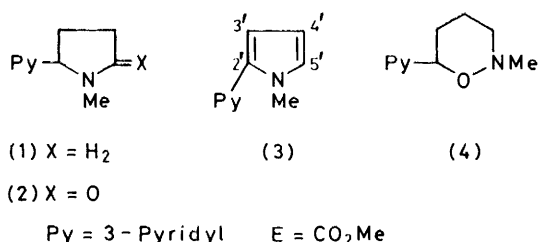


Addition Reactions of Heterocyclic Compounds. Part 70.¹ Formation of Quinolizines and Indolizines from Nicotine Derivatives and Acetylenic Esters

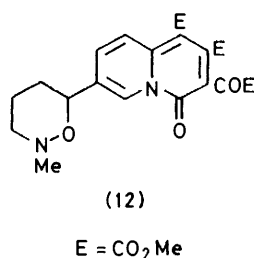
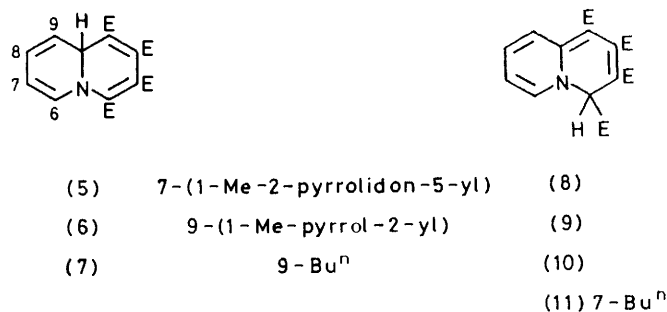
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Cotinine and other nicotine derivatives have been converted to 9a*H*- and 4*H*-quinolizines by dimethyl acetylenedicarboxylate, while cotinine itself by a series of steps has yielded 6-(1-methyl-5-oxopyrrolidin-2-yl)indolizine.

As pyridines give many novel products with dimethyl acetylenedicarboxylate,² the reactions of this ester with nicotine (1), nicotyrine (3) from the dehydrogenation of nicotine,³ cotinine (2) from the oxidative bromination and debromination of nicotine,⁴ and the oxazine (4) from the rearrangement⁵ of nicotine 1'-oxide, were examined in the hope of obtaining compounds with interesting biological properties.⁴



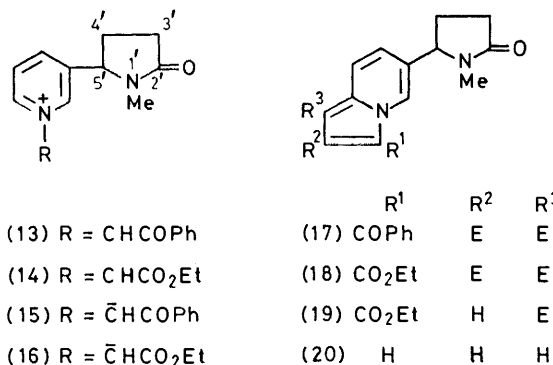
No identifiable products were obtained from nicotine and it is probable that the acetylene first attacked the pyrrolidine nitrogen atom, in the same way as it reacts with triethylamine,⁶ causing ring scission and formation of an unresolvable mixture. Cotinine (2) and nicotyrine (3), and 3-*n*-butylpyridine from the hydrogenolysis⁷ of nicotine, gave respectively the 9a*H*-quinolizines (5)–(7), and in the case of the butylpyridine also the 4*H*-



isomer (11), which were all identified by comparison of their u.v. and ¹H n.m.r. spectra with those of corresponding quinolizines from 3-methylpyridine.^{8,9} The 9a*H*-quinolizines (5)–(7) all isomerised on heating to the corresponding 4*H*-isomers (8)–(10), presumably by a [1,5] sigmatropic shift,¹⁰ and were identified by spectral comparisons with other 4*H*-quinolizines.⁸ It is interesting that it was possible to isolate (5), for other 9a*H*-quinolizines unsubstituted at positions 6 or 9 isomerise to the 4*H*-isomers during attempted isolation.²

With dimethyl acetylenedicarboxylate the oxazine (4), the proposed⁵ structure for which was confirmed by its n.m.r. spectrum, gave as the only solid the 4*H*-quinolizone (12), an analogue of 'Kashimoto's compound' (methyl 1,2-dimethoxycarbonyl-4-oxoquinolizine-3-glyoxylate) and formed in the same way.¹¹

In the hope of converting the pyridine ring of nicotine into the indolizine system, cotinine (2) was chosen as the starting material in order to avoid difficulties arising from electrophilic attack at the more basic pyrrolidine nitrogen atom of nicotine. Cotinine (2) with phenacyl



bromide, followed by sodium hydride, gave the ylide (15). This, using Boekelheide and Fahrenholtz's procedure,¹² was converted by dimethyl acetylenedicarboxylate in the presence of palladium-charcoal to the indolizine (17). In a similar way the ester (14) yielded the indolizine (18) but in poor yield. As hydrolysis and acidification of indolizine-1,2,3-tricarboxylic esters usually removes the 1- and 3-substituents only,^{12,13} the ylide (16) was treated with methyl propiolate to give (19). This diester on alkaline hydrolysis followed by refluxing with concentrated hydrochloric acid did give some of the desired indolizine (20), but the compound rapidly darkened on exposure to light and turned blue in chloroform solution,

TABLE 1

¹H N.m.r. spectra measured at 60 MHz (τ values, J in Hz) using tetramethylsilane as internal reference

Compound	Solvent	Proton resonances
(4)	CCl ₄	2-H, 1.54d; 4-H, 2.50; ^a 5-H, 2.94q; ^b 6-H, 1.63q; 2'-Me, 7.50; 3',4',5'-H ₆ , 7.0—8.9m; 6'-H, 5.30q; $J_{2,4}$ 2; $J_{4,5}$ 7.5; $J_{4,6}$ 1.7; $J_{5,6}$ 5.0; $J_{5,6'}$ 10, 2.8
(5)	CDCl ₃	6-H, 3.70d; 8,9-H ₂ , 3.9—4.2m; 9a-H, 5.17t; 1'-Me, 7.28d; 3',4',5'-H ₅ , 7.0—8.2m; (OMe) ₄ 6.01, 6.11, 6.19, 6.28; $J_{9,9a} \approx J_{8,9a} \approx 2$
(6) ^c	CDCl ₃	6-H, 3.65q; 7-H, 3.99q; 8-H, 3.87; ^d 9a-H; 5.35d; 1'-Me, 6.74; 3'-H, 4.10q; 4'-H, 4.01q; 5'-H, 3.39q; (OMe) ₄ , 6.14, 6.21, 6.32, 6.38; $J_{6,7}$ 7.2; $J_{6,8}$ 0.5; $J_{7,8}$ 6.2; $J_{8,9a}$ 1.7; $J_{3',4'}$ 3.9; $J_{3',5'}$ 1.7; $J_{4',5'}$ 2.6
(7) ^c	CDCl ₃	6-H, 3.78d; 7-H, 8-H, 4.05—4.35m; 9-CH ₃ (CH ₂) ₂ CH ₂ , 8.3—8.9m; 9-PrCH ₂ , 7.95m; 9a-H, 5.13; ^e $J_{6,7}$ 7.5; (OMe) ₄ 6.09, 6.09, 6.27, 6.29
(8)	CDCl ₃	4-H, 4.06; 6,8-H ₂ , 2.6—2.8m; 9-H, 1.36d; 1'-Me, 7.32; ^e 3',4',5'-H ₅ , 7.2—7.8m; (OMe) ₄ , 6.14, 6.27, 6.31, 6.33; $J_{8,9}$ 9
(9)	CDCl ₃	4-H, 3.85; 6-H, 2.55q; ^f 7-H, 3.06t; 8-H, 2.32q; ^f 1'-Me, 6.93; 3',4'-H ₂ , 3.83d; ^g 5'-H, 3.36t; ^g (OMe) ₄ , 6.07, 6.22, 6.28, 6.48; $J_{6,7}$ 8; $J_{6,8}$ 1; $J_{7,8}$ 6; $J_{3',5'} \approx J_{4',5'} \approx 2$
(10)	CDCl ₃	4-H, 3.94; 6-H, 2.43d; ^f 7-H, 3.06q; 8-H, 2.33d; ^f 9-CH ₃ (CH ₂) ₃ , 8.9—9.1m; 9-CH ₃ (CH ₂) ₂ CH ₂ , 8.2—8.9m; 9-PrCH ₂ , 7.35t; ^e J 8 + 8; (OMe) ₄ 6.12, 6.29, 6.35, 6.35; $J_{6,7}$ 8; $J_{7,8}$ 6
(11) ^h	CDCl ₃	4-H, 3.95; 6,8-H ₂ , 2.4—2.7m; 7-CH ₃ (CH ₂) ₂ CH ₂ , 9.06t; 7-CH ₃ (CH ₂) ₂ CH ₂ , 8.2—8.9mm; 7-PrCH ₂ , 7.50t, J 7; 9-H, 1.36d; (OMe) ₄ , 6.07, 6.22, 6.24, 6.27; $J_{8,9}$ 9
(12) ^c	CDCl ₃	6-H, 0.62q; 8-H, 2.03q; 9-H, 1.23q; 2'-Me, 7.34; 3',4',5'-H ₆ , 6.8—8.5m; 6'-H, 5.02q; J 9 + 2; (OMe) ₃ , 6.08, 6.08, 6.14; $J_{6,8}$ 1; $J_{6,9}$ 0.5; $J_{8,9}$ 9.3
(13)	D ₂ O	1-CH ₂ , 3.42s; 2,6-H ₂ , 0.97m; 4,5-H ₂ and 2,6-H ₂ of C ₆ H ₅ , 1.73m; Ar-H ₃ , 2.25m; 1'-CH ₃ , 7.21s; 3',4'-H ₄ , 2.89m; 5'-H, 4.84m
(17)	CDCl ₃	1-CO ₂ CH ₃ , 6.71; 2-CO ₂ CH ₃ , 6.13; 3-C ₆ H ₅ CO, 3.4m; 5-H, 0.39; ^e 7-H, 2.82d; 8-H, 1.55d; 1'-Me, 7.30; 3',4'-H ₄ 7.66m; 5'-H, 5.41m; $J_{5,7}$ 1; $J_{7,8}$ 9
(18)	CDCl ₃	1-CO ₂ CH ₃ , 6.07; 2-CO ₂ CH ₃ , 6.00; 3-CO ₂ CH ₂ CH ₃ , 5.62q; 3-CO ₂ CH ₂ CH ₃ , 8.61t, J 7.2; 5-H, 0.41; ^e 7-H, 2.66d; 8-H, 1.57d; 1'-Me, 7.29; 3',4'-H ₄ , 7.5m; 5'-H, 5.40m; $J_{5,7}$ 1; $J_{7,8}$ 9.0
(19)	CDCl ₃	1-CO ₂ CH ₃ , 6.10; 2-H, 2.04; 3-CO ₂ -CH ₂ CH ₃ , 5.59q; 3-CO ₂ CH ₂ CH ₃ , 8.59t, J 6.6; 5-H, 0.46; ^e 7-H, 2.83d; 8-H, 1.62d; 1'-Me, 7.30; 3',4'-H ₄ , 7.26—8.3m; 5'-H, 5.40m; $J_{5,7}$ 1; $J_{7,8}$ 9.0
(20)	CDCl ₃	1-H, 3.62m; 2-H, 3.23q; 3-H, 2.69; 5-H, 2.18; 7-H, 3.58m; 8-H, 6.63d; 1'-Me, 7.33; 3',4'-H ₂ , 7.3m; 5'-H, 4.32m; $J_{1,2}$ 4; $J_{1,3}$ 1; $J_{2,3}$ 3.2; $J_{5,7}$ 1; $J_{7,8}$ 10

^a 6 lines. ^b Some additional splitting. ^c Also at 100 MHz. ^d 8 lines. ^e Broad. ^f These assignments could be interchanged. ^g Apparent. ^h At 100 MHz.

like some other unstable indolizines.¹⁴ The structures of these indolizines were established from comparisons of their n.m.r. spectra with those of other indolizines,^{15,16}

but reduction of the cotinine analogue (20) to the corresponding nicotine has not been achieved.

EXPERIMENTAL

Instruments and chromatographic and general procedures have been described.¹ Evaporation refers to the removal of volatile material at 15 Torr using a Büchi apparatus. Analyses for new compounds are within accepted limits for C, H, and N (Table 6) and along with the u.v. (Table 3), mass (Table 4), and i.r. spectra (Table 5) are available in Supplementary Publication No. SUP 22620 (5 pp).*

The Quinolizines (5)—(12).—The nicotine derivatives, in dry acetonitrile were added to dimethyl acetylenedicarboxylate (2 equiv.) in acetonitrile at 0 °C. After 4 h at 0 °C the volatile material was evaporated off at 18 °C and the residue in benzene–chloroform chromatographed on deactivated alumina. The solid products were recrystallised from methanol and are described in Table 2.

TABLE 2

Compounds from DMAD and pyridine derivatives

Product	M.p. (°C)	Yield (%)
(5)	124—125	1.7
(6)	109—110	6.3
(7)	88—89	3.4
(8) ^b	112—115	
(9) ^a	135—138	
(10) ^d	153—155	
(11) ^c	164—167	0.6
(12) ^e	158—160	8.1

^a From (6) by heating to 50 °C in benzene for 6 h followed by chromatography on Al₂O₃ and recrystallisation from MeOH. ^b As for *a* but starting from (5). ^c Eluted after (7) from column. ^d From (7) by refluxing in benzene for 7 h, followed by recrystallisation from MeOH. ^e Recrystallisation from MeOH after 6 months at 0 °C.

3-(1-Methyl-5-oxopyrrolidin-2-yl)-1-phenacylpyridinium Bromide (13).—1-Methyl-5-(3-pyridyl)-2-pyrrolidone (2) (8.1 g), phenacyl bromide (9.2 g), and dichloromethane (150 ml) were refluxed for 2 h. The solvent was evaporated off and the residue recrystallised from ethanol–ether to give the bromide (13) (15.6 g, 90%), m.p. 141.5—143°.

Dimethyl 3-Benzoyl-6-(1-methyl-5-oxopyrrolidin-2-yl)-indolizine-1,2-dicarboxylate (17).—Sodium hydride (0.44 g) was added to a stirred solution of 3-(1-methyl-5-oxo-2-pyrrolidinyl)-1-phenacylpyridinium bromide (13) (5.4 g) in dry dimethylformamide (DMF) (50 ml). The mixture was stirred for 10 min and cooled (ice–salt bath) during the addition of dimethyl acetylenedicarboxylate (3.1 g) in dry DMF (10 ml). After stirring for 2 h, water (10 ml) was added and the mixture evaporated. Water (50 ml) and chloroform (100 ml) were added to the residue, and the organic phase and further extracts (2 × 200 ml) of the aqueous phase were combined, dried, and evaporated. The residue solidified on trituration with toluene, and recrystallisation from methanol–ether gave the diester (17) (1.6 g), m.p. 215°.

1-(Ethoxycarbonylmethyl)-3-(1-methyl-5-oxopyrrolidin-2-yl)pyridinium Bromide (14).—1-Methyl-5-(3-pyridyl)-2-pyrrolidone (2) (21.6 g), ethyl bromoacetate (20.5 g), and dichloromethane (250 ml) were refluxed for 16 h. Evaporation gave a dark oil (41.9 g) which was homogeneous on t.l.c. The n.m.r. spectrum also showed no significant impurities. The product was used without purification.

* For details of the Supplementary Publication scheme see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1978, Index issue.

3-Ethyl 1,2-Dimethyl 6-(1-Methyl-5-oxopyrrolidin-2-yl)-indolizine-1,2,3-tricarboxylate (18).—Sodium hydride (1.4 g) was added to a stirred solution of the bromide (14) (10.0 g) in dry DMF (50 ml). After 10 min, dimethyl acetylenedicarboxylate (4.4 g) in DMF (20 ml) was added to the cooled mixture. Work-up was as for (17) except that the dried chloroform solution was chromatographed on deactivated alumina (600 g, made up in chloroform). Elution with chloroform gave polymerised DMAD followed by the triester (18) which was recrystallised from toluene-hexane, m.p. 148–149° (1.2 g).

3-Ethyl 1-Methyl 6-(1-Methyl-5-oxopyrrolidin-2-yl)indolizine-1,3-dicarboxylate (19).—Potassium carbonate (5.95 g) was added to a stirred solution of the bromide (14) (14.8 g) in dry DMF (50 ml). The solution was stirred for 1 h at room temperature before the addition of methyl propiolate (7.2 g)¹⁷ in dry DMF (20 ml). The mixture was stirred for 2 h and worked up as before. Chromatography of the products on deactivated alumina gave the diester (19) as crystals from toluene-hexane (6.7 g), m.p. 176–178°.

6-(1-Methyl-5-oxopyrrolidin-2-yl)indolizine (20).—Sodium hydroxide (16.0 g) in water (20 ml) was added to a solution of the diester (19) (2.0 g) in methanol (60 ml). After refluxing for 4 h the solution was cooled and made strongly acid with hydrochloric acid. The mixture was brought to pH 10 with sodium carbonate and then extracted with chloroform (2 × 100 ml). The dried extracts were evaporated and the product was recrystallised from toluene-hexane to give as colourless crystals the indolizine (20) (200 mg), m.p. 133–134°, which turned blue on exposure to light.

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