appeared (3 days). The greenish yellow reaction mixture was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to yield a crystalline residue. The residue was shaken with ether and with a solution of $NaHCO_3$. From the aqueous layer 1.3 g of 3,5-dinitro-4-hydroxyhydrocinnamic acid was recovered. The ether layer was washed with water, dried, and evaporated to give 1.3 g of a semisolid residue. Upon trituration of this with petroleum ether, the *p*-quinol ether **5m** was obtained as yellow crystals, mp 147–149°, yield 0.52 g (51%). Tlc showed a single spot; ir (Nujol), no OH band, 1705 (COOH), 1667, 1645, and 1542 cm^{-1}. *Anal.* Calcd for $C_{27}H_{36}N_2O_8$: C, 62.77; H, 7.02; N, 5.42. Found: C, 62.88; H, 7.02; N, 5.44.

Reaction of 2,4,6-Tri-*t*-butylphenoxyl with *p*-Hydroxyacetophenone.—To a blue free-radical solution, prepared from 1.05 g (4 mmoles) of 2,4,6-tri-*t*-butylphenol in the usual manner, was added 0.27 g (2 mmoles) of *p*-hydroxyacetophenone dissolved in 20 ml of ether. The mixture was allowed to stand under nitrogen at room temperature. After 2 days,[23] the solution became greenish yellow. The reaction mixture was evaporated *in vacuo* and the residue (1.33 g) was chromatographed on silica gel (20 g). Elution with petroleum ether–benzene (1:1) gave 0.48 g of 2,4,6-tri-*t*-butylphenol as colorless crystals. Elution with benzene–ether (99:1) gave 0.623 g (78.5%) of *p*-quinol ether **5k** as yellow crystals. Recrystallization from methanol gave pale yellow prisms, mp 115–116°. *Anal.* Calcd for $C_{26}H_{36}O_3$: C, 78.74; H, 9.15. Found: C, 78.66; H, 9.05.

Further elution with benzene–ether (99:1) gave 0.112 g of a yellow crystalline solid, whose tlc showed one main spot with a minor spot of *p*-quinol ether **5k**. Recrystallization from petroleum ether gave 0.1 g (16%) of *o*-hydroxydiphenyl ether **8k** as colorless needles: mp 131–132°; ir (Nujol), 3400 (OH) and 1670 cm^{-1} (=CO). *Anal.* Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.37; H, 8.11.

Reaction of 2,4,6-Tri-*t*-butylphenoxyl with *p*-Nitrophenol.—To a blue free-radical solution, prepared from 1.05 g (4 mmol) of 2,4,6-tri-*t*-butylphenol, was added 0.28 g (2 mmol) of *p*-nitrophenol dissolved in 10 ml of benzene. The mixture was allowed to stand at room temperature under N_2 atmosphere. After 2 days the blue color of the solution still persisted. An additional 3 g of *p*-nitrophenol was therefore added to the mixture, which turned greenish yellow after 3 hr. The reaction mixture was evaporated *in vacuo* and the residue (4.65 g) was triturated with petroleum ether and filtered to remove *p*-nitrophenol. The filtrate was chromatographed on a silica gel column (20 g). Elution with petroleum ether gave 0.5 g of 2,4,6-tri-*t*-butylphenol as colorless crystals. Elution with petroleum ether–ether (98:2) gave 0.534 g (65%) of *p*-quinol ether (**5l**) as yellow crystals. Recrystallization from methanol gave yellow prisms, mp 136–138°. *Anal.* Calcd for $C_{24}H_{33}NO_4$: C, 72.15; H, 8.33; N, 3.51. Found: C, 72.23; H, 8.38; N, 3.77.

Further elution with petroleum ether–ether (98:2) gave 0.134 g (19%) of crude *o*-hydroxydiphenyl ether (**8l**) as a yellow crystalline solid. Recrystallization from petroleum ether gave colorless prisms, mp 128–129°. *Anal.* Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.33; N, 4.08. Found: C, 69.83; H, 7.48; N, 4.31.

Registry No.—**5a**, 18826-70-5; **5b**, 18826-71-6; **5c**, 18826-72-7; **5d**, 18826-73-8; **5e**, 18826-74-9; **5f**, 18826-75-0; **5g**, 18826-76-1; **5h**, 18826-77-2; **5i**, 18826-78-3; **5j**, 18826-79-4; **5k**, 18826-80-7; **5l**, 18826-81-8; **5m**, 18826-82-9; **7i**, 18826-83-0; **8a**, 18826-84-1; **8e**, 18826-85-2; **8f**, 18826-86-3; **8i**, 18826-87-4; **8k**, 18826-88-5; **8l**, 18826-89-6; **3-[4-(2-methoxyphenoxy)phenyl]propionic acid**, 18826-90-9; **10**, 18826-91-0.

Acknowledgment.—The authors wish to thank Dr. H. J. Cahnmann, National Institutes of Health, Bethesda, Md., for his helpful discussion throughout this work.

(23) When 2.7 g (20 mmoles) of the phenol was used the reaction was completed within 3 hr.

Alkaloids of the *Papaveraceae*. X. New Alkaloids From *Argemone gracilenta* Greene[1]

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Department of Chemistry, Colorado State University, Fort Collins, Colorado

Received September 19, 1968

The alkaloid content of the poppy *Argemone gracilenta* Greene has been investigated. Of the total alkaloid content, over 90% was argemonine. Other known alkaloids found were (+)-laudanidine, (−)-munitagine, muramine, protopine, (+)-reticuline, and (−)-platycerine. The structure of (−)-platycerine was unequivocally established. New natural alkaloids isolated were (−)-argemonine N-oxide, (−)-argemonine methohydroxide, and (−)-isonorargemonine.

As part of our continuing investigation of the poppy genus *Argemone*, we collected for analysis plants of *A. gracilenta* Greene, whose habitat and distribution is described[2] as being in desert terrain mainly below 1000 ft from west-central Arizona southward in the Sonoran Desert to Baja California del Sur. In a preliminary report[3] we indicated the taxonomic closeness of *A. gracilenta* to *A. munita* and *A. hispida*, using both morphological and chemical criteria. In the present report, we describe the complete alkaloid analysis of *A. gracilenta*.

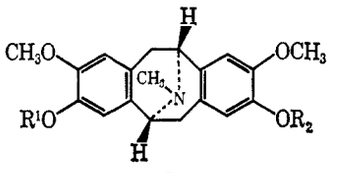
Results

A. gracilenta proved to have a relatively rich (0.33% of the dried plant) total alkaloid content and would be a prime source of (−)-argemonine (Ia) since this alkaloid represented over 90% of the total. The alkaloids (−)-munitagine (IIa), protopine, muramine, and (+)-reticuline (IIIa) were easily identified. Five additional alkaloids were also isolated and their structures were proven as indicated below (with complete details in the Experimental Section).

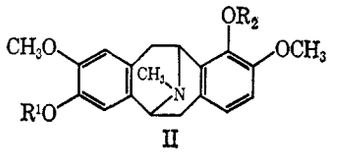
(1) Previous paper: F. R. Stermitz and R. M. Coomes, *Phytochemistry*, in press. The present work was supported by Grant GM-15424 from the U. S. Public Health Service.

(2) G. B. Ownbey, "Monograph of the Genus *Argemone* for North America and the West Indies," Memoirs of the Torrey Botanical Club, Vol. 21, The Seeman Printery, Durham, N. C., 1958.

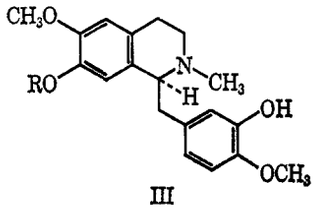
(3) F. R. Stermitz in "Recent Advances in Phytochemistry," Vol. 1, T. J. Mabry, Ed., Appleton-Century-Crofts, New York, N. Y., 1968, Chapter 5.



I



II



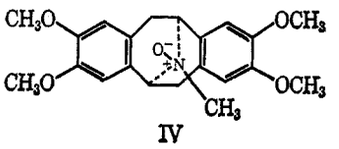
III

Ia, $R_1 = R_2 = CH_3$
b, $R_1 = H; R_2 = CH_3$
c, $R_1 = CH_3; R_2 = H$
d, $R_1 = R_2 = H$

IIa, $R_1 = R_2 = H$
b, $R_1 = R_2 = CH_3$
c, $R_1 = CH_3; R_2 = H$

IIIa, R = H
b, R = CH_3

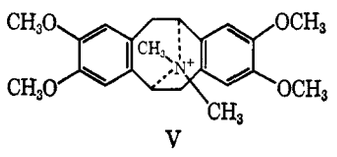
(−)-Argemonine N-Oxide.—The 1 *M* acid fraction (see Experimental Section) yielded an amorphous alkaloid (mp 140–160° with effervescence) whose mass spectrum, at first glance, appeared identical with that of Ia. The nmr spectrum in $CDCl_3$ showed the presence of four methoxyl groups as in Ia, except that they were all clearly magnetically nonequivalent, while Ia contains two pairs of equivalent methoxyls. In addition, the N-methyl absorption appeared at considerably lower field than in Ia, almost reaching the downfield position of a methyl on protonated nitrogen. The alkaloid was water soluble and the nmr spectrum in D_2O showed remarkable downfield shifts of two aromatic hydrogens and two of the methoxyl absorptions as compared with the spectrum in $CDCl_3$. Our understanding of these shifts is as yet incomplete and will be the source of a further report when suitable model compounds have been examined. Reexamination of the mass spectrum showed that although the spectrum was indeed superimposable with that of Ia up to *m/e* 355 (the molecular ion of Ia), small peaks were also present at *m/e* 369 and *m/e* 371. If the latter could be taken as the molecular ion of the unknown alkaloid, then the difference between it and Ia would be 16 mass units, most often representing an oxygen atom. These data were all consistent with an argemonine N-oxide (IV) structure for the unknown alkaloid. Synthetic IV was shown to be identical in all respects to the isolated



IV

alkaloid. Reduction of isolated IV with CH_3I yielded argemonine.

(−)-Argemonine Methohydroxide.—In work on several species of *Argemone*, we often observed by thin layer chromatography (tlc), an alkaloid (or alkaloids) which did not move from the origin in our solvent developing system. Because of the large amount of plant material used in the present work, we were able to isolate 12 mg of the unknown "0.0 R_f" alkaloid. This alkaloid proved to have a mass spectrum identical with that of Ia, but the nmr showed two N-methyl groups on protonated nitrogen as well as shifts downfield of the typical bridgehead protons in Ia. These data were consistent with a quaternary methyl salt of argemonine (V) since such salts are known[4] often to give mass spectra identical with those of the tertiary base. The correctness of this assignment was assured



V

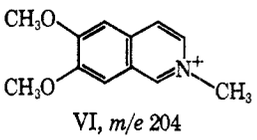
by preparation of argemonine methohydroxide, which was found to be identical with the unknown "0.0 R_f" alkaloid.

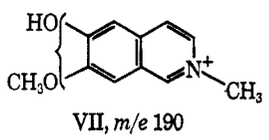
(−)-Isonorargemonine.—The pH 12.5 fraction yielded a crystalline alkaloid (mp 219–221°) whose mass spectrum and nmr and solution ir spectra proved to be identical with those of (±)-isonorargemonine (Ic), a compound we had previously synthesized[5] during the course of the structure proof of norargemonine. Thus, an addition has been made to the small list of compounds synthesized prior to their isolation from nature.

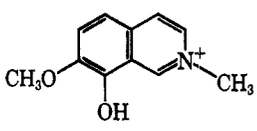
(−)-Platycerine.—Still another alkaloid isomeric with norargemonine was isolated from the pH 12.5 fraction. This compound proved to have properties identical with the alkaloid platycerine previously isolated[6] from *A. platyceras*. We confirmed the report[7] that methylation of platycerine with diazomethane yielded O,O-dimethylmunitagine[8] (IIb) and since platycerine showed a positive Gibb's test (an indication of aromatic hydrogen *para* to a phenolic OH) and a negative Millon's test (no aromatic hydrogen *ortho* to phenolic OH), the structure IIc was essentially ensured. However, we deemed it of value to obtain evidence not dependent on a color test. We were able to synthesize platycerine from munitagine (IIa) by treating the latter with a 1.5 *M* equiv of diazomethane. This yielded only (−)-platycerine and IIb. Preferential methylation of only one of the phenol groups of IIa seems best explicable as a result of the hindered nature of the phenolic group at R_2 in IIa. Perhaps more compelling evidence is provided by the mass spectrum of platycerine as compared with those of norargemonine and isonorargemonine. The latter two have identical mass spectra and show the typically high base peaks for VI and VII of equal intensity, while in the case of platycerine the *m/e* 190 peak VIII is only 30% of the intensity of the VI peak. This difference is easily explained as a result of the lesser contribution to stabil-

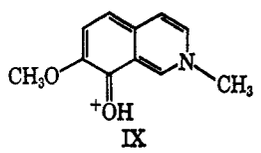
(4) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1968, pp 330–333.
(5) F. R. Stermitz and J. N. Seiber, *Tetrahedron Letters*, 1177 (1966).
(6) J. Slavik and L. Slavikova, *Collect. Czech. Chem. Commun.*, **28**, 1728 (1963). We thank Professor Slavik for a sample of platycerine.
(7) J. Slavik, L. Slavikova, and K. Haisova, *ibid.*, **32**, 4420 (1967).
(8) F. R. Stermitz and J. N. Seiber, *J. Org. Chem.*, **31**, 2925 (1966).

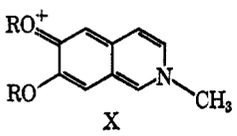
ity of the *m/e* 190 peak from the *o*-quinoid-type canonical form IX as compared to the *p*-quinoid form X in norargemonine and isonorargemonine.


VI, *m/e* 204


VII, *m/e* 190

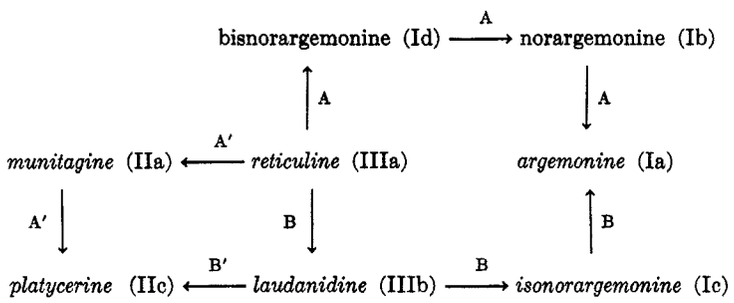

VIII, *m/e* 190


IX


X

then the cyclization product would be isonorargemonine, rather than the found norargemonine. In the present work, we have found neither bisnorargemonine nor norargemonine (the precursors to argemonine in a direct route from reticuline), but instead have found isnorargemonine and laudanidine. Thus, in *A. gracilenta* it is possible that the major biosynthetic pathway (path B) to argemonine involves methylation of reticuline prior to cyclization while in *A. hispida* it involves cyclization prior to methylation (path A). It is interesting to note that the alternative cyclization of laudanidine (similar to the alternative cyclization of reticuline to munitagine) would produce platycerine *via* path B'. However, the isolation of munitagine from *A. gracilenta* leaves the question of the pathway to platycerine completely open. As far as we are aware, in practically all other poppy alkaloid biosynthesis pathways cyclizations to the various complex ring systems (*e.g.*, morphines, aporphines, protoberberines, etc.) from a benzylisoquinoline structure have been either found or thought

SCHEME I
POSSIBLE BIOSYNTHESIS PATHWAYS[a]



[a] Alkaloids found in *A. gracilenta* are italicized.

(+)-Laudanidine.—The pH 12.5 fraction also yielded a crystalline alkaloid (mp 181–182°) whose nmr and mass spectra were characteristic of a tetrahydrobenzylisoquinoline alkaloid. The spectra were best interpreted in terms of structure IIIb and the physical properties all corresponded with those of the known (+)-laudanidine. The opium poppy, *Papaver somniferum*, was early found[9] to contain both (−)-laudanidine and (±)-laudanidine (named laudanine), but (+)-laudanidine has otherwise only been found in the *Lauraceae*: *Machilus*[10] and *Notaphoebe*.[11]

Discussion

Some rather interesting biogenetic speculations can be made regarding the alkaloids of *A. gracilenta*. These are outlined in Scheme I. Structural relationships of the alkaloids of *A. munita* and *A. hispida* allowed us to suggest[8] a biogenesis (path A) leading in sequence from (+)-reticuline to bisnorargemonine to norargemonine to argemonine. An alternative cyclization (path A') would lead from (+)-reticuline to munitagine. A key suggestion was that the free phenolic group in the benzyl portion of the tetrahydrobenzylisoquinoline was necessary for cyclization and that had reticuline been methylated to yield laudanidine prior to cyclization, to occur from reticuline or an isomer rather than laudanidine.

A comment is perhaps also in order in regard to the finding of argemonine N-oxide. Although N-oxides are common in some other alkaloid families (*e.g.*, quinolizidines), we believe ours to be the first reported occurrence of an N-oxide in the *Papaveraceae*. It is perhaps a consequence of the fact that argemonine represented over 90% of the total alkaloid content that we were able to isolate the N-oxide, its presumed metabolite.[12] Since N-oxides are thought[12] to be the precursors of N-demethylated alkaloids, we made a diligent search for N-desmethylargemonine, the finding of which would have represented the isolation from nature of the alkaloid corresponding to pavine, the synthetic[13] original of this alkaloid type. However, this attempt was unsuccessful.

Experimental Section

Melting points are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich. Instruments for spectra were Beckmann IR-5 and Perkin-Elmer 237 (ir), Perkin–Elmer 141 polarimeter (optical rotation), Varian A60-A (nmr), AEI MS-12 (mass spectra), and Bausch and Lomb Spectronic 505 (uv). The nmr chemical shifts are reported in parts per million from tetramethylsilane (TMS) in $CDCl_3$ or from 3-(trimethylsilyl)propanesulfonic acid sodium salt (TSS)

(9) O. Hesse, *Ann.*, **153**, 47 (1870); **282**, 208 (1894).
(10) M. Tomita, S.-T. Lu, and P. Lan, *Yakugaku Zasshi*, **85**, 588 (1965).
(11) S.-T. Lu, *ibid.*, **87**, 1282 (1967).
(12) J. Cymerman Craig, N. Y. Mary, N. L. Goldman, and L. Wolf, *J. Am. Chem. Soc.*, **86**, 3866 (1964).
(13) G. Goldschmiedt, *Monatsh.*, **7**, 485 (1886).

in D_2O. Thin layer chromatography (tlc) was accomplished using silica gel G plates (Brinkmann) of 250- and 2000-μ thicknesses and 3:2 benzene–methanol as developing solvent. Visualization of alkaloid spots was with iodoplatinic acid. Alkaloids were reisolated from preparative tlc plates by removal of the appropriate band of silica gel and extraction of the silica gel with methanol in a Soxhlet extractor for 4 hr. For the Millon's test 1 mg of alkaloid was suspended in a few drops of water and to this was added 2 ml of Millon's reagent (an aqueous solution 0.2 *M* in $Hg(OAc)_2$, 0.2 *M* in $NaNO_2$, 0.2 *M* in $NaNO_2$, and 0.05 *M* in acetic acid). A violet color indicated the presence of an unsubstituted aromatic position *ortho* to a phenolic OH. Gibb's tests were performed on the tlc plates and could be done either before or after spraying with iodoplatinic acid. The tlc plate was immersed in running water for a few seconds, then wetted with a saturated aqueous solution of sodium bicarbonate, warmed over a steam bath for a few seconds, and finally treated with a few drops from a pipet of an aqueous suspension of 2,6-dichloroquinonechloroimide. An immediate bright blue color at the alkaloid spot was taken as a positive test for an unsubstituted aromatic position *para* to a phenolic hydroxyl. Column chromatography was conducted using Merck 71701 aluminum oxide. An aqueous slurry of this alumina is slightly basic (*ca.* pH 9).

Isolation and Preliminary Fractionation.—Above-ground plant parts of *A. gracilenta* Greene were collected near Congress (Yavapai County), Arizona, in June 1966 and 1967. Voucher samples were deposited at the Intermountain Herbarium, Utah State University, under accession no. 111146. The dried and powdered plant material (10 kg) was treated with 2 l. of 10% aqueous $NaHCO_3$ and then with 15 l. of 1:1 *n*-butyl alcohol–benzene solution. After having stood for 3 days, the mixture was filtered and the filter cake was washed with additional butanol–benzene. The total organic solution was then extracted with 6 l. of 1 *M* H_2SO_4 in portions and the combined acid extract was made basic with excess $NaHCO_3$ and extracted with 6 l. of $CHCl_3$ in portions. The $CHCl_3$ was dried and evaporated to leave a crude alkaloid residue (33 g or 0.33%) as a thick brown semisolid. The residue was redissolved in 1 l. of 1 *M* H_2SO_4 and this was extracted with 3 l. of $CHCl_3$. The aqueous layer was then made basic to pH 12.5 with NaOH and extracted in portions with 3 l. of $CHCl_3$. The aqueous layer was then acidified with H_2SO_4 to pH 8.4 and again extracted in portions with 3 l. of $CHCl_3$. Each of the $CHCl_3$ layers were dried and evaporated to yield the following: (1) 1 *M* acid fraction, 15.9 g, (2) pH 12.5 fraction, 16.4 g, and (3) pH 8.4 fraction, 1.5 g.

The 1 *M* Acid Fraction. (−)-Argemonine, (−)-Argemonine N-Oxide, and (−)-Argemonine Methohydroxide.—The 1 *M* residue showed a single large spot on tlc at R_f 0, indicating acid salts of alkaloids. The residue was therefore redissolved in 1 *M* H_2SO_4, made basic with excess $NaHCO_3$, and extracted with four equal volumes of $CHCl_3$. The $CHCl_3$ solution was evaporated to dryness and the residue was taken up in benzene and chromatographed on an alumina column. Elution with 1:1 benzene–$CHCl_3$ yielded, after evaporation, 11 g of (−)-argemonine. A portion recrystallized from Skellysolve H and benzene (1:1) yielded colorless crystals, mp 153.5–155° (lit.[14] mp 152.5–153°), $[\alpha]^{25}D$ −203° (*c* 3.31, $CHCl_3$).

Elution of the above column with pure $CHCl_3$ yielded 210 mg of a residue showing a trace of argemonine on tlc, but mainly an alkaloid of R_f 0.25 which gave a characteristic rose color with iodoplatinic acid rather than the usual red- or blue-violet. Separation by preparative tlc yielded (−)-argemonine N-oxide as a clear glass: mp 140–160° (effervescence); $[\alpha]^{25}D$ −185° (*c* 2.81, $CHCl_3$); ir ($CHCl_3$), 3.38, 6.18, 6.62, 6.82, 7.32, 7.44, 8.63, 8.84, 9.01, 9.33, 9.88, 10.30, 10.52, 10.80, 10.98, 11.20 μ; nmr ($CDCl_3$ in ppm from TMS), 3.35 (s, 3, NCH_3), 3.78 (s, 6, OCH_3), 3.82 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 2.58–4.65 (m, 6, aliphatic ring H), 6.50 (s, 1, aromatic H), 6.54 (s, 1, aromatic H), 6.65 (s, 2, aromatic H); nmr (D_2O in ppm from TSS), 3.62 (s, 3, NCH_3), 3.80 (s, 3, OCH_3), 3.85 (s, 3, OCH_3), 4.22 (s, 3, OCH_3), 4.28 (s, 3, OCH_3), 3.0–5.1 (m, 6, aliphatic ring H), 6.68 (s, 1, aromatic H), 6.79 (s, 1, aromatic H), 7.36 (s, 2, aromatic H); mass spectrum (70 eV), *m/e* (rel intensity) 371 (1), 369 (3), 355 (45), 354 (18), 205 (10), 204 (100), 190 (8). *Anal.* Calcd for $C_{21}H_{25}NO_5 \cdot H_2O \cdot 0.5CHCl_3$: C, 58.0; H, 6.08; N, 3.08. Found: C, 57.9; H, 6.24; N, 3.00.

Treatment of (−)-argemonine N-oxide with CH_3I yielded (−)-argemonine.

Continued elution of the above alumina column with 20% CH_3OH in $CHCl_3$ yielded 12 mg of (−)-argemonine methohydroxide as an amorphous solid of R_f 0.0 which exhibited no sharp melting point, but decomposed gradually. Sufficient material for an elemental analysis was not available, but the following spectral data were obtained: $[\alpha]^{25}D$ −170° (*c* 2.81, $CHCl_3$); ir ($CHCl_3$), 3.39, 6.19, 6.82, 7.30, 7.98, 8.63, 8.91, 9.01, 9.70, 9.90, 10.02, 10.54, 11.62 μ; nmr ($CDCl_3$ in ppm from TMS), 3.67 (s, 6, $N^+(CH_3)_2$), 3.80 (s, 6, OCH_3), 3.88 (s, 6, OCH_3), 3.1–5.5 (m, 6, aliphatic ring H), 6.53 (s, 2, aromatic H), 6.82 (s, 2, aromatic H); mass spectrum (70 eV), *m/e* (rel intensity) 355 (54), 354 (36), 340 (6), 324 (5), 205 (22), 204 (100), 190 (6).

The pH 12.5 Fraction. (−)-Argemonine, Protopine, Muramine, (−)-Isonorargemonine, (+)-Laudanine, and (−)-Platycerine.—The pH 12.5 residue was dissolved in 1:1 benzene–Skellysolve H and chromatographed on an alumina column. Continuing the elution with the same solvent mixture yielded over 10 g of pure (−)-argemonine (identified as above) in the early fractions. Later fractions contained (along with more argemonine) two other alkaloids showing spots at R_f 0.38 and 0.22 on tlc. Preparative tlc allowed the isolation of 50 mg each of protopine and muramine which were identical in physical and spectral properties with authentic samples.

Continued elution of the alumina column with chloroform and methanol again yielded fractions which contained much argemonine. However, a number of fractions were sufficiently rich in three other alkaloids that these could be combined and the alkaloids separated by preparative tlc.

An alkaloid positive tlc band at R_f 0.48 was eluted to yield 100 mg of crude alkaloid which was recrystallized from 1:1 CH_3OH–H_2O to yield colorless crystals of (−)-isonorargemonine, mp 219–221°, $[\alpha]^{25}D$ −202° (*c* 3.31, $CHCl_3$). The ir (KBr) and nmr ($CDCl_3$) spectra of (−)-isonorargemonine were superimposable on those of (±)-isonorargemonine.[5] *Anal.* Calcd for $C_{20}H_{23}NO_4 \cdot H_2O$: C, 66.8; H, 7.01; N, 3.90. Found: C, 66.8; H, 6.42; N, 3.58.

A tlc band showing R_f 0.42 was also eluted to yield 140 mg of a crude alkaloid which was recrystallized twice from ethanol to yield colorless crystals of (+)-laudanidine: mp 181–182° (lit.[10] mp 184–185°, lit.[11] mp 181–182°); $[\alpha]^{25}D$ +89.5° (*c* 1.80, $CHCl_3$); nmr ($CDCl_3$ in ppm from TMS), 2.50 (s, 3, NCH_3), 2.55–3.35 (m, 7, aliphatic H), 3.58 (s, 3, OCH_3) 3.84 (s, 6, OCH_3), 6.10 (s, 1, aromatic H), 6.38–6.88 (m, 4, aromatic H); mass spectrum (70 eV), *m/e* (rel intensity) 343 (1), 342 (2), 341 (4), 206 (100). The Gibb's test and the Millon's test were both positive.

A tlc band showing R_f 0.54 was eluted to yield 52 mg of platycerine as an amorphous semisolid which we could not crystallize.[15] However, the ir ($CHCl_3$), nmr ($CDCl_3$), and mass spectra of the semisolid were identical with those of an authentic sample.[6] The ir spectrum was recorded previously;[6] nmr ($CDCl_3$ in ppm from TMS), 2.53 (s, 3, NCH_3), 2.4–4.5 (m, 6, aliphatic ring H), 3.76 (s, 3, OCH_3), 3.82 (s, 3, OCH_3), 3.83 (s, 3, OCH_3), 6.4–6.8 (m, 4, aromatic H); mass spectrum (70 eV), *m/e* (rel intensity) 341 (33), 340 (22), 204 (100), 190 (30), 170.5 (3). *Anal.* Calcd for $C_{20}H_{23}NO_4 \cdot CH_3OH$: C, 67.5; H, 7.01; N, 3.75. Found: C, 67.6; H, 7.14; N, 3.07. Platycerine gave a positive Gibb's test and a negative Millon's test.

The pH 8.4 Fraction. (+)-Reticuline and (−)-Munitagine.—Analysis of the pH 8.4 fraction by tlc showed that additional amounts of argemonine had carried over into this fraction. However, two additional bases of R_f 0.35 and 0.50 were noted.

Preparative tlc allowed isolation of 34 mg of the R_f 0.35 base which proved to be (+)-reticuline, mp 60–90°, $[\alpha]^{25}D$ +58° (*c* 1.74, ethanol). These properties were virtually identical with those of the reticuline previously isolated[8] from *A. munita* and *A. hispida* and thus indicated the presence of a mixture of (+)- and (±)-reticuline.

The R_f 0.50 base could also be isolated by preparative tlc and this yielded 30 mg of (−)-munitagine whose properties were identical with those previously[8] reported.

Synthesis of (−)-Argemonine N-Oxide.—(−)-Argemonine (350 mg) which had been isolated from *A. gracilenta* (see above) was dissolved in a minimum amount of methanol. An excess (10 ml) of 30% H_2O_2 was added and the solution allowed to stand at 25° for 1 hr. The excess peroxide was decomposed with

(14) T. O. Soine and O. Gisvold, *J. Am. Pharm. Assoc., Sci. Ed.*, **33**, 185 (1944).

(15) It was reported[6] that platycerine could be successfully crystallized from ether "in the course of several months."

platinum black and the mixture was filtered. The filtrate was evaporated to give 362 mg of nearly pure (−)-argemonine N-oxide. A portion was purified by preparative tlc to yield the pure N-oxide, mp 140–160° (effervescence), $[\alpha]^{25}D$ −152° (*c* 10.71, $CHCl_3$). The ir, nmr, and mass spectra of the prepared sample were identical with those of the isolated alkaloid (see above).

Synthesis of (−)-Argemonine Methohydroxide.—(−)-Argemonine (30 mg) which had been isolated from *A. gracilenta* (see above) was dissolved in a few drops of methanol. Methyl iodide (10 ml) was added and the solution was heated at reflux for 1 hr. The solution was evaporated to dryness, the residue was dissolved in water, and the iodide ion was precipitated with $AgNO_3$. The mixture was filtered and 30 ml of 40% aqueous NaOH was added. The resulting mixture was filtered and the filtrate was extracted with $CHCl_3$. The $CHCl_3$ solution was dried and evaporated to yield 25 mg of a semisolid whose properties were essentially identical with those of the isolated (−)-argemonine methohydroxide (see above).

Synthesis of (−)-Platycerine.—(−)-Munitagine (50 mg) which had been isolated[6] from *A. munita* was dissolved in 10 ml of methanol and a 1.5 molar equiv of diazomethane (generated from Diazald) in ether solution was added, while the solutions were kept cold in ice. The resulting solution was allowed to come to room temperature slowly and then allowed to stand for 12 hr. The solution was evaporated to dryness on a steam bath, and the residue was dissolved in 1 *M* HCl and then basified and extracted with $CHCl_3$ successively at pH 12.5 and 8.4. From the pH 12.5 extract was isolated O,O-dimethylmunitagine.[8] The residue from the pH 8.4 extract was purified by preparative tlc and yielded 13 mg of (−)-platycerine, mp 120–140° (effervescence), $[\alpha]^{25}D$ −224° (*c* 0.80, $CHCl_3$). The ir, nmr, and mass spectra were identical with those of the isolated (−)-platycerine (see above) and an authentic sample.[6]

Registry No.—(−)-Ic, 18826-67-0; (−)-IIc, 18826-68-1; (−)-IV, 18841-61-7; (−)-V, 18826-69-2.

The Synthesis of trans-β-Carotene from Retinyl Phosphonate by the Michaelis–Arbuzov Reaction

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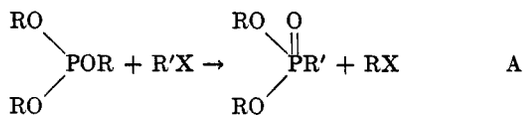
Retinyl phosphonate, which was synthesized for the first time, was condensed with vitamin A aldehyde to afford β-carotene in good yield.

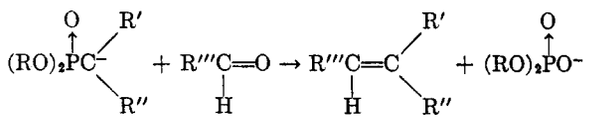
The Michaelis–Arbuzov reaction[1] provides a versatile method for the formation of carbon–phosphorus bonds by the reaction of a phosphite ester with an alkyl halide.



A

The characteristic of this reaction is the formation of a P=O bond. The mechanism involves an expansion of the valence shell of phosphorus from eight to ten electrons, made possible by the vacant 3d orbitals.

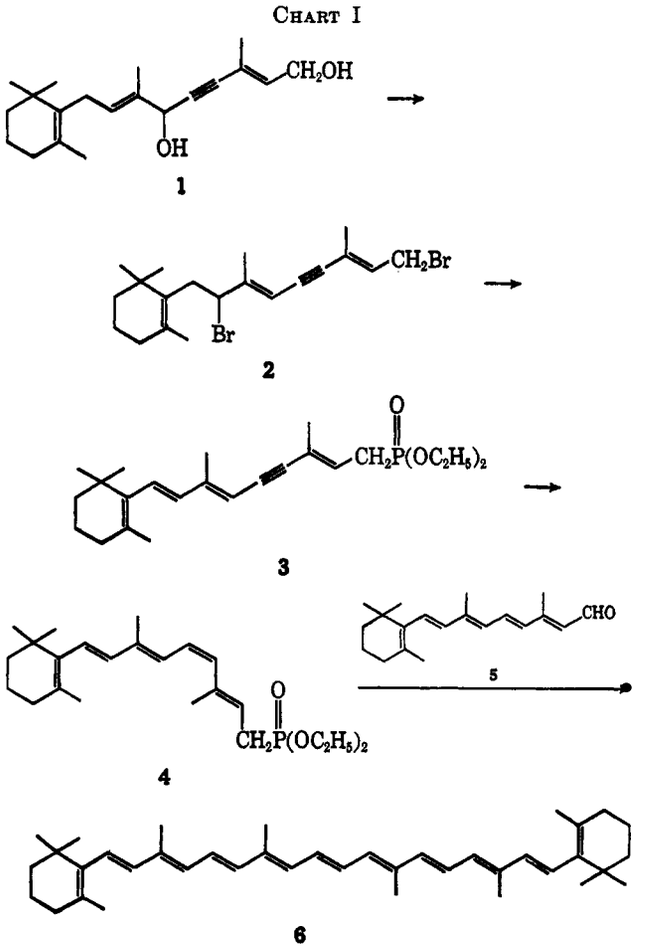
It has been demonstrated by earlier workers[2,3] that the alkyl diethyl phosphonates form carbanions which react with carbonyl compounds to afford olefins.



Since the phosphite esters have the advantage of being less expensive than triarylphosphines, the so-called Wittig reagents, it occurred to us that the Michaelis–Arbuzov reaction may be used favorably for preparing β-carotene. However, as there is no known procedure for preparing the halide from vitamin A as required by eq A, retinyl halide was eliminated as a possible precursor to retinyl phosphonate. This problem has been resolved by following the synthetic route shown in Chart I.

The C-20 diol (1), which is an intermediate of an industrial vitamin A synthesis,[4,5] was treated with phosphorus tribromide to yield the rearranged dibromide **2.**

Chart I



(1) R. G. Harvey and E. R. De Sombre, *Topics of Phosphorous Chemistry*, Vol. 1, Interscience, New York, 1964, p 57.

(2) L. Horner, H. Hoffmann, H. G. Wippel, and G. Klohre, *Chem. Ber.*, **92**, 2499 (1959).

(3) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).

(4) O. Isler, A. Ronco, W. Guex, N. C. Hindley, W. Huber, K. Dialer, and M. Kofler, *Helv. Chim. Acta*, **32**, 489 (1949).

(5) J. D. Surmatis, U. S. Patent 2,610,208 (1952).