Derivatives of 1-2*H*-Isoquinolone. V. Some Methyl and Acetyl Derivatives of 1-2*H*-Isoquinolone and of 4-Hydroxy-1-2*H*-isoquinolone (1,2)

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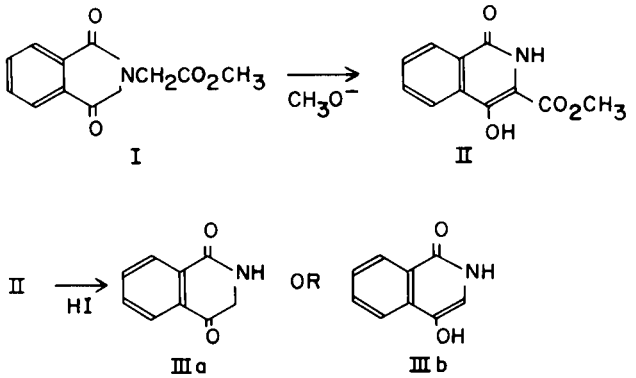
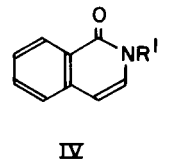
The initial paper (6) in this series described the ultraviolet absorption spectra of the product, 3-carbomethoxy-4-hydroxy-1-2*H*-isoquinolone (II), resulting from the Gabriel-Colman rearrangement of methyl phthalimidoacetate (I), and of the compound (III) formed by decarbomethoxylation of II. Tentative assignments of structure were made on the basis of these spectral studies. The observations tended to confirm Gabriel's (7) assignment of a 4-hydroxy structure to II. The spectral behavior of III, on the other hand, seemed to suggest a predominance of a 1,4-dioxo structure (IIIa) rather than of the 1-oxo-4-hydroxy structure (IIIb) proposed by Gabriel. Subsequent attempts to carry out carbonyl reactions to be expected for structure IIIa were, however, unsuccessful (8), and the chemical behavior of III was generally consistent with structure IIIb. Lombardino (9) has recently reported evidence for conclusively assigning structure IIIb. We can now report our more recent studies on the methylation and acetylation reactions of II and III, and the absorption spectra of the products of these reactions and of the methyl and acetyl derivatives of 1-2*H*-isoquinolone (IVa), which were prepared for comparison.

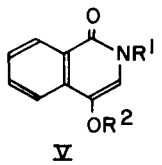


The synthesis of 1-2*H*-isoquinolone (IVa) was accomplished by the procedures described by Chichibabin. In the first procedure (10a), isoquinoline was converted to 1-aminoisoquinoline by a method essentially identical with that for the amination of pyridine (11), and the 1-aminoisoquinoline was subsequently diazotized in sulfuric acid solution. The second procedure (10b) involved the direct action of potassium hydroxide on isoquinoline at the boiling point of isoquinoline, followed by cooling and neutralization. Compound IVa was obtained by this method only when technical grade potassium hydroxide was used. The preparations of 2-methyl-1-2*H*-isoquinolone (IVb), 2-acetyl-1-2*H*-isoquinolone (IVc) and 3-methyl-1-2*H*-isoquinolone (VII) also followed previously published procedures (12,13).



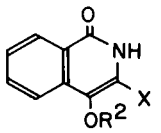
IV

a. R^1 = H
b. R^1 = CH_3
c. R^1 = $COCH_3$



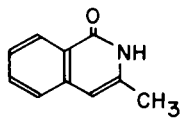
V

a. R^1 = H; R^2 = CH_3
b. R^1 = H; R^2 = $COCH_3$
c. R^1 = R^2 = $COCH_3$
d. R^1 = $COCH_3$; R^2 = CH_3



VI

a. R^2 = $COCH_3$; X = CO_2CH_3
b. R^2 = H; X = CH_3



VII

Attempts to reproduce Gabriel's (14) methylation of III by methyl iodide were unsuccessful. We were successful, however, in converting III to 4-methoxy-1-2*H*-isoquinolone (Va) by the action of dimethyl sulfate on an alkaline solution of III under a hydrogen atmosphere, with a very short reaction time. That methylation did not occur on the nitrogen atom may be demonstrated by comparison of the melting point and absorption spectra of Va with those reported for 2-methyl-4-hydroxy-1-2*H*-isoquinolone, which has been prepared by Lombardino (9). The latter compound melts at 224-227° and shows absorption maxima at 232, 261, and 315 mμ. The methylation of III could also have occurred at the carbonyl oxygen. The presence of an amide carbonyl absorption band at 6.05 μ in the infrared spectrum of Va shows that this did not occur.

The acetylations of II to form 4-acetoxy-3-carbomethoxy-1-2*H*-isoquinolone (VIa) and of III to form 4-acetoxy-1-2*H*-isoquinolone (Vb) were both readily carried out with refluxing acetic anhydride. The presence of an ester carbonyl absorption band at 5.75 μ in the infrared spectrum of Vb showed that an oxygen atom had been acetylated. The infrared spectrum of Vb also showed amide carbonyl absorption at 6.05 μ and a broad band at 3.35-3.85 μ (NH and CH_3), showing that the amide group had not been acetylated. Acetylation of Va and Vb gave, respectively, 2-acetyl-4-methoxy-1-2*H*-isoquinolone (Vd) and 2-acetyl-4-acetoxy-1-2*H*-isoquinolone (Vc). The occurrence of *N*-acetylation, rather than *O*-acetylation, in these cases, is demonstrated by the presence of two carbonyl bands in the infrared spectrum of Vd and three carbonyl bands in the spectrum of Vc. The diagnostic characteristids of the infrared absorption spectra of these compounds are summarized in Table I.

The characteristics of the ultraviolet absorption spectra are presented in Table II. In all cases there is very little difference between the spectra of the alcoholic solutions and the spectra of the aqueous-acidic solutions. The effects of basic conditions upon the spectra were variable, and the compounds have been grouped in Table II on the basis of these effects of alkaline conditions. In all cases, a high *p*H resulted in broadening of the absorption bands and loss of minor elements of the absorption spectra.

The first group of compounds in Table II consists of substances whose spectra were not significantly altered by basic conditions. These were IVa, IVb, IVc, and VII. The structure of IVa has sometimes been written in the tautomeric form of 1-isoquinolinol. This alternate form would be acidic and would be expected to show a bathochromic shift in strongly alkaline solution (*p*H$\sim$12) as the result of the formation of the anion. No such shift has been observed. The remarkable similarity of the absorption spectra of IVa to the spectra of IVb and IVc, which cannot tautomerize to acidic forms, constitutes conclusive evidence for the existence of IVa in the lactam form. For this reason, we feel that the descriptive name 1-2*H*-isoquinolone is preferable to the undescriptive term isocarbostyril as the name of this compound. These observations extend earlier studies (15) of IVa, with the same conclusions.

Similar conclusions may be drawn for 3-methyl-1-2*H*-isoquinolone (VII). The spectra of IVa and of VII were very similar below 300 mμ. The peaks above this wavelength showed small bathochromic shifts with the 3-methyl substituent. The average value of these shifts for all peaks of VII above 300 mμ, and for all conditions, was 8 mμ.

The second spectral group is composed of the 4-hydroxy compounds II, III, and VIb, and the 4-acetoxy derivatives Vb, Vc, and VIa. The acetoxy derivatives and III show appreciable bathochromic shifts in basic solution. It was expected that II and IVb should also show such bathochromic shifts, but II actually shows a 5-mμ hypsochromic shift, and the spectrum of VIb in basic solution has no peaks. The spectra of III and Vc in basic solution are fairly similar, suggesting that the shifts observed with the acetoxy derivatives may be due to partial saponification.

The spectra of III and Vc in alcoholic and acidic solutions are also sufficiently similar to conclude that these two compounds are similar in structure in nonalkaline media. Comparison of the spectra of III and of its 3-methyl derivative, VIb, shows that 3-methyl substitution contributes an 8-mμ bathochromic shift to the longest wavelength absorption band, in surprisingly good agreement with the observation obtained from comparison of IVa and VII.

The last group of compounds consists of the 4-methoxy derivatives Va and Vd. The spectra of these compounds were similar to each other, and were also similar to the spectra of III in alcoholic and acidic solutions.

TABLE I

Infrared Absorption Spectra

Compound	OH-NH Region, μ	Carbonyl Region, μ
IVa	3.3-3.6	6.06
IVb	-----	6.07
IVc	-----	5.87 (a) 6.01 (a)
VII	3.3-3.6	6.08
II	3.15-3.5	6.05-6.17
III	3.1-3.6	6.05
Va	3.35-3.65	6.05
Vb	3.3-3.85	5.75 6.05
Vc	-----	5.73 5.86 5.95
Vd	-----	5.85 5.98

(a) Reference 13.

EXPERIMENTAL

Melting points were determined with an Electrothermal melting point apparatus and are not corrected. Microanalyses were done by Midwest Microlab, Inc., Indianapolis, Indiana.

The following compounds were prepared by previously de-

TABLE II

Ultraviolet Absorption Spectra

Compound	in 95% EtOH		in dil HCl		in dil. NaOH	
	λ max, mμ	log ε max	λ max, mμ	log ε max	λ max, mμ	log ε max
IVa	247.5	3.96	----	----	----	----
	275	3.91	271	3.92	274 (a)	3.78
	282	3.94	279	3.92	280	3.82
	315 (a)	3.65	315 (a)	3.69	----	----
	323	3.70	322	3.75	322	3.70
	336 (a)	3.55	334 (a)	3.61	334 (a)	3.60
IVb	248.5	3.93	----	----	----	----
	279	3.99	276	3.90	276	3.81
	287	3.99	284	3.91	284	3.83
	315 (a)	3.66	315 (a)	3.64	315 (a)	3.65
	323.5	3.72	322.5	3.70	323	3.70
	336 (a)	3.57	333 (a)	3.58	333	3.58
IVc	224	4.82	228	4.81	----	----
	239 (a)	4.60	238 (a)	4.35	238 (a)	4.30
	247	4.21	245	4.17	246 (a)	4.21
	275	4.17	273	4.13	275 (a)	4.04
	281	4.16	280	4.12	281	4.07
	315 (a)	4.11	315 (a)	3.87	312	3.95
	323	4.19	322	3.93	321	3.93
	335 (a)	4.12	337 (a)	3.79	334 (a)	3.84
VII	----	----	228	4.16	----	----
	238 (a)	3.91	----	----	----	----
	247	3.80	246 (a)	3.77	246 (a)	3.85
	2.77	3.84	273	3.79	281	3.76
	284 (a)	3.82	280 (a)	3.77	----	----
	321 (a)	3.50	322 (a)	3.52	----	----
	330	3.55	330	3.57	330	3.58
	343 (a)	3.41	344 (a)	3.44	344 (a)	3.46
II	215	4.48	212	4.45	----	----
	272	3.71	270	3.69	----	----
	335 (a)	4.10	335	4.12	----	----
	340	4.11	340	4.11	365	4.10
III	249	3.68	248	3.71	----	----
	258 (a)	3.59	258 (a)	3.62	----	----
	273 (a)	3.49	274 (a)	3.52	266 (a)	3.40
	302	3.82	297	3.81	283 (a)	3.29
	338	3.74	334	3.75	379	3.56
Vb	226	4.22	227	4.32	----	----
	243	4.02	241 (a)	4.10	----	----
	252	3.98	250	4.03	----	----
	283	3.96	278	3.98	----	----
	290	3.96	285	3.97	----	----
	320 (a)	3.71	319 (a)	3.78	273 (a)	3.31
	328	3.74	327	3.83	282 (a)	3.11
	341 (a)	3.56	338 (a)	3.60	398	3.65

Table II - Continued

Vc	----	----	241	4.14	----	----
	251	4.06	250.5	4.04	----	----
	280	4.01	279	4.01	----	----
	289	4.00	286	4.00	257 (a)	3.62
	----	----	317 (a)	3.78	267 (a)	3.75
	329	3.79	327	3.82	332	3.82
	----	----	340 (a)	3.69	379	3.76
VIa	232 (a)	4.73	228	4.45	----	----
	254 (a)	4.35	252	4.27	----	----
	310	3.93	310	3.93	----	----
	323	4.04	323	4.05	252 (a)	4.14
	339	4.04	339	4.05	372	4.14
VIb (b)	254 (a)	3.67	252 (a)	3.80	(c)	----
	296	3.71	285	3.56	(c)	----
	346	3.42	342	3.28	(c)	----
Va	228	3.79	230	3.72	----	----
	235 (a)	3.66	235 (a)	3.70	(c)	----
	250.5	3.54	250.5	3.54	----	----
	259.5	3.47	259.5	3.50	251	3.73
	296	3.73	297	3.69	256 (a)	3.66
	335	3.56	338	3.59	323	3.65
Vd	----	----	248 (a)	3.95	----	----
	259.5	3.82	259 (a)	3.83	250	4.05
	294	4.02	292	4.01	255 (a)	3.99
	338	3.88	336	3.88	319	4.00

(a) Shoulder. (b) Reference 6. (c) No peaks.

scribed methods: 1-2*H*-isoquinolone (IVa) (10), 2-methyl-1-2*H*-isoquinolone (IVb) (12), 2-acetyl-1-2*H*-isoquinolone (IVc) (13), and 4-hydroxy-3-carbomethoxy-1-2*H*-isoquinolone (11) (16).

4-Hydroxy-1-2*H*-isoquinolone (III).

To 4.4 g. (0.02 mole) of II was added 35 ml. of colorless, constant-boiling (125°) hydroiodic acid which had been freshly distilled under hydrogen in the presence of hypophosphorous acid (17). The mixture was refluxed with stirring, under a hydrogen atmosphere, for 90 minutes. The clear, yellow solution solidified on cooling to room temperature. To the solid mass was added 100 ml. of distilled water. The mixture was rapidly heated to boiling, then immediately chilled in an ice bath. The resulting yellowish precipitate was removed by filtration, washed several times on the filter with cold, distilled water, and dried under hydrogen. The yield was 3.06 g. (94%). The ultraviolet spectra and lack of melting point below 300° were in agreement with previous reports (6,7,14).

4-Methoxy-1-2*H*-isoquinolone (Va).

To a stirred, refluxing solution of 1.61 g. (0.01 mole) of III in 50 ml. 0.4 *N* potassium hydroxide under hydrogen was rapidly added 2.52 g. (0.02 mole) of dimethyl sulfate. The color of the mixture quickly changed from deep-brown to yellow, and a precipitate appeared. After 10-15 minutes of refluxing under hydrogen, the mixture was chilled and filtered, giving 1 g. of product. Addition of dry ice to the filtrate precipitated an additional 0.5 g. The combined precipitates were recrystallized from acetone, yielding colorless crystals melting at 170-171°. The reported (14) melting point of Va is 170-171°.

4-Acetoxy-1-2*H*-isoquinolone (Vb).

A mixture of 1.3 g. (0.008 mole) of III and 10 ml. of acetic anhydride was refluxed with stirring for 30 minutes, cooled to room temperature, and diluted with 100 ml. of cold, distilled water. The mixture was chilled in an ice bath for one hour and filtered, giving 1.13 g. (69%) of yellowish crystals melting at 214-216°. Three recrystallizations from ethyl acetate gave white crystals melting at 219-220°. Repetition of this procedure with addition of 5 drops of 85% phosphoric acid gave a 70% yield.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.28; H, 4.62; N, 7.02.

2-Acetyl-4-acetoxy-1-2*H*-isoquinolone (Vc).

A mixture of 1.012 g. (0.005 mole) of Vb, 10 ml. of acetic anhydride, and 5 drops of 85% phosphoric acid was refluxed with stirring for 30 minutes. The resulting clear, green solution was cooled to room temperature and diluted with 100 ml. of cold, distilled water. The mixture was chilled and filtered, giving one g. (80%) of a white precipitate, melting at 119-120° after three recrystallizations from 1:1 acetone-chloroform.

Anal. Calcd. for $C_{13}H_{11}NO_4$: C, 63.76; H, 4.52; N, 5.70. Found: C, 63.78; H, 4.68; N, 5.51.

2-Acetyl-4-methoxy-1-2*H*-isoquinolone (Vd).

A mixture of 0.5 g. (0.0028 mole) of Va, 5 ml. of acetic anhydride, and 3 drops of 85% phosphoric acid was refluxed for 20 minutes with stirring. The yellow solution was cooled to room temperature and diluted with 50 ml. of cold, distilled water, to give a pinkish precipitate. Recrystallization of the precipitate from chloroform gave 0.32 g. (52%) of white crystals, melting at 108-109°.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.54; H, 5.28; N, 6.99.

4-Acetoxy-3-carbomethoxy-1-2*H*-isoquinolone (VIa).

A mixture of one g. (0.0045 mole) of II and 10 ml. of acetic anhydride was refluxed 1.5 hours with stirring. The deep-yellow solution yielded 1.1 g. (90%) of pale-pink precipitate on cooling and dilution with 100 ml. of cold, distilled water. The product melted at 186-187° after recrystallization from 1:1 acetone-chloroform, or from 1:1 benzene-hexane.

Anal. Calcd. for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.24; N, 5.36. Found: C, 60.47; H, 4.52; N, 5.60.

3-Methyl-1-2*H*-isoquinolone (VII) (18).

The synthesis of 3-methyl-1-2*H*-isoquinolone was accomplished from 3-methylisoquinoline, by way of the 2-oxide, following the procedure of Robison and Robison (13). Repeated recrystallization of the product from 50% ethanol yielded a fine, white powder melting very sharply at 219.0°. The melting point of VII has previously been reported as 210.5-212.5° (13) and 212-214° (19).

Anal. Calcd. for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.43; H, 5.80; N, 8.70.

Determination of Absorption Spectra.

The infrared absorption spectra were measured with a Beckman IR-5 infrared spectrophotometer, using potassium bromide pellets containing 0.3-0.4%, by weight, of the sameple.

The ultraviolet absorption spectra were determined with a Cary Model 15 recording spectrophotometer, using 1-cm. cylindrical cells and concentrations of 10^{-5} to 10^{-2} molar. The acidic and basic solutions were prepared by dilution of 10^{-2} molar stock solutions in 95% ethanol with 0.1 *N* hydrochloric acid or with 0.1 *N* sodium hydroxide. The approximate *p*H values of the acidic and basic solutions were 1 and 12, respectively.

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Received July 6, 1970

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