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UNUSUAL [3+2]-CYCLOADDITION OF ACRYLIC ACID DERIVATIVES TO 7-FORMYL-4,5,6,7-TETRAHYDRO-4,5,7-TRIMETHYLPYRROLO[3,2-*c*]-PYRIDINE UNDER MICHAEL REACTION CONDITIONS

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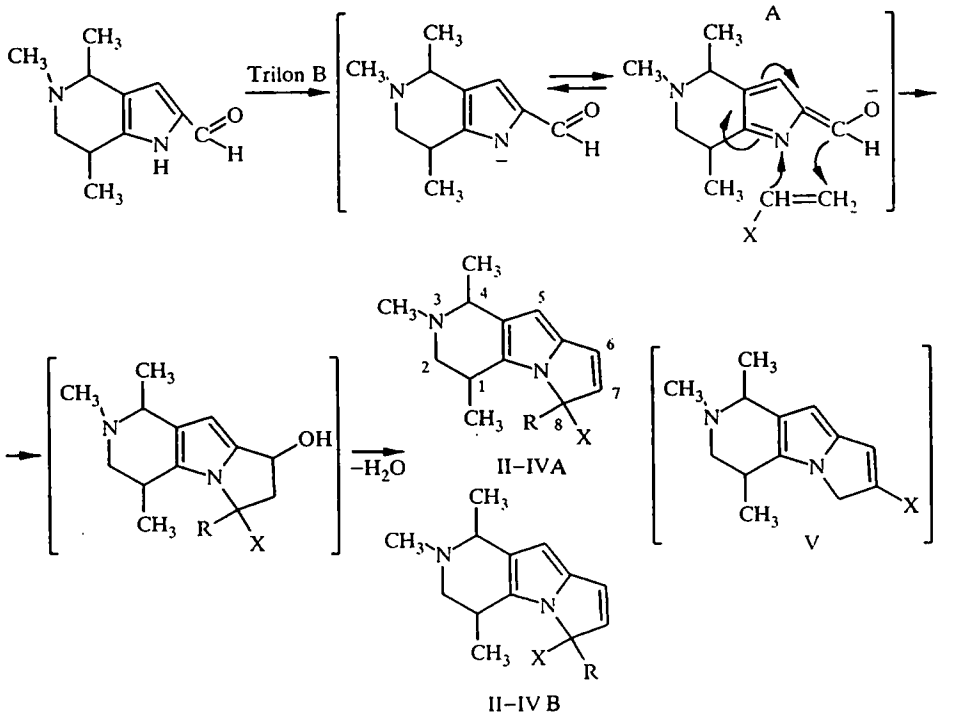
8-Substituted tetrahydropyrido[3,2-*e*]pyrrolizines are formed in the [3+2]-cycloaddition of 2-formyltetrahydropyrrolo[3,2-*c*]pyridine and acrolein, acrylonitrile, and methyl acrylate in the presence of trilon B.

Substituted and hydrogenated pyrrolizine derivatives are found as alkaloids and have strong and variegated biological activity [1, 2]. For example, mitomycin C is used in the treatment of breast cancer [3]. One of the methods of constructing the 3H-pyrrolizine ring is based on the β-R-ethylation of 2-formylpyrroles under Michael reaction conditions and subsequent cyclization of the resultant N-β-R-ethyl derivatives [4]. We attempted to use this method to construct tetrahydropyrido[4,3-*e*]pyrrolizine, a new heterocyclic system, using previously synthesized 2-formyl-4,5,6,7-tetrahydro-4,5,7-trimethylpyrrolo[3,2-*c*]pyridine [5].



II, III R = H; IV R = CH_2CH_2CN; II X = CHO; III X = CO_2CH_3; IV X = CN

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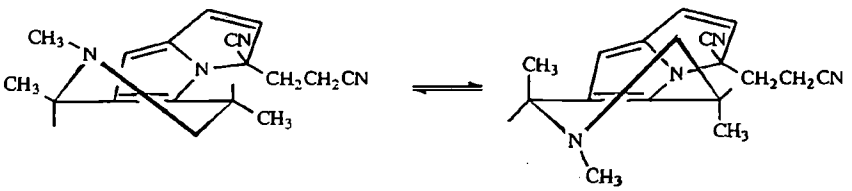
This reaction was carried out by heating the substrate in benzene at reflux in the presence of trilon B with acrolein, methyl acrylate, and acrylonitrile taken in two-fold excess as the anion acceptor. In all cases, the usual Michael reaction adducts, namely, the N-β-R-ethyl derivatives, were not formed. Products identified as 8-substituted 1,2,3,4-tetrahydropyrido[4,3-*e*]pyrrolizines II-IV were isolated in 12-20% yield.

If the products isolated result from condensation of the initial Michael reaction adducts, they should have structure V, which is not in accord to the PMR spectra. The downfield part of these spectra at 6.11-7.55 ppm is composed of three signals for protons at double bonds.

Thus, in the case of I, the reaction presumably proceeds through an anion with azafulvene structure, which is converted as the result of [3+2]-cycloaddition of the acrylic acid derivatives into a hydroxydihydropyrrolizine, whose dehydration leads to formation of II-IV. In the case of acrylonitrile, the reaction does not terminate at formation of 8-cyanopyrido[4,3-*e*]pyrrolizine, which undergoes further β-cyanoethylation at $C_{(8)}$ to give geometrical isomers IVA and IVB. This behavior is probably related to the strong electron-withdrawing effect of the CN group. Products IVA and IVB were isolated as pure compounds. GC/MS analysis indicated lack of the monoaddition products (R = H, X = CN). The IR spectra of II-IV show bands characteristic for the corresponding functional groups: 1660 cm^{-1} for CHO in II, 1710 cm^{-1} for CO_2Me in III, and 2210 cm^{-1} for CN in IVA and IVB. The keto—enol tautomerism gives rise to the band for a bound OH group at 3470 cm^{-1} in the IR spectrum of the 8-formyl derivative, II.

The PMR spectra of II-IV (Table 1) show signals for all the protons in these molecules; signals for NH protons are lacking. The PMR spectra show three signals at 6.11-7.55 ppm corresponding to 5-H-7-H in the pyrrolizine fragments. Two singlets of equal intensity are found in the spectra of II and III at 3.8-4.0 ppm, corresponding to 8-H protons with total integral intensity of 1H. This result implies formation of II and III as 1:1 mixtures of geometrical isomers relative to the arrangement of 8-R and 1-CH_3. The signals for 8-H in 3H-pyrrolizines are found at 3-4 ppm, while the signals for 6-H and 7-H are found at 6-7 ppm [6]. The presence of strong vicinal coupling between 1-H and one of 2-H protons (11.3 Hz) indicates pseudoaxial orientation of 1-H and, thus, pseudoequatorial orientation of the 1-CH_3 group. The lack of long-range $4J_{4H,2He}$ coupling indicates equatorial orientation of the 4-CH_3 group.

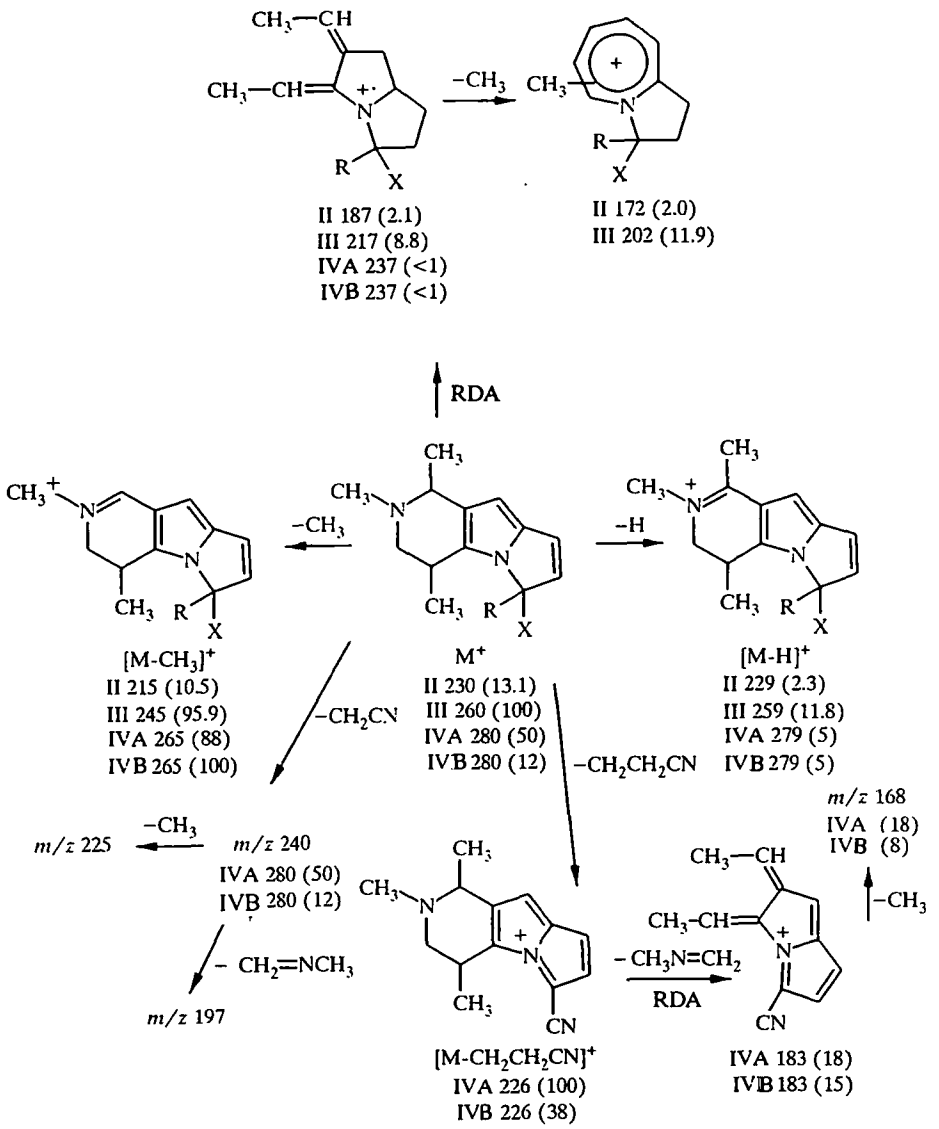
Comparison of the PMR spectra of isomers IVA and IVB indicates significant differences in the chemical shifts of the corresponding 1-H, 2-H, 4-H, 1-CH_3, and 4-CH_3 protons of the piperidine ring and methylene protons of the β-cyanoethyl fragment. The vicinal coupling constants between 1-H and 2-H also differ markedly. The spectrum of IVB lacks the strong coupling characteristic for axial—axial orientation of 1-H and one of the 2-H protons. The coupling constants for 1-H with both 2-H protons are equal; $^3J_{12}$ = 5.2 Hz. These results suggest that the bulky 8-β-cyanoethyl group and 1-CH_3 group in IVB have *cis*-orientation, which leads to deformation of the tetrahydropyridine ring as a result of steric hindrance. Rapid dynamic inversion of the piperidine ring involving a conformer with pseudoaxial orientation of the 1-CH_3 and 4-CH_3 groups cannot be excluded for IVB.



This process may account for the vicinal coupling constants of 1-H and 2-H in the spectrum of IVB.

The structures of products II-IV and exclusion of structure V were supported by ^{13}C NMR spectroscopy in the case of IVB. Three methine doublets for $C_{(5)}$, $C_{(6)}$, and $C_{(7)}$ with coupling constants $^1J_{CH}$ = 170-195 ppm and three singlets for quaternary carbons $C_{(9a)}$, $C_{(4a)}$, and $C_{(5a)}$ are found in the downfield part of the ^{13}C NMR spectrum of this isomer at 95-150 ppm characteristic for carbons with sp^2-hybridization. The singlet for $C_{(8)}$ is found at 71.34 ppm. The unusually low chemical shift of the triplet of one of the methylene carbons of the β-cyanoethylene fragment (11.57 ppm) with $^1J_{CH}$ = 133.7 Hz characteristic for the ^{13}C NMR spectrum of isomer IVB. This finding indicates steric interaction of the 1-CH_3 and 8-β-cyanoethyl groups.

The structure of II-IV is in good accord with their electron impact fragmentation. The mass spectra of these compounds show molecular ion peaks corresponding to the chemical formulas. The major decomposition channels for the M^+ ion are similar to those for tetrahydropyrrolo[3,2-*c*]pyridines [7]. The fragmentation of the molecular ions features



elimination of a CH_3 group or hydrogen from $C_{(4)}$ to give fragment ions $[M-CH_3]^+$ and $[M-H]^+$, which then undergo aromatization, losing a hydrogen or methyl group. Retro-Diels—Alder decomposition with elimination of a $CH_3N=CH_2$ group characteristic for tetrahydropyrrolo[3,2-*c*]pyridines is observed for II and III. Retro-Diels—Alder decomposition of isomers IVA and IVB occurs in the second fragmentation step from the $[M-CH_2CH_2CN]^+$ ions. The subsequent decomposition of the $[M-CH_3N=CH_2]^+$ and $[M-CH_2CH_2CN-, CH_3N=CH_2]^+$ ions features elimination of a methyl group or hydrogen atom. The presence of functional groups at $C_{(8)}$ in II and III accounts for the characteristic decomposition channels of their M^+ ions. The characteristic decomposition for II involves loss of CO and CHO to give strong fragment ions with *m/z* 202(100) and 201(80), while this process for III involves loss of CH_3O and CO_2CH_3 to give ions with *m/z* 229(9) and 201(50). The elimination of a CH_2CN fragment to give an ion with *m/z* 240 is also characteristic for decomposition of the M^+ ion of IVA and IVB. This fragment ion then loses a CH_3 group or undergoes retro-Diels—Alder decomposition. In general, the fragmentation of IVA and IVB is characterized by the same decomposition channels, while differences are observed only in the intensities of the corresponding ions. This clearly indicates that these compounds are isomers.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrophotometer for KBr pellets. The mass spectra were obtained on MKh-1303 and Kratos MS-2SFR spectrometers with direct sample inlet into the ion source. The ionizing voltage

TABLE 1. PMR Spectra of II, III, IVA and IVB in $CDCl_3$

Compound	Chemical shifts, δ, ppm (J, Hz)											
	1-H_a	2-H_a	2-H_e	4-H_a	5-H	6-H	7-H	8-H	1-CH_3	3-CH_3	4-CH_3	8-R
II	1,77 d.d.q. J_{1a2a} = 11,3 J_{1a2e} = 3,7 $J_{1a1\text{-}Me}$ = 6,7	2,26 d.d. J_{1a2a} = 11,3 J_{2a2e} = 12,5	2,88 d.d. J_{1a2e} = 3,7 J_{2a2e} = 12,5	2,94 q $J_{4a4\text{-}Me}$ = 6,7	6,33 s	6,26 d J_{67} = 0,9	7,55 d J_{67} = 0,9	3,96 s 3,94 s	1,27 d $J_{1a1\text{-}Me}$ = 6,7	2,35 s	1,42 d $J_{4a4\text{-}Me}$ = 6,7	9,71 s
III	1,73 d.d.q. J_{1a2a} = 11,3 J_{1a2e} = 3,7 $J_{1a1\text{-}Me}$ = 3,7	2,23 d.d. J_{1a2a} = 11,3 J_{2a2e} = 12,5	2,85 d.d. J_{1a2e} = 3,7 J_{2a2e} = 12,5	2,92 q $J_{4a4\text{-}Me}$ = 6,7	6,29 s	6,24 d J_{67} = 0,9	7,57 d J_{67} = 0,9	3,91 s 3,94 s	1,26 d $J_{1a1\text{-}Me}$ = 6,7	2,34 s	1,44 d $J_{4a4\text{-}Me}$ = 6,7	3,8 s
IVA	1,91 d.d.q. J_{1a2a} = 11,9 J_{1a2e} = 4,0 $J_{1a1\text{-}Me}$ = 7,0	2,38 d.d. J_{1a2a} = 1,9 J_{2a2e} = 12,8	2,80 d.d. J_{1a2e} = 4,0 J_{2a2e} = 12,8	2,96 q $J_{4a4\text{-}Me}$ = 6,4	6,40 s	6,21 d J_{67} = 0,9	7,30 d J_{67} = 0,9	—	1,12 d $J_{1a1\text{-}Me}$ = 7,0	2,34 s	1,43 d $J_{4a4\text{-}Me}$ = 6,4	$CH_aH_aCH_bH_cCN$ 1,53 (m, H_a) 2,09 (m, H_b) 2,38 (m, H_c)
IVB	2,30 t.q J_{12} = 5,2 $J_{11\text{-}Me}$ = 7,0	2,15 d.d. J_{12} = 5,2 J_{22} = 12,8	2,98 d.d. J_{12} = 5,2 J_{22} = 12,8	3,61 q $J_{44\text{-}Me}$ = 6,7	6,37 s	6,11 d J_{67} = 0,9	7,17 d J_{67} = 0,9	—	0,53 d J_{11} = 7,0	2,33 s	1,27 t $J_{44\text{-}Me}$ = 6,7	$CH_aH_bCH_cH_dCN$ 1,32 (m, H_a) 1,82 (m, H_b) 2,13 (m, H_c) 2,90 (m, H_d)

was 70 eV. The ^1H and ^{13}C NMR spectra were taken for 2% solutions (^1H NMR) and 5% solutions in $CDCl_3$ (^{13}C NMR) on a Bruker MW-400 spectrometer at 400 (^1H NMR) and 100.58 MHz (^{13}C NMR) at 20°C. Chemapol LS 5/40 alumina was used for the flash chromatography while plates coated with Alufol alumina were used for the thin-layer chromatography. The plates were developed with ion vapor.

8-Formyl-1,2,3,4-tetrahydro-1,3,4-trimethylpyrido[4,3-*e*]pyrrolizine (II). Argon was bubbled through 20 ml benzene at 45°C for 0.5 h. A solution of 0.34 g (18 mmoles) formyl derivative I in 5 ml absolute benzene and five drops of trilon B were added. After 10 min, 0.21 g (37 mmoles) acrolein was added. The mixture was left at 45°C for 9 h and monitored by thin-layer chromatography. Benzene was distilled off in vacuum. Then, 10 ml water was added and the mixture was extracted with three 20-ml portions of ether. The combined extracts were dried over magnesium sulfate. The residue (0.48 g) after removal of the ether was crystallized from a mixture of heptane and ethyl acetate to give 0.08 g (20%) yellow crystalline II, mp 118-120°C, *Rf* 0.8 (1:20 ethanol—ethyl acetate). Mass spectrum, *m/z* (I_{rel}, %): 230(M^+, 13.1), 229(2.3), 215(10.5), 187(2.1), 177(4.3), 172 (2.7), 141(10.1), 123(3.6), 122(5.0), 119(7.4), 108(8.2), 86(68), 84(100), 78(28.8), 63(28.8), 43(65). Found: C, 72.81; H, 8.01; N, 12.26%. Calculated for $C_{14}H_{18}N_2O$: C, 73.04; H, 7.82; N, 12.17%.

8-Methoxycarbonyl-1,2,3,4-tetrahydro-1,3,4-trimethylpyrido[4,3-*e*]pyrrolizine (III). A similar procedure yielded 0.07 g (13%) white crystalline III, mp 135-139°C (from hexane—ethyl acetate, dec.), *Rf* 0.8 (1:1 ethyl acetate—hexane), from 0.4 g (21 mmoles) I and 0.38 g (44 mmoles) methyl methacrylate with five drops of trilon B at 70°C over 4 h. Mass spectrum, *m/z* (I_{rel}, %): 260 (M^+, 100), 259(41.8), 245(95.9), 229(11.8), 217(8.8), 202(11.9), 130(18:2), 122(29.4), 108(29.4), 107(17.6). Found: C, 69.04; H, 7.65; N, 11.06%. Calculated for $C_{15}H_{20}N_2O_2$: C, 69.23; H, 7.63; N, 10.76%.

8-Cyano-8-β-cyanoethyl-1,2,3,4-tetrahydro-1,3,4-trimethylpyrido[4,3-*e*]pyrrolizine (IV). An analogous procedure gave 0.48 g product from 0.4 g (21 mmoles) I and 0.3 g (51 mmoles) acrylonitrile in the presence of trilon B at 80°C. Flash chromatography of the product on alumina (*H* = 3.5 cm, *d* = 4.5 cm) using 1:5 ethyl acetate—hexane as the eluent gave 0.04 g (6%) white crystalline IVB, mp 159-160°C (from hexane—ethyl acetate), *Rf* 0.6 (1:4 ethyl acetate—hexane). Mass spectrum, *m/z* (I_{rel}, %): 280 (M^+, 11), 279(3), 279(3), 265(100), 240(5), 226(38), 225(5), 224(13), 197(5), 196(8), 195(8), 183(15), 182(13), 169(7), 168(8), 167(7), 42(11). ^{13}C NMR spectrum in $CDCl_3$ (multiplicity, $^1J_{CH}$, Hz): 148.2 (s, $C_{(5a)}$), 139.9 (s, $C_{(1a)}$), 96.67 (s, $C_{(4a)}$), 121.47 (d, 192, $C_{(7)}$), 117.56 (d, 174, $C_{(5)}$), 100.96 (d, 180, $C_{(6)}$), 118.35, 116.65 (s, s, 2C≡N), 71.34 (s, $C_{(8)}$), 57.88 (d, 141, $C_{(4)}$), 55.47 (t, 134, $C_{(2)}$), 41.79 (q, 134, $CH_3N_{(3)}$), 38.49 (d, 132, $C_{(1)}$), 15.23, 14.20 (q.q, 128, 126, $CH_3C_{(4)}$, $CH_3C_{(1)}$), 11.57, 35.82 ppm (t.t, 134, 135, CH_2CH_2CN). Found: C, 72.66; H, 7.53; N, 21.0%. Calculated for $C_{17}H_{20}N_4$: C, 72.86; H, 7.14; N, 20.0%.

Then, elution with 3:1 ethyl acetate—hexane gave 0.03 g (5%) white crystalline IVA, mp 149-150°C, *Rf* 0.2 (1:1 ethyl acetate—hexane). Mass spectrum, *m/z* (I_{rel}, %): 280 (M^+, 50), 279(5), 265(88), 240(20), 226(100), 225(8), 210(15), 197(9), 196(13), 183(18), 182(11), 176(18), 169(15), 168(11), 167(13), 166(20), 42(15). Found: C, 72.44, H, 7.49; N, 20.77%. Calculated for $C_{17}H_{20}N_4$: C, 72.86; H, 7.14; N, 20.0%.

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