TABLE I—RELATIVE COLOR STABILITY OF PAPAVERINE HYDROCHLORIDE PARENTERAL SOLUTIONS WITH AND WITHOUT SODIUM EDETATE—TIME TO DISCOLOR TO A.P.H.A. COLOR STANDARD 15[a] PAPAVERINE HYDROCHLORIDE WITH NITROGEN ATMOSPHERE

Temp., °C.	No EDTA	0.005% EDTA
50	2 wk.	5 mo.
37	1 mo.	9 mo.
25	12 mo.	Colorless to date (2 yr.)

[a] Standards of American Public Health Association using solutions of platinum chloride in water. A.P.H.A. 15 is a pale yellow color.

dry heat. The glass-sealed ampuls were sealed by pull-type seals. The rubber-stoppered vials were sealed with West natural rubber stoppers and aluminum seals. Aging tests were conducted at room temperature and in ovens at 37° and 50°. Light exposure consisted of exposure to direct sunlight in a window facing south, and also by exposure on a shelf to fluorescent lights approximately 10 ft. away. Color was noted visually by observing against a white background. The N.F. XII assay procedure for papaverine hydrochloride was used in all cases. Samples of papaverine hydrochloride containing 0%, 0.005%, 0.01%, and 0.02% sodium edetate were formulated.

Samples of papaverine hydrochloride with 0.005% and no sodium edetate were stored in glass-seal ampuls and rubber-stoppered vials. Two lots of papaverine hydrochloride raw material were used for the experiments. Some ampuls of each section were exposed to light. Some contained a nitrogen atmosphere. All sections were exposed to 25, 37, and 50° temperatures. The samples were observed weekly to 2 months, then monthly to the point of discoloration.

DATA AND RESULTS

Oxygen in the air and light detract from color stability of papaverine hydrochloride solutions. The effect, however, is considerably less for sodium edetate formulations. Temperature has less effect on discoloration with the sodium edetate formulations, but still is a significant factor. It was found that color inhibition was maximum at 0.005% sodium edetate and was not improved by increasing the concentration of sodium edetate. The discoloration noted in glass-seal ampuls and rubber-stoppered vials was the same, indicating no effect from the package. No difference was seen between either of the lots of papaverine hydrochloride raw material. The type of sterilization (filtration *versus* autoclave) did not affect color formation. The amount of improvement of color stability can be seen in Table I.

CONCLUSIONS

Disodium ethylenediaminetetraacetate (sodium edetate or EDTA) successfully inhibits color formation in injectable solutions of papaverine hydrochloride at a concentration of 0.005%. Protection from light and oxygen offer additional protection. Chemical potency is still at 100% at 37° at 18 months. It is believed that the mechanism of protection is through sequestering trace quantities of heavy metals present, such as iron, which may react with chloride ions in the solution at the low pH (3.0–4.0) of these solutions. That this is so was determined by adding a tiny piece of iron oxide to each of several vials of papaverine hydrochloride which turned dark amber soon after.

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New Compounds: *N*-Substituted Tetrahydroisoquinolines

By JOSEPH SAM*

The Mannich, sodium borohydride reduction, and esterification reactions were utilized for the preparation of several *N*-substituted tetrahydroisoquinolines. Aminolysis of ethyl cyanoacetate with tetrahydroisoquinoline provided the corresponding cyanoacetamide.

SEVERAL *N*-SUBSTITUTED tetrahydroisoquinolines were prepared and screened for biological activity. The Mannich reaction with *p*-chloro- and *p*-methoxyacetophenone yielded two tetrahydroisoquinolino-ketones (I). Mannich and Lammering (1) earlier had described the preparation of unsubstituted I. The sodium borohydride reduction of I resulted in II; treatment of II*a* with 3,4,5-trimethoxybenzoyl chloride provided the corresponding ester.

The aminolysis of ethyl cyanoacetate with tetra-

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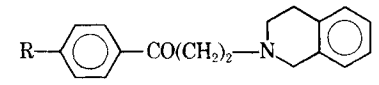
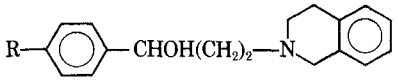
* Present address: Department of Pharmaceutical Chemistry, School of Pharmacy, University of Mississippi, University, MS 38677

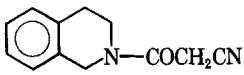


Ia, R = CH_3O
b, R = Cl



IIa, R = CH_3O
b, R = Cl

hydroisoquinoline gave a good yield (65%) of the corresponding amide III.



III

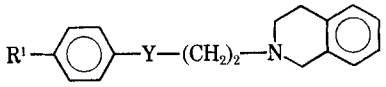
Preliminary pharmacological evaluation did not indicate any pronounced biological activity in the compounds.

and Brown (3) was followed. To a mixture of 5 Gm. of sodium borohydride and 50 ml. of methanol was added dropwise with stirring a solution of 0.1 mole of carbonyl compound. Thereafter, the mixture was refluxed for 2 hr. The methanol was distilled *in vacuo*. The residual material was treated with 200 ml. of water, extracted with ether, and dried over anhydrous sodium sulfate. The product was isolated as the base or converted to the hydrochloride in the usual manner.

α - (p - Methoxyphenyl) - γ - [3,4 - dihydro-2(1) - isoquinolyl]propyl - 3,4,5 - trimethoxybenzoate (Table I, Method C)—A solution of 6.0 Gm. (0.02 mole) of the alcohol in 150 ml. of chloroform was treated with 5.0 Gm. of 3,4,5-trimethoxybenzoyl chloride and an excess of potassium carbonate. The resulting mixture was allowed to remain at room temperature for 18 hr. Water was added to the mixture and the chloroform layer separated and dried over anhydrous potassium carbonate. A hydrochloride was prepared in the usual manner and recrystallized from a mixture of methyl ethyl ketone and ether, m.p. 163–164°.

2 - Cyanoacetyl - 1,2,3,4 - tetrahydroisoquinoline

TABLE I—*N*-SUBSTITUTED TETRAHYDROISOQUINOLINES



R'	Y	Recrystn. Solvent[a]	Method	% Yield	B.p., °C. (mm.) M.p., °C.	Molecular Formula	Anal. Calcd. C	Calcd. H	Found C	Found H
Cl	C=O	M	*A*	66	200–202	$C_{18}H_{19}Cl_2NO$[b]	64.3	5.69	64.5	5.79
CH_3O	CHOH	M–MIK	*B*	60	155–156	$C_{19}H_{24}ClNO_2$[b]	69.0	7.37	68.5	7.38
CH_3O	3,4,5-tri$CH_3OC_6H_2$-CO_2CH	E-MEK	*C*	28	163–164	$C_{29}H_{34}ClNO_6$[b]	66.0	6.49	66.2	6.62
CH_3O	C=O	...	*A*	61	81–82	$C_{19}H_{21}NO_2$	...	...	...	...
CH_3O	C=O	M–MEK	..	90[c]	184–186	$C_{19}H_{22}ClNO_2$[b]	68.8	6.68	69.2	6.85
Cl	CHOH	E–H	*B*	80	194–200 (0.4 mm.) 99–100	$C_{18}H_{20}ClNO$	71.6	6.68	71.7	6.78
Cl	CHOH	M–E	..	95[c]	184–186	$C_{18}H_{21}Cl_2NO$[b]	63.9	6.26	64.3	6.60

[a] M, methanol; MIK, methyl isobutyl ketone; E, ether; MEK, methyl ethyl ketone; H, *n*-hexane. [b] Hydrochloride. [c] From the parent amine.

EXPERIMENTAL[1]

Mannich Reaction Products (Table I, Method A)—The procedures described by Mannich and Lammering (1) and Mosettig and May (2) were followed. To a mixture of 10 ml. of concentrated hydrochloric acid were added 0.1 mole of substituted acetophenone and 10 ml. of 37% formaldehyde. The resulting mixture was heated on a steam bath with stirring for 2 hr. The hydrochloride was removed by filtration and recrystallized from a suitable solvent (Table I).

Sodium Borohydride Reduction Products (Table I, Method B)—The procedure described by Chaiken

[1] All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.

—A mixture of 13 Gm. (0.1 mole) of 1,2,3,4-tetrahydroisoquinoline and 12 Gm. (0.1 mole) of ethyl cyanoacetate was refluxed for 2 hr. and then allowed to stay at room temperature for 12 hr. The reaction mixture was treated with ether. The solid (13 Gm., 65%) was removed by filtration and recrystallized from a mixture of methanol and ether, m.p. 105–106°.

Anal.—Calcd. for $C_{12}H_{12}N_2O$: C, 72.0; H, 6.04. Found: C, 72.2; H, 6.13.

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