[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE UNIVERSITY, AMES, IOWA]

General Methods of Synthesis of Indole Alkaloids. III.[1] A Flavopereirine Synthesis[2]

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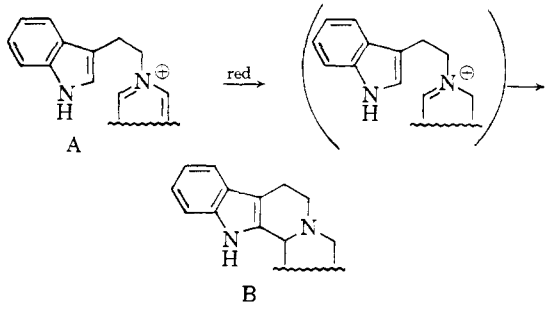
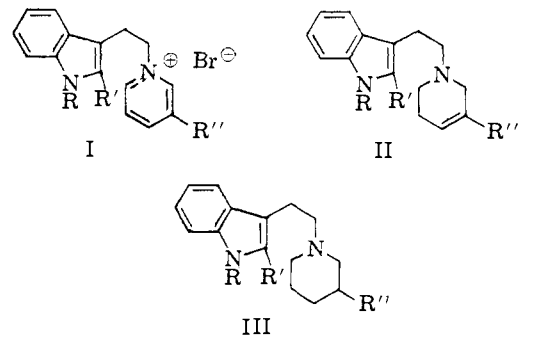
The reactions of several N-[β-(3-indolyl)-ethyl]-pyridinium salts with various metal hydrides have been investigated. Their use in a new synthesis of the alkaloid flavopereirine is reported.

As part of our search for new general methods of synthesis of indole alkaloids of part structure B, we have investigated the reductive cyclization scheme A → B. As our previously reported oxidative cyclization methods[1] indicated, the intermediate 1-piperidines undergo ready cyclization. Hence, an A → B transformation depends mainly on conversion of pyridinium salts to 1-piperideines. Two new procedures for this reduction, one by means of catalytic hydrogenation[2] and the other with the aid of metal hydrides as reducing agents, have been developed. The latter represents the subject of the present communication.



N-Alkylpyridinium salts are reduced by lithium aluminum hydride to 1-alkyl-1,2-dihydropyridines and by sodium borohydride in protic solvents to 1-alkyl-1,2,3,6-tetrahydropyridines.[4] However, reduction of N-[β-(3-indolyl)-ethyl]-pyridinium bromide (Ia) by either hydride, a case pertinent to our study, has been reported to lead exclusively to the tetrahydropyridine (IIa).[5] This striking anomaly made a reinspection of the reduction of Ia necessary.

The chemical reduction of five salts of I was investigated. Their preparation consisted of syntheses of the proper tryptophols, conversion to the tryptophyl bromides with phosphorus tribromide and treatment of the halides with the appropriate pyridines. Sodium borohydride reduction of the salts in methanol solution yielded tetrahydropyridines II. Catalytic hydrogenation of IIa, b and c led to the known[1] piperid nes IIIa,b and c, respectively. Similar reduction of IId afforded the piperidine IIId whose identity was established by its alternate synthesis *via* the reaction of methyl 1-methyl-3-indolylacetate with piperidine and lithium aluminum hydride reduction of the resulting amide. Finally hydrogenation of the ketone IIf, obtained by an acid hydrolysis of the ketal IIe, gave the known[6] piperidino ketone IIIf.



a, R = R′ = R″ = H
b, R = R′ = H, R″ = Et
c, R = R″ = H, R′ = Me
d, R = Me, R′ = R″ = H
e, R = R′ = H, R″ = CHMe[O₂(CH₂)₂]
f, R = R′ = H, R″ = Ac

These results are in conformity with previous data[4,5] and rule out the use of sodium borohydride reduction in our proposed A → B conversion. It is interesting to note that the *py*-substituted salts Ib and e are each reduced to only one double-bond isomer, IIb and e, respectively. The position of the isolated multiple bond was proven by the presence of only a single-proton signal in the p.m.r. spectra of the two compounds. In the case of IIb, it was a broad singlet at 5.46 p.p.m., while in the case of IIe, it appeared as a similar broad singlet at 5.96 p.p.m. The downfield position of the latter undoubtedly is due to the proximity of the ketal oxygen atoms to the olefinic hydrogen. Further confirmation of the position of the double bond in the tetrahydropyridine IIb came from the sharply defined p.m.r. signals characteristic of its ethyl group, methyl triplet at 1.03 p.p.m. (J = 7.2 c.p.s.) and methylene quartet at 1.35 p.p.m. (J = 7.2 c.p.s.), as contrasted with the diffuse ethyl signal of its dihydro derivative IIIb.[7]

Lithium aluminum hydride reduction of the model salt Ia followed by dilute hydrochloric acid treatment yielded two products, one of which was recognized readily to be the sodium borohydride reduction product IIa. The second product appeared to be a tetracyclic material since its p.m.r. spectrum lacked the indolic α-hydrogen signal, δ = 6.8–7.0 p.p.m., present in the spectra of all tricyclic α-unsubstituted indoles II and III.[8] This was

(1) For parts I and II see E. Wenkert and J. Kilzer, *J. Org. Chem.*, **27**, 2283 (1962), and E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, in press, respectively.

(2) This work was first presented as part of a lecture by E. W. at the 17th National Organic Chemistry Symposium of the American Chemical Society at Bloomington, Ind., June 26–29, 1961. It was supported by U. S. Army Chemical Corps contract DA 18-108-405-CML-269.

(3) Department of Chemistry, Indiana University, Bloomington, Ind.

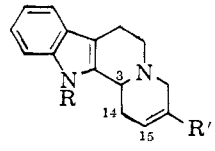
(4) J. J. Panouse, *Bull. soc. chim. France*, D.60 (1953).

(5) R. C. Elderfield, B. C. Fischer and J. M. Lagowski, *J. Org. Chem.*, **22**, 1376 (1957).

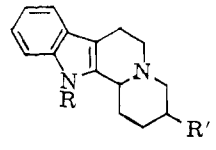
(6) E. Wenkert and B. Wickberg, manuscript in preparation.

(7) *Cf.* F. A. L. Anet, *Can. J. Chem.*, **39**, 2262 (1961).

confirmed by its transformation to the known[1] tetracycle Va on catalytic hydrogenation. As a consequence, structure IVa was assigned to the new compound. The position of its double bond could be inferred by analogy with that of substance IVb (*vide infra*) and by the absence of a downfield C(3)–H p.m.r. signal (as compared to Va) expected for the only plausible alternate structure, the 14,15-double bond isomer.



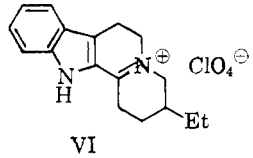
IV



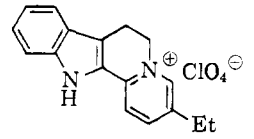
V

a, R = R′ = H
b, R = H, R′ = Et
c, R = Me, R′ = H

Lithium aluminum hydride reduction and acid treatment of the pyridinium salt Ib led to two products, one of which was the product (IIb) of sodium hydride reduction. The p.m.r. spectrum of the other product permitted assignment of structure IVb to this substance. Catalytic hydrogenation of the new compound afforded a mixture from which the known crystalline octahydroflavopereirine (Vb)[1,9] could be isolated. Mercuric acetate oxidation of the mixture yielded the 3-dehydro derivative VI. Palladium–maleic acid dehydrogenation of IVb gave the dihydroflavopereirine derivative VII.



VI



VII

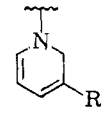
While the results from the lithium aluminum hydride reduction of the salts Ia and b are at variance with previous observation,[5] inasmuch as the reaction leads to some 1,2-dihydropyridines which in the end become tetracycles IVa and b, they confirm the production of the anomalous tetrahydropyridines IIa and b. The most likely reason for this departure from the normal mode of reduction[4] of N-alkylpyridinium salts is the action of the hydride as a base and its abstraction of the indole N_a-hydrogen atom and the capacity of the resulting indole-aluminohydride complex to carry out intramolecular reduction of its dihydropyridine sidechain. This interpretation suggests that the over-reduction might be avoided if no complex is formed because: (a) the hydride employed is not likely to act as a base or (b) the indole nitrogen atom is protected by an alkyl group, or if (c) the complex has been made non-reducing by the aluminum having had its hydrogen atoms removed. Experiments were designed to test these three possibilities of improving our A → B transformation.

On the assumption that sodium borohydride would not form a complex with the indole ring, the salt Ia was reduced by this reagent in the aprotic medium diglyme and the products exposed to acid treatment. While this reaction yielded some tetracyclic product (IVa) in contrast to the reaction in an alcoholic medium, the over-reduced substance IIa still represented the major product. Probably the intermediate BH_3 or diborane was responsible for the further reduction of the pyridine nucleus.

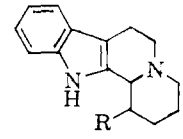
Lithium aluminum hydride reduction of the *ind*-N-methylated salt Id afforded exclusively one compound whose tetracyclic nature was established by the identity of the picrate of its catalytic hydrogenation product Vc with that of the product of *ind*-N-methylation of Va. This successful reductive cyclization speaks well for the use of *ind*-N-protecting groups in the synthesis of polycyclic systems of general structure B. Furthermore, it is strong support for the view that intramolecular hydrogen transfer processes are responsible for the previous deleterious over-reductions.

Reductions of the salts Ia and b with lithium tri-*t*-butoxyaluminum hydride were undertaken in the hope that the complex this hydride would form with the indole nucleus would possess no Al–H bonds and thus no reducing power. Indeed, the reactions led mostly to the tetracyclic substances IVa and b. The reduction of Ia yielded also small amounts of IIa, whereas that of Ib produced no tetrahydropyridine IIb. Thus it appears that the use of monohydrides may be another method for avoiding overreduction of the pyridine nucleus.

It is significant from the point of view of general synthesis that the first step of the hydride reductions of unsymmetrically substituted pyridinium salts, *e.g.*, Ib and e, takes place exclusively on the α-carbon next to the substituent. Further reactions of the resulting dienamine VIII, reductions leading to II or acid treatment finally yielding IV, involve only the central double bond of the conjugated system. As a consequence, the reductive cyclizations have afforded only a hydroflavopereirine (IVb). Complementarily another scheme of reductive cyclization leads to the isomeric system IX.[6] Furthermore, in view of the previous conversion of the tetracyclic amine Vb to flavopereirine perchlorate the present reaction sequence represents another short total synthesis of the alkaloid of *Geissospermum vellosii* and *laeve*.[10]



VIII



IX

A lithium aluminum hydride reduction of the α-methylindole derivative Ic was carried out in the hope that reductive cyclization, which in this case is blocked at the α-indole site, might occur by condensation of the pyridine nucleus with the indole

(8) *Cf.* L. A. Cohen, J. W. Daly, H. Kny and B. Witkop, *J. Am. Chem. Soc.*, **82**, 2184 (1960).

(9) N. A. Hughes and H. Rapoport, *ibid.*, **80**, 1604 (1958).

(10) For previous syntheses of flavopereirine see ref. 1 and A. LeHir, M.-M. Janot and D. van Stolk, *Bull. soc. chim. France*, 551 (1958); K. B. Prasad and G. A. Swan, *J. Chem. Soc.*, 2024 (1958); J. Thesing and W. Festag, *Experientia*, **15**, 127 (1959); H. Kaneko, *J. Pharm. Soc. Japan*, **80**, 1374 (1960); Y. Ban and M. Seo, *Tetrahedron*, **16**, 5 (1961).

α-methyl group or β-carbon atom. However, thus far the reaction has led to a tar from which only the over-reduced substance IIc could be isolated.

Experimental

Pyridinium Salts. Ia.—A reaction between 3.0 g. of tryptophol and phosphorus tribromide according to the procedure of Hoshino and Shimodaira[11] gave colorless crude tryptophyl bromide, m.p. 90–95°. A mixture of the latter and 7 ml. of pyridine was heated at 80° under nitrogen for 8 hr. Addition of ether to the cooled reaction mixture yielded a precipitate whose crystallization from ethanol–ether afforded 3.6 g. of Ia, m.p. 231–233° (lit.[5] m.p. 235–237° dec.).

Salt Ib was prepared from 4.0 g. of tryptophol and 6.0 g. of β-ethylpyridine in the above manner. Crystallization of the product from methanol–acetone gave 3.8 g. of crystals, m.p. 137–140°.

Anal. Calcd. for $C_{17}H_{19}N_2Br$: N, 8.46. Found: N, 8.34, 8.46.

Ic.—Ethyl 3-(2-methylindolyl)-acetate was prepared according to the method of Bullock and Fox.[12] Lithium aluminum hydride reduction of this ester[5] gave α-methyltryptophol, b.p. 152–156° (0.4 mm.), m.p. 53–55° on crystallization from petroleum ether–benzene (lit.[11] m.p. 55–56°). The pyridinium salt Ic was prepared from 6.4 g. of this tryptophol and pyridine in the above manner. Crystallization of the crude product, m.p. 240–243°, from methanol–ether yielded 5.0 g. of crystalline material, m.p. 241–243°.

Anal. Calcd. for $C_{16}H_{17}N_2Br$: C, 60.60; H, 5.36; N, 8.77; Br, 25.21. Found: C, 60.30; H, 5.50; N, 8.82; Br, 25.40.

Id.—3-(1-Methyl-2-carboxyindolyl)-acetic acid was prepared by the method of King and L'Ecuyer.[13] It was decarboxylated by following a recently recorded general procedure for the decarboxylation of α-indolecarboxylic acids.[14] A mixture of 2.0 g. of the diacid and 100 ml. of 5% hydrochloric acid was refluxed under nitrogen for 5 hr. The mixture was extracted with ether and the acid products extracted with 5% sodium hydroxide solution. Acidification gave a solid which on crystallization from aqueous ethanol yielded 1.6 g. of 3-(1-methylindolyl)-acetic acid, m.p. 126–128° (lit.[13] m.p. 128°). Methylation of the latter with excess diazomethane in ether produced methyl 3-(1-methylindolyl)-acetate, b.p. 129–133° (0.5 mm.). Lithium aluminum hydride reduction of 10.5 g. of this ester by the method of Eiter and Svierak[15] led to 7.8 g. of N-methyltryptophol, b.p. 122–126° (0.5 mm.) (lit.[15] b.p. 120–140° (0.01 mm.). Treatment of this tryptophol, 6.4 g., with phosphorus tribromide and thereafter with pyridine in the manner described above yielded a salt whose crystallization from dimethylformamide–benzene afforded 4.6 g. of Id, m.p. 106–108°.

Anal. Calcd. for $C_{16}H_{17}N_2Br$: N, 8.77; Br, 25.21. Found: N, 8.53; Br, 24.97.

Salt Ie was prepared from 6.0 g. of tryptophol and 13.4 ml. of β-acetylpyridine ethylene ketal[16] by the above procedure. Crystallization from methanol yielded 10.3 g. of crystalline Ie, m.p. 209–210°.

Anal. Calcd. for $C_{19}H_{21}O_2N_2Br$: C, 58.61; H, 5.40; N, 7.20; Br, 20.56. Found: C, 58.97; H, 5.53; N, 7.04; Br, 20.28.

Sodium Borohydride Reductions.—All reductions were carried out according to the procedure of Elderfield, Fischer and Lagowski[5] and the product mixtures were chromatographed on alumina.

Reduction of 200 mg. of the salt Ia gave 96 mg. of product, m.p. 147–150°. Crystallizations from petroleum ether as well as from aqueous methanol yielded IIb, m.p. 151–152° (lit.[5] m.p. 152–153°); p.m.r. spectrum ($CDCl_3$): (*ind*)–NH 8.27 p.p.m., (*ind*)–α-H 6.93 p.p.m., olefinic CH 5.47–5.93 p.p.m. Its picrate was crystallized from methanol, m.p. 173–174.5°.

Anal. Calcd. for $C_{21}H_{21}O_7N_5$: C, 55.38; H, 4.65; N, 15.38. Found: C, 55.63; H, 4.66; N, 15.40.

Reduction of 200 mg. of the salt Ib and crystallization of the product from petroleum ether gave 118 mg. of solid. Recrystallizations from the same solvent as well as from aqueous methanol yielded IIb, m.p. 119–122°; p.m.r. spectrum ($CDCl_3$): (*ind*)–NH 8.44 p.p.m., (*ind*)–α-H 6.88 p.p.m., olefinic CH 5.46 (broad) p.p.m., ethyl CH_2 1.35 p.p.m., ethyl CH_3 1.03 p.p.m.

Anal. Calcd. for $C_{17}H_{22}N_2$: C, 80.27; H, 8.72; N, 11.01. Found: C, 79.97; H, 8.43; N, 11.45.

Its picrate was crystallized from methanol, m.p. 161–163°.

Anal. Calcd. for $C_{23}H_{25}O_7N_5$: C, 57.13; H, 5.12; N, 14.49. Found: C, 57.29; H, 5.35; N, 14.59.

Reduction of 710 mg. of the salt Ic and crystallization of the crude product from petroleum ether gave 340 mg. of crystalline IIc, m.p. 124–126°; p.m.r. spectrum ($CDCl_3$): (*ind*)–NH 8.04 p.p.m., olefinic CH 5.48–5.98 p.p.m., (*ind*)–α-CH_3 2.25 p.p.m.

Anal. Calcd. for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39; N, 11.66. Found: C, 79.72; H, 8.37; N, 11.54.

Its picrate was crystallized from methanol; m.p. 176–178°.

Anal. Calcd. for $C_{22}H_{23}O_7N_5$: C, 56.28; H, 4.94; N, 14.92. Found: C, 56.51; H, 4.95; N, 15.01.

Reduction of 600 mg. of the salt Id and chromatography of the reaction mixture led to a pure liquid fraction of IId; p.m.r. spectrum ($CDCl_3$): (*ind*)–α-H 6.83 p.p.m., olefinic CH 5.47–6.00 p.p.m., (*ind*)–NCH_3 3.67 p.p.m., which was characterized as its picrate, m.p. 151–152.5° upon crystallization from methanol.

Anal. Calcd. for $C_{22}H_{23}O_7N_5$: C, 56.28; H, 4.94; N, 14.92. Found: C, 56.25; H, 5.15; N, 14.95.

Reduction of 200 mg. of the salt Ie and crystallization of the crude product from hexane–chloroform yielded crystalline IIe, m.p. 126.5–128°; p.m.r. spectrum ($CDCl_3$): (*ind*)–NH 8.63 p.p.m., (*ind*)–α-H 6.96 p.p.m., olefinic CH 5.96 p.p.m., CCH_3 1.48 p.p.m.

Anal. Calcd. for $C_{19}H_{24}O_2N_2$: C, 73.04; H, 7.74; N, 8.93. Found: C, 73.10; H, 7.45; N, 8.63.

A solution of 260 mg. of the amine IIe, 20 ml. of methanol and 6 ml. of water, to which enough 0.5 *N* hydrochloric acid had been added to bring the solution to *p*H 3, was stirred under nitrogen at room temperature for 2.5 hr. The mixture was made basic with 10% sodium hydroxide solution and was extracted with chloroform. The extract was dried over sodium sulfate and evaporated to dryness. Crystallization of the product from methanol yielded 130 mg. of the ketone IIf, m.p. 186–190°; spectra: ultraviolet (95% ethanol), λ_{max} 223 mμ (log ε 4.61), 276–278 mμ (log ε 3.72), 283 mμ (log ε 3.75) and 292 mμ (log ε 3.69), λ_{min} 256 mμ (log ε 3.46) and 289 mμ (log ε 3.65); infrared ($CHCl_3$ or Nujol), C=O 6.01(s)μ.

Anal. Calcd. for $C_{17}H_{20}ON_2$: C, 76.08; H, 7.51; N, 10.44. Found: C, 75.99; H, 7.37; N, 10.60.

A mixture of 300 mg. of the salt Ia and 1.20 g. of sodium borohydride in 20 ml. of diglyme was stirred for 2 hr. at room temperature under nitrogen. The mixture was concentrated almost to dryness under vacuum, basified with 40 ml. of 5% sodium hydroxide solution and extracted with ether. A solution of the extract, 30 ml. of *N* hydrochloric acid and 3 ml. of acetic acid were heated on a steam-bath under nitrogen for 30 min. The mixture was basified and extracted with chloroform. The extract was dried over magnesium sulfate, the solvent removed and the products chromatographed on 30 g. of deactivated alumina. The further work-up and characterization of the products followed that of the lithium aluminum hydride reduction of Ia (*vide infra*). Compounds IIa, 22 mg., m.p. 150–152°, and IVa, 12 mg., m.p. 140–143°, were obtained.

Piperidines III.—The hydrogenations of compounds II were carried out over Adams catalyst in ethanol solution.[5]

Tetrahydropyridine IIa, 95 mg., was reduced (10 mg. of platinum oxide in 20 ml. of ethanol) to IIIa, 80 mg., m.p. 149–150° (lit.[5] m.p. 151–152°) on crystallization from aqueous methanol as well as petroleum ether; picrate, m.p. 169.5–171°. Both substances had infrared and p.m.r. spectra identical with those of authentic samples[5] and

(11) T. Hoshino and K. Skimodaira, *Ann.*, **520**, 19 (1935).

(12) M. W. Bullock and S. W. Fox, *J. Am. Chem. Soc.*, **73**, 5155 (1951).

(13) F. E. King and P. L'Ecuyer, *J. Chem. Soc.*, 1901 (1934).

(14) Z. Pelchowicz and E. D. Bergmann, *ibid.*, 4699 (1960).

(15) K. Eiter and O. Svierak, *Monatsh.*, **83**, 1453 (1952).

(16) S. Sugasawa and M. Kirisawa, *Pharm. Bull. Japan*, **3**, 190 (1955).

showed no m.p. depression on admixture with the latter. (However, neither was there a m.p. depression on admixture with the starting material and its picrate, respectively.)

Hydrogenation of 100 mg. of IIb in 15 ml. of ethanol over 10 mg. of platinum oxide and crystallization of the product from petroleum ether yielded 60 mg. of IIIb, m.p. and m.m.p. 112–113.5°, spectra identical with those of an authentic sample.[1]

Reduction of 100 mg. of IIc in 20 ml. of ethanol over 12 mg. of platinum oxide and crystallization of the product from petroleum ether and aqueous methanol gave 70 mg. of IIIc, m.p. and m.m.p. 101–103°, spectra identical with those of an authentic sample.[1]

Compound IId, 150 mg., was hydrogenated (18 mg. of platinum oxide in 25 ml. of ethanol) to an oily mixture whose chromatography on alumina yielded two non-crystalline fractions. Both were converted to picrates. One gave 40 mg. of an unidentified picrate, m.p. 191–192°, which was not investigated further. The other afforded 55 mg. of IIId picrate, m.p. and m.m.p. 146–147° (with sample below) on crystallization from methanol.

Anal. Calcd. for $C_{22}H_{25}O_7N_5$: C, 56.04; H, 5.35; N, 14.86. Found: C, 56.05; H, 5.55; N, 14.91.

A mixture of 800 mg. of methyl 3-(1-methylindolyl)-acetate and 6 ml. of piperidine was refluxed under nitrogen for 40 hr. The excess piperidine was removed by distillation. A mixture of the crude product and 1.0 g. of lithium aluminum hydride in 150 ml. of ether was refluxed for 4 hr. under nitrogen. The reaction mixture was decomposed with a slurry of solid sodium sulfate saturated with water and filtered. The ether solution was dried, evaporated and the residue chromatographed on 50 g. of alumina. Elution with benzene gave an oil whose conversion to a picrate which was crystallized from methanol yielded 1.10 g. of IIId picrate, m.p. 146–147°.

A mixture of 32 mg. of IIf and 7 mg. of 10% palladium–charcoal in 100 ml. of ethanol was hydrogenated. Filtration and evaporation of the solvent yielded 30 mg. of an oil which crystallized on trituration with ether. Crystallization of the solid from ether yielded ketone IIIf, m.p. 130–132°. It gave no m.p. depression on admixture with an authentic sample[6] and its infrared spectrum was identical with that of the latter.

Lithium Aluminum Hydride Reductions.—The following procedure represents the best reaction conditions found by preliminary experiments to lead to optimum yields of products. Lithium aluminum hydride was added to a suspension of the pyridinium salt I in ether and the mixture stirred under nitrogen at room temperature for 1–2 hr. A wet sodium sulfate slurry was added and the mixture filtered. Thereupon *N* hydrochloric acid was added and the mixture heated under nitrogen on a steam-bath for 30 min. It was made alkaline and extracted with chloroform. The extract was dried over magnesium sulfate and evaporated. The residue was chromatographed on deactivated alumina. All products II were identified by m.p., m.m.p. with authentic samples from the sodium borohydride reductions of I (*vide supra*) and by comparison of infrared spectra.

The salt Ia, 200 mg., was reduced with 125 mg. of lithium aluminum hydride in 30 ml. of ether and the product treated with 20 ml. of acid. Chromatography of the crude product mixture on 50 g. of alumina and elution with 1:5 petroleum ether–benzene yielded 54 mg. of IIa, m.p. 151–152° on crystallization from petroleum ether. Elution with benzene gave 33 mg. of a new solid. Crystallizations from petroleum ether as well as aqueous methanol afforded IVa, m.p. 144–144.5°; p.m.r. spectrum ($CDCl_3$): (*ind*)-NH 7.70 p.p.m., olefinic CH 5.37–5.97 p.p.m.; picrate, m.p. 184–187° on crystallization from methanol.

Anal. Calcd. for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 79.99; H, 7.17; N, 12.63.

The reduction of 1.00 g. of Ib with 625 mg. of hydride in 200 ml. of ether and treatment of the product with 100 ml. of acid led to a mixture whose chromatography on 55 g. of alumina and elution with 50:1 benzene–ether yielded first 372 mg. of IIb, m.p. 119–122° on crystallization from aqueous methanol, then 40 mg. of mixed fractions and finally 43 mg. of a new solid. Crystallization of the latter from petroleum ether gave IVb, m.p. 143–145°: p.m.r. spectrum ($CDCl_3$), (*ind*)-NH 7.70 p.p.m., olefinic CH 5.42 (broad) p.p.m., ethyl CCH_3 1.03 p.p.m. (triplet, J = 6.8 c.p.s.).

Anal. Calcd. for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 80.71; H, 8.00; N, 11.19.

The salt Ic, 200 mg., was reduced with 125 mg. of hydride in 30 ml. of ether and the product treated with 20 ml. of acid. Chromatography of the unpromising looking crude mixture on 60 g. of alumina yielded only 45 mg. of IIc, m.p. 125–126° on crystallization from petroleum ether.

Reduction of 1.00 g. of Id with 625 mg. of hydride in 200 ml. of ether and follow-up treatment with 100 ml. of acid yielded a product whose chloroform solution was filtered through 3 g. of alumina and the solvent evaporated. A solution of the residue in 40 ml. of ethanol was hydrogenated over 40 mg. of platinum oxide. After cessation of hydrogen uptake, the solvent and catalyst were removed and the residue chromatographed on 150 g. of alumina. The only product was a homogeneous oil, 400 mg., which yielded Vc picrate, m.p. 198–200° on crystallization from methanol, identical in all respects with a sample produced in the following manner.

A mixture of 90 mg. of Va and 100 mg. of potassium in 10 ml. of dry benzene was refluxed under nitrogen for 7 hr. Upon cooling, 2 ml. of methyl iodide was added and the mixture stirred at room temperature for 16 hr. The mixture was concentrated into a molecular still, whereupon the residue was heated at 300° for 30 min. A 1:1 benzene–chloroform solution of the distillate was filtered through 3 g. of alumina and evaporated. Formation of a picrate of the residual oil, 72 mg., and crystallization from methanol led to Vc picrate, m.p. 198–200°.

Anal. Calcd. for $C_{22}H_{23}O_7N_5$: C, 56.28; H, 4.94; N, 14.92. Found: C, 56.32; H, 5.10; N, 15.00.

Reductions and Oxidations of Amines IV.—A solution of 120 mg. of IVa in 20 ml. of ethanol was hydrogenated over 10 mg. of platinum oxide. After removal of the catalyst and the solvent and crystallization of the residue from petroleum ether, 90 mg. of a solid was obtained. Recrystallization of the latter from the same solvent as well as from aqueous ethanol led to Va, m.p. and m.m.p. 151–152°. Its infrared spectrum was identical with that of an authentic sample.[1]

A similar hydrogenation of 110 mg. of IVb led to a mixture whose chromatography on 40 g. of alumina and 20:1 benzene-ether elution yielded 85 mg. of partly oily and in part solid fractions. Crystallization of the solid from ethanol afforded crystalline Vb, m.p. and m.m.p. 161–163°, whose infrared spectrum was identical with that of an authentic sample.[1] A mixture of 75 mg. of the stereoisomeric mixture Vb and 375 mg. of mercuric acetate in 6 ml. of 5% acetic acid was heated at 80° under nitrogen for 3 hr. Hydrogen sulfide treatment, work-up and perchlorate salt formation of the product followed standard procedure.[1] Crystallization of the resulting solid, 54 mg., from ethanol yielded VI, m.p. 217–220° (lit.[10] m.p. 221–223°).

Anal. Calcd. for $C_{17}H_{21}O_4N_2Cl$: C, 57.86; H, 5.96; N, 7.94. Found: C, 57.86; H, 5.99; N, 8.11.

A mixture of 45 mg. of IVb, 154 mg. of maleic acid and 22 mg. of palladium-black in 2 ml. of water was heated at 100° for 24 hr. Methanol was added to the heating mixture to dissolve all organic matter and the hot mixture filtered through glass wool. A solution of 1 g. of sodium perchlorate in 2 ml. of water was added to the filtrate, being cooled in an ice bath. The mixture was left standing in the bath for 1 hr. and the precipitate filtered, washed with cold water and dried under vacuum for 6 hr. Crystallization of the solid, 65 mg., from ethanol yielded 5,6-dihydroflavopereirine perchlorate (VII), m.p. 278–281°; ultraviolet spectrum (95% ethanol), λ_{max} 222 mμ (log ε 4.43), 252 mμ (log ε 3.99), 316 mμ (log ε 4.13) and 392 mμ (log ε 4.11), λ_{min} 243 mμ (log ε 3.94), 272 mμ (log ε 3.62) and 342 mμ (log ε 3.89).[10]

Anal. Calcd. for $C_{17}H_{17}O_4N_2Cl$: C, 58.54; H, 4.91; N, 8.03. Found: C, 58.67; H, 4.82; N, 7.81.

Lithium Tri-*t*-butoxyaluminohydride Reductions.—A mixture of 400 mg. of Ia and 1.76 g. of hydride in 25 ml. of dry tetrahydrofuran was stirred at room temperature under nitrogen for 2.5 hr. A slurry of 20 g. of sodium sulfate saturated with water was added, the mixture filtered and 20 ml. of *N* hydrochloric acid added to the filtrate. The mixture was left standing under nitrogen at room temperature for 2 hr. and then was heated on a steam-bath for 45 min. The cooled solution was brought to *p*H 12 with 10% sodium hydroxide solution and extracted with chloroform. The extract was dried over sodium sulfate and evaporated. The

residual yellow oil was chromatographed on 50 g. of alumina. This led to 90 mg. of IVa, m.p. and m.m.p. 145–146° on crystallization from petroleum ether, and 14 mg. of IIa, m.p. and m.m.p. 150–152° on crystallization from the same solvent.

A similar reduction of 210 mg. of Ib with 837 mg. of hydride yielded 58 mg. of IVb, m.p. and m.m.p. 144–146° on crystallization from petroleum ether.

The infrared and p.m.r. spectral properties of all products were identical with those of samples described above.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, URBANA, ILL.]

Stereochemistry of the Formation and Decomposition of 1-Pyrazolines[1]

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Thermal decomposition of 3-carbomethoxy-*cis*-3,4-dimethyl-1-pyrazoline (**7**) proceeds with loss of geometry to give, in addition to unsaturated products, both 1-carbomethoxy-*cis*-1,2-dimethylcyclopropane (**14**) and 1-carbomethoxy-*trans*-1,2-dimethylcyclopropane (**13**). Light-induced decomposition of the same 1-pyrazoline results in stereospecific formation in high yield of 1-carbomethoxy-*cis*-1,2-dimethylcyclopropane (**14**), together with some methyl tiglate. Formation of the latter compound arises from a formal reversal of the addition of diazomethane to an unsaturated ester. 3-Carbomethoxy-*trans*-3,4-dimethyl-1-pyrazoline (**6**) behaves analogously to pyrazoline (**7**).

Addition of diazomethane to double bonds activated by a suitable electron-withdrawing group, followed by thermal decomposition of the resulting pyrazolines, is an established route to cyclopropanes,[3-5] although the synthetic utility of the method is hampered by extensive formation of unsaturated compounds in the pyrolysis step.[3-13] von Auwers and König studied the stereochemistry of the preparation of cyclopropanes by this method, and concluded that when the intermediate pyrazolines are 1-pyrazolines, the cyclopropanes formed retain the geometry of the initial olefins.[14,15] Recent studies have focused on the more complex problem of the stereochemistry of cyclopropane formation in cases where the intermediate pyrazoline is a conjugated 2-pyrazoline.[16-18] The explanation advanced for the results of these studies is based on the assumption that 1-pyrazolines indeed decompose with retention of geometry, as reported by von Auwers and König.[15] However, major errors in the analytical results of von Auwers and König in other cases have been demonstrated,[8,9] so re-investigation of their results with presently available analytical tools probably is advisable.

Stereochemistry of 1-Pyrazoline Formation.—Formation of 1-pyrazolines by the addition of diazomethane to double bonds "activated" by electron-withdrawing groups is often described as a *cis* addition,[3-5] but only one study of this point has been made.[14] In this study the stereochemistry of the reaction was examined by the addition of diazomethane to pairs of isomeric α,β-unsaturated esters. The first pair, dimethyl citraconate and dimethyl mesaconate, on treatment with diazomethane gave two liquid 1-pyrazolines, presumably *cis*-3,4-dicarbomethoxy-3-methyl-1-pyrazoline (**1a**) and *trans*-3,4-dicarbomethoxy-3-methyl-1-pyrazoline (**2a**), respectively. These pyrazolines had identical physical constants,[14] but they were reported to give different products on pyrolysis.[15] 3,4-Dicarbomethoxy-4-methyl-2-pyrazoline (**3**) was obtained from both esters.[14] In the case of the other ester pair, treatment of dimethyl dimethylmaleate with diazomethane gave a low-melting 1-pyrazoline, supposedly *cis*-3,4-dicarbomethoxy-3,4-dimethyl-1-pyrazoline (**4**), while dimethyl dimethylfumarate and diazomethane yielded a liquid 1-pyrazoline reported to be *trans*-3,4-dicarbomethoxy-3,4-dimethyl-1-pyrazoline (**5**). Steric structures were not determined experimentally; *cis* addition was assumed because stereospecific *trans* addition could not be envisioned. No examination of the degree of stereospecificity was made. Similarly, addition of diphenyldiazomethane to dimethyl citraconate[19] and to dimethyl mesaconate[19,20] has also been reported to produce different pyrazolines (**1b** and **2b**).

In the present work addition of diazomethane to methyl angelate and to methyl tiglate produced 3-carbomethoxy-*trans*-3,4-dimethyl-1-pyrazoline (**6**) and 3-carbomethoxy-*cis*-3,4-dimethyl-1-pyrazoline (**7**), respectively. These were shown to be different by their n.m.r. spectra (Fig. 1), and by

(1) (a) Presented in part at the 138th Meeting of the American Chemical Society, New York, N. Y., Sept. 11–16, 1960; *cf.* Abstracts of Papers, p. 9P. (b) Portions of the present work dealing with the formation and photolysis of pyrazolines have appeared as a brief communication [K. L. Rinehart, Jr., and T. V. Van Auken, *J. Am. Chem. Soc.*, **82**, 5251 (1960)]. (c) The earliest brief description of the present results including pyrolyses is that of D. Wedegaertner, University of Illinois Organic Seminar Abstracts, Summer Session (June 22), 1960, p. 1.

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