Thanks are also due to Mrs. R. Shindo for IR spectral measurements, and Miss M. Ishii and Mr. K. Ikeda and Mr. K. Kakimoto for carrying out microanalyses.

Summary

N,N-Dialkyl 3-(substituted anilino)butyramides were prepared by condensing of N,N-dialkyl crotonamides or N,N-dialkyl 3-chlorobutyramides with substituted anilines.

N,N-Dialkyl 3-(N′-benzyl-substituted anilino)butyramides were prepared from N,N-dialkyl 3-(substituted anilino)butyramides and benzyl chloride.

Some of the compounds thus prepared have analgetic activities.

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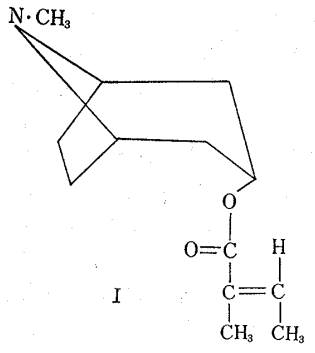
Hideo Yamaguchi and Kuniko Nishimoto: Studies on the Alkaloids of the Root of *Physalis alkekengi*. (1). Isolation of 3α-Tigloyloxytropane.

(*Osaka College of Pharmacy*[*1])

Physalis alkekengi L. *var franchettii* HORT *forma bunyardii* MAKINO which belongs to Solanaceae has been called Sanshō (or Hōzuki) in Japan and its root, named Sanshōkon, has been used as a drug which has the expectorant and antitussive actions or oxytocic action and, up to date, many studies were reported on the components of this plant. For example, physalin, a bitter principle, isolated from the fruits and the leaves,[1] and physalien (zeaxanthine dipalmitate),[2] physoxanthin and lutein[3] were also obtained from the fruits, the calyx, and the leaves. However, no systematic studies on the alkaloids have been shown except one which was reported by Haraoka, Takano and Horibe[4] in 1958. They isolated a liquid alkaloid whose picrate showed m.p. 175° in a small quantity besides physalin and suggested the existence of ethylenic double bond, carbonyl group and imino group in this alkaloid by infrared specrtra on both of free base and picrate. But no further studies were investigated by its small amount.



I

This time the authors carried out the systematic extraction and isolation of the alkaloids on the root of this plant and, as a result, besides two alkaloids, isolated an alkaloid as picrate which showed the same m.p. 176° as described by Haraoka, *et al.*[4] and its structure was confirmed to be 3α-tigloyloxytropane (I) by the following study.

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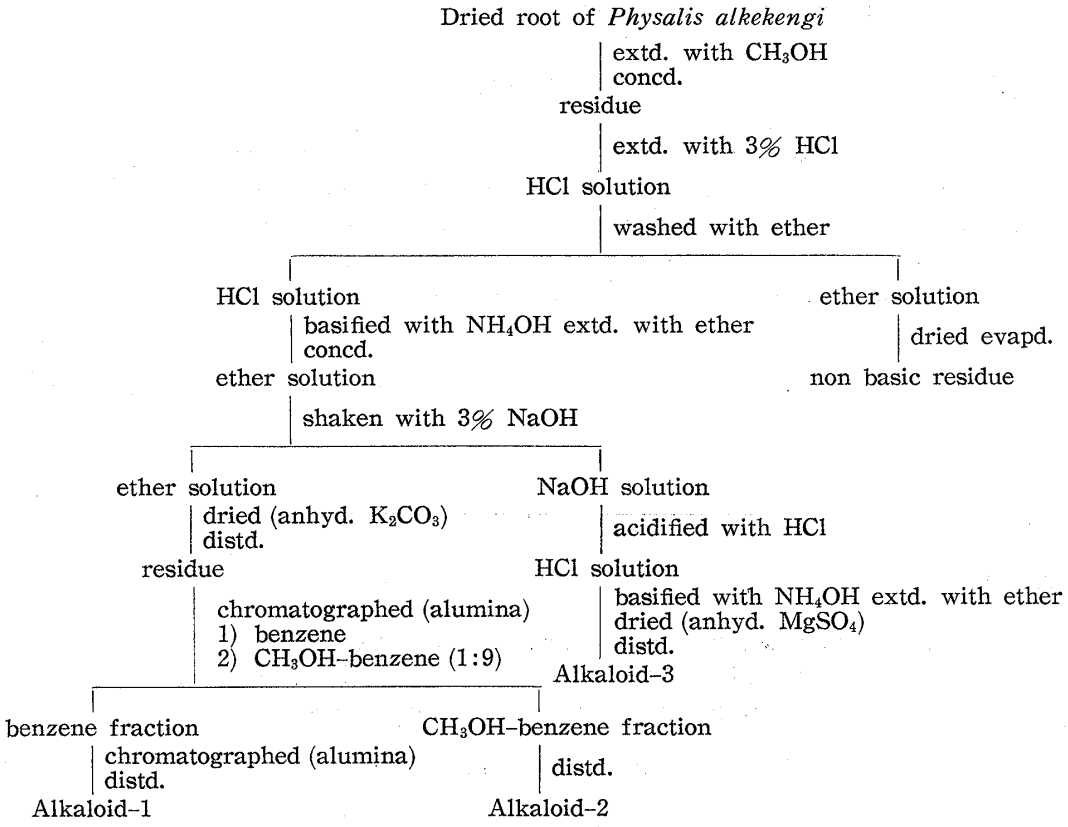
1) V. Dessaigne, J. Chautard: J. Pharm. Chim., **21**, 24 (1852); J. Pract. Pharm., **55**, 323 (1852). For the summary of literatures see W. Völksen: Arch. der Pharm., **294**, 337 (1961).
2) R. Kuhn, W. Wiegand: Helv. Chim. Acta, **12**, 499 (1929); R. Kuhn, A. Winterstein, W. Kaufmann: Ber., **63**, 1489 (1930).
3) C. Bodea, E. Nicoara: Ann., **622**, 188 (1959); *Ibid.*, **635**, 137 (1960).
4) R. Haraoka, T. Takano, S. Horibe: Yakugaku Kenkyu, **30**, 58 (1958); C. A., **53**, 20699 (1959).

TABLE I. Extraction and Isolation of Alkaloids



The plant material used was collected in Chita Peninsula. Extraction and isolation of alkaloids were followed as shown in Table I.

Alkaloid-1 was evidently distinguished from Alkaloid-2 by Thin-layer chromatography but no further study was pursued on account of its extremely small amount. Alkaloid-3, which is soluble in sodium hydroxide solution and insoluble in ammonium hydroxide, is now under investigation.

Alkaloid-2, the free base of which is an oily liquid, has b.p. 155~160° at 0.5 mm (bath temp.) and forms the picrate m.p. 176° (from acetone). It also gives the methiodide, m.p. 282~283°, and picrolonate, m.p. 205~206°. The analytical values of these three derivatives suggested $C_{13}H_{21}O_2N$ as the empirical formula of the original base. Free base gave a negative iodoform reaction and no methoxyl group was shown on crystalline methiodide. No optical rotation was seen on both of free base and methiodide. In ultraviolet spectrum, methiodide showed a maximum band at 217 mμ (log ε 3.51). The infrared spectrum of free base shows the absorptions at 2.95 μ (broad), 3.4 μ, 5.85 μ, 6.07 μ, and 8.8 μ (in liquid film) and the same absorptions are observed in methiodide. The nuclear magnetic resonance spectrum of free base shows the peaks at τ 3.18 multiplet (1H), τ 4.92 triplet (1H), τ 6.89 singlet (2H), τ 7.72 singlet (3H), τ 8.02 doublet (3H) and τ 8.16 singlet (3H). Since the peak at τ 7.72 was shifted to τ 7.19 in picrate and the free base formed easily the methiodide, it seemed likely that the original base contained an N-methyl group and the presence of imino group presumed by Haraoka, *et al.*[4] was spurious.

The attempts of acetylation and benzoylation were failed recovering the original base and the presence of hydroxyl group was rejected.

Reduction of the free base by lithium aluminum hydride afforded an oily product which gave a picrate, $C_8H_{15}ON \cdot C_6H_3O_7N_3$, whose melting point showed the unobvious decomposing point from 230° to 280°, and a methiodide, $C_8H_{15}ON \cdot CH_3I$, m.p. 349~350°.

These results lead to the presumption that this product is tropine and it was confirmed by comparing the picrate with authentic tropine picrate in the infrared spectra. Accordingly, the original base is a tropane type alkaloid and the carboxylic acid forming ester is assumed to be C_4H_7COOH containing a double bond. In nine isomers which are consistent with the above acid, tiglic acid is the most adequate one because the original base has the absorption at 5.85 μ and 8.8 μ in infrared spectrum which corresponds to α,β-unsaturated ester and shows a single proton at τ 3.18 in nuclear magnetic resonance which is appropriate for β-vinyl proton of *cis* type to carbonyl group in α,β-unsaturated ester.[5] To confirm this, the hydrolysis of the original base by dilute sodium hydroxide solution was carried out and as a result, tropine and an acid, m.p. 62.5°~63°, were obtained. The latter acid was confirmed to be tiglic acid by comparing with authentic sample in the infrared spectra and the mixed melting point determination. Consequently, the structure of the original base was determined to be 3α-tigloyloxytropane (I).

Although 3α-tigloyloxytropane is a known substance,[6~8] the data of derivatives were seldom noticed except picrate of which various melting points were described. To remove any doubt, the direct comparison by infrared spectra was made on the picrate of the original base and the authentic specimen of 3α-tigloyloxytropane picrate which was given through the generosity of Dr. W.C. Evans and as a result, it was confirmed that both samples were quite identical.

Experimental*2

Extraction and Isolation of Alkaloids——10 kg. of Dried and ground root was extracted three times with methanol under reflux (total methanol 220 L.). After filtration, the methanolic extract was concentrated under reduced pressure to give 220 g. of resinous residue. 3% HCl was added to this residue and the mixture was warmed on the hot water bath for 30 min. with continuous stirring. After standing overnight at room temperature the HCl solution was filtered. After repeating this acid-extraction process using 4 L. of 3% HCl as a total, the combined acidic solution was washed several times with ether. The aqueous phase was then basified with ammonia and extracted thoroughly with ether until the aqueous layer showed no longer positive reaction with Mayer reagent. The ethereal extract was concentrated to about 4 L. and then shaken in a separating funnel with 2.4 L. of 3% NaOH solution following 100 ml. of water to separate the fraction soluble in NaOH solution.

The NaOH solution was once acidified with HCl and then made alkaline with ammonia. The depositing base was extracted several times with ether. After drying over anhyd. $MgSO_4$, the ether was evaporated to give 0.87 g. of oily base (Alkaloid-3).

The ethereal solution from which above Alkaloid-3 was removed was concentrated to dryness after drying over anhyd. K_2CO_3 yielding 4.6 g. of oil. This oil was dissolved in benzene containing a little of acetone and chromatographed over 150 g. of alumina (Nach Brockmann). Elution was started with 600 ml. of benzene and continued with 1.4 L. of methanol-benzene (1:9) until no more residue was remained after the evaporation of the solvent. The benzene fraction was rechromatographed over alumina and eluted with benzene. Upon concentration of this benzene eluate a minor quantity of oil was obtained (Alkaloid-1).

The methanol-benzene (1:9) fraction obtained by the first chromatography was concentrated affording 3.3 g. of clear yellow oil (Alkaloid-2). This oil was converted into picrate by adding 3.4 g. of picric acid in acetone solution, whereupon a picrate of Alkaloid-2(3α-tigloyloxytropane picrate) was deposited. Recrystallized from acetone, m.p. 176°. *Anal.* Calcd. for $C_{13}H_{21}O_2N \cdot C_6H_3O_7N_3$: C, 50.44; H, 5.35; N, 12.39. Found : C, 50.43, 50.52; H, 5.58, 5.53; N, 12.76, 12.58. NMR_{CDCl_3} : τ 7.19 singlet (3H).*3

*2 All melting points are uncorrected.

*3 NMR spectra were measured at 60 Mc. in $CDCl_3$ by Varian A-60 using $(CH_3)_4Si$ as an internal reference.

5) L.M. Jackman : "Application of Nuclear Magnetic Resonance Spectroscopy," 119 (1959). Pergamon Press.
6) G. Barger, Wm. Martin, Wm. Mitchell : J. Chem. Soc., **1937**, 1820.
7) W.C. Evans, M. Wellendorf : *Ibid.*, **1959**, 1406.
8) J.D. Leary, K.L. Khanna, A.E. Schwarting, J.M. Bobbitt : Lloydia, **26**, 44 (1963).

3α-Tigloyloxytropane——The above picrate was dissolved in a small portion of acetone and chromatographed in a column containing alumina and eluted with methanol-benzene (1:9). The eluate was concentrated under reduced pressure yielding an almost colourless oil, b.$p_{0.5}$ 155~160° (bath temp.). IR λ_{max}^{liquid} μ: 3.4, 5.85, 6.07, 8.8. NMR*4: τ 3.18 multiplet (1H), τ 4.92 triplet (1H), τ 6.89 singlet (2H), τ 7.72 singlet (3H), τ 8.02 doublet (3H), τ 8.16 singlet (3H).
Methiodide: Recrystallized from methanol-acetone, m.p. 282~283° (decomp.). *Anal.* Calcd. for $C_{13}H_{21}O_2N \cdot CH_3I$: C, 46.03; H, 6.62. Found: C, 46.17, 45.78; H, 6.54, 6.73. UV: λ_{max}^{EtOH} 217 mμ (log ε 3.51).*5 IR λ_{max}^{Nujol} μ: 5.89, 6.07, 8.84.
Picrolonate: Recrystallized from acetone, m.p. 202~206°. *Anal.* Calcd. for $C_{13}H_{21}O_2N \cdot C_{10}H_8O_5N_4$: C, 56.66; H, 6.00. Found: C, 56.52; H, 6.10.

Thin-layer Chromatography on Alkaloid-1 and 3α-Tigloyloxytropane——TLC was followed by the method of Schwarting, *et al.*[8] using silica gel G., and C_2H_5OH-NH_4OH (8:2) solution. Alkaloid-1: Rf 0.2, 3α-tigloyloxytropane: Rf 0.8.

Reduction of 3α-tigloyloxytropane by Lithium Aluminum Hydride——A solution of 0.95 g. of oily Alkaloid-2 in 25 ml. of tetrahydrofuran was added dropwise to a well stirred mixture of 0.6 g. of $LiAlH_4$ and 50 ml. of anhyd. ether over a period of 1 hr. After the addition, warming and stirring were continued for further 30 min. on a water bath at 40~50°, after which the contents were decomposed by the successive addition of 1 ml. of ethyl acetate and 2 ml. of 25% NaOH. The ether-tetrahydrofuran solution was filtered by suction to separate the inorganic salts, which were washed with ether. The combined solution was dried over anhyd. K_2CO_3 and evaporated to dryness using rotatory evaporator under diminished pressure resulting 0.5 g. of oily substance. A portion of this oil (50 mg.) was lead to picrate in acetone. After recrystallizing from acetone, it shows an undefinite decomposing point from 230~280°. *Anal.* Calcd. for $C_8H_{15}ON \cdot C_6H_3O_7N_3$: C, 45.40; H, 4.90; N, 15.13. Found: C, 45.44, 45.28; H, 4.98, 4.98; N, 14.97, 14.99. Another portion of the oily reduced product (30 mg.) was dissolved in 1 ml. of methanol and refluxed with the excess of CH_3I for 30 min. Upon concentration, it afforded methiodide as colourless needles, which was recrystallized from methanol-acetone, m.p. 349~350° (decomp.). *Anal.* Calcd. for $C_8H_{15}ON \cdot CH_3I$: C, 38.17; H, 6.41. Found: C, 38.44, 38.38; H, 6.51, 6.50. IR spectra of the above mentioned picrate and methiodide were identical with those of tropine derived from atropine.*6

Hydrolysis of 3α-Tigloyloxytropane by Dilute Sodium Hydroxide Solution——0.3 g. of oily Alkaloid-2 dissolved in 3 ml. of ethanol was refluxed for 2 hr. with 2 g. of NaOH dissolved in aqueous ethanol. After removing ethanol under reduced pressure, water was added and the solution was extracted three times with ether. The ether extract was dried over anhyd. K_2CO_3 and concentrated to dryness remaining an oily base, which was converted to picrate with 0.27 g. of picric acid in acetone solution, yielding 0.3 g. of picrate, m.p. 230~280° (decomp.). The IR spectrum coinsides well with that of authentic tropine picrate.

The aqueous alkaline solution separated from tropine was acidified with HCl and extracted thoroughly with ether by salting out with NaCl. The ether extract was evaporated after drying over anhyd. $MgSO_4$. On cooling, the residual oil was crystallized as colourless pillers. By recrystallization from water, it gave m.p. 62~63.5°, which was identified with an authentic tiglic acid by mixed melting point determination and IR spectra.

The authors express their deep gratitude to Prof. M. Tomita, University of Kyoto, for his kind guidance and to Prof. V. Boekelheide, University of Oregon, and Prof. H. Inoue, University of Kyoto, for their helpful discussion. They are greatly indebted to Dr. W. C. Evans, University of Nottingham, for his kind gift of precious sample. The NMR spectra were measured by Mr. T. Shingu, University of Kyoto, and the IR spectra were determined by Dr. K. Machida, University of Kyoto, to whom the authors are grateful. They are also indebted to Takeda Chemical Industries and Nippon Shinyaku Co. for the determination of UV spectrum and optical rotations.

Summary

Systematic extraction and isolation of alkaloids were carried out on *Physalis alkekengi* L. *var franchettii* Hort *forma bunyardii* Makino. Besides two alkaloids, there was obtained an oily base, $C_{13}H_{21}O_2N$, as a chief alkaloid, which was confirmed to be 3α-tigloyloxytropane (I) as a result of detailed examinations.

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*4 NMR spectra on tropane type alkaloids were reported by J. Parello, *et al.*: Bull. soc. chim. France, **1963**, 2787.
*5 (−)-6-β-Tigloyloxytropane-3α-ol and 3α,6β-bis(tigloyloxy)tropane have their maximum absorptions at 217 mμ: W. C. Evans, *et al.*: J. Chem. Soc., **1957**, 1102; *Ibid.*, **1963**, 4348.
*6 The IR spectrum of tropine was reported by F. Uchimaru: This Bulletin, **9**, 310 (1961).