203. 4-n-*Propyl-picolinic and -pipecolinic Acids. Limitations of the Wibaut–Arens Reaction with α-Substituted Pyridine Derivatives.*

By W. Solomon.

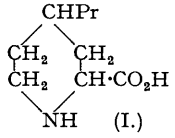
The preparation is described of 4-n-*propylpicolinic acid* (II) from 4-*n*-propylpyridine in four stages. It furnishes on reduction 4-n-*propylpipecolinic acid* (I). The failure is recorded of attempts to introduce the *n*-propyl group by the Wibaut–Arens reaction (*Rec. Trav. chim.*, 1941, **60**, 119; 1942, **61**, 59) into the 4-position of the pyridine nucleus of eight α-substituted pyridine derivatives, thus pointing to the generalisation that α-substituted pyridine derivatives, unlike pyridine itself, cannot be alkylated by this method.

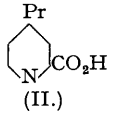
In the course of work proceeding in these laboratories it became necessary to obtain 4-n-*propylpipecolinic acid* (I). The most attractive method appeared to be the introduction of the propyl group into the 4-position of the pyridine nucleus in picolinic acid (III; R = CO_2H) using the Wibaut–Arens reaction (*loc. cit.*), followed by the reduction of the resulting acid (II). As this proved unsuccessful, attention was next turned to the possibility of introducing the propyl group into other α-substituted pyridine derivatives (III) in which R might be a group subsequently convertible into carboxyl.

Apart from picolinic acid itself (III; R = CO_2H) seven other substances were tried, namely (III; R = Me, CO_2Et, $CO{\cdot}NH_2$, CN, CH:CHPh, NH_2, and Cl), but in no case could a propyl derivative of the starting material be isolated from the products of the reaction.

The Wibaut–Arens reaction (compare *Ann. Reports*, 1941, **38**, 223; 1943, **40**, 163) is based on an original

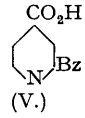
observation of Dohrn and Horsters (G.P. 390,333/1922; *Chem. Zentr.*, 1924, ii, 891) that pyridine and α-picoline on treatment with zinc dust and acetic anhydride are converted in fair yield into the respective 4-ethyl derivatives. The Dutch workers showed that analogous reactions occurred with other fatty acid anhydrides, and thus added a new, valuable method to the few unsatisfactory ones hitherto available for the preparation of 4-alkylpyridine derivatives; however, they restricted their study to unsubstituted pyridine itself. On the other hand, Dohrn and Horsters (*loc. cit.*) not only describe the preparation of 2-methyl-4-ethylpyridine from α-picoline as already stated, but lay general claim to the applicability of the reaction to " pyridine homologues." In view of the present author's results with eight α-substituted pyridine derivatives (including α-picoline) using propionic anhydride, the German claim that α-picoline could be converted into 2-methyl-4-ethylpyridine was re-examined by causing α-picoline to react with zinc dust and acetic anhydride under a variety of conditions, which included (*a*) those described in the patent, (*b*) those worked out by Wibaut and Arens for pyridine and acetic anhydride, as well as (*c*) other variations devised by the author. In no case could the desired product be isolated. More than half the picoline remained unchanged, while the greater part of the remainder became converted into high-boiling or even non-volatile, viscous material. Essentially similar results were obtained in the series of eight experiments with propionic anhydride already mentioned.


(I.)


(II.)


(III.)


(IV.)


(V.)

2-Aminopyridine (III; R = NH_2) was exceptional in its inertness, the only observable reaction being propionation: on hydrolysis the substance was recovered unchanged in almost quantitative yield. α-Stilbazole (III; R = CH:CHPh) underwent some reduction to the known 2-2′-phenylethylpyridine (III; R = $CH_2 \cdot CH_2Ph$), while 2-chloropyridine (III; R = Cl) suffered some dehalogenation. Most of the reaction mixtures were complex and it cannot be asserted that none contained any of the desired product, only that none could be isolated. It seems therefore that the patent claim is unfounded, its specific example irreproducible, and that, unlike pyridine itself, α-substituted pyridine derivatives cannot successfully be alkylated in the 4-position by means of the Wibaut–Arens reaction.

Other attempts to prepare 4-propylpicolinic acid by direct methods included some experiments on the introduction of suitable hydrocarbon residues into the 2-position in 4-propylpyridine either by means of Grignard reagents and lithium compounds, or directly. The styryl radical could not be introduced, but 2-*benzyl*-4-n-*propylpyridine* (IV; R = CH_2Ph) was prepared by the direct interaction of 4-propylpyridine with benzyl chloride in the presence of copper-bronze at 250° (cf. Maier-Bode and Altpeter, " Das Pyridin und seine Derivate," Wilhelm Knapp, 1934, p. 39). However, on oxidation with permanganate in hot aqueous acid solution, this furnished 2-*benzoyl*isonicotinic acid (V).

4-*Propylpicolinic acid* was finally obtained in orthodox fashion by a longer route from 4-propylpyridine. The latter, prepared from pyridine, propionic anhydride, propionic acid, and zinc dust by the method of Arens and Wibaut (*loc. cit.*), gave with sodamide the 2-*amino*-derivative (IV; R = NH_2) which, with nitrous and hydrobromic acids in the presence of bromine (cf. Craig, *J. Amer. Chem. Soc.*, 1934, **56**, 231), furnished 2-*bromo*-4-n-*propylpyridine* (IV; R = Br). The cyano-analogue (IV; R = CN) was obtained in an impure condition by distillation with cuprous cyanide (cf. Craig, *loc. cit.*; Tyson, *ibid.*, 1939, **61**, 184; McElvain and Goese, *ibid.*, 1941, **63**, 2283; Gilman and Spatz, *ibid.*, p. 1556). 2-*Chloro*-4-n-*propylpyridine* (IV; R = Cl) could not be made to react with cuprous cyanide. Finally, the crude cyano-compound was hydrolysed to the acid by boiling with hydrochloric acid. On catalytic hydrogenation in glacial acetic acid at atmospheric pressure at *ca.* 50°, using Adams's platinic oxide catalyst, 4-propylpicolinic acid slowly absorbed three molecules of hydrogen and furnished 4-*n*-propylpipecolinic acid (I).

Experimental.

2-*Benzyl*-4-*propylpyridine* (IV; R = CH_2Ph).—4-*n*-Propylpyridine (11·0 g.), benzyl chloride (9·9 g.), and copper-bronze powder (0·1 g.) were heated in a sealed tube at 250° for 7 hours. After cooling, there was no sign of pressure on opening the tube. The contents, a dark, viscous oil containing some crystals, were not fully soluble either in ether or in water, or in dilute or concentrated hydrochloric acid, but dissolved satisfactorily in a 2-phase mixture of ether and moderately concentrated hydrochloric acid. The two layers were separated, and the aqueous layer repeatedly extracted with more ether. In this way there was removed in the ether 0·5 g. of dark extraneous matter. The aqueous acid layer was made alkaline with sodium hydroxide, and then yielded on extraction with ether 14·05 g. of an almost black, mobile oil, which, on distillation at 18 mm., furnished a middle fraction (6·56 g.), boiling mainly at 175—190°. On re-distillation the 2-*benzyl*-4-*propylpyridine* boiled mainly at 203°/35 mm. (Found: N, 6·9. $C_{15}H_{17}N$ requires N, 6·6%). The *picrolonate* separated from acetone in yellow crystals, m. p. 171—176° (Found: N, 14·9. $C_{15}H_{17}N,C_{10}H_8O_5N_4$ requires N, 14·7%).

2-*Benzoyl*isonicotinic *Acid* (V).—2-Benzyl-4-propylpyridine (1 g.) in a little dilute sulphuric acid was treated at the boil with portions of a solution of potassium permanganate (5 g.) in water (*ca.* 75 c.c.). This occupied 3·5 hours, and more sulphuric acid was added from time to time to maintain a strongly acid reaction. The total sulphuric acid used was 12·5 g. At first the permanganate was rapidly reduced, and the solution remained colourless. Later portions were attacked more slowly and gave a permanent brown precipitate of manganese dioxide which, at the end of the reaction, was filtered off hot and washed with hot water. It weighed 2·5 g., so that 10·6 atoms of oxygen were consumed. The colourless, strongly acid filtrate was extracted with ether to yield 0·64 g. of crystalline solid which was recrystallised twice from alcohol and finally from ethyl acetate. M. p. 225—230°. 2-*Benzoyl*isonicotinic *acid* is also

soluble in acetone and dioxan, but almost insoluble in hot water, benzene, or chloroform. It dissolves sparingly in aqueous sodium carbonate or dilute hydrochloric acid, but readily in concentrated acid and in aqueous caustic alkali. It gives no colour reaction with ferric chloride (Found: C, 68·8; H, 4·2; N, 6·2. $C_{14}H_9O_3N$ requires C, 68·7; H, 4·0; N, 6·2%).

2-*Amino*-4-n-*propylpyridine* (IV; R = NH_2).—(Cf. "Organic Reactions," John Wiley & Sons, 1942, Vol. 1, p. 91.) (All apparatus was dried and appropriately protected against ingress of water.) Good quality sodamide powder (36·3 g.), xylene (distilled over sodium) (80 c.c.), and three ½-inch stainless steel ball-bearings were placed in a round-bottomed 3-necked, 500 c.c. "Quickfit" flask, which was then corked and gyrated slowly and uniformly for 6 hours about a central axis inclined to the vertical. At the end of this operation the sodamide suspension was like an emulsion. 4-*n*-Propylpyridine (97·3 g.) and a further 60 c.c. of xylene were then rapidly introduced and the flask fitted with a mercury-seal stirrer, a reflux condenser, and a thermometer reaching nearly to the bottom. The mixture turned red in the cold. The flask was heated in a metal-bath at *ca.* 140°, with stirring, the xylene being kept just below the boil (internal temperature 130—135°). The reaction is exothermic, and the internal temperature rose for a short time to a point a little higher than that of the bath. Ammonia and hydrogen were evolved, and the mixture became dark brown, thickened, and deposited some tarry matter. After 12 hours the cooled contents, a stiff black paste, were thinned out with ether and poured on ice. The resulting liquid was acidified with hydrochloric acid and the ethereal layer re-extracted with acid. The combined acid extracts were made alkaline with sodium hydroxide and the precipitated base transferred to ether. This material (116 g.) on distillation at 30 mm. gave a middle fraction (83·5 g.), b. p. 125—220°, but mainly *ca.* 150°, which crystallised in the receiver. The purity of this material was adequate for use as an intermediate (yield, 76·4%). Further quantities of this product, as well as unchanged propylpyridine, were recoverable from the first (low-boiling) fraction. On re-distillation, pure 2-*amino*-4-n-*propylpyridine* was obtained. It is highly deliquescent and difficult to handle and analyse. M. p. 37—47°; b. p. 151—156°/29 mm., 145—150°/20 mm. (Found: C, 69·7; H, 8·6; N, 21·05. $C_8H_{12}N_2$ requires C, 70·6; H, 8·9; N, 20·6%). The *picrate*, from acetone, has m. p. 199—201° (Found: C, 46·1; H, 4·4. $C_8H_{12}N_2,C_6H_3O_7N_3$ requires C, 46·0; H, 4·1%). The *acetyl* derivative separates from petroleum (b. p. 60—80°) in glistening needles, m. p. 74—75°, b. p. *ca.* 200°/37 mm. (Found: C, 67·45; H, 8·1. $C_{10}H_{14}ON_2$ requires C, 67·4; H, 7·9%).

2-*Chloro*-4-n-*propylpyridine* (IV; R = Cl).—To a solution of 2-amino-4-propylpyridine (4·5 g.) in concentrated hydrochloric acid (6·5 c.c.) cooled to − 17°, was added in portions powdered sodium nitrite (3·5 g.). Gas was evolved, some crystals deposited, and the liquid turned orange-yellow. The product was isolated by means of ether after adding ice and making alkaline with 25% sodium hydroxide. Yield, 3·9 g.; b. p. 130—132°/30 mm. (Found: C, 61·7; H, 6·5; Cl, 22·7. $C_8H_{10}NCl$ requires C, 61·7; H, 6·5; Cl, 22·8%).

2-*Bromo*-4-n-*propylpyridine* (IV; R = Br).—To a solution of 2-amino-4-propylpyridine (41·4 g.) in 60% hydrobromic acid (115 c.c.), cooled to − 17° and mechanically stirred, bromine (46 c.c., 143·5 g.), previously cooled to 0°, was added dropwise. A dark red precipitate was produced which was kept dispersed by stirring. During the later stages of the bromine addition the precipitate dissolved again. An ice-cold solution of sodium nitrite (52·5 g.) in water (80 c.c.) was then added at such a rate that the internal temperature could be kept at *ca.* 0°. Stirring was continued for a further hour. The mixture was then made alkaline with ice-cold 25% aqueous sodium hydroxide, the temperature being prevented from rising above *ca.* 20°. Extraction with ether furnished 58·3 g. of an oil which on distillation furnished 53·7 g. (88·3% of the theory) of 2-*bromo*-4-n-*propylpyridine*. For analysis, the oil was distilled again, the main bulk having b. p. 133—135°/19 mm. (Found: Br, 39·9. $C_8H_{10}NBr$ requires Br, 39·9%).

2-*Cyano*-4-n-*propylpyridine* (IV; R = CN) *and* 4-n-*Propylpicolinic Acid* (II).—The conversion of 2-bromo-4-*n*-propylpyridine into the corresponding cyano-compound requires the most careful control if a reasonable yield is to be obtained. The product always contains unchanged bromo-compound which cannot be wholly removed by fractionation. The crude product (containing about 20% of bromo-compound) was hydrolysed to 4-propylpicolinic acid and the 2-bromo-4-propylpyridine recovered. The reaction was carried out as follows: 2-Bromo-4-propylpyridine and ⅔ of its weight of dried cuprous cyanide, in a distillation flask connected to a condenser and receiver, were agitated and very gently heated with a small flame until a black homogeneous oil formed. When the temperature of the oil reached about 120° a vigorous reaction suddenly set in. At this moment the system was evacuated as rapidly as possible to about 20 mm. and the products of reaction distilled briskly. The crude distillate was redistilled once and then hydrolysed by boiling under reflux for 7 hours with 2 vols. of hydrochloric acid (17%). The product was basified, extracted with ether (to recover 2-bromo-4-propylpyridine which was reprocessed), reacidified, neutralised with ammonia, and treated with copper sulphate solution in slight excess. Crude *copper* 4-*propylpicolinate* separated as a bluish-grey precipitate (yield 80 g. from 160 g. of bromo-compound; 40·9% of theory); it forms large brilliant blue needles from alcohol, m. p. 305° (decomp.) and is almost insoluble in water, acetone, or chloroform [Found: C, 55·2; H, 5·2; Cu, 15·45. $(C_9H_{10}O_2N)_2Cu$ requires C, 55·2; H, 5·1; Cu, 16·2%]. The free *acid* was obtained by passing hydrogen sulphide for many hours through a boiling suspension of the finely powdered copper salt (42 g.) in 50% alcohol (1200 c.c.); the copper sulphide thus formed was colloidal and, after evaporation of the alcohol, was removed by a twice repeated treatment of the boiling solution with charcoal (2 g.), followed by filtration through kieselguhr. The filtrate on evaporation left a crystalline residue (36·3 g.) which after several crystallisations from acetone formed colourless pyramids, m. p. 104—107° (Found: C, 65·6; H, 6·7; N, 8·45. $C_9H_{11}O_2N$ requires C, 65·4; H, 6·7; N, 8·5%).

4-n-*Propylpipecolinic Acid* (I).—The foregoing acid in acetic acid solution at *ca.* 50°, and in the presence of highly active Adams's platinic oxide catalyst, absorbs hydrogen at atmospheric pressure slowly, and the absorption is liable to tail off unless periodically reactivated either by the addition of more catalyst or by flushing the system with oxygen. 4-Propylpicolinic acid (29 g.) in glacial acetic acid (250 c.c.) was reduced under the conditions stated in the presence of 1·4 g. of catalyst. Total absorption, 11·8 l. at N.T.P.; calc. for substance and 1·4 g. catalyst, 12·0 l. The catalyst was filtered off, the acetic acid removed under reduced pressure, and the crystalline residue triturated with ethyl acetate. On filtering, a solid was obtained, which still smelled of acetic acid, even after much washing with ethyl acetate in which it is almost insoluble. The acetic acid was driven off by drying for several hours at 110°; the 4-n-*propylpipecolinic acid* so obtained (yield amost quantitative) separated from alcohol in gleaming white felted needles, m. p. 284° (decomp.) after softening. It is soluble in water, alcohol, benzene, and chloroform, but very sparingly in ether, ethyl acetate, or acetone (Found: C, 62·9; H, 9·9; N, 8·25. $C_9H_{17}O_2N$ requires C, 63·1; H, 10·0; N, 8·2%). The N-*benzoyl* derivative prepared by the method of Steiger (*J. Org. Chem.*, 1944, **9**, 396) is an oil which, on esterification with methyl alcohol and hydrogen chloride, furnished *methyl* N-*benzoyl*-4-n-*propylpipecolinate*, a straw-coloured, viscous oil, b. p. 190°/0·2 mm., 232—234°/16 mm., and 244—246°/25·5 mm. (Found: C, 70·7; H, 8·35. $C_{17}H_{23}O_3N$ requires C, 70·55; H, 8·0%).

The author is much indebted to Messrs. A. W. Stokes and H. Waddington, and his thanks are due to A. Bennett for the microanalyses.

THE WELLCOME LABORATORIES OF TROPICAL MEDICINE, LONDON, N.W.1 [*Received, April 5th,* 1946.]