in determining unreacted monomer in the rate experiments summarized in Tables II and III. Estimation of the probable maximum unsaturation in the polymer is complicated by the fact that the minimum in the completely saturated polymer spectrum corresponding approximately to the monomer ultraviolet maximum is not a point of zero absorption but rather is a "valley" between absorption maxima. In the polymers investigated, this minimum was lower than the corresponding minimum in 1,3-dimethyl-2-ethyl-5-*t*-butylbenzene, which suggests that there is a very little unsaturation in the polymer. This probably amounts to less than one double bond for every twenty polymer molecules. However, even if the total absorption of the polymer at 2450 Å. is attributed to unsaturation, the polymer contains only 0.8% of the original aliphatic double bonds of the monomer which still corresponds to only one double bond for every four polymer molecules (mol. wt. 5200).

The infrared spectra of the polymer and 1,3-dimethyl-2-ethyl-5-*t*-butylbenzene should be very similar, if the polymer results from normal addition polymerization. Comparison of the two spectra shows that this is the case. All of the infrared absorption maxima in the spectrum of the polymer have their counterparts in the spectrum of 1,3-dimethyl-2-ethyl-5-*t*-butylbenzene, with the exception of small peaks at 9.3 and 13.2μ. Absorption at 6.35, 6.9 and 13.4μ is considerably attenuated in the spectrum of the polymer compared to that of 1,3-dimethyl-2-ethyl-5-*t*-butylbenzene; and peaks at 7.6, 9.15, 9.4, 10.35, 12.75 and 14.4μ in the spectrum of the latter are not in evidence in the polymer spectrum. The peak at 13.4μ and all of those listed in the second group are also absent in the spectra of the series of hydrocarbons in which the ethyl group of 1,3-dimethyl-2-ethyl-5-*t*-butylbenzene is replaced by methyl, *n*-decyl and *n*-octadecyl[13]; but all have their counterparts in the spectrum of 1,3,5-trimethyl-2-ethylbenzene.[20] Therefore, their absence is to be expected in a normal addition-type polymer. The intense absorption at 11.5μ, which is present in the spectra of 2,6-dimethyl-4-*t*-butylstyrene, its polymer and its ethyl analog, is due to the vibration of the isolated nuclear hydrogens in the 4- and 6-positions in and out of the plane of the ring. Its presence indicates that the relationship of the alkyl groups on the nucleus and the structure of this part of the monomer molecule are unchanged by the polymerization.

Acknowledgments.—The author wishes to express his appreciation to Mr. R. D. Clark for spectra and spectrographic analyses and to Dr. L. L. Ferstandig for performing early polymerization experiments and for helpful discussion.

(20) K. C. Bryant, G. T. Kennedy and E. M. Tanner, *J. Chem. Soc.*, 2389 (1949).

RICHMOND, CALIFORNIA

[CONTRIBUTION FROM THE FRUIT AND VEGETABLE CHEMISTRY LABORATORY, WESTERN UTILIZATION RESEARCH BRANCH, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

Plant Polyphenols. I. The Polyphenolic Constituents of the Pellicle of the Walnut (*Juglans regia*)[1]

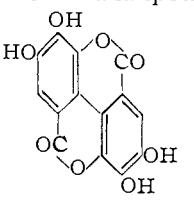
BY LEONARD JURD

RECEIVED FEBRUARY 16, 1956

A study of the natural antioxidants in walnut pellicles has been undertaken. Ellagic acid, methyl gallate, gallic acid and a tannin were isolated from extracts of the pellicle. The tannin was composed chiefly of four polyphenolic esters or glucosides, and on hydrolysis gave ellagic acid, gallic acid, methyl gallate and glucose. Preferential oxidation of these pyrogallol derivatives in the pellicle probably aids in stabilizing walnut kernel constituents against decomposition.

In recent years it has become increasingly apparent that many naturally occurring polyphenolic compounds may function as antioxidants or be involved as substrates in the enzymic browning of plant tissues. Relatively few investigations into the nature of the natural phenolic substrates, however, have been reported,[2] although catechol compounds have been suggested as possible substrates and the reaction of polyphenol oxidases with such catechol derivatives as caffeic acid esters, catechins and flavonols has been proved.[3] In this Laboratory it has been observed that the oxidative deterioration of walnut kernels is inhibited by the presence of an intact pellicle (skin). It was of interest, therefore, to determine the nature of the compounds responsible for the protective properties of the pellicle. Previous work on walnuts has been limited to the isolation by Daglish[4] and others of an α-hydrojuglone glucoside from the leaves and pericarp. This was proved to be 1,5-dihydroxy-4-glucosidoxynaphthalene.[5] Bate-Smith[6] recently reported that an extract of the seed coat produced cyanidin when boiled with acids.

From the ether-soluble fraction of methanolic extracts of the pellicle a yellow crystalline phenol, $C_{14}H_6O_8$, was obtained. The reactions of this phenol indicated the presence of a 4,4'-dihydroxybiphenyl and a lactone grouping, and furthermore it gave a blue ferric coloration indicative of a pyrogallol nucleus. The properties of the phenol agreed closely with those reported for ellagic acid (I), a compound isolated from the ellagitannins found in various Terminalia species.[7]



I

Direct comparison of the spectra, R_f values, fluorescence and color reactions on paper chromatograms of

(1) Presented at Meeting of Biological Chemistry Section, American Chemical Society, April, 1956, Dallas, Texas. Financial support for this work was provided by the California Walnut Growers Association.

(2) M. A. Joslyn and J. D. Ponting, "Advances in Food Research," Vol. 3, Academic Press, Inc., New York, N. Y., 1951, p. 1.

(3) E. C. Bate-Smith, ref. 2, Vol. 5, 1954, p. 261.

(4) C. Daglish, *Biochem. J.*, **47**, 452 (1950).

(5) N. F. Hayes and R. H. Thomson, *J. Chem. Soc.*, 904 (1955).

(6) E. C. Bate-Smith, *Biochem. J.*, **58**, 122 (1954).

(7) F. M. Dean, "Progress in the Chemistry of Organic Natural Products," Vol. IX, Springer-Verlag, Vienna, 1949, p. 283.

the natural phenol and synthetic ellagic acid prove them to be identical. The mixed melting point of their acetates confirmed this identity.

Two additional phenols were isolated from the ether solution. One of these was not extracted with aqueous sodium bicarbonate. Analysis of this phenol and its acetate indicated the presence of one methoxyl and three hydroxyl groups and established its empirical formula as $C_8H_8O_4$. Complete methylation of the phenol gave a methyl ether which produced 3,4,5-trimethoxybenzoic acid on alkaline hydrolysis. The methoxyl in the parent phenol was therefore present as a carbomethoxy group. From these data it was apparent that the phenol was methyl gallate, and this was confirmed by direct comparison with authentic methyl gallate.[8] The second phenol was extracted with sodium bicarbonate. Its acidic nature, blue ferric reaction, and close connection with methyl gallate suggested its identity as gallic acid, a conclusion confirmed by mixed melting point, spectrophotometric and paper chromatographic comparison with authentic gallic acid.

Most of the phenolic material in the methanol extract was obtained from the acetone-soluble fraction of the extract as an amorphous brown powder amounting to 5–10% of the pellicle. Two-dimensional paper chromatograms of this powder revealed four closely related phenols as the chief components of the mixture, the elementary composition of which was C, 52.4; H, 3.60; MeO, 0.93%. It exhibited typical tannin reactions, giving precipitates with gelatin and lead acetate solutions and a blue-black color and precipitate with ferric chloride. Complete hydrolysis of the tannin with mineral acids gave approximately 50% of its weight as ellagic acid, 15% as gallic acid, a small quantity of a dark red pigment and an undetermined but considerable quantity of glucose. Mild partial hydrolysis with water alone gave methyl gallate and gallic acid, while hydrolysis with aqueous sodium bisulfite or vacuum sublimation gave pyrogallol, methyl gallate, gallic acid and ellagic acid. Consideration of these data suggests that, although relatively small quantities of ellagic acid, methyl gallate and gallic acid occur uncombined in the pellicle, the polyphenolic constituents of the tannin are simply esters or glucosides formed by the combination of these three phenols in varying amounts with glucose. In confirmation, it was found that acid hydrolysis of the total methanol extract gave ellagic acid amounting to 4% of the pellicle. The carbomethoxy group present in the methyl gallate and the tannin was not introduced by methanolysis during the extraction process since acetone extraction of the pellicle also gave methyl gallate and a tannin identical with that obtained by methanolic extraction. Further work on the separation and characterization of the individual polyphenol esters constituting the tannin is in progress.

The presence of these easily oxidizable pyrogallol derivatives suggests that the stabilizing or protective effect of the pellicle of the walnut kernel may be due to the preferential oxidation of these compounds.

(8) The melting point of methyl gallate is incorrectly recorded as 157° in Heilbron's "Dictionary of Organic Compounds" and in the Merck Index, 6th Ed. (1952).

Experimental

Separation of Constituents in Methanol Extracts of Pellicle.—Powdered walnut pellicles (1500 g.) were extracted in a Soxhlet-type apparatus with low-boiling petroleum ether for 24 hr. and then with methanol for 48 hr. The methanol extract was concentrated to a sirup which was added slowly to warm ether (3000 cc.). After standing overnight the clear ether solution (E) was decanted from the gum which had precipitated. The gum was successively extracted with boiling acetone (A) (4 × 800 cc.) and methanol (500 cc.), leaving an insoluble residue (S).

Ether Extract (E).—The ether solution (E) was washed with water (2 × 300 cc.). The aqueous layer was then extracted repeatedly with ethyl acetate (5 × 600 cc.), the combined ethyl acetate extracts being dried, concentrated to 400 cc. and allowed to stand. Ellagic acid slowly crystallized in yellow needles, m.p. >360° (3.2 g.). The ether solution, after washing with water, was extracted with 5% sodium bicarbonate solution (2 × 50 cc.), dried and evaporated to an oil. Chromatograms of the oil indicated the presence of one phenolic compound which was separated by the addition of saturated methanolic lead acetate (300 cc.) to a solution of the oil in warm methanol (500 cc.). The precipitated lead salt was collected, suspended in methanol and treated with hydrogen sulfide. Evaporation of the filtrate from the lead sulfide gave a mass of felted needles of methyl gallate (3.6 g.). The sodium bicarbonate extract of the ether solution was acidified with hydrochloric acid and re-extracted with ether. Evaporation of the ether solution gave crude gallic acid as a brown gum which crystallized from water in slightly brown needles (0.42 g.).

Acetone Extract (A).—The acetone solution (A) was concentrated to a gum which was repeatedly extracted with boiling ethyl acetate (4 × 500 cc.). An amorphous brown solid remained undissolved (42 g.) (tannin A). The ethyl acetate extracts were combined, concentrated to 500 cc. and added to boiling *n*-hexane (3000 cc.). An amorphous cream solid separated (34 g.) (tannin B).

Solid (S).—The solid (S) was suspended in warm water (100 cc.) and filtered. The water-insoluble residue was crystallized from aqueous pyridine. Ellagic acid separated in yellow needles, m.p. >360° (2.8 g.).

Characterization of Constituents. Ellagic Acid.—The walnut phenol identified as ellagic acid was almost insoluble in water and the usual organic solvents. It was purified, however, by crystallization from pyridine and recrystallization from large volumes of methanol, thereby being obtained in yellow needles, m.p. >360°.

Anal. Calcd. for $C_{14}H_6O_8$: C, 55.6; H, 2.02. Found: C, 55.2; H, 2.25.

The phenol sublimed when heated in vacuum gave a blue ferric chloride reaction and a yellow solution in warm 5% aqueous sodium hydroxide. On cooling the alkaline solution the sodium salt crystallized in yellow needles. The phenol gave a positive Greissmeyer reaction, its solution in concentrated nitric acid containing nitrous acid developing an intense blood red color on dilution with water.

Synthetic ellagic acid was prepared from gallic acid by the method of Perkin and Nierenstein.[9] It crystallized from pyridine and from methanol in yellow needles, m.p. >360°, and gave color reactions identical with those described for the natural phenol.

Anal. Calcd. for $C_{14}H_6O_8$: C, 55.6; H, 2.02. Found: C, 55.0; H, 2.15.

Ellagic acid tetraacetate was prepared from the natural and synthetic ellagic acid by heating with acetic anhydride and sulfuric acid for 1 hr. The acetate of the natural product crystallized from acetic anhydride in colorless needles, m.p. 335°, undepressed on admixture with synthetic ellagic acid tetraacetate.

The tetramethyl ether of the natural acid was prepared by the addition of an ethereal solution of diazomethane to a suspension of the acid in methanol. Recrystallized from acetic anhydride, the product had m.p. 341° (ellagic acid tetramethyl ether, lit.[10] m.p. 340–343°). The methyl

(9) A. G. Perkin and M. Nierenstein, *J. Chem. Soc., Trans. Sec.*, **87**, 1412 (1905).

(10) F. E. King, T. J. King and J. M. Ross, *J. Chem. Soc.*, 1333 (1955).

ether did not react with ferric chloride and sodium bicarbonate. It dissolved slowly in cold sodium hydroxide solutions and was recovered on acidification.

Natural and synthetic ellagic acid had identical R_f values in water (R_f 0), *n*-butyl alcohol saturated with water (R_f 0.28) and *n*-butyl alcohol/acetic acid/water (R_f 0.33) on descending chromatograms on Whatman No. 1 paper. Ellagic acid gave a bright blue fluorescence in ultraviolet light, changing to a yellow-green with ammonia vapor.

Methyl Gallate.—The walnut phenol identified as methyl gallate crystallized from ether–hexane solutions in slightly brown prisms, m.p. 195°, undepressed on admixture with synthetic methyl gallate. It gave a blue ferric reaction and its alkaline solutions rapidly changed to dark brown.

Anal. Calcd. for $C_8H_8O_5$: C, 52.5; H, 4.40; 1 MeO-, 16.9. Found: C, 52.4; H, 4.61; MeO-, 16.9.

On paper chromatograms the natural and synthetic methyl gallate had identical R_f values in 5% aqueous acetic acid (R_f 0.54) and in *n*-butanol/acetic acid/water (R_f 0.87).

The acetate of the walnut phenol, prepared by the action of acetic anhydride and sodium acetate, crystallized from aqueous acetone in colorless needles, m.p. 126.5° (triacetyl methyl gallate, lit. m.p. 122°).

Anal. Calcd. for $C_{28}H_{28}O_{16}$: C, 54.2; H, 4.55; 1 MeO-, 10.0. Found: C, 54.5; H, 4.69; MeO-, 9.91.

The walnut phenol was methylated with methyl iodide and potassium carbonate in acetone. It crystallized from *n*-hexane in colorless flat needles, m.p. 85° (methyl trimethyl gallate, lit. m.p. 84°). The methyl ether was dissolved in warm 5% aqueous sodium hydroxide. On acidification colorless needles separated which, after recrystallization from aqueous methanol, had m.p. 165°, undepressed on admixture with authentic 3,4,5-trimethoxybenzoic acid.

Gallic Acid.—The phenol identified as gallic acid had m.p. 259°, undepressed on admixture with authentic gallic acid. The natural and authentic gallic acid had identical R_f values in 5% aqueous acetic acid (R_f 0.50) and in *n*-butyl alcohol–acetic acid–water (R_f 0.74). Identical ultraviolet absorption spectra were obtained in neutral and in alkaline solutions (Table I).

Ultraviolet Light Absorption Spectra.—The ultraviolet spectra of the phenols were measured on a Beckman model DU spectrophotometer using 1-cm. quartz cells. The spectra were determined in absolute ethanol and in absolute ethanol saturated with sodium acetate. The data are summarized in Table I.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF WALNUT PHENOLS

Phenol	EtOH λ_{max}	EtOH log ϵ	EtOH–NaAc[a] λ_{max}	EtOH–NaAc[a] log ϵ
Ellagic acid (walnut)	366	3.93	355	4.06
	255	4.60	277	4.54
			255	4.46
Ellagic acid (synthetic)	366	4.00	355	4.03
	255	4.70	277	4.53
			255	4.44
Methyl gallate (walnut)	275.5	4.32		
	217	4.72		
Methyl gallate trimethyl ether (walnut)	265	3.97		
	214.5	4.47		
Gallic acid (walnut)	272.5	4.02	259	4.32
Gallic acid (authentic)	272.5	4.06	258	4.30
Pyrogallol (authentic)	267			

[a] Excess of powdered sodium acetate added to the cell.

Tannin B.—Two-dimensional paper chromatograms of tannin B showed that it consisted chiefly of four phenols with only traces of other phenolic compounds. It did not contain methyl gallate and gallic acid, although a trace of ellagic acid was present. The tannin precipitated gelatin from aqueous solution, formed a slight precipitate with bromine water and gave a blue-black ferric chloride reaction. It did not give the Greissmeyer reaction with nitric acid nor did it give a positive Molisch carbohydrate test. When its solution in dilute hydrochloric acid was warmed for a few minutes it gave a positive Molisch test. When the tannin was boiled with dilute hydrochloric acid under a layer of amyl alcohol the alcohol layer assumed a deep red anthocyanin-like color. Treated with a drop of 1% alcoholic vanillin solution and concentrated hydrochloric acid, the tannin gave a cherry-red coloration identical with that given by a dilute solution of *d*-epicatechin.

Vacuum Sublimation.—Tannin B (1.0 g.) was vacuum sublimed for 1 hr. immersed in an oil-bath maintained at 220–230°. A yellow oil collected on the condenser. The condenser was changed and the tannin residue was heated over a small flame. A crystalline sublimate was then obtained which, recrystallized from methanol, had m.p. >360°. Two-dimensional paper chromatograms of this compound in *n*-butyl alcohol saturated with water (R_f 0.28) and water (R_f 0), and its blue fluorescence in ultraviolet light indicated its identity with ellagic acid. The spectra of the compound in ethanol, λ_{max} 366, 256 mμ, and in ethanolic sodium acetate, λ_{max} 359, 278, 254 mμ, confirmed this identity.

The oil which had sublimed was dissolved in ether (50 cc.), and the solution was extracted with 5% sodium bicarbonate solution (2 × 10 cc.). The bicarbonate solution was acidified and re-extracted with ether. This ether extract was concentrated and studied chromatographically on paper. Alone or with added gallic acid only one spot was obtained in *n*-butyl alcohol–water (R_f 0.50) and water (R_f 0.45). The spectrum of the spot was determined directly on the paper strip after chromatography by the method of Bradfield and Flood.[11] It had λ_{max} 278 mμ. Authentic gallic acid, similarly chromatographed, had λ_{max} 278 mμ. The original ether solution was evaporated to a gum after the bicarbonate washing. Two-dimensional paper chromatograms on Whatman No. 1 paper showed the presence of two phenolic compounds. The R_f values of spot 1, 0.71 in *n*-butyl alcohol–water and 0.43 in water, and of spot 2, 0.68 in *n*-butyl alcohol–water and 0.62 in water, indicated their identity with methyl gallate and pyrogallol, respectively. When the gum was co-chromatographed with methyl gallate and/or pyrogallol the same two spots only were obtained. Determined directly on the paper strips spots 1 and 2 had λ_{max} 283 and λ_{max} 270 mμ, respectively. Methyl gallate and pyrogallol had λ_{max} 282 and λ_{max} 269, respectively.

Acid Hydrolysis.—A solution of tannin B (5.0 g.) in *N* aqueous sulfuric acid (50 cc.) was heated under reflux for 20 hr. The crystalline precipitate (2.20 g.) was collected and recrystallized from pyridine. It separated in yellow needles, m.p. >360°. The spectrum fluorescence and R_f values of this compound proved that it was ellagic acid. The aqueous acid filtrate from the crude ellagic acid was extracted continuously with ether for 18 hr. Evaporation of the filtered ether solution gave a mass of brown needles (0.90 g.) which, when recrystallized from water, had m.p. 259–260°, undepressed on admixture with gallic acid. This compound had λ_{max} 273 mμ in absolute ethanol and gave one spot when co-chromatographed with gallic acid. The aqueous acid solution was then neutralized with barium carbonate and the barium salts were filtered. A portion of the filtrate was added to a solution of phenylhydrazine in dilute acetic acid–sodium acetate, and the mixture was heated in a steam-bath for 30 minutes. On cooling a yellow osazone separated. It was recrystallized from methanol as yellow needles, m.p. 203°, undepressed on admixture with glucosazone.

The total available ellagic acid in the pellicles was determined by extracting this material (100 g.) in a Soxhlet extractor with methanol for 48 hr. The extract was evaporated to a gum which was dissolved in water (50 cc.) and sulfuric acid (5.0 cc.). A layer of *n*-butyl alcohol (25 cc.) was added and the mixture was heated under reflux for 5 hr. After standing at room temperature for 24 hr., the crude ellagic acid (4.0 g.) was collected by filtration and recrystallized from pyridine. Walnut kernels (120 g.), similarly extracted and hydrolyzed, gave 0.60 g. of crude ellagic acid.

Partial Hydrolysis with Water.—A solution of tannin B (1.0 g.) in distilled water (10 cc.) was heated under reflux for 16 hr., cooled, filtered and extracted with ether (3 × 20 cc.). The ether solution was washed with sodium bicarbonate solution, dried and evaporated to a gum (a). Acidification of the bicarbonate solution and re-extraction with ether gave a small quantity of a crystalline solid (b) on

(11) A. E. Bradfield and A. E. Flood, *J. Chem. Soc.*, 4740 (1952).

evaporation of the ether. By procedures previously described, *viz.*, co-chromatography with added methyl gallate and gallic acid, the identity of (a) and (b) as methyl gallate and gallic acid, respectively, was established.

Hydrolysis with Aqueous Sodium Bisulfite.—A solution of tannin B (1.0 g.) and sodium bisulfite (2.0 g.) in water (20 cc.) was heated under reflux for 6 hr., cooled and filtered from a yellow crystalline sodium salt (0.34 g.). The filtrate was extracted with ether, acidified and re-extracted with ether. Two-dimensional paper chromatograms showed the presence of pyrogallol and methyl gallate in the first ether extract and gallic acid in the second ether extract. The crystalline sodium salt, suspended in warm water and treated with hydrochloric acid, gave ellagic acid, m.p. >360°, λ_{max} 366, 256 mμ in ethanol.

Tannin A.—Paper chromatograms showed the presence of the same phenolic constituents in both tannin A and B, although in different relative amounts. Tannin A gave a positive Molisch carbohydrate test and appeared to contain free carbohydrate.

Acknowledgment.—The author wishes to thank L. M. White for performing the elementary analyses.

PASADENA, CALIF.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

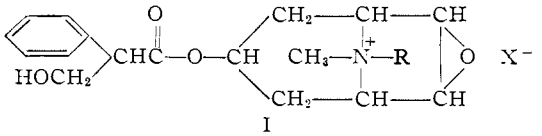
Antispasmodics. VIII. Scopolamine Derivatives

BY ROBERT BRUCE MOFFETT AND BROOKE D. ASPERGREN

RECEIVED FEBRUARY 2, 1956

A variety of derivatives of scopolamine have been prepared and tested for their antispasmodic and gastric antisecretory activities. These include several quaternary salts (analogs of Pamine Bromide[1,2]) and a number of O-acyl esters of scopolamine and their salts. Aposcopolamine, desoxyscopolamine, 6-hydroxytropine tropate and an ester of scopoline together with their methobromides were also made and tested. Of the above, O-acetylscopolamine methobromide appears to be the most active anticholinergic, but several other O-acyl scopolamines show interesting properties. Most of these compounds are new but a few that have been previously reported are here more completely characterized.

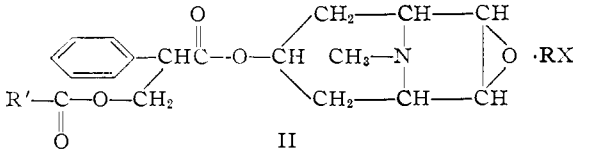
The excellent properties of Pamine Bromide[1] as a visceral antispasmodic and gastric antisecretory agent[3] have prompted us to prepare a number of other derivatives of scopolamine. Besides the methyl bromide several other quaternary salts (I) were prepared. Some of these have been previously reported[4,5] but for the most part without analytical data.



I

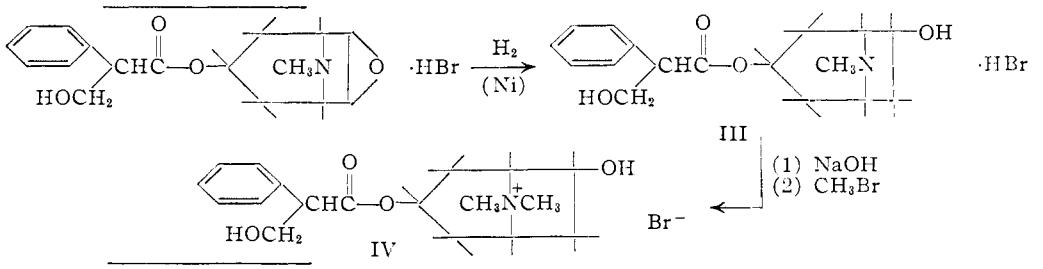
Pamine Bromide[1] was also prepared from radioactive (C^{14}) methyl bromide. This was used by Dr. William L. Miller[6] in studies of the metabolic disposition and excretion of Pamine in dogs.

O-Acetylscopolamine and its hydrobromide (II, R′ = CH_3, RX = HBr) were reported many years ago.[2,7] Recently an Australian patent specification[8] described this hydrobromide, giving considerably different properties from the older literature



II

but without analytical data. We have repeated the preparation and our results confirm the Australian work except that our melting point was nine degrees higher. The methyl bromide quaternary salt (II, R′ = CH_4, RX = CH_3Br) was also prepared and found to have excellent anticholinergic properties (Table I). Its clinical investigation is under way. Besides the acetate, a number of other O-esters of scopolamine salts (II) were prepared. These esters were made by the action of a large excess of the acid anhydride or the acid chloride and pyridine on scopolamine hydrobromide. In the case of the phenylurethan, scopolamine base was treated with phenyl isocyanate.



III

IV

The epoxide ring of scopolamine hydrobromide has been hydrogenated by Fodor and Kovacs,[9] but they hydrolyzed the product to *dl-trans*-6-hydroxy-

(1) The Upjohn Company brand of Scopolamine Methyl Bromide (I, R = CH_3, X = Br).

(2) O. Hesse, *J. prakt. Chem.*, [ii] **64**, 353 (1901).

(3) F. E. Visscher, P. H. Seay, A. P. Tazelaar, Jr., W. Veldkamp and M. J. VanderBrook, *J. Pharmacol. Exp. Therap.*, **110**, 188 (1954); J. B. Kirsner and W. L. Palmer, *J. Am. Med. Assoc.*, **151**, 798 (1953); J. B. Kirsner, E. Levin, and W. L. Palmer, *Gastroenterology*, **26**, 852 (1954).

(4) E. Schmidt, *Arch. Pharm.*, **232**, 409 (1894).

(5) H. Wick, *Arch. exper. Path. Pharmacol.*, **213**, 485 (1951).

(6) W. L. Miller, J. J. Krake and M. J. VanderBrook, to be published elsewhere.

(7) E. Schmidt, *Arch. Pharm.*, **230**, 207 (1892).

(8) Australian Spec. 12181 (1952).

(9) G. Fodor and O. Kovacs, *J. Chem. Soc.*, 2341 (1953).