1004. *Condensation of Ethyl 2- and 4-Pyridylacetate with Aromatic Carbonyl Compounds.*

By D. R. Bragg and D. G. Wibberley.

Ethyl 2- and 4-pyridylacetate have been caused to react with a series of aromatic aldehydes in ethanol with piperidine as a catalyst. The normal product was an α-pyridylcinnamate, but *o*-aminobenzaldehyde yielded 3-pyridylquinolin-2-ols and salicylaldehyde yielded 3-pyridylcoumarins. Benzaldehyde has also been condensed with ethyl 2- and 4-pyridylacetate methiodides, the product from the former salt being a derivative of ethyl *cis*-cinnamate; the *trans*-isomer has been obtained by the action of methyl iodide on ethyl α-2′-pyridylcinnamate.

Attempts to condense aromatic ketones with ethyl 2- and 4-pyridylacetate failed, but the methiodide of the latter ester with *o*-aminoacetophenone produced 4-methyl-3-4′-pyridylquinolin-2-ol methiodide.

Ethyl 2- and 4-pyridylacetate have been known since 1936, and methods are available for their preparation in good yield from the corresponding picolines. In spite of this, and of the numerous examples in the literature concerning the condensations of 2- and 4-picolines [1] and of their methiodides, little work appears to have been carried out on the condensations of pyridylacetates with aldehydes or ketones. The only such reactions known to the authors are the condensation by Kakimoto *et al.*[2] of ethyl 4-pyridylacetate with benzaldehyde in the presence of acetic anhydride to yield ethyl α-4′-pyridylcinnamate and that by Hartmann and Bosshard [3] of the sodio-derivative of ethyl 3-pyridylacetate with benzaldehyde to yield ethyl α-3′-pyridylcinnamate. It is well known [4] that whereas 2- and 4-picoline with benzaldehyde give good yields of styrylpyridines only in the presence of acetic anhydride or zinc chloride as catalyst, the corresponding methiodides give excellent yields of the styrylpyridine methiodides by treatment with the aldehyde in boiling alcohol in the presence of piperidine. Roberts [5] suggested that reaction occurs on incipient ionisation of a hydrogen atom of the methyl group. This explains why milder conditions suffice for the methiodides since quaternisation facilitates proton release. Aromatic aldehydes having a strong electron-attracting group in the *ortho*- or *para*-position give better yields than does benzaldehyde in reactions with 2- or 4-picoline but in the piperidine-catalysed reactions of the methiodides, *o*- and *p*-nitrobenzaldehyde, for example, give slightly smaller yields than benzaldehyde; *p*-dimethylaminobenzaldehyde, on the other hand, gives excellent yields with the quaternary salts.[6] Phillips [7] suggested that the dominating factor in condensations involving methiodides is the structure of the final product. He has shown that where the product can be written as a resonating ion in which a major contribution to stability could reasonably be expected from the styryl portion of the molecule, then this product is obtained in excellent yield.

We prepared ethyl 2-pyridylacetate by the method of Woodward and Kornfeld,[8] and ethyl 4-pyridylacetate by Hey and Wibaut's method.[9] In the present work we have shown that these esters condense with aromatic aldehydes in alcohol in presence of piperidine as catalyst, to yield ethyl α-2′- and -4′-pyridylcinnamate. However, aromatic aldehydes having a substituent capable of reaction with the ethoxycarbonyl group gave

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[1] Elderfield, " Heterocyclic Compounds," Wiley, New York, 1950, Vol. I, p. 493.
[2] Kakimoto, Nishie, and Yamamoto, *J. Tuberculosis*, 1959, **7**, 76.
[3] Hartmann and Bosshard, *Helv. Chim. Acta*, 1941, **24**, 28.
[4] Ref. 1, p. 496.
[5] Roberts, *Chem. and Ind.*, 1947, 658.
[6] Doja, *J. Indian Chem. Soc.*, 1940, **17**, 347; 1942, **19**, 125.
[7] Phillips, *J. Org. Chem.*, 1947, **12**, 333.
[8] Woodward and Kornfeld, *Org. Synth.*, 1949, **29**, 44.
[9] Hey and Wibaut, *Rec. Trav. chim.*, 1953, **72**, 525.

cyclised products. Thus *o*-aminobenzaldehyde formed 3-2′- and -4′-pyridylquinolin-2-ol, a reaction which may be regarded as an example of the Friedländer synthesis of quinolin-2-ols; and salicylaldehyde yielded 3-2′- and 3-4′-pyridylcoumarin, which may be regarded as a modification of the Perkin coumarin synthesis. The yields varied with the substituents in the aldehyde molecule, being in the sequence 2-OH $>$ 4-NMe_2 $>$ H $>$ 2-NH_2 $>$ 4-NO_2 $>$ 2-NO_2, and, with each aldehyde, ethyl 4-pyridylacetate gave a better yield than its 2-isomer. Quaternisation of ethyl 4-pyridylacetate before reaction with *o*-aminoacetophenone afforded 4-methyl-3-4′-pyridylquinolin-2-ol methiodide, where previously no reaction had occurred. The same procedure, however, was not successful with the 2-isomer and neither acetophenone nor *o*-hydroxyacetophenone reacted with ethyl 2- or 4-pyridylacetate or with their methiodides. Quaternisation of the esters before reaction with benzaldehyde did not increase the yields.

From the experiments it may be deduced that electron attraction by the ethoxycarbonyl group increases the incipient ionisation of the methylene group in the pyridylacetic esters to such an extent that the reactions proceed well under the influence of piperidine as catalyst.

Both the *cis*- and the *trans*-form of ethyl α-2′-pyridylcinnamate methiodide have been obtained. Methyl iodide and ethyl α-2′-pyridylcinnamate gave an isomer of the product from benzaldehyde and ethyl 2-pyridylacetate methiodide; the former has a lower m. p. and the principal peak in its ultraviolet absorption curve is at a shorter wavelength, suggesting that the aromatic rings are not co-planar (cf. Braude *et al.*[10]) and this isomer is ethyl *trans*-α-2′-pyridylcinnamate, (*i.e.*, *trans*-cinnamate but *cis*-styrylpyridine).

Horwitz [11] noted a similar phenomenon in condensations of quinaldinium salts with a series of aldehydes, which yield *trans*-2-styrylquinolinium salts having main absorption peaks in the ultraviolet spectra at wavelengths 25—75 mμ longer than those of the *cis*-2-styrylquinolinium salts obtained by condensation of quinaldine with the same aldehydes followed by quaternisation with the appropriate halide or methosulphate. It is unlikely that reaction with methyl iodide affects the configuration of ethyl α-2′-pyridylcinnamate and so it must be assumed that it also has the *trans*-cinnamate configuration.

The bulky methiodide group in ethyl 2-pyridylacetate methiodide has forced a *cis*-cinnamate configuration in its condensation product with benzaldehyde. No such steric effect obtains in ethyl 4-pyridylacetate methiodide and only one isomer, presumably the *trans*-cinnamate, has been obtained by both methods. In the formation of the quinolinols it is not necessary to postulate that *cis*- or *trans*-α-2′-pyridylcinnamates are first formed since cyclisation of the intermediate aldol followed by loss of water from the resulting 3,4-dihydro-4-hydroxyquinolinols and 3,4-dihydro-4-hydroxycoumarins would give the same products.

EXPERIMENTAL

General Procedure for Condensation of Ethyl 2- and 4-Pyridylacetate or their Methiodides with Carbonyl Compounds.—The pyridylacetic ester, or its methiodide (0·01 mol.), the carbonyl compound (0·012 mol.), piperidine (0·5 g.), and ethanol (10·0—15·0 ml.) were refluxed together for 17—18 hr. or, in the case of salicylaldehyde, until the bumping caused by the separated solid became prohibitive. Liquid products were isolated by distillation, and solid products by filtration, after evaporation of the solution to half bulk. Where no crystallisation occurred under these conditions, it was induced in most cases by trituration with water and acetone or alcohol, except for methiodides for which dry ether was used.

Ethyl trans-*α-2′-Pyridylcinnamate.*—Ethyl 2-pyridylacetate and benzaldehyde yielded *ethyl* trans-*α-2′-pyridylcinnamate* (46%), b. p. 160—161°/1·0 mm. (Found: C, 75·9; H, 6·0; N, 5·6. $C_{16}H_{15}NO_2$ requires C, 75·9; H, 6·0; N, 5·5%).

Ethyl α-4′-Pyridylcinnamate.—Ethyl 4-pyridylacetate and benzaldehyde yielded ethyl α-4′-pyridylcinnamate (75%), b. p. 175—176°/2·3 mm. (Found: C, 76·2; H, 6·0; N, 5·6%).

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[10] Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890.

[11] Horwitz, *J. Amer. Chem. Soc.*, 1955, **77**, 1687.

Kakimoto *et al.*[2] obtained the oil in 52% yield, b. p. 190°/3·0 mm., by condensation of the same reactants in the presence of acetic anhydride.

Ethyl trans-*α-2'-Pyridylcinnamate Methiodide.*—Ethyl *trans*-α-2'-pyridylcinnamate (0·4 g.) and methyl iodide (5·0 ml.) were refluxed together on the water bath for 2 hr. The mixture was evaporated to give the trans-2-*methiodide* (0·62 g., 100%), m. p. 200—201° (decomp.), which crystallised from ethanol in yellow needles, m. p. 200—201° (decomp.), $\lambda_{max.}$ (in EtOH) 272 mμ (log ε 4·39) (Found: C, 51·9; H, 4·9; N, 3·7. $C_{17}H_{18}INO_2$ requires C, 51·7; H, 4·6; N, 3·8%).

Ethyl cis-*α-2'-Pyridylcinnamate Methiodide.*—Ethyl 2-pyridylacetate methiodide, m. p. 81—82° [prepared in quantitative yield by refluxing (2·0 hr.) ethyl 2-pyridylacetate and methyl iodide], and benzaldehyde yielded the cis-2-*methiodide* (35%) which crystallised from ethanol as pale yellow needles, m. p. 227—228° (decomp.), $\lambda_{max.}$ (in ethanol) 331 mμ (log ε 4·17) (Found: C, 51·9; H, 4·3; N, 3·8%). The mixed m. p. with the *trans*-2-methiodide was 192—196°.

Ethyl α-4'-Pyridylcinnamate Methiodide.—(*a*) Ethyl α-4'-pyridylcinnamate (1·2 g.) and methyl iodide (10·0 ml.) were refluxed on the water bath for 2 hr. to give the 4-*methiodide* (1·87 g., 100%), m. p. 195—197° (decomp.), which separated from ethanol as bright yellow prisms, m. p. 197—198° (decomp.), $\lambda_{max.}$ (in EtOH) 262 mμ (log ε 4·13) (Found: C, 52·0; H, 4·6; N, 3·5%).

(*b*) Ethyl 4-pyridylacetate methiodide (prepared in quantitative yield), m. p. 103—104°, with benzaldehyde yielded the 4-methiodide (42%) which crystallised from ethanol as bright yellow prisms, m. p. 197—198° (decomp.) alone and on admixture with the product from (*a*) (Found: C, 51·5; H, 4·6; N, 3·7%).

Ethyl p-*Dimethylamino-α-2'-pyridylcinnamate.*—Ethyl 2-pyridylacetate and *p*-dimethylaminobenzaldehyde yielded *ethyl* p-*dimethylamino-α-2'-pyridylcinnamate* (76%), which crystallised from aqueous acetone as deep yellow needles, m. p. 127—128° (Found: C, 73·2; H, 6·6; N, 9·5. $C_{18}H_{20}N_2O_2$ requires C, 72·9; H, 6·8; N, 9·45%).

Ethyl 4-pyridylacetate and *p*-dimethylaminobenzaldehyde yielded *ethyl* p-*dimethylamino-α-4'-pyridylcinnamate* (89%), which crystallised from aqueous ethanol as deep yellow needles, m. p. 101—102° (Found: C, 73·5; H, 7·0; N, 9·4%).

Ethyl 2-Nitro-α-4'-pyridylcinnamate Hydrochloride.—Ethyl 4-pyridylacetate reacted with *o*-nitrobenzaldehyde in the normal manner. The resulting brown solution was evaporated to dryness and stirred with a mixture of dilute hydrochloric acid and chloroform. Basification of the acidic layer gave only a slight precipitate but evaporation of the chloroform layer gave a semi-solid residue from which the *hydrochloride* (4·2%) was isolated by trituration with acetone. Crystallisation from acetone–ethanol gave needles, m. p. 183—184° (decomp.) (Found: Cl, 10·7; N, 8·5. $C_{16}H_{15}ClN_2O_4$ requires Cl, 10·6; N, 8·4%).

A similar condensation with *p*-nitrobenzaldehyde gave the corresponding 4-*nitro-hydrochloride* (13%) as needles (from acetone), m. p. 147—149° (decomp.) (Found: Cl, 10·6; N, 8·4%). *p*-Nitrobenzaldehyde (80%), m. p. 105—106°, was recovered.

3-2'-*Pyridylquinolin*-2-*ol.*—Ethyl 2-pyridylacetate and *o*-aminobenzaldehyde yielded 3-2'-*pyridylquinolin*-2-*ol* (30%) which crystallised from ethanol as needles, m. p. 236—237°, $\lambda_{max.}$ (in EtOH) 300 mμ, 351 mμ (log ε 4·07, 4·04) (Found: C, 75·7; H, 4·4; N, 12·8%; equiv., 220. $C_{14}H_{10}N_2O$ requires C, 75·7; H, 4·5; N, 12·7%; equiv., 222). By addition of water to the mother liquor an unidentified by-product (0·6 g.) was obtained which crystallised from alcohol as needles, m. p. 137—138°.

3-4'-*Pyridylquinolin*-2-*ol.*—Ethyl 4-pyridyl acetate and *o*-aminobenzaldehyde yielded 3-4'-*pyridylquinolin*-2-*ol* (44%) which crystallised from aqueous ethanol as needles, m. p. 234—235°, $\lambda_{max.}$ (in EtOH) 294, 349 mμ (log ε 4·15, 4·01) (Found: C, 75·7; H, 4·6; N, 12·8%; equiv., 218). The mixed m. p. with the 2-isomer was 218—224°. By addition of water to the mother liquor a by-product (0·55 g.) was obtained which crystallised from ethanol as needles, m. p. 137—138° alone and on admixture with the by-product above.

4-*Methyl*-3-4'-*pyridylquinolin*-2-*ol Methiodide.*—Ethyl 4-pyridylacetate methiodide and *o*-aminoacetophenone yielded 4-*methyl*-3-4'-*pyridylquinolin*-2-*ol methiodide* (17%) which crystallised from aqueous ethanol as pale yellow needles, m. p. 315—316° (decomp.) (Found: C, 50·6; H, 3·9; N, 7·7. $C_{16}H_{15}IN_2O$ requires C, 50·8; H, 4·0; N, 7·4%).

3-2'-*Pyridylcoumarin.*—Ethyl 2-pyridylacetate and salicylaldehyde in 7 hr. at the b. p. yielded 3-2'-*pyridylcoumarin* (75%), which crystallised from ethanol as needles, m. p. 141—142° (Found: C, 75·3; H, 4·1; N, 6·2%; equiv., 227. $C_{14}H_9NO_2$ requires C, 75·35; H, 4·1; N, 6·3%; equiv., 223).

3-4′-*Pyridylcoumarin.*—Ethyl 4-pyridylacetate and salicylaldehyde in 2 hr. at the b. p. yielded 3-4′-*pyridylcoumarin* (94%) which crystallised from ethanol as needles, m. p. 228—229° (Found: C, 75·4; H, 4·2; N, 6·3%, equiv., 214).

The authors are indebted to Professor G. R. Clemo for suggestions which initiated the work.

PHARMACY DEPARTMENT, SUNDERLAND TECHNICAL COLLEGE,
SUNDERLAND, CO. DURHAM.

[*Received, June 5th,* 1961.]