The cesium salt of **1a** was prepared using aqueous cesium carbonate. The infrared spectrum of the salt had no OH bands; carboxylate bands at 6.2 and 7.3 μ were present.

Anal. Calcd for $C_7H_4N_2O_3FCs$: C, 26.60; H, 1.28; N, 8.87. Found: C, 26.77; H, 1.46; N, 9.56.

N-(2-Carboethoxyphenyl)-N′-*p*-toluenesulfonyldiimide N-oxide (2b) was prepared from ethyl 2-nitrosobenzoate and chloramine-T according to the procedure of Farrar and Gulland.[6] It was recrystallized from chloroform–hexane, mp 90–92°.

Anal. Calcd for $C_{16}H_{16}N_2O_5S$: C, 55.16; H, 4.63; N, 8.04. Found: C, 55.04; H, 4.75; N, 8.00.

The uv spectrum (ethanol) had λ_{max} 224 and 277 mμ (ϵ_{max} 18,800 and 9700).

Preparation of N-(2-Carboxyphenyl)-N′-*p*-toluenesulfonyldiimide N-Oxide (1b).—A 3.48-g sample of **2b** in a mixture of 5 ml of water and 55 ml of methanol containing 14 mmoles of sodium methoxide was stirred overnight. The mixture was poured into water and acidified, and the solid removed by filtration. Two recrystallizations of the solid (chloroform–ethyl acetate) gave 1.8 g of **1b**, mp 195–196° dec.

Anal. Calcd for $C_{14}H_{12}N_2O_5S$: C, 52.49; H, 3.78; N, 8.75. Found: C, 52.65; H, 4.14; N, 8.69.

The infrared spectrum of **1b** (Nujol mull) had an –OH peak at 3.13 μ and a sharp carbonyl peak at 5.82 μ.

The uv spectrum (ethanol) had λ_{max} 224 and 262 mμ (ϵ_{max} 17,100 and 8100). In 0.1 *N* sodium hydroxide in ethanol, λ_{max} 228 mμ (ϵ 13,700) and $\lambda_{shoulder}$ 272 mμ (ϵ 7300) were observed.

The cesium salt of **1b** had no –OH absorption in its infrared spectrum. Bands due to the carboxylate group were at 6.2 and 7.35 μ.

Esterification of 1b. A. With Acidic Methanol.—A mixture of 15 ml of 1,2-dichloroethane, 0.80 g of **1b**, 1 ml of methanol, and two drops of concentrated sulfuric acid was refluxed for 6 hr. The mixture was cooled and washed with H_2O and 10% aqueous sodium bicarbonate. The residue obtained upon evaporation of the organic layer was recrystallized from ethanol. Thus, N-(2-carbomethoxyphenyl)-N′-*p*-toluenesulfonyldiimide N-oxide, mp 125–127°, was obtained.

Anal. Calcd for $C_{15}H_{14}N_2O_5S$: C, 53.9; H, 4.22; N, 8.38. Found: C, 53.8; H, 4.43; N, 8.21.

The uv spectrum (ethanol) had λ_{max} 225 and 277 mμ (ϵ_{max} 18,600 and 9300).

B. With Acidic Ethanol.—When ethanol was substituted for methanol in the procedure A, and the mixture was refluxed for 24 hr, **2b**, mp and mmp 90–92°, was produced.

C. With Diazomethane.—To 0.5 g of **1b** in 50 ml of tetrahydrofuran (THF) at 0° was added an excess of ethereal diazomethane. When gas evolution ceased, the THF was removed at reduced pressure. The residue, recrystallized from ethanol, had mp 123–125° and an infrared spectrum identical with the methyl ester produced by procedure A.

Pyrolysis of the Cesium Salt of 1a.—A 0.32-g (1 mmole) sample of the cesium salt of **1a** was heated at 180–190° in 15 ml of triglyme. After 2 hr, the closed tube was vented into a calibrated volume. A total of 29 cc of gas, 79% N_2 and 23% CO_2 by mass spectrum was collected. An additional 16 cc of CO_2 was collected by quickly pumping the gases from the solution into a −196° trap.

When 0.63 g of the cesium salt was heated in 10 ml of *o*-dichlorobenzene for 2 hr at 170°, 70 cc of gas was obtained. This was 9% N_2O, 37% CO_2, and 54% N_2, as determined by mass spectrum.

Pyrolysis of 1b and its Cesium Salt.—When 0.45 g of the cesium salt of **1b** in 15 ml of dichlorobenzene was heated (180°) for 2 hr, 22 cc of gas, 73% N_2 and 27% CO_2, was collected. Degassing into a −196° trap collected another 10 cc of gas (99% CO_2 and 1% NO by mass spectrum).

From 0.32 g of **1b** (1 mmole) in 15 ml of triglyme (200°, 1 hr), 20 cc of gas, 75% N_2 and 25% CO_2, was collected.

Reaction of Anthracene and Sodium Salt of 1a.—To 4 mmoles of the sodium salt of N-(2-carboxyphenyl)-N′-fluorodiimide N-oxide, prepared from 0.75 g of the free acid, was added 1.2 g of anthracene and 25 ml of dichlorobenzene. The mixture was refluxed 4 hr. Excess dichlorobenzene was removed at 1 mm; excess anthracene was removed with maleic anhydride as usual.[3] The solid residue obtained after this treatment was chromatographed on silica gel. Elution was carried out with pentane containing increasing (2, 3, 5, 10%) methylene chloride. Anthracene (63 mg) and triptycene (18 mg) were recovered from the column. The triptycene had mp 251–253° (lit.[3] mp 254°) and infrared and nmr spectra identical with those reported.[3]

When 0.62 g of the cesium salt of **1a**, 0.72 g of anthracene, and 25 ml of triglyme were heated 3 hr at 180–190°, and the reaction worked up as described above, only 5 mg (1%) of triptycene was isolated.

Reaction of Anthracene and 1b.—A mixture of 0.64 g of **1b** (2 mmoles), 0.72 g of anthracene, and 25 ml of triglyme was heated (190–200°) for 3 hr. The mixture was cooled, poured into water, and extracted with hexane. The residue from the hexane was freed of anthracene as usual.[3] Chromatography of the final residue on silica gel gave 0.129 g of triptycene, mp 251–253°.

Reaction of 1b and 1,2,3,4-Tetraphenylcyclopentadienone.—Four mmoles, 1.28 g, of **1b**, 1.92 g (5 mmoles) of tetraphenylcyclopentadienone and 25 ml of triglyme was heated at 200° for 3 hr. The mixture was cooled and chromatographed on silica gel. Elution was carried out with pentane–methylene chloride (20:1, 5:1, 2:1). The first fraction eluted was 1,2,3,4-tetraphenylnaphthalene 0.426 g, mp 205–207° (lit.[3] mp 204°). The nmr spectrum corresponded to that reported.[3]

Registry No.—**1a**, 15037-76-0; **1a** cesium salt, 15037-77-1; **1b**, 15037-78-2; **1b** cesium salt, 15037-79-3; **2a**, 15037-80-6; **2b**, 15037-81-7; N-(2-carbomethoxyphenyl)-N′-*p*-toluenesulfonyldiimide N-oxide, 15037-82-8; triptycene, 477-75-8; 1,2,3,4-tetraphenylnaphthalene 751-38-2; benzyne, 462-80-6.

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Synthesis of Isoquinolines. VII. 4-Hydroxy-1,2,3,4-tetrahydroisoquinolines[1]

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In our original paper describing a new synthesis of 1,2,3,4-tetrahydroisoquinolines[3] (**1** → **2** → **5**), we postulated that the reaction proceeded through a 1,2-dihydroisoquinoline such as **3** (Scheme I). This postulate was based upon the facts that the products of acid treatment of **2** gave dimers characteristic of 1,2-dihydroisoquinolines and that reaction of **2** with benzaldehyde in acid yielded 4-benzylisoquinolines,[4] again a reaction best described through a 1,2-dihydroisoquinoline intermediate.

It now appears that such is not the case under the conditions used. When derivatives of **2** were dissolved in 6 *N* hydrochloric acid and the acid was evaporated under vacuum, 4-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochlorides (**4**) were obtained in good yield. On hydrogenolysis with hydrogen and palladium-on-

(1) (a) Paper VI: J. M. Bobbitt, D. N. Roy, A. Marchand, and C. W. Allen, *J. Org. Chem.*, **32**, 2225 (1967). (b) This work was supported by Grant CA-3905 from the National Cancer Institute of the National Institutes of Health, Public Health Service, and by Contract DA-49-193-MD-2948 from the U. S. Army Medical Research and Development Command, Publication 151.

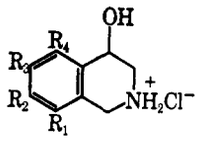
(2) Abstracted in part from the M.S. Thesis of J. C. S., The University of Connecticut, Storrs, Conn., 1966.

(3) J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, **30**, 2247 (1965).

(4) J. M. Bobbitt, D. P. Winter, and J. M. Kiely, *ibid.*, **30**, 2459 (1965).

TABLE I

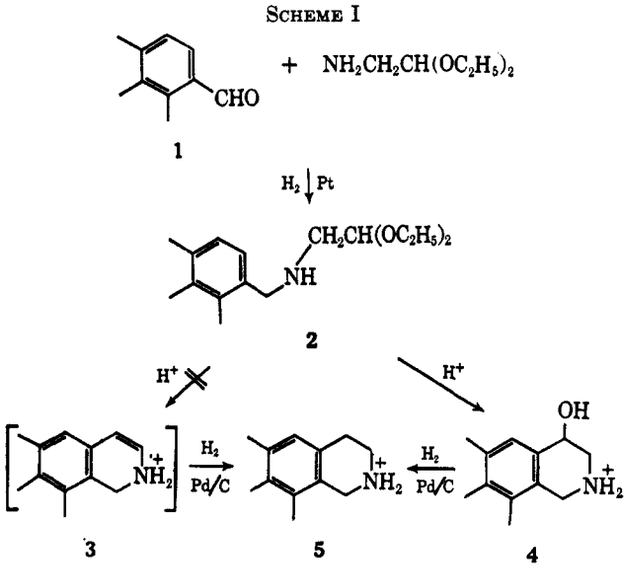
4-HYDROXY-1,2,3,4-TETRAHYDROISOQUINOLINES



Compd	R_1	R_2	R_3	R_4	Yield,[a] %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % Cl	Found, % C	Found, % H	Found, % N	Found, % Cl
6	H	OCH_3	OH	H	77	183–186	51.94	6.06	6.06	15.02	51.88	6.08	5.94	15.56
7	H	OCH_2O		H	62	187–190	52.24	5.24	6.10	15.47	52.53	5.57	6.38	15.78
8	OH	H	H	OH	81	195–197	49.66	5.52	6.44	16.32	49.97	5.20	6.03	16.72
9	OH	OCH_3	H	H	60	203–205	51.94	6.06	6.06	15.02	51.64	6.00	6.09	15.21

[a] Yields are based upon the starting aldehydes.

SCHEME I



carbon, compounds **4** gave the tetrahydroisoquinolines, **5**, as originally described. In this respect, it should be noted that Vinot[5] obtained 4-ethoxy-1,2,3,4-tetrahydroisoquinolines from treatment of **2** with boron trifluoride. The isolation of the derivatives of **4** aids in the elucidation of the original proposed reaction sequence and also constitutes a useful synthetic path to a class of compounds not normally available.[6] The path is quite similar to one attempted by Young and Robinson[7] who obtained low yields of materials which might have been 4-hydroxytetrahydroisoquinolines. Attempts to repeat the work of these authors for comparison purposes were not successful.

Crystalline 4-hydroxy-1,2,3,4-tetrahydroisoquinolines (**6–9**) were isolated in the yields shown in Table I. Compound **6** was characterized as a picrate and free base. The four compounds **6–9** were hydrogenolyzed to the 1,2,3,4-tetrahydroisoquinolines, **5**. One of the tetrahydroisoquinolines, 5,8-dihydroxy-1,2,3,4-tetrahydroisoquinoline, is a new compound and represents the first time that we have carried out a cyclization *ortho* to a phenol group. The preparation of 6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline constitutes an additional application of our general method.[3] In several cases, the 4-hydroxy compounds were not isolable, although, judging from their conversion to 1,2,3,4-tetrahydroisoquinoles,[3] they were almost surely present. These were 7-hydroxy-6-methoxy-, 7-hydroxy- and 7-methoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinolines.

The structure proof of compounds **6–9** is based upon their nmr spectra and their oxidation with periodate.[8] The protons on C-3 and C-4 should give rise to an ABX pattern assuming that those on C-3 are sufficiently different, due to the ring system, to couple with one another. In actual fact, the C-3 protons appeared as a triplet in **6** and as a quartet in **7**, **8**, and **9** in the region τ 6.3–6.7. The additional lines were probably lost in the noise of the spectrum. The proton at C-4 consistently appeared as the expected asymmetric triplet in the region τ 4.9–5.2 in all of the compounds. The protons at C-1 appeared as a singlet in **6** and **7** at τ 5.6–5.8. In the compounds **8** and **9** which contain a substituent on C-8, the situation is somewhat different. The ring system is apparently held in such a position that the two protons are different and form an AB pattern centered at τ 5.7. The two center peaks were readily apparent and one of the side peaks (J = 13 cps) could be observed. The other side peak of the pattern was not observed. The aromatic protons were exactly as predicted for the various arrangements.

One of the alternate structures for **4** would be a 3-hydroxy isomer arising from an acid dehydration followed by a rehydration. If structure **4** is correct as written, it is a 2-amino alcohol and should react with 1 *M* equiv of periodate to yield 1 *M* equiv of formaldehyde. If **4** is the 3-hydroxy isomer it should not react to any extent. Since phenols are known to react[9] with periodate, reliable quantitative data was obtainable on **7** which did, in fact, react with the predicted amount of oxidant. Formaldehyde was assayed by the method of Reeves.[10] Yields of the methone varied from 40 to 71%. The reason for these poor yields in a method which is generally quantitative is not known.

Experimental Section[11]

4-Hydroxy-1,2,3,4-tetrahydroisoquinolines (4).—Substituted N-benzylaminoacetaldehyde diethyl acetals, **2**, were prepared from the appropriate benzaldehydes, **1**, in 0.02-mole quantities by the procedure previously described.[3] The oily bases were dis-

(5) N. Vinot, *Ann. Chim.* (Paris), [13], **3**, 461 (1958); *Bull. Soc. Chim. France*, 617 (1960).

(6) 4-Hydroxy-N-methyl-1,2,3,4-tetrahydroisoquinoline was prepared by I. G. Hinton and F. G. Mann, *J. Chem. Soc.*, 599 (1959), by a rather laborious synthesis.

(7) P. C. Young and R. Robinson, *ibid.*, 274 (1933).

(8) J. M. Bobbitt, *Advan. Carbohydrate Chem.*, **11**, 1 (1956).

(9) E. Adler, I. Falkehag, and B. Smith, *Acta Chem. Scand.*, **16**, 529 (1962).

(10) R. E. Reeves, *J. Am. Chem. Soc.*, **63**, 1476 (1941).

(11) All melting points were taken on a Kofler hot-stage apparatus and are corrected. The microanalyses were performed by H. Fröhofer of the Organic Chemistry Institute of the University of Zürich, Switzerland. The nmr spectra were measured on a Varian A-60 instrument and the shifts are measured from tetramethylsilane as an external standard.

solved in 100 ml of 6 *N* hydrochloric acid and allowed to stand at room temperature for 14–18 hr. The acid solution was concentrated to about 50 ml on a rotary vacuum evaporator. At this point the products precipitated and were separated by filtration and washed with cold absolute ethanol. The compounds could be recrystallized with difficulty and considerable loss from ethanol. Since recrystallization did not seem to raise the melting points and the compounds were homogeneous on tlc (1:25 ammonia–methanol on silica gel G), the crude products were judged pure and were analyzed directly.

Derivatives of 6.—The picrate of **6** was prepared from the hydrochloride and recrystallized from ethanol to yield an analytical sample, mp 185–187°.

Anal. Calcd for $C_{16}H_{16}N_4O_{10}$: C, 45.29; H, 3.80; N, 13.20. Found: C, 45.25; H, 4.01; N, 13.40.

The free base of **6** was prepared by basification, with ammonia, of a concentrated aqueous solution of the hydrochloride. It melted at 218–219° and was washed with cold ethanol prior to analysis.

Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.98; H, 6.99; N, 7.22.

1,2,3,4-Tetrahydroisoquinolines (5).—The 4-hydroxy-1,2,3,4-tetrahydroisoquinolines in 0.02-mole amounts were dissolved in the minimum of cold 6 *N* hydrochloric acid and an amount of 5% palladium-on-carbon equal to the weight of the compound was added. Hydrogenation was carried out at atmospheric pressure and room temperature. The catalyst was removed by filtration and the acid solutions were evaporated to small volumes. Addition of ethanol caused precipitation of the 1,2,3,4-tetrahydroisoquinoline hydrochlorides. In the case of the compounds derived from **8** and **9**, an appreciable amount of product remained with the catalyst and was removed by washing it with boiling methanol which was subsequently added to the aqueous filtrates.

6-Hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (derived from **6**) was obtained in 90% yield and melted at 259–260° (lit.[3] mp 260–263°).

6,7-Methylenedioxy-1,2,3,4-tetrahydroisoquinoline was obtained in 85% yield andm elted at 276–278° (lit.[12] mp 315°). An analytical sample was recrystallized from ethanol.

Anal. Calcd for $C_{10}H_{12}NO_2Cl$: C, 56.20; H, 5.62; N, 6.56; Cl, 16.63. Found: C, 56.59; H, 5.82; N, 6.67; Cl, 17.02.

5,8-Dihydroxy-1,2,3,4-tetrahydroisoquinoline was obtained in 40% yield. The analytical sample was recrystallized from ethanol and melted at 265–267°.

Anal. Calcd for $C_9H_{12}NO_2Cl$: C, 53.60; H, 5.96; N, 6.95; Cl, 17.62. Found: C, 53.39; H, 6.08; N, 7.16; Cl, 17.89.

8-Hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline was obtained in 85% yield and melted at 280–282° (lit.[3] mp 280–283°).

Periodate Oxidation of 7.—Compound **7** (0.1114 g) was dissolved in 5 ml of water and combined with 5 ml of 0.3 *M* sodium metaperiodate. Aliquots of 2 ml were removed at timed intervals and analyzed by the arsenite method.[13] The results were 1 min, 1.05 *M* equiv of periodate; 5 min, 1.08; 15 min, 1.12, and 25 min, 1.20.

The formaldehyde assay[10] was carried out on compounds **6** to **9** with the following results: **6**, 66% of formaldehyde formed; **7**, 40%; **8**, 71%; and **9**, 46%. In each case the methone of formaldehyde obtained was identical with an authentic sample.

Registry No.—**6** (free base), 15051-98-6; **6**, 15051-99-7; **6** picrate, 15052-00-3; **7**, 15052-01-4; **8**, 15052-02-5; **9**, 15052-03-6; 6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline, 1011-43-4; 6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, 15052-05-8; 5,8-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, 15052-06-9; 8-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline, 1610-72-6.

Acknowledgment.—In addition to the financial aid previously acknowledged, the authors are indebted to Drs. S. J. Huang and D. N. Roy of this department for many helpful discussions.

(12) J. S. Buck, *J. Am. Chem. Soc.*, **56**, 1769 (1934). The discrepancy between these melting points is not readily explained. The nmr spectrum of this compound was in complete agreement with the several similar materials prepared in this laboratory.[3]

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3-Substituted Amino-4,5-Disubstituted 1,2,4-4H-Triazole and Aldehyde from 1-Acylsemicarbazide[1]

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Symmetrical diacylhydrazines react with primary amines in the presence of anhydrous zinc chloride to afford 3,4,5-trisubstituted 1,2,4-4H-triazoles[3]. We have now found that 1-benzoylsemicarbazide (Ia) and 1-isonicotinylsemicarbazide (Ib) react with primary amines in the presence of anhydrous zinc chloride to give 3-substituted amino-4,5-disubstituted 1,2,4-4H-triazoles (II). The structure of the triazole (IIa) was confirmed by unambiguous syntheses from 1-benzoyl-4-phenylsemicarbazide (IIIa) as well as from 2-anilino-5-phenylfuradiazole[4] in the presence of aniline and anhydrous zinc chloride. The formation of the triazoles II presumably occurs by initial formation of the semicarbazide III (Scheme I).

A characteristic decomposition of I has also been observed at 260–270° in the presence of anhydrous sodium carbonate giving rise to the aldehyde V in about 15 to 18% yield along with ammonia, carbon monoxide, and nitrogen. This reaction depends on the nature of acyl group; an alkarylacylsemicarbazide (Id) fails to afford the corresponding aldehyde under similar conditions. The formation of the aldehyde evidently proceeds *via* the acyldiimide (IV), reminiscent of the McFadyen and Stevens[5] reaction, but unlike the latter, decomposition of I could not be effected in solvents like ethylene glycol or cyclohexanol. The yield of the aldehyde could not be improved by using potassium carbonate.

It has been observed that 1-acylsemicarbazide–4-substituted 1-acylsemicarbazide can be prepared in good yield by heating a mixture of acylhydrazine and urea or substituted urea in aqueous or alcoholic medium. An attempt to prepare Ib by refluxing isonicotinic acid hydrazide and ureathane was unsuccessful. However a different reaction was observed resulting in the formation of symmetrical diisonicotinylhydrazine[6] (VI) and 2-(4-pyridyl)-1,3,4-oxadiazol-5-one[7] (VII). The product, VI, has obviously been formed by the interaction of two molecules of the hydrazide with elimination of one molecule of hydrazine,[8] whereas VII appears to be formed through the cyclization of the intermediate 1-isonicotinyl-2-carbethoxyhydrazine.[7]

(1) Presented in part at the Joint Convention of the Indian Chemical Society and Chemical Research Committee of the Council of Scientific and Industrial Research, Aligarh, India, 1965. See also S. Dutta, B. P. Das, and U. P. Basu, *Current Sci. India*, **34**, 18 (1965).

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