[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

SYNTHETIC APPROACHES TO IPECAC ALKALOIDS. II. A SYNTHESIS OF 4-CARBOMETHOXY-5-ETHYL-2-METHYLPYRIDINE[1, 2]

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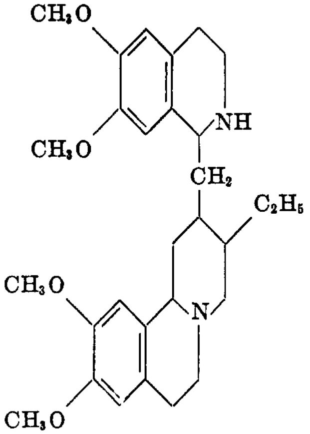
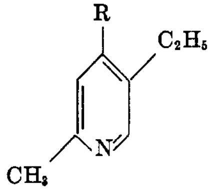
As a preliminary stage in a program (1) of synthetic and stereochemical studies on emetine (I) and other ipecac alkaloids, we have had occasion to investigate methods of synthesis of 4-carbomethoxy-5-ethyl-2-methylpyridine (IIb). This paper describes the synthesis of IIb, as well as a number of incidental observations of some theoretical interest.



I



IIa: R = H
b: R = CO_2CH_3
c: R = NH_2
d: R = N_2^+
e: R = Cl

An attractive starting material for the preparation of IIb was the commercially available "aldehyde collidine," (5-ethyl-2-methylpyridine, IIa). Two methods were considered for the introduction of the carbomethoxy group into position 4. The first was an adaptation of the procedure (2) for preparing ethyl isonicotinate, involving pyrolysis of the product from pyridine, ethyl chloroformate, and zinc. This method is analogous to those elegantly developed (3–5) for preparing 1,4-diacyl-1,4-dihydropyridines (and from them, 4-alkylpyridines) by the sequence Pyridine + $(RCO_2O + Zn \rightarrow III \rightarrow IV \rightarrow V$ (6). However, despite the claim in the patent literature (5) that 2-methylpyridine gave 4-ethyl-2-methylpyridine, it now seems to be established (7, 8, 20) that the reaction fails, or at best, gives

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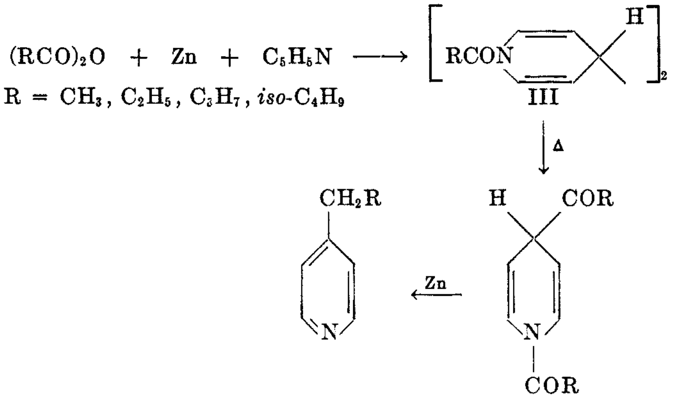
only small yields, with 2-alkylpyridines. We therefore did not attempt this approach.


$(RCO)_2O + Zn + C_5H_5N \longrightarrow$

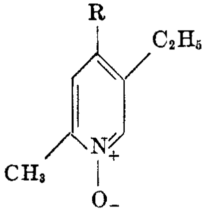
$R = CH_3, C_2H_5, C_3H_7$, *iso*-C_4H_9

III

IV

V

The second method was designed to take advantage of the general susceptibility of pyridine-1-oxides to nitration at C_4, and of established procedures for modification of the nitro group (9–12). Accordingly, IIa was converted to the oxide (VIa) with hydrogen peroxide in acetic acid. Nitration of the oxide gave a nitro compound which we formulate as 5-ethyl-2-methyl-4-nitropyridine-1-oxide (VIb) (i) by analogy to other pyridine-1-oxide nitrations (9–12), and (ii) by comparison of its ultraviolet spectrum and that of the derived amine (IIc) (obtained from VIa with iron in acetic acid) with those of suitable model compounds (Table I). While the spectra of VIa and 4-nitropyridine-1-oxide were very similar, spectra of 2- and 3-nitropyridine-1-oxides were not available for comparison. However, more conclusive evidence was afforded by comparison of the spectrum of IIc with those of 2-, 3- and 4-aminopyridine. Table I demonstrates that the spectrum of our amine closely reproduced that of 4-aminopyridine, in both neutral and basic solution, but was unmistakably different from that of 2- or 3-aminopyridine.



VIa: $R = H$
b: $R = NO_2$
c: $R = NH_2$
d: $R = N_2^+$
e: $R = CN$
f: $R = CO_2H$
g: $R = CO_2CH_3$

We first attempted replacement of the amino function of IIc with cyano by a Sandmeyer reaction. However, the corresponding diazonium salt was extremely unstable, and rapidly evolved nitrogen, even at −14°. We attribute this reactivity to the powerful electron-attracting inductive and mesomeric effects of the ring nitrogen (enhanced by protonation in the acid solution) which activate the diazonium group toward nucleophilic displacement. Such instability of 2- and 4-pyridinediazonium salts has been noted previously (13–15).

TABLE I

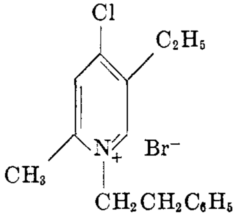
ULTRAVIOLET ABSORPTION SPECTRA

Compound	Medium	λ_{max} (mμ)	$\log \epsilon$
VIb	95% EtOH	240, 326	4.04, 4.00
4-Nitropyridine-1-oxide[a]	EtOH	235, 330	4.0, 4.2
IIc	95% EtOH	247.5, 267	3.97, 3.92
4-Aminopyridine[c–e]	EtOH	244, 265[b]	4.15, 3.50
IIc	0.01 *N* NaOH in 95% EtOH	246, 267[b]	4.11, 3.60
4-Aminopyridine[c–e]	0.01 *N* NaOH in 95% EtOH	245,[b] 262	3.85, 4.00
3-Aminopyridine[c–e]	95% EtOH	240, 300	4.00, 3.50
3-Aminopyridine[c–e]	0.01 *N* NaOH in 95% EtOH	232, 290	3.80, 3.48
2-Aminopyridine[c–e]	95% EtOH	235, 294	4.1, 3.6
2-Aminopyridine[c–e]	0.01 *N* NaOH in 95% EtOH	230, 285	3.9, 3.6

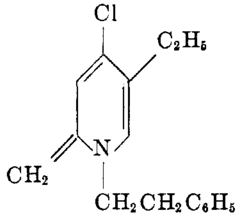
[a] den Hertog and Combé, *Rec. trav. chim.*, **71,** 745 (1952). [b] Shoulder. [c] Steck and Ewing, *J. Am. Chem. Soc.*, **70,** 3397 (1948). [d] Bliznyukov, *Zhur. Obshchei Khim.*, **22,** 1204 (1952); *Chem. Abstr.*, **47,** 403 (1953). [e] Ashley, Buchanan, and Easson, *J. Chem. Soc.*, 60 (1947).

However, the chloro compound IIe was obtained in good yield by diazotization of IIc at low temperatures in the presence of saturated hydrochloric acid.

We were unable to find examples of direct conversion of a 4-chloropyridine to a 4-cyanopyridine in the literature. Although 2-halopyridines have been converted to 2-cyanopyridines, usually by distillation of the halide with dry cuprous cyanide (16–18), the yields have often been low. We therefore attempted to activate the chlorine of IIe by quaternizing the base with 2-phenylethyl bromide, in the hope that the more reactive quaternary salt might suffer nucleophilic displacement of the 4-chloro substituent under milder conditions than those which apparently were necessary with the free bases. However, the results were unsatisfactory. When the quaternary salt (VII) was dissolved in aqueous alcoholic potassium cyanide, the solution became deep red. That this behavior was due to the formation of an anhydro base (VIII) was evident from (i) the fact that the same color was produced from VII and aqueous potassium hydroxide; (ii) the color disappeared when the solution was acidified; (iii) the colored substance was readily extracted into chloroform. The anhydro base was unstable and, upon standing or being warmed in solution, it gave rise to intractable materials.

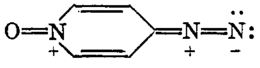


VII



VIII

The desired cyano compound was finally prepared by taking advantage of the greater stability of the diazonium salt (VId) from the 4-amino-1-oxide (VIc). Selective hydrogenation (9) of the 4-nitro-1-oxide (VIb) in neutral ethanol over 30% palladium-charcoal gave the amine (VIc) with the oxide function still intact. The corresponding diazonium salt (VId) was converted to the nitrile VIe with cuprous cyanide under typical Sandmeyer conditions. The greater stability of the diazonium salt VId compared to that of IId is attributable to resonance interaction between the oxide and diazonium groups, exemplified by the contributing resonance structure IX. A similar interaction undoubtedly accounts for the fact that although the oxide VIa readily formed salts, the 4-nitro-1-oxide VIb was an extremely weak base, and did not react detectably with dry hydrogen chloride in benzene.


IX

Basic hydrolysis of the nitrile (VIe) gave the acid (VIf), which was converted to the methyl ester (VIg). Hydrogenation of VIg, in acetic acid containing a trace of acetic anhydride, over 30% palladium-charcoal, gave 4-carbomethoxy-5-ethyl-2-methylpyridine as an oil. The substance was characterized as the picrate.

The yields for the stages of the sequence were IIa → VIa (92%); VIa → VIb (87%); VIb → VIc (quantitative); VIc → VIe (43%); VIe → VIf (96%); VIf → VIg (72%); VIg → IIb (91%). It is likely that several successive stages could be run without isolation of the intermediates, and the uniformly good to excellent yields make the scheme not prohibitively inconvenient, despite its length.

EXPERIMENTAL[4]

5-Ethyl-2-methylpyridine-1-oxide (VIa). A mixture of 100 g. (0.825 mole) of 5-ethyl-2-methylpyridine (Eastman Kodak), 82 cc. of 30% hydrogen peroxide, and 500 cc. of glacial acetic acid was heated on the steam-bath for 3½ hours, with mechanical stirring. An additional portion of 65 cc. of hydrogen peroxide was added and heating and stirring were continued for an additional eight hours. The reaction mixture was allowed to remain at room temperature for 12 hours and then was concentrated *in vacuo* to a volume of 150 cc. Then 100 cc. of water was added, the mixture was again concentrated to 150 cc. in volume and was treated with 300 cc. of chloroform. The resulting mixture was warmed on the steam-bath and treated with portions of a slurry of water and potassium carbonate until gas evolution ceased.

The mixture was filtered, the filtrate was separated into aqueous and chloroform phases, the aqueous phase was extracted with several portions of fresh chloroform, and the combined chloroform solutions were dried over sodium carbonate and concentrated. The residue was distilled *in vacuo* to give 104 g. (92% yield) of VIa as a colorless liquid, b.p. 93° at 0.2 mm., $n_D^{27.5}$ 1.5610, reported (19) b.p. 147° at 11 mm., n_D^{26} 1.5634.

The *picrate*, yellow needles from ethanol, had m.p. 106–107.2°.

The *neutral oxalate*, prepared from VIa and oxalic acid in isopropyl alcohol, was recrystallized from benzene to give white prisms, m.p. 98.3–99.2°.

Anal. Calc'd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69.

Found: C, 59.14; H, 6.99; N, 7.97.

5-Ethyl-2-methyl-4-nitropyridine-1-oxide (VIb). To an ice-cold mixture of 25 cc. of fuming nitric acid (specific gravity 1.59) and 25 cc. of conc'd sulfuric acid (specific gravity 1.84) was added portionwise 8.0 g. (0.584 mole) of VIa. The solution was warmed slowly and

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[4] The microanalyses were performed by Mr. W. J. Schenck. Melting points were not corrected. The ultraviolet spectra were taken with the Beckman spectrophotometer, Model DU.

cautiously to 75°, where it was allowed to remain for one hour with periodic stirring. The temperature was then raised to 97° and the mixture was heated at that temperature for one hour. If the temperature is not controlled as specified, the reaction becomes uncontrollably vigorous.

The reaction mixture was cooled to room temperature, poured into 100 g. of crushed ice and kept cold in an ice-bath while concentrated sodium hydroxide was added, with stirring. Water (*ca.* 150 cc.) was added during the addition to dissolve enough of the precipitated salt to facilitate stirring. When the mixture was at *p*H 4, the voluminous pale yellow precipitate was filtered off, and the mother liquor (A) was set aside. The precipitate was washed with warm water to remove inorganic salt, and then was filtered and dried to give 4.46 g. of light yellow needles, m.p. 72–79°. The mother liquor was combined with (A) and the whole was extracted with six 50-cc. portions of chloroform. Evaporation of the dried (sodium sulfate) extracts afforded a second crop of VIb which, after being washed with water and dried, weighed 4.77 g. and melted at 72–77°. The combined crude yield was thus 9.23 g. (87%). Alternate recrystallizations from chloroform-ligroin and from aqueous methanol gave pale-yellow needles, m.p. 79.6–80.3°.

Anal. Calc'd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38.
Found: C, 52.60; H, 5.53; N, 15.50.

The ultraviolet spectrum has been described in the theoretical section. VIb did not give a precipitate when its benzene solution was saturated with hydrogen chloride gas.

4-Amino-5-ethyl-2-methylpyridine (IIc). The procedure was a modification of that used by Taylor and Crovetti (12) for the preparation of 4-amino-3-methylpyridine.

A solution of 8.23 g. of VIb in 50 cc. of acetic acid was added during 30 minutes to a stirred suspension of 25 g. of iron powder in 200 cc. of hot acetic acid. The reaction was vigorously exothermic but easily controlled by regulation of the rate of addition. The mixture then was heated on the steam-bath (with stirring) an additional 1½ hours, cooled, and diluted with 100 cc. of water. Concentrated sodium hydroxide solution was added, with cooling, until the mixture was at *p*H 10. The pasty green mass was stirred with 100 cc. of methanol, filtered through diatomaceous earth ("Hyflo Super-Cel"), the filter cake thoroughly washed with water and then with ether, and the combined filtrates exhaustively extracted with 18 portions of chloroform (total 450 cc.). The chloroform extract was evaporated and the resulting cream-colored solid was dissolved in benzene. Hydrogen chloride was passed into the benzene solution until no further precipitation occurred. The precipitate, 5.64 g. (72%) of the *hydrochloride of IIc*, melted at 258° (dec.). The crude hydrochloride was used directly in the diazotization step (*vide infra*). An analytical sample was prepared by recrystallization from ethanol.

Anal. Calc'd for $C_8H_{13}ClN_2$: C, 55.65; H, 7.59; N, 16.30.
Found: C, 55.31; H, 7.91; N, 16.40.

The *free base* (IIc) was liberated by treating an aqueous solution of the hydrochloride with sodium hydroxide. Recrystallization from aqueous methanol yielded long white needles which after drying *in vacuo*, had m.p. 88.3–89.5°.

Anal. Calc'd for $C_8H_{12}N_2$: C, 70.54; H, 8.88; N, 20.57.
Found: C, 70.20; H, 9.24; N, 20.84.

When IIc was recrystallized from aqueous solvents and not dried *in vacuo*, a substance, presumably a *hydrate*, m.p. 67.5–69°, was obtained.

The ultraviolet behavior of IIc is discussed in the text.

4-Chloro-5-ethyl-2-methylpyridine (IIe). A solution of 2.5 g. of the hydrochloride of IIc in concentrated hydrochloric acid was cooled to −10° in an ice-salt bath and saturated with gaseous hydrogen chloride. The temperature was lowered to −14° and solid sodium nitrite (5.0 g.) was added in portions, with stirring. Each addition caused vigorous gas evolution, although the temperature remained constant at −14°. Stirring was continued at this temperature for an additional hour, during which time very little nitrogen was evolved. The brown solution was allowed to come to room temperature, with stirring, during five hours and then was diluted with water. With cooling, 30% sodium hydroxide was added until the solution was neutral and the cloudy mixture was extracted with chloroform. The extracts were dried over sodium carbonate, evaporated, and the residue was distilled to give 1.79 g. (79%) of a colorless liquid, b.p. 38.2–39° at 1 mm., n_D^{25} 1.5170.

Anal. Calc'd for $C_8H_{10}ClN$: C, 61.67; H, 6.47; Cl, 22.77.

Found: C, 61.46; H, 6.41; Cl, 22.86.

The *picrate*, prepared in ethanol and recrystallized from benzene-ligroin, had m.p. 131–132.2°.

4-Chloro-5-ethyl-2-methyl-1-(2-phenylethyl)pyridinium bromide (VII). A mixture of 0.96 g. of IIe and 3.54 g. of 2-phenylethyl bromide was heated for 18 hours on the steam bath. The addition of ethyl acetate caused precipitation of a brown solid. Another crop was obtained by evaporation of the mother liquor and heating of the residue for an additional two hours. The combined crops were recrystallized from isopropyl alcohol (Norit) to give 1.09 g. of the bromide, m.p. 170–173°, with softening at 165°.

An *iodide* was prepared by adding 48% hydriodic acid to a solution of the bromide in the minimum quantity of water. This substance retained a persistent yellow color after repeated recrystallization. It was converted to a *chloride* by heating an ethanolic solution with silver chloride, filtering, and evaporating the ethanol. The solid residue was dissolved in chloroform and was reprecipitated with ethyl acetate to give white prisms, m.p. 157-162.5° to a red liquid. Recrystallization from a mixture of 95% ethanol and ethyl acetate gave a substance, presumably a hydrate of the chloride, m.p. 83–87°.

When a solution of the iodide in 95% ethanol was treated with picric acid and the resulting precipitate was recrystallized from a mixture of ethanol, water and chloroform, a *picrate monohydrate*, well-defined, amber prisms, m.p. 153–154.5°, was obtained.

Anal. Calc'd for $C_{22}H_{21}ClN_4O_7 \cdot H_2O$: C, 51.92; H, 4.56.

Found: C, 52.24; H, 4.94.

Aqueous ethanolic solutions of the bromide gave an immediate deep red color with potassium cyanide or hydroxide. Attempts to isolate discrete products from these solutions were fruitless.

4-Amino-5-ethyl-2-methylpyridine-1-oxide (VIc) was prepared by catalytic hydrogenation of the nitro compound (VIb) in ethanol over 30% palladium-charcoal, according to the method used by Ochiai (9) for preparing 4-aminopyridine-1-oxide. The rate of hydrogenation diminished markedly after the consumption of the theoretical quantity (3 moles) needed for reduction of the nitro group. After filtration of the catalyst and evaporation of the solvent, the residue was taken up in *tert*-butyl alcohol and the amine was precipitated by adding ligroin. In several runs, the yields were quantitative. The product so obtained was a white solid, m.p. 197–221°. The melting point range of the crude product is not necessarily indicative of impurity, since the melting point of pure material, obtained by recrystallization from *tert*-butyl alcohol, varies. In one case, white prisms, m.p. 209.5–212°, were obtained. Another sample had m.p. 200–203°. Both samples showed identical infrared spectra, both gave picrates of identical m.p. and mixture m.p. (177.5–181.5°), and both gave the correct analysis for VIc.

Anal. Calc'd for $C_8H_{12}N_2O$: C, 63.13; H, 7.95.

Found: C, 63.40; 63.13; H, 7.82; 7.44.

4-Cyano-5-ethyl-2-methylpyridine-1-oxide (VIe). To a vigorously stirred, ice-cooled solution of 6.0 g. of 4-amino-5-ethyl-2-methylpyridine-1-oxide in 6.6 cc. of concentrated sulfuric acid and 19.8 cc. of water, an aqueous solution of sodium nitrite was added until the reaction mixture gave an immediate positive test for nitrous acid with starch-iodide paper. At this point, the yellow solution was evolving gas at a very slow rate. With cooling and stirring, the solution was slowly neutralized with sodium hydroxide, water being added to dissolve any precipitated salt.

The reaction mixture was kept ice-cold and was added dropwise during one hour to a stirred ice-cooled solution of 5.28 g. of cuprous cyanide and 7.68 g. of potassium cyanide in 40 cc. of water. Each drop caused vigorous evolution of gas. The brown mixture was stirred an additional ten minutes, during which time no gas evolution was apparent.

The reaction mixture was extracted with 15 portions of chloroform, and the extracts were dried over sodium carbonate and evaporated. The residue was taken up in hot ethyl acetate and the solution was treated with ligroin, whereupon 2.43 g. of a brown solid, m.p. 98.5–103.5°, separated. Evaporation of the mother liquor gave an additional 1.58 g. of a sticky orange solid, m.p. 87–102°. Recrystallization of the crude product from a variety of solvents produced sharp-melting material, but failed to remove the color completely. Accordingly, 3.50 g. of the crude nitrile was chromatographed in benzene on an alumina column. The column was developed with benzene and was eluted with chloroform-benzene (3:1). The orange impurity moved more slowly on the column than the nitrile, and the eluate was collected until the orange material had moved to the bottom of the column. The eluate was concentrated and treated with ligroin, whereupon 2.38 g. (43%) of VIe, buff plates, m.p. 104.8–106.2°, was obtained. Vacuum sublimation afforded the pure nitrile, m.p. 107.2–108.3°.

Anal. Calc'd for $C_9H_{10}N_2O$: C, 66.65; H, 6.22.
Found: C, 66.85; 6.48.

4-Carboxy-5-ethyl-2-methylpyridine-1-oxide (VIf). A mechanically stirred suspension of 1.27 g. of VIe in 14 cc. of 15% sodium hydroxide was warmed slowly to 75° and held at that temperature for one hour. The solution became brown and homogeneous after 20 minutes. Upon being cooled in ice and adjusted to *p*H 1 with concentrated hydrochloric acid, the reaction mixture deposited 1.34 g. (96%) of the acid, m.p. 193–195°. Recrystallization from ethanol gave material of m.p. 193.8–194.5°.

Anal. Calc'd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12.
Found: C, 59.49; H, 6.38.

4-Carbomethoxy-5-ethyl-2-methylpyridine-1-oxide (VIg) was prepared by boiling a mixture of 0.72 g. of VIf, 1.5 cc. of concentrated sulfuric acid, and 25 cc. of methanol for 12 hours at reflux. The reaction mixture was concentrated, diluted with 25 cc. of water, neutralized with sodium bicarbonate, and extracted with chloroform. Evaporation of the dried (sodium carbonate) extract left an oil which crystallized upon cooling. This material was washed with ligroin to give 0.56 g. (72%) of the crude methyl ester (VIg) as a pale yellow solid, m.p. 60–61.5°. It was hydrogenated without further purification.

4-Carbomethoxy-5-ethyl-2-methylpyridine (IIb). A solution of 0.21 g. of VIg in 15 cc. of acetic acid containing 0.7 cc. of acetic anhydride was stirred with 30% palladium-charcoal in an atmosphere of hydrogen. The theoretical quantity of gas was absorbed in seven hours. The catalyst was filtered off and the bulk of the solvent was removed *in vacuo*. The residue was dissolved in 15 cc. of water, shaken with excess sodium carbonate, and then was extracted with chloroform. Evaporation of the dried (sodium carbonate) extracts under a stream of nitrogen afforded 0.18 g. (91%) of a pale brown oil.

The *picrate*, prepared in ethanol, had m.p. 110–112° when crude. Recrystallization from methanol and from benzene raised the m.p. to 114.2–115.5°.

Anal. Calc'd for $C_{16}H_{16}N_4O_9$: C, 47.06; H, 3.95.
Found: C, 47.02; H, 3.78.

SUMMARY

4-Carbomethoxy-5-ethyl-2-methylpyridine, an intermediate for projected syntheses of ipecac alkaloids, has been synthesized from a commercially available starting material, 5-ethyl-2-methylpyridine.

Los Angeles 7, California

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NOTICE TO AUTHORS

On and after September 1, 1955, the Journal will accept *Notes*; the Journal will accept *Communications to the Editor* received on or after November 1, 1955 for publication in Volume 21. See revised Notice to Authors for details.

Effective with Volume 21, the Journal will use a double column format with a page size approximately 6½″ by 9″. Authors should consider this in connection with graph sizes, and table compositions.