Reissert Compound Studies. XXXI. Emetine Analogs Based on the Reaction of the Reissert Anion with 1,3,4,6,7,11b-Hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-2-ones

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Reaction of the Reissert anion with the carbonyl group of 1,3,4,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-2-one and with 3-ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxy-11b*H*-benzo[*a*]quinolizin-2-carboxaldehyde give emetine analogs. This anion does not react with the carbonyl group of 3-alkyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-2-one but instead gives a rearrangement product and the benzoquinolizinone cyanohydrin.

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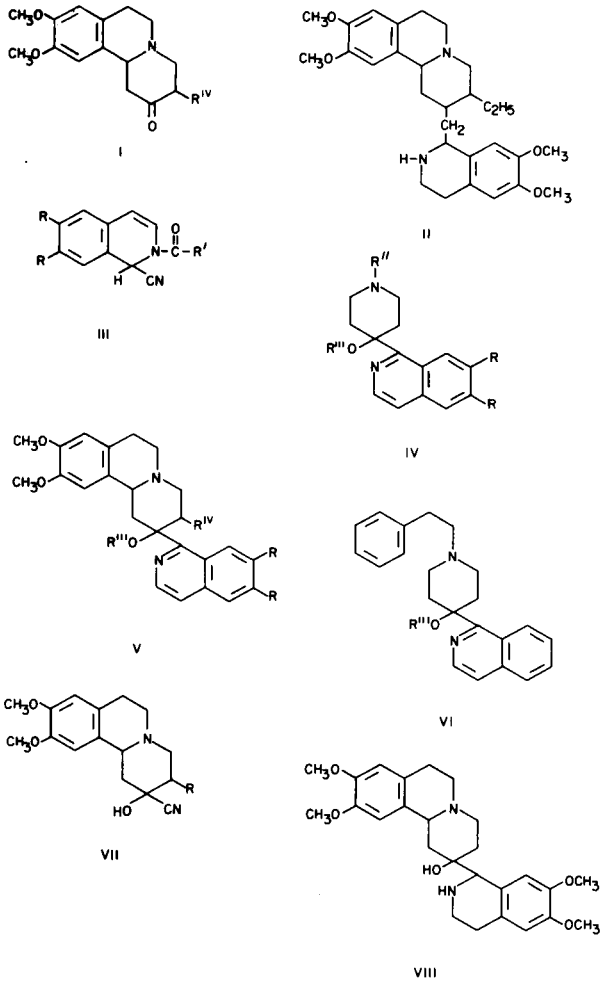
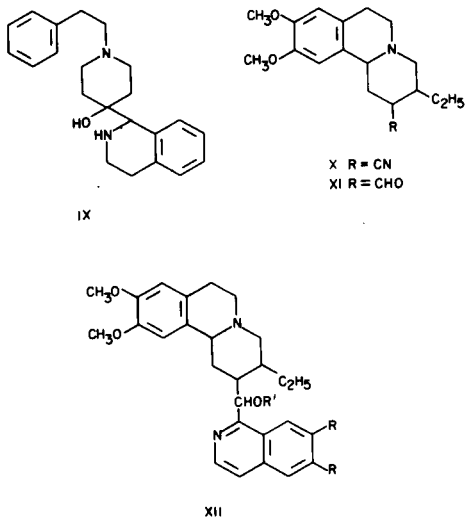
Not only is the chemistry of the 1,3,4,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-2-one ring system (I) (1) of interest in itself but it provides a convenient and attractive intermediate for the synthesis of emetine (II) and emetine analogs. In view of our demonstration (2) that the anion of 2-benzoyl-1,2-dihydroisoquinaldonitriles (III)



(Reissert compounds (3)) react with 1-substituted-4-piperidones to give esters and alcohols of the type IV (R''' = COR' or H), we felt that it would be on interest to study the reaction of the anion III with (I) to give emetine analogs (V) lacking the one carbon bridge between the benzoquinolizine and isoquinoline units. In fact, our previously reported (2) compound (VI) of the type IV derived from (1-(2-phenylethyl)-4-piperiodone could be considered such an analog.



Reaction of I (R'''' = H) with III (R' = C_6H_5, R = H) in the presence of sodium hydride proceeded smoothly to give the benzoate V (R = R'''' = H, R''' = COC_6H_5). In a similar manner, the acetyl Reissert compound (III, R' = CH_3, R = H) gave the corresponding acetate (V). In the course of preparing this latter compound an acetate of the type IV was prepared from 1-benzyl-4-piperidone. The Reissert compound derived from 6,7-dimethoxyisoquinoline also reacted with 1,3,4,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-2-one I (R'''' = H) to give V

($R = OCH_3$, $R'''' = H$, $R''' = COC_6H_5$). The esters V ($R''' = COC_6H_5$) readily underwent hydrolysis to the corresponding alcohols.

In order to obtain closer analogs of emetine lacking the methylene bridge, the reaction of the Reissert anion with the 3-ethylbenzoquinolizinone system (I, $R'''' = C_2H_5$) was attempted. The only products isolated from this reaction (4) were 1-benzoylisoquinoline and the cyanohydrin VII ($R = C_2H_5$). This cyanohydrin was identical to that obtained (5) by reaction of the hydrochloride of I ($R'''' = C_2H_5$) with sodium cyanide in water. It would thus appear that the 3-ethyl group decreased the reactivity of the ketone carbonyl (I) sufficiently so that the anion of III ($R = H$, $R' = C_6H_5$) underwent rearrangement (3) to 1-benzoylisoquinoline with the liberation of cyanide ion which in turn led to the formation of the dimethylformamide insouble cyanohydrin VII ($R = C_2H_5$). In support of this we found that I ($R'''' = C_2H_5$) and sodium cyanide react in the presence of sodium hydride-dimethylformamide to form VII ($R = C_2H_5$). When the same reaction was attempted with the 3-methyl ketone (I, $R'''' = CH_3$), the products were again 1-benzoylisoquinoline and the cyanohydrin VII ($R = CH_3$). Attempted reaction of I ($R'''' = CH_3$) with III ($R = H$, $R' = C_6H_5$) in acetonitrile with 50% sodium hydroxide and triethylbenzylammonium chloride gave over 90% recovery of unreacted I.

Although the failure of the 3-alkylbenzoquinolizinones (I) to give emetine models lacking the methylene bridge caused abandonment of this approach, some aspects of the chemistry of V ($R''' = R'''' = H$, $R = OCH_3$) and VI ($R''' = H$) were studied in a preliminary manner. Several attempts to dehydrate these alcohols by standard methods failed. In one such attempt the sulfate ester of VI was obtained. This ester was recovered unchanged from a number of attempted eliminations. Catalytic hydrogenation of these two alcohols gave VIII and IX respectively.

In an alternative approach to emetine analogs, involving similar chemistry, the nitrile X, which had been obtained (5) from I ($R'''' = C_2H_5$) by reaction with tosylmethyl isocyanide, was reduced with diisobutyl aluminum hydride to the aldehyde XI. Through a sequence similar to that noted above the anion of the Reissert compounds III ($R' = C_6H_5$; $R = H$ and OCH_3) were reacted with XI to give after hydrolysis of the benzoates, the alcohols XII ($R = H$; $R = H$ and OCH_3).

EXPERIMENTAL

2(1-Isoquinolinyl)-1,3,4,6,7,11b-hexahydro-9,10-dimethoxybenzo-[*a*]quinolizin-2-ol Benzoate (V, $R = R'''' = H$, $R''' = COC_6H_5$).

A solution of I ($R'''' = H$) (1.3 g., 0.005 mole) and 2-benzoyl-1,2-dihydroisoquinaldonitrile (III, $R = H$, $R' = C_6H_5$) (1.6 g., 0.0075 mole) in dimethylformamide (30 ml.) was treated with sodium hydride in oil (0.4 g., 0.01 mole) and stirred one hour at room temperature. The mixture was poured over ice (400 ml.), and salt added to cause flocculation. The solids were filtered, dissolved in chloroform, dried with sodium sulfate, and the chloroform evaporated to give a tan solid. The solid was chromatographed on alumina with methylene chloride and recrystallized from hexane to give 1.3 g. (52%) of V ($R = R'''' = H$, $R''' = COC_6H_5$), m.p. 113-116°; ir (potassium bromide): 1720 cm^{-1}; nmr δ 8.6 (m, 2H), 8.2 (m, 2H), 7.5 (m, 7H), 6.7 (d, 2H), 3.9 (s, 6H), 3.7-1.0 (m, 11H).

Anal. Calcd. for $C_{31}H_{30}N_2O_4$: C, 75.32; H, 6.07; N, 5.66. Found: C, 75.08; H, 6.29; N, 5.15.

2(1-Isoquinolinyl)-1,3,4,6,7,11b-hexahydro-9,10-dimethoxybenzo-[*a*]quinolizin-2-ol Acetate (V, $R = R'''' = H$, $R''' = COCO_3$).

A solution of I ($R'''' = H$) (2.6 g., 0.01 mole) and 2-acetyl-1,2-dihydroisoquinaldonitrile (III, $R = H$, $R' = CH_3$) (2.1 g., 0.011 mole) in dimethylformamide (75 ml.) was treated with 50% sodium hydride in oil (0.5 g., 0.012 mole) and stirred at room temperature for one hour. The mixture was poured over ice and filtered. Recrystallization from hexane gave 2.6 g. (60%) of V ($R = R'''' = H$, $R''' = COCH_3$), m.p. 180-182°; ir (potassium bromide): 1725 cm^{-1}.

Anal. Calcd. for $C_{26}H_{28}N_2O_4$: C, 72.27; H, 6.48. Found: C, 72.26; H, 6.44.

Synthesis of IV ($R = H$, $R'' = CH_2C_6H_5$, $R''' = COCH_3$).

Using the above procedure, 1-benzyl-4-piperidone and III ($R = H$, $R' = CH_3$) gave a 70% yield of IV ($R = H$, $R'' = CH_2C_6H_5$, $R''' = COCO_3$), m.p. 148-150° (from methanol); ir (potassium bromide): 1705, 110 cm^{-1}.

Anal. Calcd. for $C_{23}H_{24}N_2O_2$: C, 76.68; H, 6.66. Found: C, 76.55; H, 6.68.

2(1-(6,7-Dimethoxyisoquinolinyl))-1,3,4,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-2-ol Benzoate (V, $R = OCH_3$, $R''' = COC_6H_5$, $R'''' = H$).

A solution of the ketone I ($R'''' = H$) (2.6 g., 0.01 mole) and 2-benzoyl-1,2-dihydro-6,7-dimethoxyisoquinaldonitrile (III, $R = OCH_3$, $R' = C_6H_5$) (3.2 g., 0.015 mole) in dimethylformamide (40 ml.) was treated with sodium hydride 50% in oil (0.7 g., 0.015 mole) and stirred one hour at room temperature. The mixture was poured over ice and filtered to give a white solid. The solid was dissolved in chloroform and dried over magnesium sulfate. The dried chloroform solution was chromatographed on a silica gel column and recrystallized from hexane to give 3.0 g. (54%) of V ($R = OCH_3$, $R''' = COC_6H_5$, $R'''' = H$), m.p. 141-143°; ir (potassium bromide): 1720 cm^{-1}.

Anal. Calcd. for $C_{33}H_{34}N_2O_6$: C, 71.50; H, 6.13; N, 5.05. Found: C, 71.90; H, 6.40; N, 5.05.

2(1-Isoquinolinyl)-1,3,4,6,7,11b-hexahydro-9,10-dimethoxybenzo-[*a*]quinolizin-2-ol (V, $R = R''' = R'''' = H$).

A solution of the ester (V, $R'''' = R = H$; $R''' = COC_6H_5$) (1.5 g., 0.003 mole) in ethanol (50 ml.) and water (50 ml.) was treated with potassium hydroxide (4 g.) and refluxed one hour. The ethanol was distilled and the solution cooled and filtered to give a brown solid. The solid was chromatographed on silica gel with acetone and recrystallized from benzene-hexane to give 1.3 g. (93%) of V ($R = R''' = R'''' = H$), m.p. 184-185°; ir (potassium bromide): 3200, 1125 cm^{-1}; nmr: δ 8.8 (s, 1H), 8.41 (d, 1H), 7.61 (m, 4H), 6.5 (d, 2H), 4.1 (s, 1H), 3.8 (d, 6H), 3.6-1.5 (m, 11H).

Anal. Calcd. for $C_{24}H_{26}N_2O_3$: C, 73.86; H, 6.66; N, 7.18. Found: C, 73.90; H, 6.60; N, 7.09.

2-(1-(6,7-Dimethoxyisoquinolinyl))-1,3,4,5,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-2-ol (V, R'''' = R''' = H, R = OCH_3).

A solution of the ester (V, R'''' = H, R = OCH_3, R''' = COC_6H_5) (2.5 g., 0.0045 mole) in ethanol (50 ml.) was added to a solution of potassium hydroxide (4.0 g.) in water (50 ml.) and refluxed one hour. The ethanol was removed by distillation, the solution cooled and filtered to give after recrystallization from isopropanol, 1.5 g. (75%) of V (R'''' = R''' = H, R = OCH_3), m.p. 113-115°; ir (potassium bromide): 3400 cm^{-1}; nmr: δ 7.7 (s, 1H), 7.4 (d, 2H), 7.0 (s, 1H), 6.5 (s, 1H), 4.0 (d, 6H), 3.9 (s, 3H), 3.8 (s, 3H), 3.1-2.2 (m, 13H); ms: m/e (%) 451 (4), 450 (10), 338 (8), 266 (23), 265 (100), 232 (52), 220 (14), 219 (69), 218 (14), 206 (40), 205 (35), 192 (12), 190 (13), 44 (15), 43 (17), 37 (27), 34 (38), 28 (42), 18 (46), 17 (46).

Anal. Calcd. for $C_{26}H_{30}N_2O_5$: C, 69.35; H, 6.66; N, 6.22. Found: C, 69.01; H, 6.62; N, 6.19.

3-Ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-2-one Cyanohydrin (VII, R = C_2H_5).

A solution of I, (R'''' = C_2H_5) (2.89 g., 0.01 mole) and 2-benzoyl-1,2-dihydroisoquinaldonitrile (III, R = H, R′ = C_6H_5) (3.2 g., 0.15 mole) in dimethylformamide (40 ml.) was treated with 50% sodium hydride in oil (1.0 g., 0.022 mole) and stirred one hour at room temperature. The mixture was poured over ice and filtered. The precipitate was dissolved in chloroform and the dried chloroform solution was evaporated to give after chromatography the starting ketone (I, R'''' = C_2H_5) and 1-benzoylisoquinoline. After standing at room temperature for an additional three days, the filtrate deposited 1.5 g. of colorless crystals, m.p. 118-120° (from benzene-hexane); ir (potassium bromide): 3400 cm^{-1}; nmr: δ 6.8 (d, 2H), 4.0 (d, 6H), 3.8-1.4 (m, 13H), 1.2 (m, 3H); ms: m/e (%) 316 (3), 315 (3), 289 (65), 288 (100), 260 (15), 246 (65), 232 (10), 205 (35), 191 (88), 190 (32), 176 (35), 55 (18), 42 (20), 28 (50), 27 (45), 26 (44), 18 (45).

Anal. Calcd. for $C_{18}H_{24}N_2O_3$: C, 68.37; H, 7.59; N, 8.86. Found: C, 68.32; H, 7.57; N, 8.78.

A solution of the ketone I (R'''' = C_2H_5) (2.3 g., 0.008 mole) and sodium cyanide (0.75 g., 0.015 mole) in dimethylformamide (20 ml.) was treated with sodium hydride 50% in oil (0.5 g., 0.011 mole) and stirred one hour at room temperature. The mixture was poured into water (200 ml.) and allowed to stand at room temperature for 5 days. Filtration yielded 1.75 g. of the cyanohydrin VII (R = C_2H_5). Mixed melting point with the compound reported above, showed no depression, and the two samples were identical spectroscopically. Both samples were also identical with the cyanohydrin obtained (5) by reaction of I (R'''' = C_2H_5) hydrochloride with sodium cyanide in water.

3-Methyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-2-one Cyanohydrin (VII, R = CH_3).

A solution of the ketone (I, R = CH_3) (2.75 g., 0.01 mole) and 2-benzoyl-1,2-dihydroisoquinaldonitrile (III, R = H, R′ = C_6H_5) (3.0 g., 0.012 mole) in dimethylformamide (30 ml.) was treated with 50% sodium hydride in oil (0.5 g., 0.011 mole) and stirred one hour at room temperature. The mixture was poured over ice and filtered to give a brown gum which was dissolved in chloroform, dried, and chromatographed on silica gel giving 1-benzoylisoquinoline, identified by comparison of its infrared spectrum with that of a known sample, (1.1 g.) and unreacted ketone (I, R = CH_3) (0.25 g.). After one week the filtrate deposited 2.75 g. of yellow needles (VII, R = CH_3), m.p. 140-143° (from benzene-hexane); ir (potassium bromide): 3300, 2210 cm^{-1}.

Anal. Calcd. for $C_{17}H_{22}N_2O_3$: N, 9.27. Found: N, 9.27.

1-(2-Phenylethyl)-4-(1-isoquinolinyl)-piperidine-4-ol Sulfate Ester (VI, R''' = SO_3H).

1-(2-Phenylethyl)-4-(1-isoquinolinyl)-piperidine-4-ol (VI, R''' = H) (2) (2.5 g.) was dissolved in concentrated sulfuric acid (10 ml.) and heated on a steambath for 30 minutes. The solution was cooled, ice was added and it was made alkaline with ammonium hydroxide. A white solid was filtered, m.p. 298°; ir (potassium bromide): 3350, 1150 cm^{-1}.

Anal. Calcd. for $C_{22}H_{24}N_2O_4S \cdot H_2O$: C, 61.40; H, 6.04; N, 6.50. Found: C, 61.61; H, 5.88; N, 6.36.

2-(1-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolinyl))-1,3,4,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-2-ol (VIII).

A solution of V (R''' = R'''' = H, R = OCH_3) (0.5 g.) in 1*N* sulfuric acid (20 ml.) was refluxed 3.5 hours and cooled. A white precipitate formed and was filtered. The precipitate was dissolved in methanol-water, platinum oxide (0.2 g.) added and the mixture shaken under 40 pounds of hydrogen pressure overnight. The catalyst was filtered and methanol removed *in vacuo*. The aqueous solution was made basic with 15% sodium hydroxide and extracted with chloroform. The chloroform extracts were dried and evaporated to give at tan solid. Recrystallization from petroleum ether gave 0.4 g. (78%) of VIII, m.p. 108-110°; ir (potassium bromide): 3350 cm^{-1}; nmr: δ 6.6 (m, 4H), 3.9 (d, 12H), 3.5-0.9 (m, 18H).

Anal. Calcd. for $C_{26}H_{34}N_2O_5$: C, 68.70; H, 7.54; N, 6.16. Found: C, 68.82; H, 7.63; N, 5.79.

1-(2-Phenylethyl)-4-(1-(1,2,3,4-tetrahydroisoquinolinyl))-piperidine-4-ol (IX).

1-(2-Phenylethyl)-4-(1-isoquinolinyl)-piperidine-4-ol (VI, R = H) (2) (3.0 g., 0.009 mole) was dissolved in a mixture of water (150 ml.) and concentrated hydrochloric acid (10 ml.). Platinum oxide (0.2 g.) was added and the mixture shaken under 40 pounds of hydrogen pressure overnight. The catalyst was filtered, the aqueous solution cooled in an ice bath and made basic with potassium carbonate. Chloroform extraction and recrystallization of the residue from hexane gave 2.8 g. (84%) of IX, m.p. 123-124°; ir (potassium bromide): 3400 cm^{-1}; nmr: δ 7.3 (s, 5H), 7.2 (s, 4H), 3.9 (s, 2H), 3.4-1.2 (m, 17H).

Anal. Calcd. for $C_{22}H_{28}N_2O$: C, 78.53; H, 8.39; N, 8.33. Found: C, 78.57; H, 8.43; N, 8.28.

3-Ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxy-11b*H*-benzo[*a*]-quinolizin-2-carboxaldehyde (XI).

A solution of the nitrile (X) (5) (3.0 g., 0.01 mole) in anhydrous toluene (150 ml.), under nitrogen, was cooled in ice and diisobutyl aluminum hydride 25% in toluene (8 ml., 0.012 mole) added *via* a syringe. The mixture was stirred one hour cold and then 1*N* sulfuric acid (50 ml.) added. The layers were separated and the toluene re-extracted with 1*N* sulfuric acid. The acid extracts were combined, cooled in ice and made basic with potassium carbonate. Extraction with chloroform yielded a yellow oil from which 2.0 g. (66%) of a white solid recrystallized from hexane, m.p. 98-99°; ir (potassium bromide): 2650, 1700 cm^{-1}; nmr: δ 9.5 (s, 1H), 7.0 (d, 2H), 3.9 (s, 6H), 3.3-0.9 (m, 16H); ms: m/e (%) 304 (33), 303 (63), 302 (60), 300 (40), 299 (40), 290 (20), 275 (40), 274 (60), 272 (20), 260 (17), 259 (40), 247 (23), 246 (60), 232 (13), 230 (47), 296 (47), 205 (100), 192 (50), 191 (80), 190 (67), 177 (20), 176 (40), 146 (13), 91 (11), 55 (17), 41 (17), 28 (23), 18 (28).

Anal. Calcd. for $C_{18}H_{25}NO_3$: C, 71.30; H, 8.25. Found: C, 71.17; H, 8.18.

The aldehyde (XI) was converted to its oxime, m.p. 173-175

(from isopropanol); ms: m/e (%) 319 (6) 318 (28), 317 (40), 303 (14), 302 (44), 301 (94), 300 (10), 299 (11), 274 (14), 260 (11), 246 (26), 244 (12), 242 (12), 230 (10), 206 (31), 205 (100), 192 (22), 191 (85), 190 (64), 177 (17), 176 (27), 147 (10), 45 (17), 41 (12), 28 (53), 18 (34).

Anal. Calcd. for $C_{18}H_{26}N_2O_3$: C, 67.94; H, 8.17; N, 8.80. Found: C, 67.85; H, 8.25; N, 8.79.

α(1-Isoquinolinyl)-3-ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxy-11b*H*-benzo[*a*]quinolizin-2-methanol (XII, R = R′ = H).

A mixture of the aldehyde XI (1.5 g., 0.005 mole) and Reissert compound, 2-benzoyl-1,2-dihydroisoquinaldonitrile (III, R = H; R′ = C_6H_5) (1.5 g., 0.0058 mole), in dimethylformamide (20 ml.) was treated with 50% sodium hydride in oil (0.3 g., 0.007 mole) and stirred at room temperature for one hour. The mixture was poured over ice and filtered. The solid obtained was chromatographed on alumina. The benzene fractions yielded 1-benzoylisoquinoline (0.2 g.). Methylene chloride yielded condensation product plus more 1-benzoylisoquinoline. The methylene chloride fractions were rechromatographed on alumina with methylene chloride to give the ester (XII, R = H, R′ = COC_6H_5) which was hydrolyzed by refluxing in a mixture of water (25 ml.) and ethanol (25 ml.) containing potassium hydroxide (4 g.). Removal of the ethanol followed by filtration gave a tan solid which was recrystallized from 2-propanol to give 0.5 g. (23%) of XII (R = R′ = H), m.p. 168-170°; ir (potassium bromide): 3350 cm^{-1}.

Anal. Calcd. for $C_{27}H_{32}N_2O_3$: C, 75.02; H, 7.40. Found: C, 75.04; H, 7.39.

α(1-(6,7-Dimethoxyisoquinolinyl))-3-ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxy-11b*H*-benzo[*a*]quinolizin-2-methanol Benzoate (XII, R = OCH_3, R′ = COC_6H_5).

The crude aldehyde XI (3.0 g., 0.01 mole) and 2-benzoyl-1,2-dihydro-6,7-dimethoxyisoquinaldonitrile (III, R = OCH_3, R′ = C_6H_5) (3.2 g., 0.01 mole) were dissolved in dimethylformamide (30 ml.), treated wiht 50% sodium hydride in oil (0.5 g., 0.011 mole) and stirred at room temperature for one hour. The mixture was poured over ice (400 ml.) and filtered. The crude solid was dissolved in chloroform and dried. Evaporation of the chloroform gave a brown oil which was introduced onto a silica gel column. Methylene chloride gave 6,7-dimethoxyisoquinaldonitrile (0.5 g.) and acetone gave after recrystallization from hexane 2.5 g. (41%) of the ester, m.p. 103-106°; ir (potassium bromide): 1720 cm^{-1}; ms: m/e (%) 597 (1), 596 (1), 504 (2), 493 (3), 492 (10), 476 (9), 475 (11), 474 (25), 303 (12), 302 (13), 275 (15), 274 (70), 273 (33), 272 (100), 271 (42), 270 (42), 269 (12), 268 (11), 258 (18), 256 (13), 247 (15), 246 (87), 244 (31), 242 (19), 203 (24), 190 (58), 176 (18), 120 (20), 105 (38), 77 (29), 55 (15), 51 (10).

Anal. Calcd. for $C_{36}H_{40}N_2O_6 \cdot H_2O$: C, 70.34; H, 6.88; N, 4.56. Found: C, 70.41; H, 7.01; N, 4.71.

A solution of the aldehyde, XI, (0.5 g., 0.0016 mole) in acetonitrile (5 ml.) was added to a solution of the Reissert compound, III (R′ = C_6H_5, R = OCH_3) (0.55 g., 0.0017 mole) in 50% sodium hydroxide (8 ml.) and the mixture treated with triethylbenzylammonium chloride (0.02 g.). After stirring at room temperature for one hour the mixture was poured into water (250 ml.). The aqueous solution was extracted with chloroform, the chloroform extracts dried and evaporated to give the ester (0.75 g., 75% yield) indentical with that reported above.

α(1-(6,7-dimethoxyisoquinolinyl))-3-ethyl-1,2,3,4,6,7-hexahydro-9,10-dimethoxy-11b*H*-benzo[*a*]quinolizin-2-methanol (XII, R′ = H, R = OCH_3).

A solution of the ester above, XII (R′ = COC_6H_5, R = OCH_3), (2.5 g., 0.0042 mole) in ethanol (100 ml.) and water (100 ml.) was treated wiht potassium hydroxide (4 g.) and refluxed for one hour. The ethanol was removed by distillation and the aqueous solution extracted with chloroform. The chloroform extracts were dried and introduced onto a silica gel column. Chloroform elution gave unhydrolyzed ester (0.1 g.) and acetone gave 1.9 g. (92%) of the alcohol, (XII, R′ = H, R = OCH_3), m.p. 158-160°; ir (potassium bromide): nmr: δ 8.3 (d, 1H), 7.4 (m, 4H), 6.4 (s, 1H), 6.1 (s, 1H), 5.7 (s, 1H), 5.7 (s, 1H), 4.0 (s, 6H), 3.9 (s, 3H), 3.8 (s, 3H), 3.5-1.4 (m, 13H), 1.2 (t, 3H); ms: m/e (%) 193 (6), 492 (20), 477 (10), 474 (5), 304 (10), 303 (25), 302 (29), 291 (10), 290 (16), 275 (24), 274 (100), 273 (30), 272 (100), 271 (27), 270 (34), 258 (19), 256 (10), 254 (10), 246 (46), 245 (11), 244 (44), 242 (17), 232 (6), 230 (16), 219 (24), 218 (28), 217 (12), 206 (16), 205 (51), 204 (17), 203 (16), 191 (58), 190 (100), 189 (18), 176 (25), 174 (15), 146 (15), 117 (10), 91 (10), 85 (17), 83 (34), 59 (20), 43 (42), 41 (23), 28 (10).

This alcohol gave a dihydrochloride salt, m.p. 220-226° (isopropanol-ether); ir (potassium bromide): 3350, 2700 cm^{-1}.

Anal. Calcd. for $C_{29}H_{38}Cl_2N_2 \cdot 2H_2O$: C, 57.93; H, 6.99; Cl, 11.79; N, 4.66. Found: C, 57.58; H, 6.55; Cl, 11.71; N, 4.70.

The alcohol was also converted to its tosylate, m.p. 220-221° (from chloroform-hexane); ir (potassium bromide): 1200 cm^{-1}; ms: m/e (%) 476 (10), 475 (28), 474 (6), 473 (6), 471 (6), 469 (8), 468 (6), 461 (12), 460 (17), 454 (17), 296 (14), 285 (29), 273 (41), 272 (35), 371 (100), 270 (14), 269 (29), 267 (17), 285 (11), 257 (44), 255 (21), 253 (12), 244 (12), 243 (56), 241 (21), 229 (18), 227 (18), 205 (20), 204 (17), 203 (17), 202 (52), 190 (21), 189 (30), 188 (13), 185 (22), 175 (14), 159 (11), 155 (23), 92 (10), 91 (51), 44 (12), 41 (10), 39 (10).

Anal. Calcd. for $C_{36}H_{42}N_2O_7S \cdot 2H_2O$: C, 63.36; H, 6.74. Found: C, 63.21; H, 6.37.

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