converted into the 3,5-dinitrobenzoate which melted at 78.5–79.5° after crystallization from ethanol.

Anal. Calcd. for $C_{27}H_{40}O_{16}N_2$: C, 58.66; H, 7.30; N, 5.07. Found: C, 58.61; H, 7.27; N, 5.22.

γ-Acetoxy-γ,γ-dicarbethoxybutyraldehyde, VI.—This reaction was carried out essentially as described for compound III. The crude product was not distilled. However, it formed a 2,4-dinitrophenylhydrazone which melted at 114–115° after crystallization from ethanol.

Anal. Calcd. for $C_{18}H_{22}O_{10}N_4$: C, 47.55; H, 4.89; N, 12.33. Found: C, 47.69; H, 4.86; N, 12.33.

The Addition of Ethyl Bromomalonate to Acrolein: A. In the Presence of Sodium Ethoxide.—Ethyl bromomalonate (47.6 g.) was added to an alcoholic solution containing 200 cc. of absolute ethanol and 80 mg. of sodium. The resulting alcoholic solution was cooled to 0° and 11.5 g. of acrolein was added dropwise. After the acrolein had been added it was observed that the reaction mixture was acidic. Hence, an additional 0.5 g. of metallic sodium dissolved in ethanol was added. The reaction mixture was still acidic and an additional 4 g. of metallic sodium dissolved in approximately 100 cc. of absolute ethanol was added. The reaction mixture was permitted to stand in the refrigerator overnight. A considerable quantity of precipitate was noted, and it was removed by filtration. The resulting light brown filtrate was evaporated *in vacuo*. The residual oil was diluted with benzene and an additional quantity of the inorganic precipitate was removed by filtration. The benzene solution was extracted with three 70-cc. portions of water and then dried over anhydrous sodium sulfate. After filtration the benzene was removed by distillation *in vacuo* yielding a residual light yellow oil. The treatment of a portion of this residual oil with 2,4-dinitrophenylhydrazine yielded a crystalline derivative which melted at 137–139°. Recrystallization from absolute ethanol increased the melting point to 141.5–142.5°. However, this 2,4-dinitrophenylhydrazone did not contain bromine. Elementary analysis indicated that it was the 2,4-dinitrophenylhydrazone of 4,4-dicarbethoxy-3-butenal.

Anal. Calcd. for $C_{16}H_{18}O_8N_4$: C, 48.75; H, 4.61; N, 14.21. Found: C, 48.61; H, 4.60; N, 13.81.

A portion of the above residual light yellow oil (29 g.) was distilled *in vacuo*. The main fraction (13 g.) was collected at 78–85° (0.05–0.06 mm.). A portion (4.4 g.) of the distilled product was dissolved in 25 cc. of absolute ethanol, and 0.4 g. of 5% palladium-on-charcoal was added. The reduction was carried out at an initial pressure of 27 pounds of hydrogen and after twenty minutes the reduction was complete. The catalyst was removed by filtration and a portion of the alcoholic filtrate was employed in the preparation of the 2,4-dinitrophenylhydrazone which melted at 75–76° after crystallization from ethanol. There was no depression in the melting point when mixed with the 2,4-dinitrophenylhydrazone of γ,γ-dicarbethoxybutyraldehyde.

B. In the Presence of Tributylamine.—Ethyl bromomalonate (43.2 g.) was dissolved in 220 cc. of absolute ethanol and the solution was cooled to 2°. Tributylamine (0.5 g.) was added. Acrolein (10.5 g.) was added over a fifteen-minute period. No appreciable increase in the temperature of the reaction mixture was observed. After ninety minutes an additional quantity (0.15 g.) of tributylamine was added. The resulting reaction mixture was placed in the refrigerator overnight and then acidified with 5 cc. of glacial acetic acid. After filtration the filtrate was concentrated *in vacuo* to yield a brown oil. The residual oil was dissolved in 200 cc. of benzene and the benzene solution was washed with four 60-cc. portions of water. After drying over anhydrous sodium sulfate the benzene was removed by distillation *in vacuo* yielding 40.4 g. of a light yellow oil. The resulting oil was subjected to distillation under diminished pressure, and the desired fraction was collected at 97–100° (0.12 mm.), $n^{25}D$ 1.4665. A portion of the distilled product was treated with 2,4-dinitrophenylhydrazine and the resulting 2,4-dinitrophenylhydrazone was obtained in the form of light yellow platelets melting at 81–82.5°. After purification by recrystallization from absolute ethanol, the product melted at 82.5–83.5°.

Anal. Calcd. for $C_{16}H_{19}O_8N_4Br$: C, 40.42; H, 4.02; N, 11.79; Br, 16.82. Found: C, 40.82; H, 4.16; N, 11.75; Br, 16.82.

Summary

1. The 1,4-addition reaction involving malonate systems and acrolein has been extended to ethyl malonate and ethyl cyanoacetate which possess two α-hydrogen atoms and the resulting aldehydo compounds have been characterized.

2. The addition reactions of ethyl hexylmalonate, ethyl decylmalonate, ethyl acetoxymalonate and ethyl bromomalonate to acrolein have been described.

3. The structure of γ,γ-dicarbethoxybutyraldehyde, resulting from the 1,4-addition of ethyl malonate to acrolein, has been proved by an unequivocal synthesis.

MINNEAPOLIS, MINNESOTA RECEIVED JUNE 19, 1948

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY OF THE NATIONAL RESEARCH COUNCIL]

The Papilionaceous Alkaloids. V. *Baptisia minor*, Lehm.[1]

BY LÉO MARION AND W. F. COCKBURN

Baptisia minor, Lehm., is blue-flowered like *B. australis*, but smaller-leaved and it has for many years been taken as identical with the latter although it had originally been considered as specifically distinct. Recently it has again been claimed to be a species (*B. vespertina*),[2] still more recently a variety of *B. australis*[3] and, finally, it has been restored to specific rank.[4] It was, therefore, of interest to investigate the alkaloids of this plant. The results of the chemical study now reported support the more recent taxonomical evidence that the plant is specifically distinct from *B. australis*.

In common with *B. australis*,[5] *B. minor* contains *d*-sparteine, cytisine and N-methylcytisine, but it also contains anagyrine, baptifoline and alkaloid P4, all three of which are absent in the former. While alkaloid P4 is present in insufficient amount to permit satisfactory characterization, baptifoline, which is also present in *B. per-*

(1) Published as National Research Council Bull. No. 1732.

(2) P. A. Rydberg, "Flora of the Prairies and Plains of Central North America," The New York Botanical Garden, 1938, p. 456.

(3) M. L. Fernald, *Rhodora*, **39**, 312 (1937).

(4) Mary M. Larisey, *Ann. of the Missouri Botan. Garden*, **27**, 119 (1940).

(5) L. Marion and J. Ouellet, THIS JOURNAL, **70**, 691 (1948).

foliata,[6] seems to be the main alkaloid of *B. minor*. Baptifoline has been characterized by the preparation of a number of salts; although the salts are readily obtained, the base is difficult to crystallize as it seems to undergo some decomposition during the process. Its melting point and those of its salts were depressed by admixture with thermopsine and its corresponding salts.

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Experimental

The plant used in this investigation was grown at the Dominion Experimental Farm, Ottawa, through the courtesy of Dr. H. A. Senn, which is gratefully acknowledged. The dried and ground material (wt. 2157 g.) was extracted in soxhlets with methanol and the extract worked up as described previously.[5] It yielded an ether extract (A) containing non-basic material and a chloroform extract (B) containing the crude alkaloids.

Isolation of a Neutral Substance.—The ether extract (A) on evaporation, yielded a substance that crystallized from boiling methanol in rosettes of pale yellow needles, m.p. 231°.[7] This substance, which is soluble in aqueous sodium hydroxide, was not further investigated.

Anal. Calcd. for $C_{12}H_{14}O_8$: C, 50.35; H, 4.82. Found: C, 50.70, 50.86; H, 5.17, 5.05.

The chloroform extract (B) of the bases was evaporated to dryness and the residue digested with 10% hydrochloric acid (1 l.). The resulting solution was cooled, filtered through charcoal and extracted repeatedly with ether. It was then alkalized with ammonia and extracted with chloroform for thirty hours in a continuous liquid–liquid extractor. Removal of chloroform from the extract by distillation left the bases as a brown gum (wt. 6 g.). Distillation of the bases under reduced pressure (0.1 mm.) yielded the following fractions: I, b.p. up to 130°; II, b.p. 130–165°; III, b.p. 165–185°; IV, b.p. 185–230°; V, an undistilled residue. The residue was dissolved in dilute hydrochloric acid, the solution filtered, alkalized with ammonia and the liberated base recovered by extraction with chloroform and refractionated by distillation. It yielded another distillate which was combined with the corresponding fractions of the first distillate.

Isolation of *d*-Sparteine.—Fraction I consisted of an oil which on cooling separated into an upper colorless layer and a lower yellow layer. No mechanical separation was attempted, but the oil was dissolved in methanol and added to a solution of twice its own weight of picric acid in methanol. A picrate separated which, after several recrystallizations from boiling methanol, consisted of long yellow needles, m.p. 207–208°. Admixture with an authentic sample of *d*-sparteine dipicrate did not alter the melting point although admixture with *l*-sparteine dipicrate caused a depression. The base recovered from the picrate was a colorless oil, b.p. 80–90° (0.1 mm.), having $[\alpha]^{20}D$ + 17.0° (*c*, 1.029 in absolute ethanol). A small quantity of the free base was dissolved in methanol and the solution made just acid to congo red by the dropwise addition of 65% perchloric acid. The solution was evaporated almost to dryness, the residue dissolved in water and a few drops of ammonia added. A perchlorate crystallized immediately which, after recrystallization from methanol, melted at 173° either alone or after admixture with *d*-sparteine perchlorate. Altogether, 390 mg. of *d*-sparteine was isolated (0.018% yield).

Isolation of Cytisine.—Fraction II, an almost colorless oil, crystallized on standing. It was dissolved by refluxing with ether. On cooling, the solution deposited a crystalline base which after recrystallization from ether consisted of colorless needles melting at 155–156°, either alone or after admixture with an authentic sample of cytisine. The ether mother liquor was evaporated to dryness, the residue dissolved in methanol and added to a methanolic solution of picric acid. A picrate separated which, after several recrystallizations from boiling water, was obtained as feathery aggregates of yellow crystals, m.p. 288–289°. Admixture with cytisine picrate failed to depress the melting point.

Anal. Calcd. for $C_{11}H_{14}ON_2 \cdot C_6H_3O_7N_3$: C, 48.70; H, 4.08. Found: C, 48.54, 48.62; H, 4.18, 4.07. Total weight of cytisine, 270 mg. (yield, 0.013%).

Isolation of N-Methylcytisine.—The mother liquors from the purification of sparteine and cytisine were combined, the free base liberated and fractionally distilled. Besides further quantities of sparteine and cytisine, the distillate yielded a yellow oil, b.p. 130–145° (0.1 mm.), which was converted in methanolic solution to a picrate which, after recrystallization from methanol, melted at 234° either alone or after admixture with an authentic sample of N-methylcytisine picrate. The base recovered from a small quantity of the picrate, was converted to the perchlorate in methanolic solution by the usual procedure. A perchlorate crystallized as colorless needles; its melting point, 282°, was not depressed by admixture with an authentic sample of N-methylcytisine perchlorate; total weight of base, 17 mg. (yield, 0.0008%).

Isolation of Anagyrine.—Fraction III, a thick, yellow oil, was dissolved in methanol and the solution neutralized with 65% perchloric acid. The crystalline perchlorate that separated was recrystallized from boiling methanol; it consisted of fine, colorless needles, m.p. 315°, either alone or after admixture with an authentic sample of anagyrine perchlorate.[8]

Anal. Calcd. for $C_{15}H_{20}ON_2 \cdot HClO_4$: C, 52.25; H, 6.10. Found: C, 52.14; H, 6.24.

The base, liberated from a small quantity of the perchlorate, was converted in methanolic solution to the picrate which crystallized as yellow prisms. It melted at 249–251° and in admixture with anagyrine picrate (m.p. 253°), at 251–252°; weight of anagyrine, 34 mg. (yield, 0.0016%).

Isolation of Baptifoline.—Fraction IV, a yellow glass, was dissolved in methanol and the solution made just acid to congo red by the addition of 65% perchloric acid. Addition of ether to the resulting solution caused the separation of a brown oil from which the supernatant liquid was decanted. A mixture of ether and ethyl acetate was added to the oil and the mixture cooled in Dry Ice, with stirring, until the oil had solidified. The brown solid so obtained was boiled with a small quantity of methanol which removed the brown color, leaving a white crystalline solid that dissolved slowly in boiling methanol, from which it crystallized in hexagonal or triangular plates, m.p. 289.5°, $[\alpha]^{16}D$ −89.05° (*c*, 1.415 in water).

Anal. Calcd. for $C_{15}H_{20}O_2N_2 \cdot HClO_4$: C, 49.91; H, 5.86; N, 7.76. Found: C, 50.75, 50.65; H, 6.00, 5.93; N, 7.25, 7.14.

A small quantity of the above perchlorate was dissolved in water, the solution alkalized with ammonium hydroxide and extracted with chloroform. The base, left after evaporation of the chloroform, was dissolved in methanol and added to a methanolic solution of picric acid. A picrate separated as fine yellow needles which melted at 145° with evolution of gas, resolidified and melted again at 256°. Recrystallization from methanol failed to alter either of these two melting points. The picrate was dried *in vacuo* at 140° for analysis.

Anal. Calcd. for $C_{15}H_{20}O_2N_2 \cdot C_6H_3O_7N_3$: C, 51.52; H, 4.73; N, 14.31. Found: C, 51.30, 51.45; H, 4.33, 4.43; N, 12.69, 12.83.

A portion of the picrate was decomposed by shaking with

(6) L. Marion and F. Turcotte, THIS JOURNAL, **70**, 3253 (1948).

(7) All melting points are corrected.

(8) L. Marion and J. Ouellet, THIS JOURNAL, **70**, 3076 (1948).

hydrochloric acid and ether and the base obtained by alkalizing the aqueous solution with ammonia and extracting with chloroform. The redistilled base was dissolved in methanol, the solution neutralized to congo red with methanolic hydrogen chloride, concentrated to a small volume and diluted dropwise with acetone, just short of incipient turbidity. On standing, the solution deposited the base hydrochloride which after several recrystallizations from methanol–acetone consisted of rosettes of small, colorless needles, m. p. 322–323°. The hydrochloride which is soluble in chloroform can be sublimed unchanged and a small quantity was isolated from the original distillate.

Anal. Calcd. for $C_{15}H_{20}O_2N_2 \cdot HCl$: C, 60.67; H, 7.12; N, 9.44. Found: C, 60.68, 60.86; H, 6.98, 7.02; N, 8.83.

The pure base was liberated from the perchlorate; it crystallized from acetone–ligroin in parallelogram-shaped plates, m.p. 210°, $[\alpha]^{18}D$ −147.7° (*c*, 0.325 in absolute ethanol).

Anal. Calcd. for $C_{15}H_{20}O_2N_2$: C, 69.18; H, 7.74; N, 10.76. Found: C, 68.83, 68.63; H, 7.44, 7.60; N, 10.74. Total weight of baptifoline 380 mg. (yield, 0.018%). Owing to the difficulties of isolation, the yield given is probably low.

This base and its salts, in admixture with baptifoline isolated from *B. perfoliata*[6] and its corresponding salts, showed no depression in melting points.

Isolation of Alkaloid P4.—Refractionation of the base recovered from the baptifoline perchlorate mother liquors yielded an oil, b.p. 175–200° (0.05 mm.), from which a perchlorate was obtained as sheaves of colorless needles, m.p. 286°. This melting point was depressed by admixture with the perchlorates of anagyrine, cytisine or baptifoline. Insufficient material was obtained, however, for further investigation.

The mother liquors from the purification of the various fractions were systematically worked up and refractionated, but no bases other than those already described could be isolated. In all cases, the yields given are the final figures after complete examination of the residues.

Summary

1. *Baptisia minor*, Lehm., has been found to contain six alkaloids, three only of which are present in *B. australis*, *i.e.*, *d*-sparteine, cytisine and N-methylcytisine.

2. The remaining three bases are anagyrine, baptifoline and alkaloid P4. Baptifoline, first found in *B. perfoliata*, has been better characterized.

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[CONTRIBUTION FROM THE SOUTHERN RESEARCH INSTITUTE AND BRISTOL LABORATORIES]

Local Anesthetics: N-Dialkylaminoalkylimides of Naphthalic and Diphenylmaleic Acids

BY ALBERT M. MATTOCKS[1a] AND OLIVIA S. HUTCHISON[1b]

It has been reported by Moore and Rapala[1] that N-dialkylaminoalkylphthalimides are effective local anesthetics. In view of this and the fact that compounds containing larger aromatic nuclei frequently possess greater activity than their benzene analogs, it was believed important that N-dialkylaminoalkylimides of aromatic acids with large nuclei be investigated.

N-Dialkylaminoalkylimides of naphthalic and diphenylmaleic acids were synthesized by treating the corresponding dialkylaminoalkyl chlorides with sodium or potassium salts of the imides, or by the reaction of the dialkylaminoalkylamines with anhydrides.[1]

Pharmacological screening for local anesthetic activity was carried out in rabbits by the corneal and intradermal wheal tests. Subcutaneous toxicity ranges were determined on mice.

Experimental

Syntheses

N-Diethylaminoethylnaphthalimide.—A solution of 9.94 g. (0.152 mole) potassium hydroxide (85%) in 200 cc. alcohol was added to a hot alcoholic solution of 30 g. (0.152 mole) of naphthalimide,[2] and the mixture was stirred with gentle heating until quantitative precipitation had occurred, also about 37 g. (0.26 mole) diethylaminoethyl chloride was added and the mixture refluxed for thirty minutes. The grayish salt gradually reacted, going into solution with the appearance of an orange color. After it had cooled to room temperature, the solution was filtered to remove potassium chloride and the alcohol evaporated at reduced pressure. The residue was then subjected to a pressure of 1 mm. and a temperature of 100° to remove excess diethylaminoethyl chloride. The residual solid was redissolved in alcohol and treated with excess alcoholic hydrogen chloride; on cooling, yellow crystals of N-diethylaminoethylnaphthalimide hydrochloride precipitated. The product was recrystallized from isopropanol.

N-Dimethylaminoethylnaphthalimide and N-morpholinoethylnaphthalimide were prepared by the above procedure.

N-Diethylaminopropylnaphthalimide.—A mixture of 30 g. (0.152 mole) of naphthalic anhydride[3] and 19.7 g. (0.152 mole) of diethylaminopropylamine was heated at 165° for one hour. This mixture was then transferred to a beaker and dissolved in a mixture of equal parts isopropanol and benzene. The solution was washed with water and dried over sodium sulfate, the solvents and unreacted amine were removed by vacuum distillation, and the residue was redissolved in hot alcoholic hydrogen chloride. On cooling, yellow crystals of N-diethylaminopropylnaphthalimide hydrochloride precipitated. The product was recrystallized from isopropanol.

N-Diethylaminoethyldiphenylmaleimide.—Twenty grams (0.092 mole) of diphenylmaleimide[4] was added to a solution of sodium methoxide (prepared by dissolving 2.13 g. (0.092 mole) of sodium in 100 cc. of absolute methanol), the mixture was stirred at room temperature for one hour, and 25 g. (0.185 mole) of diethylaminoethyl

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(1b) The authors gratefully acknowledge the assistance of Anne Stelzenmuller who carried out the toxicity tests and of Mathilde Ramsey who performed the analyses.

(1) M. B. Moore and R. T. Rapala, THIS JOURNAL, **68**, 1657 (1946).

(2) G. F. Jaubert, *Ber.*, **28**, 360 (1895).

(3) C. Graebe and E. Gfeller, *ibid.*, **25**, 652 (1892).

(4) P. M. Bartholdy, *ibid.*, **40**, 4400 (1907).