroxyl groups in the molecule. Because the carbonyl group is located in any reasonable molecular model close to one of the hydroxyl group, this difference can be interpreted as a result of some interaction between these two groups. However, the methods employed are not capable of giving an unequivocal solution in the problem of selecting a simple structure for this tautomeric substance.

The disodium salt of I treated with carbon dioxide under controlled conditions afforded a crystalline monosodium salt. Methylation of the latter with methyl iodide resulted in the same monosodium salt monomethyl ether (I, X = Na, X′ = CH_3) as was obtained from diazomethane methylation of III and it yielded the same benzoyl or *p*-nitrobenzoyl derivatives.

It was found that fusion above the m. p. or distillation *in vacuo* of the free disalicylidene-

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[1] Department of Chemistry, Princeton University, Princeton, New Jersey.

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[3] Heilbron and Buck, *J. Chem. Soc.*, 1500 (1921).

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