TABLE VIII—CHLORPROTHIXENE RECOVERED FROM HUMAN URINE[a]

Time, hr.	Adult Male Subject I	II	III
	mcg./ml.		
4	0.14	0.55	3.33
8	1.46	3.76	7.59
12	1.48	4.45	3.99
24	4.19	2.32	2.26
48	2.21	0.88	1.14
72	1.19	0.20	0.35
Total recovered, mg.	3.6	3.4	3.6

[a] Each subject received 50 mg. chlorprothixene by mouth.

concentration of chlorprothixene measured in the urine over a 72-hr. period varied considerably from one subject to another (Table VIII). The total amount excreted in the urine by the three subjects during the 72 hr. was less variable: 3.4 to 3.6 mg.

Although the method for analysis which has been described does not distinguish between chlorprothixene and its sulfoxide metabolite, this lack of specificity is not likely to carry medical or legal importance. Sensitivity of the method is sufficient to permit the analyst to detect the drug and its metabolites in the urine 3 days after an individual has taken a single 50-mg. dose.

SUMMARY

A quantitative ultraviolet spectrophotometric procedure has been developed for the determination of chlorprothixene and its principal sulfoxide metabolite in biologic specimens. In the procedure, the drug is oxidized with buffered permanganate to a carbonyl derivative which has a well-defined ultraviolet absorption spectra. The method is sensitive and the combined ultraviolet spectrum of the oxidation products is sufficiently specific to establish qualitative identification of the drug. Results of a study to establish the excretion pattern of chlorprothixene and its metabolites in man, as well as their distribution in the tissues, and biologic fluids of the rat are presented.

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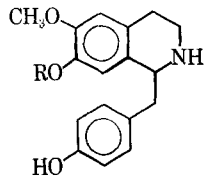
1-Benzyl-1,2,3,4-tetrahydroisoquinolines

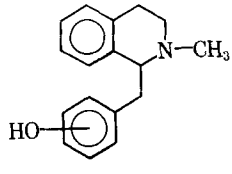
By JOSEPH SAM and A. J. BEJ*

The syntheses of 1-benzyl-1,2,3,4-tetrahydroisoquinolines, particularly phenolic derivatives, are described. Preliminary pharmacological data also are reported.

NUMEROUS CHEMICAL and biological investigations have been conducted with synthetic as well as naturally occurring 1-benzylisoquinolines (1). Limited biological information is available, however, on phenolic 1-benzyl-1,2,3,4-tetrahydroisoquinolines. Kupchan and co-workers (2) noted weak analgesic activity with (−)-*N*-normarmepavine (I*a*). Colacurine (I*b*) was tested for curare-like activity in dogs but manifested no activity (3). Both of these alkaloids are secondary amines. Often the biological activity of secondary amines are lower than the corresponding *N*-methyl or tertiary amines (4). Accordingly, a program was initiated to synthesize and evaluate phenolic 1-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinolines (II) for biological activity.



I*a*, R = CH_3
b, R = H



II

DISCUSSION

The relationship of phenolic 1-benzyl-2-methyl-1,2,3,4-tetrahydroisoquinolines, both structurally (not sterically) and biogenetically (5), to morphine (III) gave additional impetus to the investigation. In this connection, Besendorf and co-workers (6) noted pronounced analgesic activity in 6,7-dimethoxy-1-(4-chlorophenethyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (IV).

The preparation of 1-(4-hydroxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (V) was investigated

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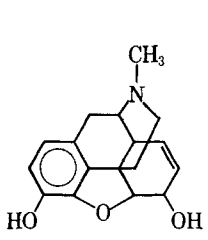
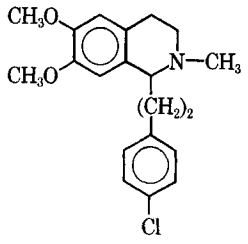
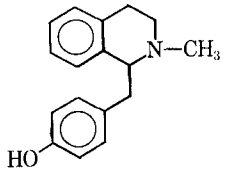
* Present address: Department of Pharmaceutical Chemistry, University of Rhode Island, Kingston, RI 02881



III



IV



V

via (*a*) the Bischler-Napieralski reaction, (*b*) the Grignard reaction, (*c*) the Reissert compound, and (*d*) the reaction of pseudobases with 2- and 4-nitrotoluenes.

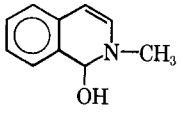
Kondo and Ishiwata (7) reported a 51% yield for the cyclization of VI to the corresponding 3,4-dihydroisoquinoline (VII) using phosphorus oxychloride. By using a mixture of phosphorus oxychloride and phosphorus pentoxide, a 70–80% yield of VII was obtained. Polyphosphoric acid on the other hand did not effect cyclization of VI at 190°. (Scheme I.)

The reduction of 1-(4-methoxybenzyl)-3,4-dihydroisoquinoline methiodide (VIII) with sodium borohydride gave the corresponding tetrahydroisoquinoline (IX). Demethylation of IX was effected with either 48% hydrobromic acid or 47% hydroiodic acid to yield V.

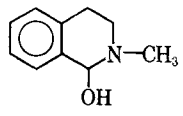
The treatment of isoquinoline methiodide (X) with 4-methoxybenzylmagnesium chloride, followed by reduction with sodium borohydride provided an alternate route to IX. The intermediate dihydro derivative (XI) was isolated but not identified. The reaction of 4-methoxybenzylmagnesium chloride with 3,4-dihydroisoquinoline methiodide (XII) also gave the tetrahydroisoquinoline (IX).

The reaction of pseudobases, XIII and XIV (obtained from isoquinoline methiodide and 3,4-dihydroisoquinoline methiodide, respectively), with 2- and 4-nitrotoluenes also was investigated. The condensation of isoquinoline methiodide (X) with 2-nitro-5-benzyloxytoluene (XV) according to the procedure described by Weisbach and co-workers (8) gave XVI. The platinum oxide reduction of XVI yielded XVII. The reaction of 4-nitrotoluene with either X or XIV, however, resulted only in the recovery of 4-nitrotoluene. (Scheme II.)

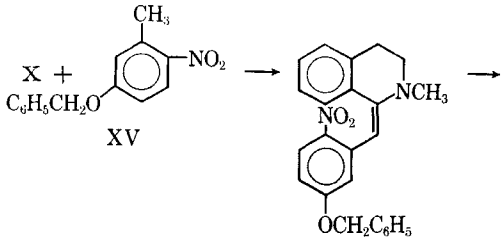
A final method of preparation of V involved initially the condensation of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline (Reissert compound) (XVIII) with 4-benzyloxybenzyl chloride (XIX) or bromide



XIII

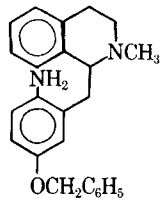


XIV

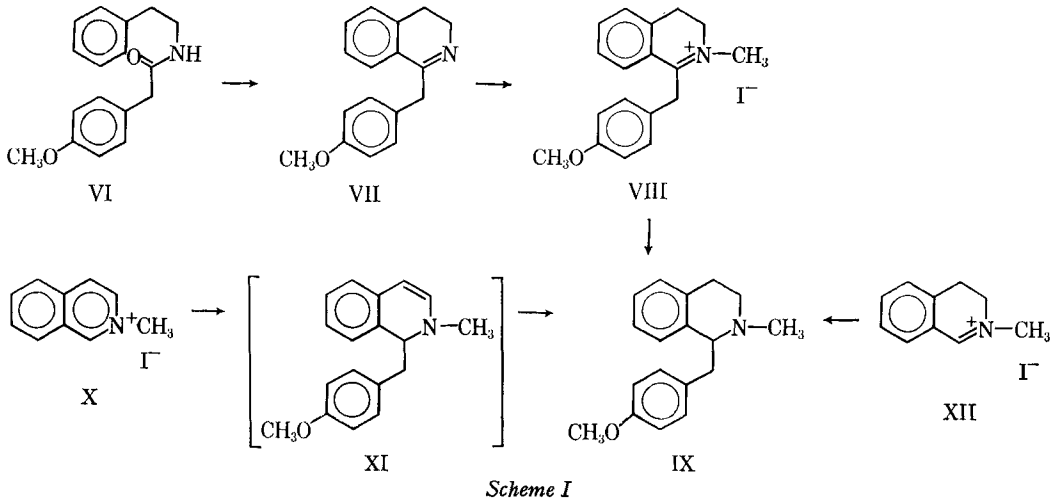


XV XVI

Scheme II



XVII



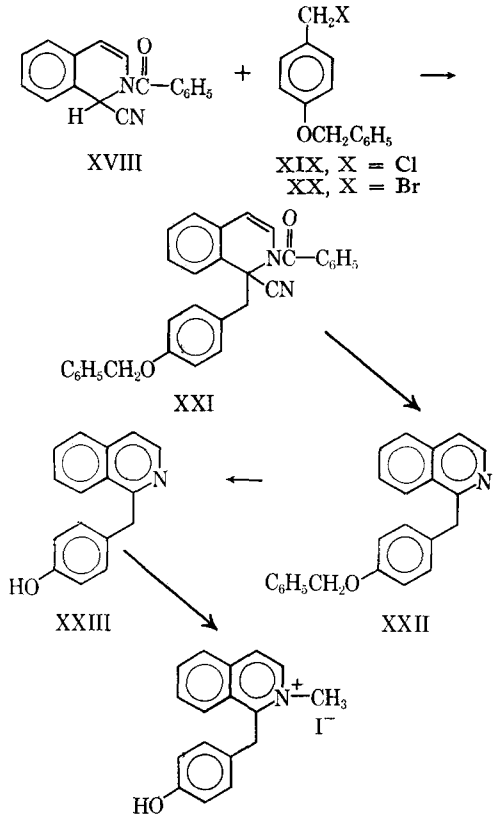
VI VII VIII X XI XII IX

Scheme I

(XX). Alkaline hydrolysis of XXI gave 1-(4-benzyloxybenzyl)isoquinoline (XXII). Heating XXII with 20% hydrochloric acid gave XXIII. The latter was converted to the methiodide (XXIV) and reduced to the desired product (V) with sodium borohydride. (Scheme III.)

Gibson and Popp (9) reported the preparation of XXII and XXIII from XVIII and 4-benzyloxybenzaldehyde. Ikehara (10) reported the synthesis of XXIII by the condensation of 1-chloroisoquinoline with 4-methoxyphenylacetonitrile, followed by demethylation.

Pharmacological Results[1]—Compounds V, XVI, and XVII have been investigated by a gross symptomological procedure in albino mice after intraperitoneal injection. There was little or no significant effect and no lethality with up to 680 mg./Kg. of XVI. However, compound XVII caused early deaths with excitation and clonic convulsions, and had an LD_{50} of 68 mg./Kg. Lower doses showed signs of CNS inhibitory actions; 2.0 and 20 mg./Kg. yielded significant prolongation of hexobarbital sleeping time. In the writhing test for analgesia, an ED_{50} of 11.5 mg./Kg. was noted. In a few albino rats, compound XVII appeared to produce drowsiness and partial analgesia at 10–20 mg/Kg., while at 46 mg./Kg. there was first sedation and later excitation and convulsions. An LD_{50} of 153 mg./Kg. was noted for V. In lethal dosage it produced multiple strong clonic convulsions and terminal tonic convulsion. In lower dosage symptoms of exophthalmos, immobility (catatonia-like), and loss of cutaneous pain reflexes were noted. At 100 mg./Kg., V reduced by 50% the number of writhing responses in the phenylquinone writhing test for analgesic action.



Scheme III

EXPERIMENTAL[2]

N-Phenethyl-4-methoxyphenylacetamide (VI)—The procedure utilized by Decker and Kropp (11) for the preparation of *N*-phenethylphenylacetamide was followed.

A mixture of 16.6 Gm. (1.0 mole) of 4-methoxyphenylacetic acid and 12.1 Gm. (1.0 mole) of β-phenethylamine was fused at 180° and the melt maintained at that temperature for 9 hr. The resulting homogeneous melt was poured into a mortar. The material, which solidified on cooling, was pulverized and recrystallized from ethanol. There was obtained 14.7 Gm. (55%) of a white crystalline solid, m.p. 96–97.5°. [Lit. (7) m.p. 95°.]

1-(4-Methoxybenzyl)-3,4-dihydroisoquinoline Methiodide (VIII)—A mixture of 26 Gm. (0.1 mole) of *N*-phenethyl-4-methoxyphenylacetamide (VI), 25 Gm. (0.22 mole) of phosphorus pentoxide, 23 Gm. (0.15 mole) of phosphorus oxychloride, and 200 ml. of dry toluene was refluxed at 130–135° for 3.5 hr. After 1 hr., 17 Gm. (0.11 mole) of phosphorus oxychloride was added to the reaction mixture. The reaction mixture was cooled to room temperature. The toluene layer was decanted from the brownish semisolid. The latter was treated with crushed ice and then extracted with 10 L. of boiling water. The water extract was divided into five portions; each portion was basified with 20% sodium hydroxide solution, and each portion was extracted with three 300-ml. portions of ether. The combined ether extract was washed with water and dried over anhydrous potassium carbonate. Distillation of the ether under reduced pressure gave 16 Gm. (70%) of the 3,4-dihydro free base. The latter was transferred to a pressure bomb (glass) and treated with 20 ml. of methyl iodide and then heated on an oil bath maintained at 50–55° for 6 hr. The crude solid was recrystallized from ethanol to yield 19 Gm. (50%) of product, m.p. 198–200°. Recrystallization twice from ethanol gave a pale yellow crystalline solid, m.p. 207–209°.

Anal.—Calcd. for $C_{18}H_{20}INO$: C, 54.98; H, 5.12; I, 32.38; N, 3.56. Found: C, 55.04; H, 5.34; I, 32.40; N, 3.34.

1-(4-Methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (IX)—*Method A*—A stirred solution of 6.25 Gm. (0.017 mole) of 1-(4-methoxybenzyl)-3,4-dihydroisoquinoline methiodide (VIII) in 150 ml. of methanol was treated with 7 Gm. of sodium

[1] The authors are grateful to Dr. Marvin Davis, Department of Pharmacology, School of Pharmacy, University of Mississippi, for the pharmacological data.

[2] Melting points were taken in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer model 137 G Infracord spectrophotometer using potassium bromide pellets unless otherwise indicated. The NMR spectrum of V was obtained by means of the Varian A-60A spectrometer using tetramethylsilane (TMS) as the internal standard and deuterochloroform as the solvent. The shifts were measured on the τ-scale relative to the internal standard TMS (τ 10.0). Assignment of protons in a certain area is based on correct integral information from the NMR spectrum.

borohydride in small portions. The resultant mixture was stirred at room temperature for 45 min. and then concentrated under reduced pressure. The residue was treated with 500 ml. of 2% sodium hydroxide and extracted with four 100-ml. portions of ether. The ether extract was washed with 200 ml. of water and dried over anhydrous potassium carbonate. The ether was concentrated under reduced pressure to yield 3.2 Gm. (45%) of pale yellow oil. A picrate was prepared in the usual manner and recrystallized from ethanol, m.p. 159–160.5°.

Anal.—Calcd. for $C_{24}H_{24}N_4O_8$: C, 58.07; H, 4.87; N, 11.30. Found: C, 58.08; H, 4.84; N, 11.32.

Method B—The procedure utilized by Schnider and Grüssner (12) for the preparation of 1-(4-methoxybenzyl)-2-methyl-1,2,5,6,7,8-hexahydroisoquinoline was followed. A stirred ice-cooled suspension of 41 Gm. (0.15 mole) of isoquinoline methiodide (X) in 200 ml. of dry ether was treated dropwise over a 30-min. period with 4-methoxybenzylmagnesium chloride [prepared from 23.4 Gm. (0.15 mole) of 4-methoxybenzyl chloride according to the general method of Van Campen (13) and coworkers]. The resultant mixture was stirred at room temperature for 1 hr. and then poured into 1 Kg. of crushed ice and water containing 30 Gm. of ammonium chloride. The mixture was made alkaline with ammonium hydroxide. The ether layer was separated and the aqueous layer further extracted with ether. The combined ether solution was extracted with seven 100-ml. portions of cold 10% hydrochloric acid. The acid extract was made alkaline with cold ammonium hydroxide and extracted with four 200-ml. portions of ether. The ether extract, after drying over anhydrous sodium sulfate, was concentrated under reduced pressure. Trituration of the residual semisolid with ethanol gave 7 Gm. (17%) of the dihydro compound (XI) as an amorphous solid, m.p. 68–73°. This compound changed to reddish brown when exposed to air, and attempts to purify the substance proved abortive.

A solution of 4 Gm. (0.014 mole) of the above solid in 150 ml. of methanol was treated in portions with 5 Gm. of sodium borohydride and then stirred at room temperature for 2.5 hr. The product was isolated as in method *A* to give 2.3 Gm. (57%) of pale yellow oil. A picrate, m.p. 159–160.5°, showed no depression on admixture with a sample obtained by method *A*. The infrared spectra were identical.

Method C—The procedure employed in method *B* was followed using a mixture of 10 Gm. (0.037 mole) of 3,4-dihydroisoquinoline methiodide (XII) (14), 50 ml. of absolute ether, and 4-methoxybenzoylmagnesium chloride [prepared from 5.8 Gm. (0.037 mole) of 4-methoxybenzyl chloride]. The mixture was treated as in method *B* to yield 1.8 Gm. (17%) of product. The picrate was prepared in the usual manner, m.p. 159–160°. A mixed melting point with the picrate obtained from either method *A* or *B* was undepressed. The infrared spectra were identical.

1-(2-Nitro-5-benzyloxybenzal)-2-methyl-1,2,3,4-tetrahydroisoquinoline (XVI)—The procedure described by Weisbach and co-workers (8) for the preparation of 1-(2-nitrobenzal)-2-methyl-1,2,3,4-tetrahydroisoquinoline was followed. To a warm stirred solution of 1.86 Gm. (0.08 mole) of sodium in 70 ml. of absolute ethanol (commercial ethanol refluxed with calcium oxide and distilled) were added 7.2 Gm. (0.26 mole) of isoquinoline methiodide and 13 Gm. (0.52 mole) of 2-nitro-5-benzyloxytoluene (XV). The resultant solution was kept at room temperature for 24 hr. and then in a refrigerator for 48 hr. The solid that separated was removed by filtration and recrystallized from ethanol to give 8 Gm. (80%) of product, m.p. 102.5–103.5°.

Anal.—Calcd. for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.73; N, 7.25. Found: C, 74.63; H, 5.64; N, 7.18.

1-(2-Amino-5-benzyloxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline Dihydrochloride (XVII)—A modified procedure of Weisbach and co-workers (8) was followed. A mixture of 10.5 Gm. (0.025 mole) of 1-(2-nitro-5-benzyloxybenzal)-2-methyl-1,2,3,4-tetrahydroisoquinoline (XVI), 1 Gm. of platinum oxide, and 250 ml. of absolute ethanol was shaken with hydrogen (initial pressure 40 p.s.i.) in a low pressure Parr hydrogenator for 2 hr. The uptake of hydrogen was essentially complete after the first 15 min. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. Ethanolic hydrogen chloride was added to the residual oil; the resulting solution was kept in a refrigerator for 48 hr. The ethanol was distilled under reduced pressure and the residue treated with 40 ml. of ethanol. The ethanol was again distilled under reduced pressure. The residue was successively treated with three 40-ml. portions of ethyl acetate and finally with 40 ml. of dry benzene; each time the solvent was distilled under reduced pressure. The crude solid was recrystallized from a mixture of methanol and ethyl acetate with the aid of charcoal to give 10.2 Gm. (97%) of product, m.p. 213.5–214.5° dec.

Anal.—Calcd. for $C_{24}H_{28}Cl_2N_2O$: C, 66.80; H, 6.54; Cl, 6.43; N, 6.49. Found: C, 66.79; H, 6.70; Cl, 16.36; N, 6.41.

4-Benzyloxybenzyl Alcohol—To a suspension of 21 Gm. (0.1 mole) of 4-benzyloxybenzaldehyde in 150 ml. of methanol was added dropwise with stirring a solution of 2 Gm. of sodium borohydride in 2 ml. of 2 *N* sodium hydroxide and 18 ml. of water at 18–25°. The reaction mixture was stirred at room temperature for 3 hr. The ethanol was distilled under reduced pressure and the residue diluted with 100 ml. of water and extracted with 600 ml. of ether. The ether solution, after drying over anhydrous magnesium sulfate, was concentrated under reduced pressure. The residue was recrystallized from petroleum ether (30–60°) to give 20 Gm. (95%) of product, m.p. 85–86°. [Lit. (15) m.p. 85–86°.]

1-(4-Benzyloxybenzyl)-2-benzoyl-1,2-dihydroisoquinoaldonitrile (XXI)—*Method A*—The procedure utilized by Kershaw and Uff (16) for the preparation of 1-(4-methoxybenzyl)-2-benzoyl-1,2-dihydroisoquinoaldonitrile was followed. To a cooled (0°) and stirred solution of 2.76 Gm. (0.01 mole) of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline (Reissert compound) (17) and 2.3 Gm. (0.01 mole) of 4-benzyloxybenzyl chloride (XIX) (15) in 50 ml. of *N*,*N*-dimethylformamide maintained in a nitrogen atmosphere was added 0.24 Gm. (0.01 mole) of a 50% dispersion of sodium hydride in mineral oil. The mixture was stirred at 0° for 1 hr. and at room temperature for 2 hr. The reaction mixture was poured onto 500 Gm. of crushed ice. The product was removed by filtration and recrystallized twice

from absolute ethanol; 3.1 Gm. (70%) of product was obtained, m.p. 144–146°. The infrared spectrum in Nujol possessed a rather weak band for the amide carbonyl group at 6.05 μ, possibly due to an interaction of the oxygen atom of the amide with the carbon atom of the cyano group. This was supported by a very weak absorption at 4.16–4.54 μ, the frequency range in which absorption due to a cyano group is observed.

Anal.—Calcd. for $C_{31}H_{24}N_2O_2$: C, 81.56; H, 5.34; N, 6.14. Found: C, 81.31; H, 5.47; N, 6.21.

Method B—The procedure described in method *A* was followed using 4-benzyloxybenzyl bromide (XX) instead of 4-benzyloxybenzyl chloride (XIX), m.p. 144–146°.

1-(4-Benzyloxybenzyl)isoquinoline (XXII)—The procedure utilized by Boekelheide and Weinstock (18) for the preparation of 1-methylisoquinoline was followed. A solution of 4.5 Gm. (0.01 mole) of 1-(4-benzyloxybenzyl)-2-benzoyl-1,2-dihydroisoquinaldonitrile (XXI) in 70 ml. of methanol was treated with 1.12 Gm. (0.02 mole) of sodium hydroxide in 8 ml. of water and then refluxed for 3.5 hr. The cooled mixture was diluted with 75 ml. of water and extracted with three 200-ml. portions of ether. The ether extract was dried over anhydrous magnesium sulfate. The ether was concentrated under reduced pressure; the residue was recrystallized from ethanol to yield 2.3 Gm. (69%) of product, m.p. 122–123°. [Lit. (9) m.p. 121–122°.]

1-(4-Hydroxybenzyl)isoquinoline (XXIII)—A mixture of 3.25 Gm. (0.01 mole) of 1-(4-benzyloxybenzyl)isoquinoline (XXII) and 100 ml. of 20% hydrochloric acid was heated on a steam bath for 1.5 hr. The reaction mixture was washed with two 30-ml. portions of chloroform and then basified with 28% ammonium hydroxide. The solid was removed by filtration, washed with water, and recrystallized from ethyl acetate to yield 1.5 Gm. (65%) of product, m.p. 180–182°. [Lit. (9) m.p. 177–179°.]

1-(4-Hydroxybenzyl)isoquinoline Methiodide (XXIV)—A solution of 0.9 Gm. (0.004 mole) of 1-(4-hydroxybenzyl)isoquinoline (XXVIII) and 15 ml. of methyl iodide in 10 ml. of methanol was refluxed for 3 hr. and then poured into ether. The solid was removed by filtration and recrystallized from methanol to yield 0.95 Gm. (82%) of product, m.p. 224–227°.

1-(4-Hydroxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (V)—*Method A*—The method utilized by Craig and associates (19) for the preparation of 1-alkyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines was followed. A mixture of 3.5 Gm. (0.013 mole) of 1-(4-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (IX) and 40 ml. of 48% hydrobromic acid (redistilled over a trace of 50% hypophosphorous acid and mixed with the latter in the proportion of 1 Gm. of 50% hypophosphorous acid to 100 Gm. of 48% hydrobromic acid) was gently refluxed at 135–140° in a current of nitrogen for 6 hr. The reaction mixture was basified with 28% ammonium hydroxide and extracted with four 100-ml. portions of benzene. The benzene extract was dried over anhydrous sodium sulfate and then distilled under reduced pressure to yield a pale yellow solid, m.p. 72–82°. The crude product was chromatographed on 25 Gm. of neutral Woelm alumina (activity I) prepared in benzene and eluted with 240 ml. of benzene, 210 ml. of acetone, 180 ml. of ethyl acetate, and finally with 180 ml. of methanol. The evaporation of the methanol eluents gave 0.420 Gm. (33%) of product, m.p. 130–132°. Recrystallization from carbon tetrachloride with the aid of charcoal gave product, m.p. 133.5–134.5°.

Anal.—Calcd. for $C_{17}H_{19}NO$: C, 80.6; H, 7.56; N, 5.59. Found: C, 80.8; H, 7.54; N, 5.82.

Method B—The procedure described in method *A* was followed using 47% hydriodic acid instead of 48% hydrobromic acid, m.p. 133.5–134.5°.

Method C—The procedure utilized by Gibson and co-workers (20) for the preparation of 1-(4-hydroxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline was followed. A mixture of 0.7 Gm. (0.0019 mole) of 1-(4-hydroxybenzyl)isoquinoline methiodide (XXIV), 2 Gm. of sodium borohydride, 2 ml. of water, and 80 ml. of methanol was refluxed with stirring for 2 hr. Most of the methanol was distilled under reduced pressure, and the residue poured onto ice. The mixture was adjusted to pH 8 and extracted with two 50-ml. portions of ether. The ether extract was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was recrystallized from carbon tetrachloride to yield 0.5 Gm. (100%) of product, m.p. 132.5–134°. A mixed melting point with the sample obtained *via* the Bischler-Napieralski reaction was undepressed.

The nuclear magnetic spectrum (NMR) of V in deuterochloroform showed three *N*-methyl protons (singlet τ = 7.49), six ring methylene protons (multiplet centered at τ 7.1), one tertiary proton (triplet τ = 6.1), and eight aromatic protons (τ 2.75–3.5), which is consistent with the structure.

1-(4-Benzoyloxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline—To a solution of 0.25 Gm. (0.001 mole) of 1-(4-hydroxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (V) in 10 ml. of 1 *N* sodium hydroxide was added 0.2 Gm. (0.001 mole) of benzoyl chloride. The mixture was shaken vigorously for 10 min. and then extracted with two 20-ml. portions of chloroform. The chloroform extract was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residual oil (0.25 Gm., 70%) was converted to a picrate in the usual manner and recrystallized from methanol, m.p. 201.5–203°.

Anal.—Calcd. for $C_{30}H_{26}N_4O_9$: C, 61.43; H, 4.47; N, 9.55. Found: C, 61.60; H, 4.57; N, 9.62.

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Plasticizers in Medical Application I

Analysis and Toxicity Evaluation of Dialkyl Benzenedicarboxylates

By JAY NEMATOLLAHI, WALLACE L. GUESS, and JOHN AUTIAN

A series of dialkyl and dicycloalkyl benzenedicarboxylates (phthalates, isophthalates, terephthalates), of which some have been employed as plasticizers, were synthesized and purified. Thin-layer chromatography and infrared spectrometry were employed as methods of detection and identification of these compounds. Toxicity tests were conducted using mammalian cell cultures and limited mouse studies. The low molecular weight esters and their isomers manifested toxic responses while the esters containing alkyl groups C_6 to C_9 were devoid of toxic effect. The di-*n*-decyl phthalate and terephthalate also elicite toxic actions to cells. Results from this study indicate the need for good quality control procedures to prevent the access of potentially toxic plasticizers in devices for medical and paramedical applications.

A NUMBER of polymeric materials require the presence of one or more plasticizers to impart a degree of softness and flexibility not inherent in the parent polymer. The concentration of the plasticizer may vary from a rather small percentage to as high as 60%, depending upon the desired final properties. Selection of a plasticizer (or plasticizers) for a specific plastic is dependent upon a number of considerations; the initial consideration is that it will impart to the final plastic the optimum properties desired at a minimum cost consistent with quality production. If the plastic material is to be used as a food wrap or a container, the degree of migration of the plasticizer to the food and the toxicity profile of the migrated ingredient must be evaluated under the Food Additive Amendment. Development and use of the plasticized polymeric materials for various medical, pharmaceutical, and dental applications such as tubing, catheters, containers, and protective films raises the question as to the toxic potential of migrated plasticizer which may enter the patient by routes other than oral. In this regard, consideration must also be given to the exact composition of the "migrated ingredient" since it may actually be composed of the intact plasticizer, degraded products of the plasticizer, impurities in the plasticizer, and other additives such as stabilizing agents, antioxidants, degraded products of the additives, and impurities in the additives.

Within the past 5 years, a number of published reports (1–3) have demonstrated that certain types of polyvinyl chloride (PVC) devices could produce toxic effects if one or more ingredients migrated from the device into tissue or into an injectable solution.

Recent investigations (4) on a group of PVC blood bags revealed that certain ingredients were migrating from the plastic into acid citrate dextrose solutions. The combined ingredients were found to be toxic to mammalian cell cultures. Further investigations on the "leached" ingredients showed the presence of several chemicals, presumably plasticizers together with their degradation products. A frequently employed plasticizer in the PVC plastic used for the manufacture of the blood bags was found to be di(2-ethylhexyl)phthalate. Others such as dialkyl sebacates and epoxidized soybean oil were also detected in the PVC.

When a combined chemical and spectrophotometric method was employed for the detection and identification of these additives, it became obvious that a mixture of homologs of a few di-

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