New Compounds: Isoquinoline Derivatives as Simple Emetine Models

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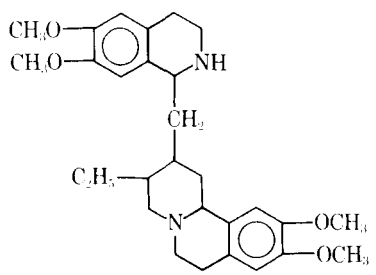
Abstract □ Several new isoquinolines were prepared using Reissert compounds. A few compounds were screened, and they exhibited no antineoplastic activity.

Keyphrases □ Isoquinoline derivatives, various—synthesized, evaluated for antineoplastic activity □ Antineoplastic activity—various isoquinoline derivatives evaluated □ Structure–activity relationships—various isoquinoline derivatives evaluated for antineoplastic activity

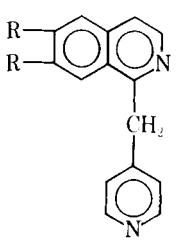
In view of the antineoplastic activity of emetine (I), the preparation of simple models of this system was studied.



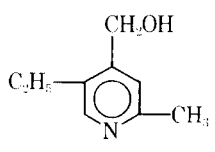
I

DISCUSSION

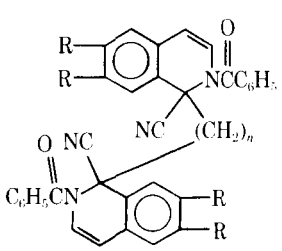
Reaction of the anion of the Reissert compounds derived from isoquinoline and 6,7-dimethoxyisoquinoline with 4-picolyl chloride gave, after hydrolysis, II and III. These compounds can be considered as models containing three of the five rings of emetine. During preliminary studies to extend this reaction, IV was prepared by reduction of the corresponding 4-methoxycarbonyl compound (1).



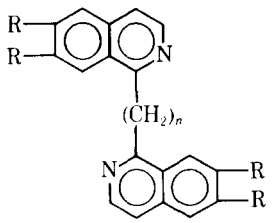
II: R = H
III: R = CH_3O



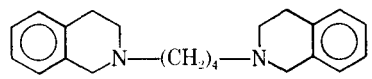
IV



Va: R = H, n = 3
Vb: R = H, n = 4
Vc: R = H, n = 5
VI: R = OCH_3, n = 3

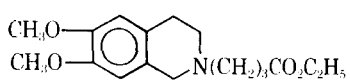


VIIa: R = H, n = 3
VIIb: R = H, n = 4
VIII: R = OCH_3, n = 3

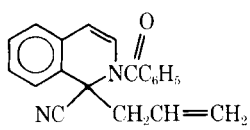


IX

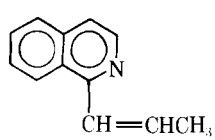
In an attempt to prepare models with the two isoquinoline units separated by three carbons as in emetine, the Reissert adduct Va, formed by reaction of the anion of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline with 1,3-dibromopropane (2), was hydrolyzed to VIIa. This compound was converted to its mono methiodide, which had a T/C value of 120% at 12.5 mg/kg against the P-388 lymphocytic leukemia and of 117% at 12.5 mg/kg against the L-1210 lymphoid leukemia. This same sequence was repeated to give, *via* VI, VIII as its hydrochloride. This compound had no activity (T/C = 104% at 100 mg/kg) against the P-388 lymphocytic leukemia. Compounds Vb, Vc, VIIb, and XIII were also prepared.



X



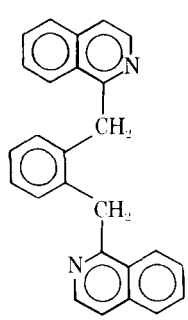
XI



XII

Attempts to form a 4-bromobutylisoquinolinium salt from 1,4-dibromobutane and isoquinoline gave only the bis adduct, which was reduced by catalytic hydrogenation to IX as its dihydrobromide. This compound had no activity (T/C = 102% at 50 mg/kg) against the L-1210 lymphoid leukemia.

Compound X was prepared by reduction of the quaternary salt obtained from 6,7-dimethoxyisoquinoline and ethyl γ-bromobutyrate. Also, reaction of the anion of the isoquinoline Reissert compound with allyl chloride gave an adduct (XI), which, on base hydrolysis, underwent isomerization to yield XII rather than the expected 1-allylisoquinoline.



XIII

EXPERIMENTAL

Reaction of Isoquinoline Reissert Compound with 4-Picolyl Chloride Hydrochloride: Preparation of 1-(4-Picolyl)-1-cyano-2-benzoyl-1,2-dihydroisoquinoline—A stirred slurry of 1.64 g (0.01 mole) of 4-picolyl chloride hydrochloride in 30 ml of dimethylformamide and 0.50 g (0.01 mole) of 50% sodium hydride in oil was added to a solution of 0.50 g (0.01 mole) of 50% sodium hydride in oil and 2.6 g (0.01 mole) of isoquinoline Reissert compound in 30 ml of dimethylformamide. The mixture was stirred for 1 hr and then poured over 500 g of cracked ice. The insoluble material was chromatographed on alumina with chloroform to give a white solid (0.70 g), which was recrystallized from cyclohexane–benzene, mp 137–138°; IR (KBr): 1670 and 1610 cm^{-1}; NMR ($CDCl_3$): δ 8.32 (2H), 7.40–6.70 (11H), 6.40 (1H), and 3.60 (2H) ppm.

Anal.—Calc. for $C_{23}H_{17}N_3O$: C, 78.61; H, 4.87; N, 11.96. Found: C, 78.71; H, 4.99; N, 11.96.

Base Hydrolysis of 1-(4-Picolyl)-1-cyano-2-benzoyl-1,2-dihydroisoquinoline—The title compound (2.00 g, 0.0057 mole) was heated in a solution of 8 g (0.14 mole) of potassium hydroxide in 25 ml of water and 25 ml of ethanol for 30 min. The ethanol was removed, and the water solution was extracted with chloroform. The chloroform extracts were evaporated to dryness, and the residue (0.92 g of II) was recrystallized from cyclohexane, mp 86–87°; IR (KBr): 1600 cm^{-1}; NMR ($CDCl_3$): δ 8.50 (2H), 7.50 (5H), 4.60 (1H), and 2.10 (1H) ppm.

Anal.—Calc. for $C_{12}H_{15}N_2$: C, 81.78; H, 5.49; N, 12.71. Found: C, 81.89; H, 5.61; N, 12.79.

Reaction of 1-Cyano-2-benzoyl-1,2-dihydro-6,7-dimethoxyisoquinoline with 4-Picolyl Chloride Hydrochloride—To a slurry of 1.64 g (0.01 mole) of 4-picolyl chloride hydrochloride in 30 ml of dimethylformamide, cooled in an ice bath and under a nitrogen atmosphere, was added 0.60 g (0.012 mole) of 50% sodium hydride in oil; the reaction was then stirred for 10 min. To the solution of 4-picolyl chloride were added 3.22 g (0.01 mole) of the 6,7-dimethoxyisoquinoline Reissert compound and 0.60 g (0.012 mole) of 50% sodium hydride in oil, and the reaction was stirred for 2.5 hr. Then the reaction was poured over ice and filtered to give 3.45 g (83%). The crude material was recrystallized from ethanol–dioxane, mp 192–193°; IR (KBr): 1660 cm^{-1}.

Anal.—Calc. for $C_{25}H_{21}N_3O_3$: C, 72.97; H, 5.14. Found: C, 72.84; H, 5.12.

Hydrolysis of 1-(4-Picolyl)-1-cyano-2-benzoyl-1,2-dihydro-6,7-dimethoxyisoquinoline—A solution of 1.55 g (0.004 mole) of the title compound, 25 ml of water, 25 ml of ethanol, and 8.5 g (0.15 mole) of potassium hydroxide was refluxed for 4.5 hr. The ethanol was removed *in vacuo*, water was added, and the mixture was filtered to give 1.05 g (100%) of III. This material was recrystallized from ethyl acetate, mp 159–160°; IR (KBr): 2950 and 1610 cm^{-1}; NMR ($CDCl_3$): δ 8.50 (2H), 7.2 (6H), 4.6 (2H), and 4.0 (6H) ppm.

Anal.—Calc. for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75. Found: C, 72.73; H, 5.84.

Reduction of 4-Methoxycarbonyl-5-ethyl-2-methylpyridine—To a solution of 0.50 g of lithium aluminum hydride in 10 ml of ether was added a solution of 3.40 g (0.022 mole) of 4-hydroxymethyl-5-ethyl-2-methylpyridine in 10 ml of ether at a rate to maintain reflux. The solution was then heated at reflux for 1 hr. To the reaction mixture was then added 5 ml of ethyl acetate, and the solution was refluxed for 15 min. To the cooled solution was added 20 ml of 6 *N* HCl, and the solution was stirred for 10 min. The layers were separated, and the ether layer was washed with 5% HCl. The acid extracts were made basic by the addition of sodium carbonate, and the aqueous solution was extracted with chloroform. The chloroform extracts were dried (sodium carbonate) and evaporated to give 1.60 g (53%) of the alcohol IV, mp 89–90°, from ligroin.

Anal.—Calc. for $C_9H_{13}NO_3$: C, 71.48; H, 8.66. Found: C, 71.61; H, 8.58.

Preparation of 1,3-Bis(1-isoquinolyl)propane (VII*a*)—To 11 g (0.02 mole) of 1,3-bis(1-cyano-2-benzoyl-1,2-dihydroisoquinolinyl)propane were added 150 ml of 95% ethanol and 150 ml of a 16% KOH solution. The mixture was refluxed on a steam bath for 2 hr, the ethanol was distilled, and the resulting mixture was poured into ice. Salt was added, and 4.25 g of VII*a* precipitated and was recrystallized from ligroin, mp 96–97°.

Anal.—Calc. for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08. Found: C, 84.58; H, 5.93.

Preparation of VII*a* Monomethiodide—A mixture of 2.25 g (0.0075 mole) of VII*a* and 30 ml of methyl iodide was heated on a steam bath for a few minutes. Ether was added to give 4.30 g (100%) of white solid, which was recrystallized from 95% ethanol, mp 233–235°.

Anal.—Calc. for $C_{22}H_{21}IN_2$: C, 60.00; H, 4.80; I, 28.82; N, 6.36. Found: C, 59.87; H, 4.85; I, 28.75; N, 6.47.

Reaction of 1-Cyano-1,2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinoline with 1,3-Dibromopropane—To a mixture of 6.4 g (0.02 mole) of the Reissert compound and 2.02 g (0.01 mole) of 1,3-dibromopropane in 40 ml of dimethylformamide, under nitrogen in an ice bath, was added 1.10 g (0.023 mole) of 50% sodium hydride in oil; the reaction was then stirred for 2 hr. The reaction mixture was poured onto ice and filtered to give a quantitative yield of 1,3-bis(2-benzoyl-6,7-dimethoxy-1-isoquinolyl)propane (VI), which could not be crystallized, mp 84–100°; IR (KBr): 1660 cm^{-1}.

Hydrolysis of VI—A mixture of 3.5 g (0.004 mole) of VI, 17% KOH, and some ethanol was heated on a steam bath for 3 hr and allowed to stand overnight. The ethanol was removed *in vacuo*, and the solution was filtered to give 1.00 g (46%) of VIII. The solid was suspended in acetone, and a few drops of concentrated hydrochloric acid were added. The mixture was heated on a steam bath for a few minutes, cooled, and filtered to give the dihydrochloride hydrate of VIII. The compound was recrystallized from 95% ethanol, mp 229–230°; IR (KBr): 1640 and 1620 cm^{-1}; NMR (dimethyl sulfoxide-d_6): 3.0–4.0 (18H), 8.0 (*AB* quartet, 4H), 7.2 (4H), and 5.0 (H_2O) ppm.

Anal.—Calc. for $C_{25}H_{26}N_2O_4 \cdot H_2O \cdot 2HCl$: C, 58.94; H, 5.93; Cl, 13.92; N, 5.49. Found: C, 59.03; H, 5.92; Cl, 13.89; N, 5.61.

Alkylation of Additional Reissert Compounds—In a procedure similar to that described for VI, 1,4-bromobutane gave V*b* (99%), mp 200–201° from 95% ethanol; IR (KBr): 1680 and 1650 cm^{-1}.

Anal.—Calc. for $C_{38}H_{30}N_4O_2$: C, 79.42; H, 5.26; N, 9.75. Found: C, 78.95; H, 5.66; N, 9.80.

The use of 1,5-dibromopentane permitted the isolation of V*c* in a 94% yield, mp 185–187° from 95% ethanol; IR (KBr): 1680 and 1650 cm^{-1}.

Anal.—Calc. for $C_{39}H_{32}N_4O_2$: C, 79.57; H, 5.48. Found: C, 79.43; H, 5.45.

Hydrolysis of Reissert Adducts—In a procedure similar to that described for VI, V*b* yielded VII*b*, mp 119–120°; IR (KBr): 1630, 1580, and 1650 cm^{-1}.

Anal.—Calc. for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.20; H, 6.32; N, 8.75.

This compound forms a dihydrochloride salt, mp 262–265°.

Anal.—Calc. for $C_{22}H_{20}N_2 \cdot 2HCl$: C, 68.57; H, 5.76; Cl, 18.40; N, 7.27. Found: C, 68.57; H, 5.71; Cl, 18.33; N, 7.29.

Similarly, α,α′-*o*-xylyene(1-cyano-2-benzoyl-1,2-dihydroisoquinoline) (2) gave XIII, mp 146–147°.

Anal.—Calc. for $C_{26}H_{20}N_2$: C, 86.63; H, 5.59. Found: C, 86.66; H, 5.54.

Preparation of 1,4-Bis(*N*-1,2,3,4-tetrahydroisoquinolyl)butane (IX)—A mixture of 4.3 g of 1,4-dibromobutane and 2.6 g of isoquinoline was heated on a steam bath for 15 min, and acetone was then added. Filtration and recrystallization from ethanol gave 2.1 g of the diquaternary salt as the dihydrate, mp 262–263°.

Anal.—Calc. for $C_{22}H_{22}Br_2N_2 \cdot 2H_2O$: C, 51.78; H, 5.13; Br, 31.32; N, 5.49. Found: C, 51.83; H, 5.38; Br, 31.20; N, 5.54.

A mixture of 3.31 g of IX in 100 ml of ethanol with 50 mg of platinum oxide was hydrogenated. The mixture was made basic, filtered, and acidified with 47% hydrobromic acid. Partial concentration *in vacuo* gave, after recrystallization from ethanol–ether, 2.1 g of IX dihydrobromide, mp 242–245°.

Anal.—Calc. for $C_{22}H_{30}Br_2N_2$: C, 54.78; H, 6.27; Br, 33.14; N, 5.81. Found: C, 54.67; H, 6.41; Br, 33.23; N, 5.72.

2-(3-Ethoxycarbonylpropyl) - 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (X) Hydrobromide—A mixture of 3.78 g (0.02 mole) of 6,7-dimethoxyisoquinoline and 3.90 g (0.02 mole) of ethyl γ-bromobutyrate was heated on a steam bath for 15 min. The resultant tacky residue was heated with acetone to give 4.10 g (54%), mp 160–165°. The solid was converted to the picrate for analysis, mp 123–125° from ethanol; IR (KBr): 1725 cm^{-1}; NMR (dimethyl sulfoxide-d_6): 10.2 (1H), 8.90 (A_2B_2, 2H), 8.1 (2H), 5.0 (2H), 3.6–4.2 (12H), and 1.2 (3H) ppm.

Anal.—Calc. for $C_{23}H_{24}N_4O_{11}$: C, 51.87; H, 4.54; N, 10.52. Found: C, 52.06; H, 4.48; N, 10.41.

A solution of 3.00 g (0.0085 mole) of the salt, 50 ml of absolute ethanol, and 5 mg of platinum oxide was shaken under hydrogen for 6 hr. The solution was filtered and taken to dryness, and the residue was treated with ether to give 2.40 g (79%) of X hydrobromide. The product was recrystallized from acetone, mp 173–174°; IR (KBr): 1725 cm^{-1}.

Anal.—Calc. for $C_{17}H_{26}BrNO_4$: C, 52.58; H, 6.75; N, 3.60. Found: C, 52.57; H, 6.55; N, 3.59.

Hydrolysis of this ester gave the acid hydrobromide, mp 220–222°.

Anal.—Calc. for $C_{15}H_{22}BrNO_4$: C, 50.01; H, 6.16; N, 3.89. Found: C, 49.82; H, 6.34; N, 3.89.

Reaction of Reissert Anion with Allyl Chloride—To 10.4 g (0.04 mole) of 2-benzoyl-1-cyano-1,2-dihydroisoquinoline in 100 ml of dimethylformamide and 8.0 g of allyl chloride was added 2.00 g of 50% sodium hydride in oil, and the mixture was stirred for 1 hr. The reaction mixture was poured over ice and allowed to stand overnight. The solution was extracted with chloroform, and the chloroform extracts were washed with water. The dried (sodium sulfate) chloroform extracts were taken to dryness *in vacuo*, and the residue was recrystallized from 95% ethanol to give 6.7 g (55%) of 1-allyl-2-benzoyl-1-cyano-1,2-dihydroisoquinoline (XI), mp 98–100°; IR (KBr): 1680 cm^{-1}; NMR (CCl_4): δ 7.5 (9H), 6.4 (1H), 5.6 (1H), 5.4 (1H), 5.2 (2H), and 3.1 (2H) ppm.

Anal.—Calc. for $C_{20}H_{16}N_2O$: C, 79.97; H, 5.37; N, 9.33. Found: C, 80.08; H, 5.43; N, 9.37.

Hydrolysis of X—A solution containing 3.00 g (0.01 mole) of X, 35 ml of water, 5 ml of ethanol, and 12 g of potassium hydroxide was refluxed for 48 hr. The basic reaction mixture was poured into 200 ml of water, and the aqueous solution was extracted with chloroform. The chloroform extracts were extracted with 5% HCl, the acid extracts were made basic with sodium carbonate, and the basic solution was extracted with chloroform. The dried (sodium sulfate) extracts were distilled at 88°/0.1 mm to give 1.24 g (73%) of 1-isoquinolylpropene (XII). The compound was converted to the picrate for analysis, mp 180–182°; IR (NaCl): 3080 and 1650 cm^{-1}; NMR (CCl_4): δ 8.0 (8H) and 1.9 (3H) ppm.

Anal.—Calc. for $C_{18}H_{14}N_4O_7$: C, 54.27; H, 3.54; N, 14.06. Found: C, 53.51; H, 3.63; N, 13.92.

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ACKNOWLEDGMENTS

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COMMUNICATIONS

Unusual Reversible Attack by Sodium Bisulfite on Physostigmine

Keyphrases □ Sodium bisulfite—effect on physostigmine molecule in solution □ Physostigmine—effect of sodium bisulfite on molecule in solution □ Antioxidants—sodium bisulfite, effect on physostigmine molecule in solution □ Ophthalmic cholinergics—physostigmine, effect of sodium bisulfite on molecule in solution

To the Editor:

Sodium bisulfite is used as an antioxidant in ophthalmic preparations containing physostigmine. Although physostigmine was shown to be stable in the presence of sodium bisulfite (1), the previous study was mainly concerned with the catalytic effect of the antioxidant on the hydrolysis rate of the carbamate linkage of the drug.

We recently observed interesting reactions between physostigmine and bisulfite. When sodium bisulfite solutions ranging in concentration from 0.01 to 0.4 *M* were mixed with 1×10^{-4} *M* physostigmine at pH 5.5 directly into the spectrophotometric[1] cell, the absorbance at 330 nm rapidly increased. At this wavelength and concentration, physostigmine has no absorbance; sodium bisulfite was present in both the sample and the blank. A semilog plot of $(A_\infty - A_t)$ against time resulted in a first-order plot (Fig. 1). The observed first-order rate constants depended on the bisulfite concentration (Fig. 2). Furthermore, at a given physostigmine concentration and in the presence of varying bisulfite concentrations, the equilibrium absorbance at 330 nm changed as a function of the bisulfite concentration (Fig. 3), indicating that an equilibrium condition existed between the species involved.

The ^{13}C-NMR spectra of aqueous solutions of physostigmine and physostigmine containing excess sodium bisulfite (molar ratio 2:1) indicate that the reaction between the two species involved an attack by bisulfite on carbon-10a of physostigmine. As seen from the NMR spectra (Fig. 4), the signal from carbon-10a (δ 98.92 ppm) disappeared when bisulfite was added. Instead, two new signals were observed, δ 88.74 and 92.32 ppm, suggesting the formation of two new species.

Since carbon-10a is partly responsible for the optical activity of physostigmine, one would anticipate changes in the optical rotation of physostigmine upon the addition

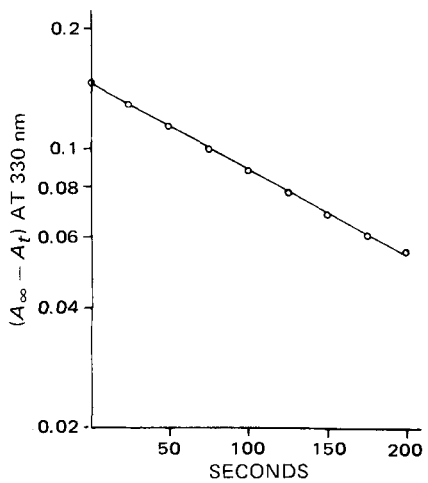

Figure 1—*Semilog plot of* $(A_\infty - A_t)$ *at 330 nm against time at pH 5.5 and 25°. Sodium bisulfite = 4.87* $\times 10^{-2}$ *M; physostigmine = 2.5* $\times 10^{-3}$ M.

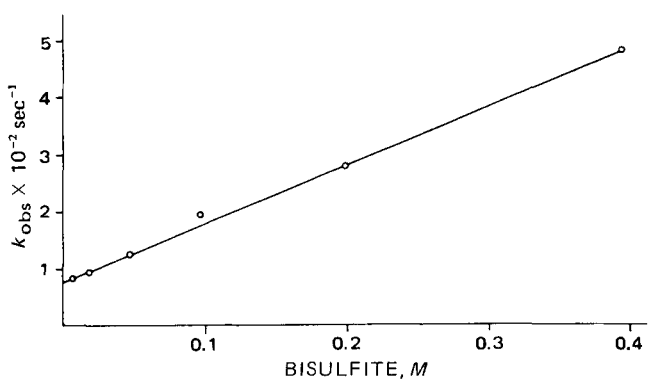

Figure 2—*Dependency of the observed first-order rate constant at pH 5.5 on bisulfite concentration.*

[1] Cary 15 recording spectrophotometer.