treatment with alcoholic potassium hydroxide followed by acidification furnished a substance, in which it was believed that a lactone ring had been opened, while boiling with alkali provided a steam-volatile base together with a nitrogen-containing acid. Precise experimental details for these reactions were not recorded nor were any physical constants listed with the exception of the melting point (m.p. 105°) of the alkaloid itself. As no further publications on this subject have appeared since 1925, we have repeated the isolation of this substance and have established its structure.[7]

In our hands, julocrotine showed m.p. 108–109°, $[\alpha]_D$ −9° (chloroform), −50° (methanol), and the analytical results were more in concordance with the empirical formula $C_{18}H_{24}N_2O_3$ rather than Anastasi's[5] $C_{19}H_{26}N_2O_3$. In the strict sense of the word, julocrotine is not really an alkaloid since it does not possess any titratable basic nitrogen atom and we were unable to prepare any salts of it. The ultraviolet absorption spectrum was typical of an isolated benzene ring, while the infrared spectrum contained characteristic bands at 2.93 μ (sharp), 5.76 μ (weak to medium), 5.93 μ (strong), and 6.65 μ (strong). The absorption in the carbonyl region did not appear to be due to a ketonic function, since the substance exhibited only a plain negative optical rotatory dispersion curve.[8] Functional group analysis indicated the absence of a methoxyl function and the presence of two C-methyl groups. Paper chromatographic analysis[9] of the volatile acids from the Kuhn-Roth oxidation revealed the formation of both acetic and propionic acids, whereupon it may be concluded that julocrotine contains both a C-methyl and a C-ethyl group.

The presence of a benzene ring, already suggested by the ultraviolet absorption of julocrotine, was confirmed by catalytic hydrogenation with platinum oxide in acetic acid. This resulted in the uptake of three molar equivalents of hydrogen and the formation of hexahydrojulocrotine (II), which was now transparent in the ultraviolet.

Of considerable diagnostic value was the lithium aluminum hydride reduction of julocrotine ($C_{18}H_{24}N_2O_3$), leading to an oxygen-free base, $C_{18}H_{30}N_2$ (subsequently shown to be III), which now lacked the four characteristic infrared bands of julocrotine at 2.93, 5.76, 5.93, and 6.65 μ. In contrast to the nonbasic julocrotine, the lithium aluminum hydride reduction product contained two basic nitrogen functions as demonstrated by the formation of a dipicrate and a dimethiodide. The loss of the three oxygen atoms with the simultaneous generation of two basic nitrogens can be rationalized[10] most readily by the presence in julocrotine of an amide as well as of an imide moiety, the infrared bands at 5.76 and 5.93 μ being assigned to them. The presence of at least one secondary amide is indicated by the sharp band at 2.93 μ in julocrotine as well as the absorption at 6.65 μ attributable[11] to the N—H deformation of secondary amides.

Catalytic hydrogenation of the base $C_{18}H_{30}N_2$ (III) again caused the uptake of three equivalents of hydrogen with production of a hexahydro base $C_{18}H_{36}N_2$ (IV), which could also be obtained from hexahydrojulocrotine (II) by treatment with lithium aluminum hydride. The empirical formula of the saturated base $C_{18}H_{36}N_2$ (IV) requires that in addition to the benzene nucleus, there be present in julocrotine a second ring. For the sake of simplicity, we shall present the further discussion of the degradative evidence in terms of the eventually established formulation I for julocrotine, its lithium aluminum hydride reduction product being III, while their respective hexahydro derivatives can be represented by expressions II and IV.

The ready availability of the basic transformation product $C_{18}H_{30}N_2$ (III) suggested application of the classic Hofmann degradation and for this purpose the base was transformed into its "dimethiodide" V[12] and then boiled with 40% potassium hydroxide. The neutral product of this reaction was presumably styrene (VI), since upon oxidation with permanganate at room tempera-

(1) Paper XXIV in the series "Alkaloid Studies" (preceding paper, B. Gilbert, L. D. Antonaccio, A. A. P. G. Archer, and C. Djerassi, *Experientia*, **16**, 61 (1960)), and paper V in the series "Estudios sobre Plantas" (preceding paper, O. O. Orazi and R. A. Corral, *Anales Asoc. Quím. Argentina*, **44**, 193 (1956)).

(2) The work at Wayne State University was supported by grant No. H-2574 from the National Heart Institute, National Institutes of Health, U. S. Public Health Service.

(3) (a) Department of Chemistry, Stanford University, Stanford, Calif.; (b) Facultad de Química y Farmacia, Universidad Nacional de la Plata, La Plata, Argentina.

(4) Recipient of a Fulbright travel grant while on leave from the University of Kyoto.

(5) C. Anastasi, *Anales Asoc. Quim. Argentina*, **13**, 348 (1925).

(6) Subsequently, this alkaloid was also encountered in other *Julocroton* species such as J. *subpannosus* and J. *camporum* (unpublished results of A. Novelli cited by A. Novelli and O. O. Orazi, *Rev. Farmacéutica (Buenos Aires)* **92**, 109 (1950)).

(7) For preliminary communication see T. Nakano, C. Djerassi, R. A. Corral, and O. O. Orazi, *Tetrahedron Letters*, No. **14**, 8 (1959).

(8) See C. Djerassi, *Optical Rotatory Dispersion: Applications to Organic Chemistry*, McGraw-Hill Book Co., New York, 1960, especially chapter 16.

(9) C. F. Garbers, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, **37**, 1336 (1954); H. Bickel, H. Schmid and P. Karrer, *Helv. Chim. Acta*, **38**, 649 (1955).

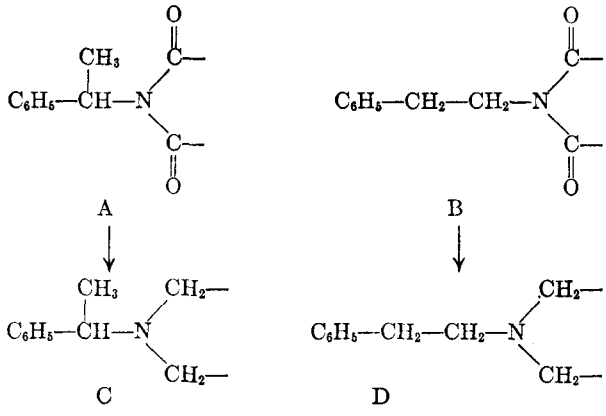
(10) For pertinent references see J. Rudinger and M. Ferles, *Hydrid Lithno-Hlinity*, Czechoslovak Academy, Prague, 1956, pp. 411–450; N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience, New York, 1956, Chap. 10.

(11) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Wiley, New York, 1958, 2nd ed., Chap. 12.

(12) The substance is actually formulated (see V) as the monomethiodide of the hydroiodide of the *N*-methylated base.

ture it furnished benzoic acid. The basic companion product was represented by an optically active amine $C_{12}H_{26}N_2$, which was further characterized as its dipicrate. The amine was saturated (no hydrogen uptake upon attempted hydrogenation with platinum oxide in acetic acid solution) and by analysis was shown to contain two *N*-methyl functions. On the basis of structure I (*vide infra*) for julocrotine, we formulate it, therefore, as 1-methyl-3-(*N'*-methyl-*N'*-β-methylbutyl)aminopiperidine (VII).

At this stage of our knowledge of julocrotine, the results of the Hofmann degradation can only be interpreted as implying the presence of partial structure A or B in the parent substance, lithium aluminum hydride treatment converting it into C or D, which upon quaternization and Hofmann elimination would yield styrene (VI) and a basic fragment corresponding in terms of empirical formula to VII.



A secure differentiation between partial structures A and B should be possible by hydrolytic cleavage of the imide linkage, which would then yield[13] either α- or β-phenylethylamine. Indeed, when julocrotine was heated under reflux with methanolic potassium hydroxide, β-phenylethylamine (VIII) could be isolated, whereupon it can be concluded that partial structure B must be represented in the complete expression for julocrotine.

The next question, namely whether the imide moiety in B was cyclic or open chain, could be answered by the results of the same alkali cleavage experiment. The principal product of this alkaline hydrolysis was acidic and upon methylation, followed by crystallization and resaponification could be separated into two isomeric acids, which we have named julocrotic acid-A and acid-B. Their structures will be discussed below in connection with synthetic studies, but at this point it need only be emphasized that the empirical formula ($C_{18}H_{26}N_2O_4$) of these two acids, which contained no basic nitrogen atom, when contrasted with that ($C_{18}H_{24}N_2O_3$) of julocrotine itself, clearly showed that they must have arisen by *alternate hydrolytic opening of an unsymmetrical cyclic imide.*

In order to determine the size of the imide ring, *N*-β-phenylethylsuccinimide and *N*-β-phenylethylglutarimide were synthesized and their infrared spectra determined. The former exhibited a weak band at 5.63 μ and a strong one at 5.85 μ, while the corresponding bands of *N*-β-phenylethylglutarimide occurred at 5.78 μ (weak) and 5.96 μ (strong).[14] As noted in the beginning of the present article, the infrared spectrum of julocrotine (I) is characterized by a weak band at 5.76 μ and a very strong one at 5.93 μ. It follows, therefore, that julocrotine must be a substituted glutarimide derivative. The *N*-β-phenylethylglutarimide portion of the molecule accounts for thirteen of the eighteen carbon atoms of julocrotine; at least four carbon atoms are represented by the secondary amide function, whose presence has already been demonstrated (infrared spectrum and course of lithium aluminum hydride reduction), and the C-methyl and C-ethyl groupings (from the paper chromatographic results of the Kuhn-Roth oxidation). Hence only one carbon atom remains to be defined.

Anastasi[5] has already remarked on the liberation of volatile acids from the dilute sulfuric acid treatment of julocrotine. While his assumption of the presence of butyric and valeric acids is not tenable on the basis of the structural information already accumulated, the isolation and definite characterization of a volatile acid would appear to afford the remaining clue to the complete structure elucidation of julocrotine. In our hands, the optimum conditions for the complete acid hydrolysis of julocrotine involved heating for twenty-four hours with a mixture of dioxane and concentrated hydrochloric acid. Aside from β-phenylethylamine (VIII), there was obtained a volatile acid as well as an amino acid. The volatile acid was identified as (+)-α-methylbutyric acid (IX) by direct comparison with authentic specimens of the anilide and *p*-bromoanilide of (+)-α-methylbutyric acid. The amino acid proved to be identical with L-(+)-glutamic acid (X), thus establishing unambiguously structure I for julocrotine.

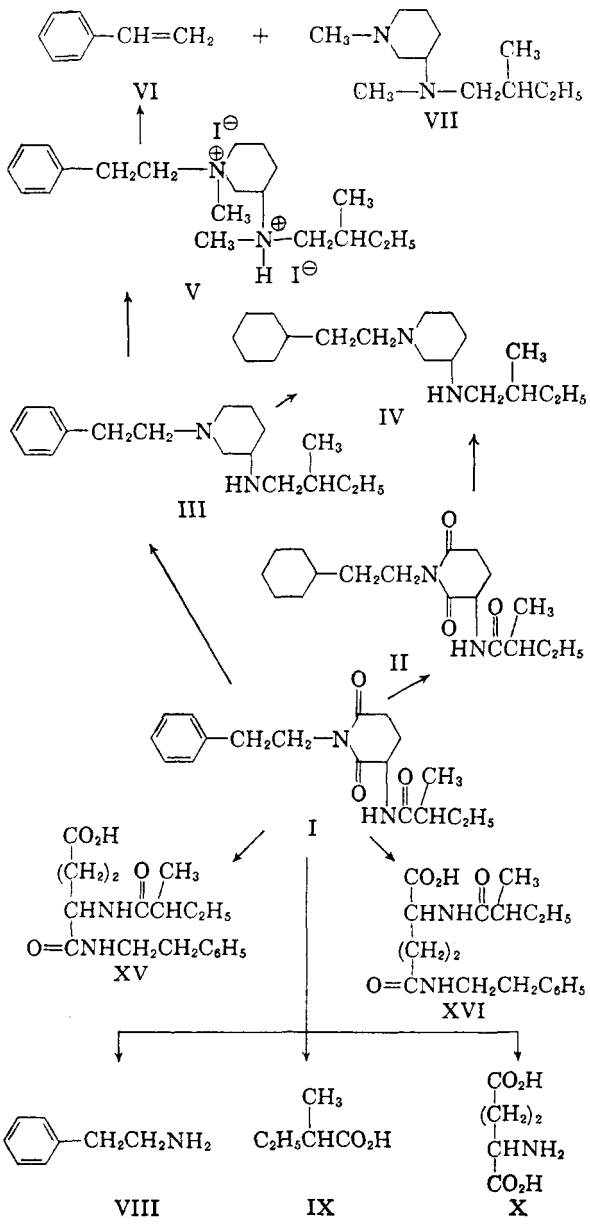
In an attempt to synthesize julocrotine, L-(+)-glutamic acid (X) was transformed into its diethyl ester and treated with (+)-α-methylbutyryl chloride. The resulting *N*-α-methylbutyryl glutamic acid diethyl ester (XIIa) was heated[15] with β-phenyl-

(13) It should be recalled that already Anastasi (Ref. 5) had noted the liberation of an unidentified volatile base upon heating julocrotine with alkali.

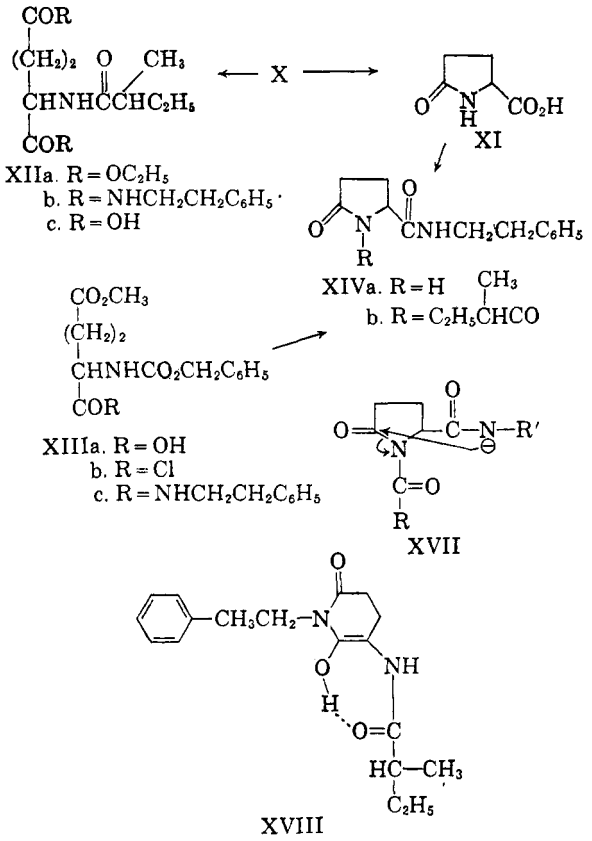
(14) Subsequent to these measurements, there appeared two articles in which the positions of the infrared bands of a number of other substituted succinimides and glutarimides were reported: H. K. Hall and R. Zbinden, *J. Am. Chem. Soc.*, 80, 6428 (1958); V. M. Clark, A. W. Johnson, I. O. Sutherland, and A. Todd, *J. Chem. Soc.*, 3283 (1958).

(15) See R. Child and F. L. Pyman, *J. Chem. Soc.*, 2010 (1929).

ethylamine, but the only product was the corresponding β-phenylethylamide XIIb. As an alternate procedure, the diethyl ester XIIa was hydrolyzed to *N*-α-methylbutyryl glutamic acid (XIIc), which was then transformed to the anhydride by heating with acetic anhydride. The crude anhydride was immediately heated without a solvent with β-phenylethylamine to yield predominantly the diamide XIIb in partially racemized form. From the mother liquors, there was isolated in poor yield a substance, whose analysis coincided with that of julocrotine and whose infrared spectrum was very similar to that of natural julocrotine (I). However, it melted over a wide range (m.p. 96–105°) and its rotation ($[\alpha]_D$ +2.7° *vs.* −50° for julocrotine) indicated extensive racemization of at least one asymmetric center. It would appear, therefore, that the synthetic compound was structurally but not stereochemically identical with julocrotine.



The relative ease of racemization (under alkaline conditions) of amides of glutamic acid has already been commented upon in the literature.[16] This appears to be true at times under acidic conditions as well since in the dioxane–hydrochloric acid cleavage of julocrotine (I), the resulting L-(+)-glutamic acid (X) was usually partially racemized. On the other hand, natural L-(+)-glutamic acid (X) or the diethyl ester of *N*-α-methylbutyryl glutamic acid (XIIa) yielded optically pure L-(+)-glutamic acid under the same conditions. It is conceivable that partial racemization is facilitated in cyclic imides of glutamic acid by hydrogen bonding in an intermediate such as XVIII.



As an alternate synthetic approach leading to julocrotic acid, γ-methyl *N*-carbobenzyloxy-L-glutamate (XIIIa)[17] was converted into its acid chloride XIIIb and thence, by addition of β-phenylethylamine, into its β-phenylethylamide XIIIc. In an attempt to remove the carbobenzyloxy blocking group, the amide XIIIc was subjected to hydrogenolysis with palladium black in methanol

(16) (a) E. Sondheimer and R. W. Holley, *J. Am. Chem. Soc.*, 76, 2467 (1954); *J. Am. Chem. Soc.*, 79, 3767 (1957); (b) A. R. Battersby and J. C. Robinson, *J. Chem. Soc.*, 259 (1955).

(17) W. E. Hanby, S. G. Waley, and J. Watson, *J. Chem. Soc.*, 3239 (1958); R. A. Boissonnas, S. Guttmann, P. A. Jaquenoud, and J. P. Waller, *Helv. Chim. Acta*, 38, 1491 (1955).

containing a small amount of acetic acid. Evaporation of the solution to dryness and recrystallization afforded in 54% yield a very weakly basic product. The analysis indicated that cyclization had occurred, possibly during the evaporation of the hydrogenolysis solution, and the structure of 2-ketopyrrolidine-5-carboxylic acid β-phenylethylamide (XIVa) was proved by direct comparison with an authentic specimen prepared by successive treatment of 2-ketopyrrolidine-5-carboxylic acid[18] (XI) with thionyl chloride and then with β-phenylethylamine.

The above pyrrolidone XIVa was now acylated with (+)-α-methylbutyryl chloride to *N*-(α-methylbutyryl)-2-ketopyrrolidine-5-carboxylic acid β-phenylethylamide (XIVb). Alkaline hydrolysis of this pyrrolidone afforded in 32% yield an acid, m.p. 120–122°, $[\alpha]_D$ +10.7°, methyl ester, m.p. 148–149°, $[\alpha]_D$ −3.4°, which proved to be identical with julocrotic acid-A (and its methyl ester), the prodiminant product of the alkaline cleavage of julocrotine (I). Julocrotic acid-A can be either the α-glutamyl (XV) or γ-glutamyl (XVI) amide and a probable differentiation seems possible with the following information. Thus, it has been shown[19] that 1-acyl-2-ketopyrrolidine-5-carboxylic acid amides of type XIVb may give rise to a mixture of the direct cleavage product, the α-glutamyl derivative, and the rearranged γ-isomer. The latter is usually[20] the predominant hydrolysis product of glutarimides of the type exemplified by julocrotine (I) and Battersby and Robinson[19] have pointed out that rearrangement of acylpyrrolidones to glutarimides is clearly feasible through the path indicated in XVII.

While julocrotic acid-A was obtained only in 32% yield by alkaline hydrolysis of the pyrrolidone XIVb, countercurrent distribution of the mother liquors provided only a trace of a second isomer which was insufficient for further work. In the alkaline cleavage of julocrotine (I), in addition to julocrotic acid-A, a second isomer, julocrotic acid-B could be isolated. It has been pointed out[19,20] that the γ-isomers (*e.g.* XVI) are considerably stronger acids than the α-isomers (*e.g.* XV). Using this criterion, julocrotic acid-A (pK_a 6.3) should be assigned structure XVI and julocrotic acid-B (pK_a 6.95) should be represented by XV. It appears, therefore, that alkaline hydrolysis of *N*-(α-methylbutyryl)-2-ketopyrrolidine-5-carboxylic acid β-phenylethylamide (XIVb) proceeds to a considerable extent by rearrangement (*via* XVII) to afford julocrotic acid-A (XVI).[21] It is pertinent to mention that saponification of the methyl ester of julocrotic acid-A (XVI) is not accompanied by rearrangement.

Finally, it is worth noting that while the occasional occurrence of glutamine and two related amides of glutamic acid has been mentioned in the phytochemical literature,[22] julocrotine (I) represents a rather unique structure among plant products.

EXPERIMENTAL[23]

Isolation of julocrotine (I). The dried and powdered roots (1 kg.) of *Julocroton montevidensis* Klotzsch[24] were heated under reflux for 6 hr. with 4 l. of alcohol, the mixture was filtered and the process was repeated three times. The combined extracts were evaporated to dryness and the residue (75 g.) was extracted continuously in a soxhlet extractor with petroleum ether (b.p. 60–70°). Upon cooling, a precipitate separated which was combined with a second crop obtained upon concentration of the mother liquors, thus totalling 13 g. Two recrystallizations from ether–petroleum ether afforded 6.2 g. of faintly colored julocrotine, m.p. 103–105°. The analytical sample, obtained after sublimation at 160–165°/0.25 mm. and repeated recrystallization, exhibited m.p. 108–109°, $[\alpha]_D$ −9° (*c*, 1.24 in chloroform), −50.1° (*c*, 1.19 in methanol), $\lambda_{max}^{CHCl_3}$ 2.93 (sharp), 5.76 (w), 5.93 (s), 6.65 μ (s), $\lambda_{max}^{C_2H_5OH}$ 252, 258, 264, and 268 mμ, log ε 2.43, 2.44, 2.30, and 2.18, $\lambda_{min}^{C_2H_5OH}$ 250, 256, 263, and 267 mμ, log ε 2.41, 2.37, 2.27, and 2.16; R.D.[8] in methanol (*c*, 0.691): $[\alpha]_{589}$ −49°, $[\alpha]_{500}$ −74°, $[\alpha]_{400}$ −150°, $[\alpha]_{350}$ −205°, $[\alpha]_{300}$ −362°. Electrometric titration[25] did not show any titratable basic nitrogen nor did titration with perchloric acid in acetic acid solution.

Anal. Calcd. for $C_{18}H_{24}N_2O_3$: C, 68.32; H, 7.64; N, 8.85; O, 15.17; C—CH_3, 4.75; mol. wt., 316. Found: C, 68.09; H, 7.72; N, 9.03; O, 15.41; OCH_3, 0.0; C—CH_3, 6.11;[26] Rast mol. wt., 309.

Hexahydrojulocrotine (II). Julocrotine did not consume any hydrogen at 30° in methanol solution in the presence of 5% palladized charcoal, but when 17.2 mg. of I was hydrogenated in 5 cc. of acetic acid with platinum oxide catalyst at 30° and atmospheric pressure, 3 equivalents of hydrogen were taken up within 20 min. The catalyst was filtered, the filtrate was made basic with ammonia solution and the product was extracted with ether. After washing, drying, and evaporation, the residue was recrystallized from ether-hexane to afford 13 mg. of colorless crystals, m.p. 94–95°, $[\alpha]_D$ −5.2° (*c*, 0.98 in chloroform), which did not exhibit any selective absorption in the ultraviolet; $\lambda_{max}^{CHCl_3}$ 2.93 (sharp), 5.76 (w), 5.93 (s) and 6.65 μ (s).

Anal. Calcd. for $C_{18}H_{30}N_2O_3$: C, 67.04; H, 9.37; N, 8.68; O, 14.88. Found: C, 66.79; H, 9.33; N, 8.40; O, 14.93.

(18) E. Abderhalden and K. Kautzsch, *Z. Physiol. Chem.*, **68**, 487 (1910).

(19) A. R. Battersby and J. C. Robinson, *J. Chem. Soc.*, 2076 (1955). See also G. Amiard, R. Heymes and L. Velluz, *Bull. Soc. Chim. France*, 97 (1956).

(20) D. W. Clayton, G. W. Kenner, and R. C. Sheppard, *J. Chem. Soc.*, 371 (1956).

(21) In our preliminary communication (Ref. 7), julocrotic acid-A had been assigned tentatively structure XV since *p*K measurements had not been performed at that time.

(22) W. Karrer, *Konstitution und Vorkommen der organischen Pflanzenstoffe*, Birkhäuser, Basel, 1958, pp. 404 and 967.

(23) Melting points were determined on the Kofler block. We are indebted to Miss B. Bach for the infrared spectra and to Dr. A. Bernhardt, Mülheim, Germany, for the microanalyses.

(24) We are indebted to Prof. José F. Molfino and Prof. Manuel G. Escalante for botanical identification of material collected by Mr. Carlos A. Sieyra in Entre Rios, Argentina, and by Mr. A. G. Schulz in Chaco, Argentina.

(25) Grateful acknowledgment is made to Dr. H. Boaz of Eli Lilly & Co. for the electrometric titrations.

(26) Paper chromatographic determination (Ref. 9) showed the presence of acetic and propionic acids.

1-β-Phenylethyl-3-(β-methylbutyl)aminopiperidine (III). A solution of 0.5 g. of julocrotine in 200 cc. of ether was added to 1.1 g. of lithium aluminum hydride dissolved in 150 cc. of ether and the mixture was heated under reflux for 22 hr. The excess reagent was decomposed with ethyl acetate, a concentrated aqueous solution of sodium sulfate was added to precipitate inorganic salts followed by the addition of anhydrous sodium sulfate. The solution was filtered, extracted with 5% hydrochloric acid, the latter was made basic with dilute ammonia and again extracted with ether. After drying, the ether was evaporated and the resulting 0.44 g. of oil was distilled at a bath temperature of 110–120°/0.005 mm., $[\alpha]_D$ −12.6° (*c*, 1.47 in chloroform), −4.4° (*c*, 1.27 in methanol). The characteristic infrared bands listed above for julocrotine had disappeared.

Anal. Calcd. for $C_{18}H_{30}N_2$: C, 78.77; H, 11.01; N, 10.28; C—CH_3, 5.48. Found: C, 78.10; H, 10.92; N, 9.84; C—CH_3, 8.10.

The *dipicrate* was obtained by treatment of a portion of III with picric acid in ethanol-ether followed by recrystallization from methanol; m.p. 186–187°.

Anal. Calcd. for $C_{18}H_{30}N_2 \cdot 2C_6H_3N_3O_7$: C, 49.17; H, 4.95; N, 15.29. Found: C, 49.39; H, 5.29; N, 15.14.

1-β-Cyclohexylethyl-3-(β-methylbutyl)aminopiperidine (IV). (a) *By catalytic hydrogenation of 1-β-phenylethyl-3-(β-methylbutyl)aminopiperidine* (III). The catalytic hydrogenation of III (17.2 mg.) was performed exactly as described above for julocrotine and the total crude product was dissolved in methanol and a few drops of concd. hydrochloric acid were added. After evaporation to dryness and two recrystallizations from methanol-acetone, the *dihydrochloride* melted at 285–286° dec. in sealed capillary.

Anal. Calcd. for $C_{18}H_{36}N_2 \cdot 2HCl \cdot 0.5H_2O$: C, 59.64; H, 10.84; N, 7.73; Cl, 19.56. Found: C, 59.31; H, 10.37; N, 8.38; Cl, 19.30.

The above hydrochloride was dissolved in a few drops of water, a saturated aqueous solution of sodium picrate was added and the resulting precipitate of the *dipicrate* was recrystallized from methanol whereupon it exhibited m.p. 178–180°.

Anal. Calcd. for $C_{18}H_{36}N_2 \cdot 2C_6H_3N_3O_7$: C, 48.77; H, 5.73; N, 15.17. Found: C, 48.57; H, 5.67; N, 14.85.

(b) *By lithium aluminum hydride reduction of hexahydrojulocrotine* (II). Hexahydrojulocrotine (140 mg.) was reduced with lithium aluminum hydride as described above for julocrotine and the resulting basic oil was distilled at 100–110°/0.008 mm. The oil yielded a hydrochloride, m.p. 285–286° dec. and a dipicrate, m.p. 178–180°, which proved to be identical by mixture melting point determination with the specimen described under (a).

Hofmann degradation of 1-β-phenylethyl-3-(β-methylbutyl)-aminopiperidine (III). A solution of 0.3 g. of the amine III and 0.9 g. of methyl iodide in 10 cc. of methanol was heated under reflux for 1 hr. After standing overnight at room temperature, addition of acetone and ether caused the separation of 0.17 g. of crystals. The filtrate was treated again with 0.3 g. of methyl iodide yielding a further 0.26 g. of crystals. Recrystallization from methanol afforded the analytical sample of the methiodide *N*-methyl hydroiodide V[12] of m.p. 226–227°.

Anal. Calcd. for $C_{20}H_{36}I_2N_2$: C, 43.02; H, 6.48; N, 5.06; I, 45.46. Found: C, 42.59; H, 6.82; N, 4.82; I, 45.75.

The above salt (1.59 g.) was boiled for 2 hr. with 80 cc. of 40% aqueous potassium hydroxide solution and after cooling, the mixture was extracted with ether. The organic layer was extracted with 5% aqueous hydrochloric acid which was made alkaline with dilute ammonia and extracted with ether. The ether solution was washed with water until neutral, dried, and evaporated to afford 0.54 g. of *1-methyl-3-(N'-methyl-N'-β-methylbutyl)aminopiperidine* (VII), which was distilled at a bath temperature of 70–80°/1.5 mm., $[\alpha]_D$ +7° (*c*, 0.76 in methanol). Microhydrogenation with platinum oxide in acetic acid confirmed the absence of any double bond.

Anal. Calcd. for $C_{12}H_{26}N_2$: C, 72.66; H, 13.21; N, 14.12; 2N—CH_3, 15.19. Found: C, 72.09; H, 13.12; N, 14.68; N—CH_3, 16.31.

A small amount of the amine was dissolved in ether and treated with a solution of picric acid in ethanol-ether. Recrystallization of the resulting precipitate from ethanol-acetone afforded the *dipicrate*, m.p. 227–228°.

Anal. Calcd. for $C_{12}H_{26}N_2 \cdot 2C_6H_3N_3O_7$: C, 43.90; H, 4.91; N, 17.06; O, 34.11; 2 N—CH_3, 4.57. Found: C, 43.63; H, 5.00; N, 17.15; O, 34.17; N—CH_3, 4.99.

The original ether solution (after extraction with 5% hydrochloric acid) was dried and to it was added at room temperature over a period of 6 hr. a 4% solution of potassium permanganate in acetone until the purple color persisted (*ca.* 50 cc.). After acidification with 5% hydrochloric acid, the excess reagent was decomposed by the addition of sodium sulfite, the resulting clear solution was washed with water, and the organic layer was extracted with 10% aqueous sodium bicarbonate. Acidification of this extract followed by ether extraction afforded 0.15 g. of *benzoic acid*, m.p. 121–122°. Identity was established in the usual manner.

Alkali cleavage of julocrotine. Isolation of β-phenylethylamine (VIII) *and julocrotic acids* (XV, XVI). Julocrotine (1.76 g.) was heated under reflux for 3 hr. with 100 cc. of 10% methanolic potassium hydroxide in a current of nitrogen. The mixture was diluted with water, most of the methanol was removed *in vacuo* and the solution was extracted thoroughly with ether. The latter was washed with 5% hydrochloric acid, the washings were made alkaline and re-extracted with ether. Evaporation yielded 0.11 g. of a basic oil which was transformed into its picrate (m.p. 168–169°) undepressed upon admixture with β-phenylethylamine picrate. Furthermore, an oxalate was obtained (m.p. 197–198° after recrystallization from aqueous ethanol), whose melting point was undepressed when mixed with authentic β-phenylethylamine oxalate.

Anal. Calcd. for $2C_8H_{11}N \cdot C_2H_2O_4$: C, 65.03; H, 7.27; N 8.42. Found: C, 65.02; H, 7.58; N, 8.37.

The original aqueous alkaline solution was acidified with hydrochloric acid and extracted with ethyl acetate. The acidic material obtained upon evaporation of the washed and dried ethyl acetate solution was directly methylated with ethereal diazomethane to afford 1.61 g. of a crystalline mass of methyl ester. Two recrystallizations from benzene-ether gave 0.45 g. of *julocrotic acid-A* (XVI) *methyl ester*, m.p. 148–149°, $[\alpha]_D$ −4.0° (*c*, 0.97 in methanol), $\lambda_{max}^{CHCl_3}$ 2.99, 3.10, 5.75, 6.00, and 6.62 μ, the ultraviolet absorption spectrum being very similar to that of julocrotine.

Anal. Calcd. for $C_{19}H_{28}N_2O_4$: C, 65.49; H, 8.10; N, 8.04; O, 18.36; OCH_3, 8.90. Found: C, 65.63; H, 7.85; N, 8.20; O, 18.20; OCH_3, 8.48.

A portion of the methyl ester was saponified by heating under reflux for 1 hr. with 25 cc. of 5% methanolic sodium hydroxide solution. After acidification and extraction with ethyl acetate, there was obtained *julocrotic acid-A* (XVI), which exhibited after recrystallization from ether–ethyl acetate m.p. 119–122°, $[\alpha]_D$ +14.4° (*c*, 0.973 in methanol), $\lambda_{max}^{CHCl_3}$ 2.82, 3.03, 5.75, 5.98, and 6.55 μ; R.D.[8] in methanol (*c*, 0.627): $[\alpha]_{589}$ +12.1°, $[\alpha]_{500}$ +17.5°, $[\alpha]_{400}$ +32.5°, $[\alpha]_{350}$ +52.3°, $[\alpha]_{300}$ +96.3°. Methylation with diazomethane regenerated the original methyl ester, m.p. 148–149°, thus showing that saponification of the methyl ester to the acid had not involved any rearrangement.

Anal. Calcd. for $C_{18}H_{26}N_2O_4$: C, 64.64; H, 7.83; N, 8.37; O, 19.13; mol. wt., 334. Found: C, 64.20; H, 7.78; N, 8.60; O, 19.21; OCH_3, 0.0; pK_a 6.3[25] (initial *p*H in 66% dimethylformamide solution 4.6; mol. wt. 325 by electrometric titration).

The mother liquors from the crystallization of julocrotic acid-A methyl ester deposited 50 mg. of crystals, which after recrystallization from benzene-ether had m.p. 133–134°. The infrared spectrum was identical with that of julocrotic acid-A methyl ester, but a mixture melting point

was depressed to 116–124° and it is conceivable (see also Discussion) that this may represent partially racemized material. Lack of substance precluded further work.

Anal. Found for $C_{19}H_{28}N_2O_4$: C, 65.52; H, 8.16; N, 8.02; O, 18.32; OCH_3, 8.46.

Further concentraton of the filtrate produced 100 mg. of gel-like crystals, which were hydrolyzed directly with 5% methanolic sodium hydroxide to yield after recrystallization from ether–ethyl acetate 70 mg. of *julocrotic acid-B* (XV), m.p. 133.5–135°, $[\alpha]_D$ +10.9° (*c*, 0.275 in methanol), λ_{max}^{Nujol} 3.05, 5.85, 5.98, 6.10 μ (insolubility in chloroform precluded measurements in that solvent); R.D. in methanol (*c*, 0.474): $[\alpha]_{589}$ +10.5°, $[\alpha]_{500}$ +15.6°, $[\alpha]_{400}$ +28.6°, $[\alpha]_{300}$ +69.6°.

Anal. Found for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.90; N, 8.51; O, 19.21; OCH_3, 0.0; pK_a 6.95[25] (initial *p*H in 66% dimethylformamide solution 5.1; mol. wt. by electrometric titration 321).

Acid hydrolysis of julocrotine. A solution of 1.3 g. of julocrotine was heated under reflux with a mixture of 70 cc. of dioxane and 21 cc. of concd. hydrochloric acid for 24 hr., diluted with water and extracted with chloroform (*extract A*). The aqueous layer was evaporated to dryness *in vacuo*, taken up in water, made alkaline (*p*H 9–11) with aqueous sodium hydroxide and extracted with ether (*extract B*). The aqueous solution was now acidified to Congo Red with hydrochloric acid and again evaporated to dryness under reduced pressure. The residue was dissolved in 200 cc. of water and transferred to a 29 × 2.7 cm. column of Amberlite IRA-400 (80 g.) in the chloride form, which had been transformed to the acetate by treating with 3*M* sodium acetate solution until no further turbidity developed in the filtrate on addition of an acidic solution of silver nitrate; prior to use, the resin was washed thoroughly with water. Elution from the resin column was performed with 0.5*N* aqueous acetic acid. Evaporation to dryness under diminished pressure and recrystallization of the residue from aqueous ethanol afforded 0.41 g. of *glutamic acid* (X), m.p. 184–185°, $[\alpha]_D$ +17.2° (*c*, 0.888 in 1*N* aqueous hydrochloric acid).[27]

Anal. Calcd. for $C_5H_9NO_4$: C, 40.81; H, 6.16; N, 9.52; O, 43.59. Found: C, 40.79; H, 6.24; N, 9.45; O, 43.27.

A mixture melting point determination with authentic L-(+)-glutamic acid (m.p. 195–196°, $[\alpha]_D$ +32.1° (*c*, 0.89 in 1*N* aqueous hydrochloric acid) showed no depression. The two specimens gave identical infrared spectra (Nujol) as well as identical R_f values by paper chromatography (descending technique) on Whatman No. 1 paper using the solvent system *n*-butyl alcohol-acetic acid–water (4:1:2).

The chloroform *extract A* was washed with 2% sodium hydroxide, the alkaline washes were acidified and extracted with chloroform to afford after distillation 0.40 g. of an acid. This was heated under reflux for 30 min. with 0.6 g. of thionyl chloride, cooled, a solution of 2.5 g. of *p*-bromoaniline in 30 cc. of benzene was added, and the mixture warmed on the steam bath for a few minutes. The benzene solution was then washed with dilute acid, sodium hydroxide, water, dried, evaporated, and recrystallized from ether-hexane to give 0.46 g. of (+)-*α-methylbutyric acid* (IX) *p*-bromoanilide, m.p. 133–134°, $[\alpha]_D$ +31.3° (*c*, 0.78 in acetone). An authentic sample, prepared in identical fashion from (+)-α-methylbutyric acid derived from optically active amyl alcohol, exhibited m.p. 135–136°, $[\alpha]_D$ +31.4° (*c*, 0.735 in acetone); no depression in melting point was encountered upon mixing the two samples.

Anal. Calcd. for $C_{11}H_{14}BrNO$: C, 51.57; H, 5.50; Br, 31.19; N, 5.46; O, 6.25. Found: C, 51.31; H, 5.25; Br, 31.01; N, 5.30; O, 6.05.

In a second experiment, the volatile acid was transformed into its *anilide*, m.p. 98–99° (after sublimation and recrystallization from ether–petroleum ether (b.p. 40–60°)), $[\alpha]_D$ +39.5° (*c*, 0.87 in acetone), which was shown to be identical by direct comparison with an authentic specimen.[28]

The *ether extract B* was dried and evaporated to afford 0.39 g. of a basic oil which was transformed directly in its picrate (0.62 g.), m.p. 168–169°, undepressed when mixed with a sample of *β-phenylethylamine* picrate.

Attempted synthesis of julocrotine. (+)-α-Methylbutyryl chloride (1.3 g.)[29] was added to 5.0 g. of L-(+)-glutamic acid diethyl ester[30] in 20 cc. of benzene and the solution was kept at room temperature overnight before washing with 5% hydrochloric acid and then with 2% sodium hydroxide. The dried benzene solution was evaporated and the residue was recrystallized from ether-hexane, giving 2.6 g. of *N-α-methylbutyryl glutamic acid diethyl ester* (XIIa), m.p. 48–49°, $[\alpha]_D$ −17.1° (*c*, 1.07 in methanol), $\lambda_{max}^{CHCl_3}$ 2.93, 5.77 (s) and 5.95 (s) μ, λ_{max}^{Nujol} 3.05, 5.76, and 6.07 μ; R.D. in methanol (*c*, 0.088): $[\alpha]_{589}$ −23°, $[\alpha]_{400}$ −50°, $[\alpha]_{300}$ −86°, $[\alpha]_{265}$ −118°.

Anal. Calcd. for $C_{14}H_{25}NO_5$: C, 58.51; H, 8.77; N, 4.87; O, 27.84. Found: C, 58.80; H, 8.72; N, 5.34; O, 27.51.

The above diethyl ester XIIa (5.0 g.) was saponified by heating under reflux for 2 hr. with 250 cc. of 5% methanolic potassium hydroxide, diluted with water, acidified with 22 cc. of concd. hydrochloric acid, and evaporated to dryness *in vacuo*. The residue was extracted with hot acetone, filtered from sodium chloride, the acetone was evaporated, and the *N-α-methylbutyryl glutamic acid* (XIIc) was recrystallized from ether-hexane; yield, 3.98 g., m.p. 110–112°, $[\alpha]_D$ −3.4° (*c*, 0.52 in methanol).

Anal. Calcd. for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06; O, 34.60; neut. equiv., 115. Found: C, 51.65; H, 7.34; N, 6.26; O, 34.78; neut. equiv., 114.

The diethyl ester XIIa (2.0 g.) was heated[15] at 190° for 7 hr. under an air condenser with 2.4 g. of β-phenylethylamine (VIII). The crystalline mass possessed m.p. 192–194° after recrystallization from methanol and its infrared spectrum indicated the formation of the bisamide XIIb. Since further heating of such amides in the succinic acid series[15] had been shown to lead to cyclization with elimination of 1 equivalent of β-phenylethylamine, the entire product was heated for a further 6 hr. at 220°. Recrystallization of the total material from acetone-methanol furnished 0.8 g. of the *bisamide* XIIb, m.p. 193–194°, $[\alpha]_D$ +9.7° (*c*, 1.013 in methanol), $\lambda_{max}^{CHCl_3}$ 2.94, 3.04, and 6.00 μ. The mother liquor remained as a brown oil and no pure product could be isolated from it.

Anal. Calcd. for $C_{26}H_{35}N_3O_5$: C, 71.36; H, 8.06; N, 9.60; O, 10.97. Found: C, 71.77; H, 7.96; N, 9.83; O, 10.85.

As an alternate approach to the production of the desired glutarimide I, 1.75 g. of the *N-α*-methylbutyryl glutamic acid (XIIc) was boiled for 5 min. with 3 cc. of acetic anhydride and then evaporated to dryness *in vacuo* leaving the corresponding anhydride ($\lambda_{max}^{CHCl_3}$ 2.94, 5.50, 5.65, and 5.93 μ) as a viscous oil. This was heated at 170° for 1 hr. with 0.9 g. of β-phenylethylamine, cooled, taken up in benzene, and then washed successively with 5% hydrochloric acid, 2% sodium hydroxide, and water, dried, and evaporated. Recrystallization from methanol-ether afforded 0.22 g. of the *bisamide* XIIb, m.p. 187–192°, $[\alpha]_D$ +1.5° (*c*, 1.102 in methanol), $\lambda_{max}^{CHCl_3}$ 2.94, 3.04, and 6.00 μ. The melting point range could not be sharpened on further recrystallization and judging from the rotation partial racemization seemed to have occurred.

(27) In one experiment a rotation of +31.8° was obtained, but in two successive ones the rotations were considerably lower and indicated partial racemization (see Discussion section). Identical acid treatment of XIIa or of L-(+)-glutamic acid followed by purification through Amberlite afforded optically pure glutamic acid.

(28) R. H. Baker and L. E. Linn, *J. Am. Chem. Soc.*, **70**, 3721 (1948).

(29) J. Kenyon, H. Phillips, and V. P. Pittman, *J. Chem. Soc.*, 1080 (1935).

(30) E. Fischer, *Ber.*, **34**, 453 (1901).

Anal. Calcd. for $C_{26}H_{38}N_2O_3$: C, 71.36; H, 8.06; N, 9.60. Found: C, 71.15; H, 7.73; N, 9.60.

The combined mother liquors were evaporated to dryness and the residue (1.0 g.) was chromatographed on 36 g. of Merck acid-washed alumina. From the 1:1 benzene–ether eluates there was obtained 87 mg. of colorless crystals, m.p. 95–105°, $[\alpha]_D$ +2.7° (*c*, 1.01 in methanol), $\lambda_{max}^{CHCl_3}$ 2.93 (sharp), 5.73 (w), 5.93 (s) and 6.51 (s) μ; R.D.[8] in methanol (*c*, 0.113): $[\alpha]_{589}$ +11°, $[\alpha]_{400}$ +14°, $[\alpha]_{300}$ +25°, $[\alpha]_{275}$ +32°. The infrared spectrum of this product was very similar but not identical with that of natural julocrotine (I) and a mixture melting point showed m.p. 95–103°. It appears that the synthetic material represents partially racemized julocrotine and repeated recrystallization did not afford sharper melting crystals.

Anal. Calcd. for $C_{18}H_{24}N_2O_3$: C, 68.32; H, 7.64; N, 8.85. Found: C, 68.61; H, 7.51; N, 8.97.

Synthesis of julocrotic acid-A (XVI). To an ice-cold solution of 1.0 g. of γ-methyl *N*-carbobenzyloxy-L-glutamate (XIIIa)[17] in 5 cc. of anhydrous ether was added in portions with stirring 0.71 g. of powdered phosphorus pentachloride. After 20 min., a solution of 5.0 g. of β-phenylethylamine in 20 cc. of benzene was added dropwise with stirring and while cooling in ice water. The mixture was left overnight at room temperature, diluted with benzene, and washed first with 5% hydrochloric acid and then with 2% sodium hydroxide. The organic layer was washed with water, dried, evaporated (*in vacuo*), and the residue was recrystallized from ether-hexane to yield 1.02 g. of *γ-methyl N-carbobenzyloxy-L-glutamate α-(β-phenylethyl)amide* (XIIIc), m.p. 124–125°, $[\alpha]_D$ −8.6° (*c*, 1.106 in chloroform), $\lambda_{max}^{CHCl_3}$ 2.92, 5.75 (s) and 5.93 (s) μ.

Anal. Calcd. for $C_{22}H_{26}N_2O_5$: C, 66.31; H, 6.58; N, 7.03; O, 20.08. Found: C, 66.15; H, 6.36; N, 7.29; O, 20.11.

The above carbobenzyloxy derivative XIIIc (3.0 g.) was submitted to hydrogenolysis by dissolving in 140 cc. of 90% aqueous methanol containing a few drops of acetic acid and shaking the solution in a current of hydrogen at atmospheric pressure and room temperature in the presence of 0.9 g. of palladium black. After 8 hr., the solution was filtered and evaporated to dryness *in vacuo*. The residue was taken up in chloroform, dried over anhydrous potassium carbonate, again evaporated to dryness and crystallized from ether, leading to 0.563 g. of *2-ketopyrrolidine-5-carboxylic acid β-phenylethylamide* (XIVa), m.p. 140–142°. The mother liquor was evaporated to dryness, taken up in 5% aqueous hydrochloric acid, washed with ether, the aqueous phase was made alkaline with ammonia and extracted with chloroform. The latter was dried, evaporated to dryness[31] and the residue was crystallized from ether to afford an additional 0.521 g. of crystals, m.p. 140–142°. The analytical sample showed the same melting point, $[\alpha]_D$ −47° (*c*, 1.115 in chloroform), $\lambda_{max}^{CHCl_3}$ 2.93, 3.01, 5.83 (s), 5.95 (s), and 6.50 (s) μ.

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06; O, 13.73. Found: C, 66.84; H, 6.86; N, 11.98; O, 14.03; OCH_3, 0.0.

As an alternate approach to this substance, 0.4 g. of 2-ketopyrrolidine-5-carboxylic acid (XI) (prepared[18] from L-(+)-glutamic acid and possessing the following constants: m.p. 153–154°, $[\alpha]_D$ −11.2° (*c*, 1.06 in water), +3.9° (*c*, 1.02 in methanol)) was heated for 30 min. at 55° with 0.54 g. of thionyl chloride, the mixture was cooled and treated with a solution of 2.2 g. of β-phenylethylamine in 20 cc. of benzene. After standing for 20 min. at room temperature, the mixture was worked up in the usual manner and furnished 0.49 g. of XIVa, m.p. 138–139°, $[\alpha]_D$ −44.4° (*c*, 1.06 in chloroform). Identity with the above described specimen was demonstrated by mixture melting point determination and infrared comparison.

A solution of 1.972 g. of 2-ketopyrrolidine-5-carboxylic acid β-phenylethylamide (XIVa) and 3.0 g. of (+)-α-methylbutyryl chloride in 50 cc. of dry pyridine was kept at room temperature overnight and then diluted with benzene. After washing with dilute acid and base, water, drying, evaporating, and crystallizing from ether-hexane, there was obtained 2.2 g. of *N-(α-methylbutryl)-2-ketopyrrolidine-5-carboxylic acid β-phenylethylamide* (XIVb) with m.p. 102–104°. Repeated recrystallization provided the analytical sample, m.p. 105–107°, $[\alpha]_D$ −24.1° (*c*, 1.02 in methanol), $\lambda_{max}^{CHCl_3}$ 2.97, 3.04, 5.72 (s), 5.93 (s), and 6.55 (s) μ. Although the compound is isomeric with julocrotine (I) and possesses the same melting point, a mixture melting point showed a marked depression (m.p. 50–70°) and the infrared spectra were quite different.

Anal. Calcd. for $C_{18}H_{24}N_2O_3$: C, 68.32; H, 7.64; N, 8.85. Found: C, 68.12; H, 7.45; N, 8.92.

Hydrolysis of XIVb (0.983 g.) was effected by heating under reflux for 1 hr. with 50 cc. of 5% methanolic potassium hydroxide. The reaction mixture was concentrated *in vacuo* to remove most of the methanol and the residue was taken up in water, washed with ether, acidified with hydrochloric acid to Congo Red, and then extracted with ethyl acetate. The extract was dried, evaporated, and the residue was crystallized from ether–ethyl acetate to furnish crystals with m.p. 100–115°. Further recrystallization from ethyl acetate provided 0.332 g. of *julocrotic acid-A* (XVI), m.p. 120–122°, $[\alpha]_D$ +10.7° (*c*, 0.746 in methanol), $\lambda_{max}^{CHCl_3}$ 2.82, 3.03, 5.75, 5.98, and 6.55 μ. Identity with julocrotic acid-A derived from natural julocrotine (I) was established by infrared comparison and mixture melting point determination.

Anal. Calcd. for $C_{18}H_{26}N_2O_4$: C, 64.64; H, 7.83; N, 8.37. Found: C, 64.12; H, 7.41; N, 8.60.

Methylation with diazomethane in ether containing a small amount of methanol followed by recrystallization from ether-chloroform-hexane led to the *methyl ester*, m.p. 148–149°, undepressed when mixed with the methyl ester of julocrotic acid-A, $[\alpha]_D$ −3.4° (*c*, 0.902 in methanol). The infrared spectra were also identical.

Anal. Calcd. for $C_{19}H_{28}N_2O_4$: C, 65.49; H, 8.10; N, 8.04. Found: C, 65.14; H, 7.91; N, 8.35.

N-β-Phenylethylglutarimide. To 1.09 g. of glutarimide in 20 cc. of absolute ethanol was added a solution of 0.4 g. of potassium metal in 20 cc. of ethanol. The solution was evaporated to dryness under reduced pressure and the residue was heated with 2.2 g. of β-phenylethyl bromide for 3 hr. at 180–200°. The reaction mixture was poured into water, extracted with ether, washed, dried, and evaporated. Crystallization from ether-hexane produced 0.907 g. of the desired glutarimide, m.p. 84–85°, $\lambda_{max}^{CHCl_3}$ 5.78 (w) and 5.96 (s) μ.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45; O, 14.73. Found: C, 71.78; H, 6.98; N, 6.47; O, 14.90.

N-β-Phenylethylsuccinimide. Succinimide (1.0 g.) was treated exactly as described above for glutarimide and led to 0.953 g. of product, m.p. 130–131°, $\lambda_{max}^{CHCl_3}$ 5.63 (w) and 5.85 (s) μ. The same substance (m.p. 133–134°) had already been obtained earlier[15] by heating diethyl succinate with β-phenylethylamine.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.82; H, 6.45; N, 6.89; O, 15.75. Found: C, 70.82; H, 6.51; N, 6.99; O, 15.76.

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(31) We believe that the material extracted with acid was the primary amine corresponding to XIIIc, which cyclized during the evaporation step.